INNOVATIONS
In Cancer Prevention and Research Conference

PROGRAM & ABSTRACTS

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CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

NOVEMBER 13-14

2017

RENAISSANCE HOTEL
AUSTIN, TEXAS

The 2017 CPRIT INNOVATIONS IN CANCER PREVENTION AND RESEARCH PROGRAM AND ABSTRACTS BOOK is published by the Cancer Prevention and Research Institute of Texas (CPRIT).

Printed in the United States.

INNOVATIONS V
In Cancer Prevention and Research Conference

Program Guide

Abstracts

Academic Research

Product Development Research

Prevention

CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

ABOUT CPRIT

Texas voters overwhelmingly approved a constitutional amendment in 2007 establishing the Cancer Prevention and Research Institute of Texas and authorizing the state to issue $3 billion in bonds to fund groundbreaking cancer research and prevention programs and services in Texas. CPRIT's goal is to expedite innovation in cancer research and product development, and to enhance access to evidence-based prevention programs throughout the state.

CPRIT's objective is to position Texas as a world-class leader in research and prevention through collaboration with a variety of entities, including public and private institutions of higher education, governmental and nongovernmental organizations, and private companies and others involved in the fight against cancer. CPRIT supports innovation in the selection of research projects emphasizing immediate or long-term medical breakthroughs; product development translational opportunities for research, and prevention services and health education for citizens with culturally appropriate information about ways in which their risks of developing and dying from cancer can be reduced. CPRIT accepts applications and awards grants for a wide variety of cancer-related research and for the delivery of cancer prevention programs and services by public and private entities located in Texas.

To date, CPRIT has awarded more than $1.89 billion in grants to Texas researchers, institutions and organizations. CPRIT provides funding through its academic research, prevention and product development research programs. Programs made possible with CPRIT funding have reached all 254 counties of the state, brought 135 distinguished researchers to Texas, advanced scientific and clinical knowledge, and provided more than 4 million life-saving education, training, prevention and early detection services to Texans.

More information about CPRIT is available at www.cprit.texas.gov. Follow CPRIT on Twitter @CPRITTexas and Facebook.

CPRIT OVERSIGHT COMMITTEE

CPRIT is governed by nine dedicated Texans who together comprise the Oversight Committee. Oversight Committee members are appointed by the Governor, the Lieutenant Governor, and the Speaker of the House to serve staggered terms. The Oversight Committee meets at least once every quarter.

Will Montgomery, Dallas, Presiding Officer

Donald “Dee” Margo, El Paso, Assistant Presiding Officer

Amy Mitchell, Austin, Secretary

Angelos Angelou, Austin

David Cummings, MD, San Angelo

Pete Geren, Fort Worth

Ned Holmes, Houston

Mahendra C. Patel, MD, San Antonio

Craig Rosenfeld, MD, Dallas

CPRIT EXECUTIVE TEAM

CPRIT’s efforts are guided by an executive team that is committed to fulfilling CPRIT’s mission to find and fund the best cancer prevention, academic research, and product development research projects in Texas.

Wayne Roberts, *Chief Executive Officer*

Kristen Doyle, *Deputy Executive Officer and General Counsel*

Vince Burgess, *Chief Compliance Officer*

Rebecca Garcia, PhD, *Chief Prevention and Communications Officer*

James K.V. Willson, MD, *Chief Scientific Officer*

Michael Lang, *Chief Product Development Officer*

Heidi McConnell, *Chief Operating Officer*

SCHEDULE AT A GLANCE

MONDAY, NOVEMBER 13

8:30 A.M. **9:00 A.M.**	Opening Session Ballroom A	***CPRIT: Today and Tomorrow*** Wayne Roberts, Chief Executive Officer, CPRIT ***Welcome - CPRIT Oversight Committee Presiding Officer*** Will Montgomery, CPRIT
9:05 A.M. **9:50 A.M.**	Opening Session Ballroom A	***Precision Medicine in Cancer Prevention, Screening, and Treatment: The HPV Paradigm*** Douglas Lowy, MD, National Cancer Institute (NCI)
10:00 A.M. **11:30 A.M.**	General Session Ballroom A	***Evolving Developments In Immunotherapy: A Look at the Future*** Moderator: Patrick Hwu, MD, UT MD Anderson Cancer Center Harpreet Singh, PhD, Immatics US, Inc. Helen Heslof, MD, Baylor College of Medicine Jennifer Wargo, MD, MMSc, UT MD Anderson Cancer Center
11:30 A.M. **12:30 P.M.**	*Lunch Provided* Ballroom B & Arbor	*No Program*
12:30 P.M. **1:30 P.M.**	**Concurrent Session** Academic Research & Prevention Ballroom A	***Epigenome-Environment Interactions — Impact on Cancer Risk and Targets for Prevention*** Cheryl Lyn Walker, PhD, Baylor College of Medicine Margaret Kripke, PhD, UT MD Anderson Cancer Center
	Product Development Research Glass Oaks	***Product Development Research Company Showcase*** Moderator: Mike Lang, CPRIT
1:45 P.M. **2:45 P.M.**	**Concurrent Session** Academic Research & Prevention Ballroom A	***Liquid Biopsies: State of the Science for Early Detection, Diagnosis*** Moderator: Stanley R. Hamilton, MD, UT MD Anderson Cancer Center Anirban Maitra, MBBS, UT MD Anderson Cancer Center Victor Ugaz, PhD, Texas A&M University
	Product Development Research Glass Oaks	***Product Development Research Company Showcase - cont'd***
3:00 P.M. **4:45 P.M.**	**Concurrent Session** Posters Rio Grande Hall	***Poster Group A***
	Product Development Research Glass Oaks	***Product Development Research Company Showcase - cont'd***

TUESDAY, NOVEMBER 14

8:00 A.M. **8:45 A.M.**	Opening Session Ballroom A	***When Precision Medicine Is Not So Precise*** Neil Spector, MD, Duke Cancer Institute
8:45 A.M. **10:00 A.M.**	General Session Ballroom A	***Diet, Obesity, Lifestyle and Cancer: Risk and Survival*** Moderator: Ross Brownson, PhD, Washington University in St. Louis Charles S. Fuchs, MD, MPH, Yale Cancer Center, Smilow Cancer Hospital Graham A. Colditz, DrPH, MD, MPH, Washington University in St. Louis
10:00 A.M. **11:30 A.M.**	Posters Rio Grande Hall	***Poster Group B***
11:30 A.M. **12:30 P.M.**	*Lunch Provided* Ballroom B & Arbor	*No Program*
12:30 P.M.	**Concurrent Session** Academic Research Ballroom A	***Progress on Childhood Cancer Research*** Moderator: Stephen X. Skapek, MD, UT Southwestern Medical Center Abbey Berenson, MD, PhD, UT Medical Branch at Galveston Barry Maurer, MD, PhD, Texas Tech University Health Sciences Center Brendan Lee, MD, PhD, Baylor College of Medicine James Amatruda MD, PhD, UT Southwestern Medical Center Joshua Mendell, MD, PhD, UT Southwestern Medical Center Peter Houghton, PhD, UT Health Science Center at San Antonio
	Prevention Wedgwood	***Dissemination and Implementation Science for Cancer Control: Realizing the Potential of Discoveries*** Ross Brownson, PhD, Washington University in St. Louis
1:15 P.M.	Product Development Research Glass Oaks	***Clinical Trial Design*** George Peoples, COL (ret), MD, FACS, Cancer Insight and the Cancer Vaccine Development Program (CVDP), Metis Foundation

TUESDAY, NOVEMBER 14

1:20 P.M. – **2:05 P.M.**

Concurrent Session

Academic Research

Ballroom A — ***Progress on Childhood Cancer Research - cont'd***

Prevention

Wedgwood — ***Approaches to Community Needs Assessment and Stakeholder Engagement***
Billy U. Philips, PhD, MPH, Texas Tech University Health Sciences Center
Kenneth Stewart, PhD, Angelo State University

Product Development Research

Glass Oaks — ***High Cancer Drug Prices: Causes, Patient Impact and Potential Solutions***
Hagop M. Kantarjian, MD, UT MD Anderson Cancer Center

2:25 P.M. – **3:10 P.M.**

Concurrent Session

Academic Research

Ballroom A — ***Update on CPRIT-Funded Core Facility Research***
Moderator: James K.V. Willson, MD, CPRIT
Funda Meric-Bernstam, MD, UT MD Anderson Cancer Center
Gaudenz Danuser, PhD, UT Southwestern Medical Center
Martin M. Matzuk, MD, PhD, Baylor College of Medicine, Ben Taub General Hospital
Michael Scheurer, PhD, MPH, Baylor College of Medicine

Prevention

Wedgwood — ***Dissemination and Implementation – Strategies and Examples***
Moderator: Rebecca Garcia, PhD, CPRIT
Jane Bolin, PhD, JD, BSH, Texas A&M Health Science Center
Lorraine Reitzel, PhD, FAAHB, University of Houston
Maria Fernandez, PhD, UT Health Science Center at Houston
Rakhshanda Rahman, MD, FRCS, FACS, Texas Tech University Health Sciences Center

Product Development Research

Glass Oaks — ***Start-up Trials and Tribulations***
Moderator: Matt McManus, MD, PhD, Asuragen, Inc.
Fahar Merchant, PhD, Medicenna Therapeutics, Inc.
Harpreet Singh, PhD, Immatics US, Inc.
Jon Northup, Beta Cat Pharmaceuticals, LLC

3:15 P.M. – **4:00 P.M.**

Concurrent Session

Academic Research

Ballroom A — ***CPRIT Academic Research RFA Funding Mechanisms***
James K.V. Willson, MD, CPRIT

Prevention

Wedgwood — ***Dissemination and Implementation – Strategies and Examples - cont'd***

Product Development Research

Glass Oaks — ***Start-up Trials and Tribulations - cont'd***

DETAILED SESSION DESCRIPTIONS AND SPEAKER INFORMATION

MONDAY, NOVEMBER 13

8:30 – 9:00 AM - OPENING SESSION

Where: **Ballroom A** ***CPRIT: Today and Tomorrow***

Wayne Roberts
Chief Executive Officer
Cancer Prevention and Research Institute of Texas

Wayne Roberts was named Chief Executive Officer of the Cancer Prevention and Research Institute of Texas (CPRIT) in November 2013 after serving since December 2012 as the Interim Executive Director.

Prior to four years with The University of Texas Health Science Center at Houston as Associate Vice President for Public Policy, Mr. Roberts' career was weighted towards public finance and budget, especially with respect to higher education. He held numerous senior positions under Governor Rick Perry in which, among other things, he authored the white paper and draft legislation creating the Texas Emerging Technology Fund to catalyze economic development, including transferring research conducted at universities to the Texas marketplace.

Mr. Roberts served Governor George W. Bush as Deputy and Acting State Budget Director. He was Lieutenant Governor Bob Bullock's special assistant for budget and human services following 18 years with the Legislative Budget Board.

He received a B.A.with honors and special honors in government from The University of Texas at Austin and a masters from the Lyndon B. Johnson School of Public Affairs at UT.

Welcome - CPRIT Oversight Committee Presiding Officer

Will Montgomery
Presiding Officer, Oversight Committee
Cancer Prevention and Research Institute of Texas

Mr. Montgomery is a partner at Jackson Walker LLP, where his practice focuses on commercial litigation and arbitration. He is experienced in all aspects of litigation, including jury and non-jury trials, arbitration, and mediation.

In recent comments, he expressed a personal stake in helping to steer CPRIT toward success in championing treatments and cures for cancer: "Cancer is a scourge that has touched families throughout Texas, including my own," Montgomery told *D Healthcare Daily.* "My father was a cancer researcher, ironically contracting cancer late in his life. My brother recently died of cancer. I am honored to have the opportunity to serve the state and to help accomplish CPRIT's mission to educate, prevent, and discover causes and possible cures for cancer."

Mr. Montgomery was admitted to the Texas State Bar in 1984. He received his BA and his MA degrees from Stanford University. He received his JD degree from the University of Chicago.

9:05 – 9:50 AM - OPENING SESSION

Where: **Ballroom A** Topic: ***Precision Medicine in Cancer Prevention, Screening, and Treatment: The HPV Paradigm***

Precision (personalized) medicine often refers to interventions for the treatment of established disease, such as cancer. However, the principles of precision medicine – interventions based on a molecular understanding of disease – are equally relevant to cancer prevention and screening. Recognition of HPV infection as the main cause of cervical cancer and a high proportion of several other cancers has led to several successful etiology-based interventions. They include: 1) primary prevention of HPV-associated cancers by FDA-approved HPV vaccines; 2) secondary prevention of cervical cancer by FDA-approved HPV-based screening; and 3) treatment of HPV-associated cancer by candidate interventions directed against HPV-encoded proteins in the cancer. The treatment approach may improve the outlook and clinical outcome for patients who develop HPV-associated cancers, while the prevention and screening approaches have the long-term potential to eliminate these cancers as a worldwide public health problem. The relevance of these advances to other cancers, including tumors not attributable to infectious oncogenic agents, will be discussed.

Douglas Lowy, MD
Chief, Laboratory of Cellular Oncology and Senior Investigator Head, Signaling and Oncogenesis Section
National Cancer Institute

Since 2010, Dr. Lowy has helped to lead NCI's key scientific initiatives. A cancer researcher for more than 40 years, Dr. Lowy received the National Medal of Technology and Innovation from President Obama in 2014 for his research that led to the development of the human papillomavirus (HPV) vaccine. As chief of the Laboratory of Cellular Oncology in the Center for Cancer Research at NCI, Dr. Lowy's research includes the biology of papillomaviruses and the regulation of normal and neoplastic growth. For his pioneering work, Dr. Lowy has received numerous honors in addition to the National Medal, including the 2017 Lasker-DeBakey Clinical Medical Research Award, the 2011 Albert B. Sabin Gold Medal Award and the Federal Employee of the Year Award in 2007 from the Partnership for Public Service.

10:00 – 11:30 AM - GENERAL SESSION

Where: **Ballroom A** Topic: ***Evolving Developments In Immunotherapy: A Look at the Future***

Creative new ways to stimulate the immune system against cancer, including molecularly engineering T-cells continue to emerge daily. The dramatic and long-lasting results seen in responding patients have bolstered the efforts of the scientific community. Attend this session to hear the current state of the art in immunotherapy as well as future directions.

Moderator

Patrick Hwu, MD
Head of the Division of Cancer Medicine; Chair, Departments of Melanoma and Sarcoma Medical Oncology
The University of Texas MD Anderson Cancer Center

Dr. Hwu is a tumor immunologist focused on the areas of vaccines, adoptive T-cell therapies, and immune resistance. His research and clinical efforts have led to insights and advances in the understanding of the interactions between tumors and the immune system, and the development of cellular therapies. He is the principal investigator on several peer-reviewed grants including NIH translational immunotherapy R01s. Based on the work in his lab, several ongoing clinical trials have resulted, including a trial of T-cells gene-modified to enhance resistance against TGF-b. Most recently, his preclinical studies have focused on combinations of immune checkpoint blockade and T-cell therapy, as well as rational combinations of targeted therapies and immunotherapies. In recognition of his outstanding contributions to cancer research, Dr. Hwu has held endowed positions since joining the institution. He currently holds the Sheikh Mohammed Bin Zayed Al Nahyan Distinguished University Chair at MD Anderson.

Speakers

Harpreet Singh, PhD
Chief Executive Officer
Immatics US, Inc.

With help from a CPRIT grant, Dr. Singh co-founded Immatics US, Inc. As Immatics Biotechnologies GmbH managing director and chief scientific officer, he is dedicated to the translation of science into highly innovative cancer immunotherapeutics. At Immatics GmbH, Dr. Singh leads a team dedicated to target and TCR discovery, immunology, manufacturing, and translational development. Dr. Singh holds numerous patents and is the co-author of 30 publications in peer-reviewed journals, including *Nature Medicine, Nature Biotechnology, Journal of Experimental Medicine, and Brain and Blood*.

Helen Heslop, MD
Associate Director for Clinical Research
Dan L. Duncan Cancer Center, Baylor College of Medicine

Dr. Heslop oversees several peer-reviewed clinical research projects, including: an NCI-funded program project grant (Enhancing T-Cell Therapy of Cancer), a SPORE grant in Lymphoma, and a Leukemia and Lymphoma Society Specialized Center of Research (SCOR) award. A Doris Duke Distinguished Clinical Scientist, Dr. Heslop has extensive experience in mentoring both clinical and laboratory trainees. She has extensive experience with clinical cell therapy studies, and serves with Dr. Malcolm Brenner and Bambi Grilley as sponsor for more than 20 active cell and gene therapy INDs.

Jennifer Wargo, MD, MMSc
Associate Professor, Department of Surgical Oncology, Division of Surgery and Department of Genomic Medicine, Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center

Dr. Wargo's research focuses on critical studies to better understand the effects of BRAF inhibition on immune responses in melanoma, and establishing a unique set of serial tumor biopsies and blood samples from patients enrolled in clinical trials on BRAF inhibitors. Through analysis of these samples, she has contributed significantly to the world literature regarding resistance mechanisms and the effect of targeted therapy on anti-tumor immunity. In September 2013, MD Anderson Cancer Center recruited Dr. Wargo to continue this work and to build a program to collect serial biopsies in patients with melanoma and other cancers on targeted therapy and immunotherapy, and to better understand responses to therapy and to develop novel strategies to combat resistance.

11:30 AM – 12:30 PM - LUNCH PROVIDED - NO PROGRAM

Where: **Ballroom B & Arbor**

12:30 – 1:30 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH/PREVENTION

Where: **Ballroom A** Topic: ***Epigenome-Environment Interactions — Impact on Cancer Risk and Targets for Prevention***

Our expanding knowledge about the role of epigenomic alterations in cancer has opened the door for understanding how epigenome-environment interactions drive the development of this disease, and provided new opportunities for identifying strategies that can exploit epigenomic plasticity for cancer prevention. Importantly, environmental exposures that occur early in life can have a profound effect on the epigenome of developing tissues, altering the epigenome in ways that persist long after the initial exposure. This type of "developmental reprogramming" of the epigenome can persist into adulthood, and dramatically increase cancer risk across the life course. To address this important new area of research, Baylor College of Medicine has established the Center for Precision Environmental Health, where faculty work to understand the causes of cancer and other diseases through research at the intersection of genetics/epigenetics, environmental health and data science (GxExD). Attend this session to hear more about recent insights into how the environment affects cancer risk, and how our growing knowledge in the area of epigenome-environment interactions is presenting new opportunities for interventions targeting the epigenome to reduce cancer risk.

Cheryl Lyn Walker, PhD
Director, Center for Precision Environmental Health
Baylor College of Medicine

A renowned molecular biologist, Dr. Walker joined the faculty of Baylor College of Medicine to develop its Center for Precision Environmental Health. She also currently directs the NIEHS Center for Translational Environmental Health Research, and serves on the board of Scientific Advisors for the National Cancer Institute and is a member of the National Academy of Sciences, Medicine and Engineering Committee on Gulf War and Health. An international leader in environmental carcinogenesis and elucidating molecular mechanisms of disease, Dr. Walker's studies on the role of the epigenome in gene-environment interactions have yielded significant insights into mechanisms by which early life exposures influence health and disease across the life course. Her work has also led to the discovery of new tumor suppressor functions in the cell and a dual role for the cell's epigenetic machinery in regulating both chromatin and the cytoskeleton. She has been recognized with the Dallas-Ft. Worth Living Legend Faculty Achievement Award in Basic Research from MD Anderson Cancer Center, the Cozzarrelli Prize from the National Academy of Sciences, the 2015 Outstanding Distinguished Scientist Award from Sigma Xi, and the 2016 Leading Edge in Basic Research Award from the Society of Toxicology.

Margaret Kripke, PhD
Professor Emerita
The University of Texas MD Anderson Cancer Center

Best known for her work in immunology of skin cancer, Dr. Kripke showed that chronic exposure to UV radiation produces cancers that are highly antigenic and that immune alterations induced by UV are responsible for tumor survival and spread. She discovered that mice exposed to UV radiation develop a selective, systemic immune suppression, and her work led to a new field of photoimmunology. Dr. Kripke's research has provided insight into how an immune system compromised by UV radiation contributes to the development of melanoma and increased vulnerability to infectious diseases.

Dr. Kripke established a new basic research department at The University of Texas MD Anderson Cancer Center and later served as vice president for academic programs and executive vice president and chief academic officer. She has been a leader in many organizations dedicated to research and collaboration and has contributed substantially to the field of environmental science. She served as CPRIT's Chief Scientific Officer from 2012 to 2015.

12:30 – 1:30 PM - CONCURRENT SESSION 2 - PRODUCT DEVELOPMENT RESEARCH

Where: **Glass Oaks** Topic: ***Product Development Research Company Showcase***

CPRIT has invested in the development of over 30 novel cancer products including immunotherapies, drugs, biologics, molecular diagnostics, devices, and services. This session provides an opportunity for attendees to hear about the research and development of promising new products and services. Company representatives will provide 15-minute overviews of their innovative new offerings. Each company will have a table set up in the Glass Oaks Ballroom to answer questions and interact with attendees.

Mike Lang
Chief Product Development Research Officer
Cancer Prevention and Research Institute of Texas

Mike Lang leads CPRIT's product development research program, designed to accelerate the progression of new cancer drugs, diagnostics, and therapies from the laboratory into clinical practice. His multi-state experience includes founding and serving as chief executive officer of a cancer diagnostic company, serial entrepreneurship, and managing a portfolio for an early stage investment. Prior to joining CPRIT in November 2015, Mr. Lang was the founder and CEO of NanoVision, a cancer diagnostics company. He headed business development at the venture capital-funded wound healing company Gilatech, where he led its novel biomaterial therapy. Lang oversaw a company restructuring as president of Dallas-based Galt Medical, served as a product manager at Johnson & Johnson, and was vice president of business development at BioEnterprise, where he directed the startup and growth of early stage firms. Mr. Lang has a BS in biomedical engineering from Northern Arizona University and a MBA from Arizona State University.

1:45 – 2:45 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH/PREVENTION

Where: **Ballroom A** Topic: ***Liquid Biopsies: State of the Science for Early Detection, Diagnosis***

Liquid biopsies to test for tumor products in blood and other body fluids promise a less invasive way of evaluating patients with cancer than traditional methods. Although numerous companies currently market liquid biopsies, commercial applications remain largely limited to improving treatment selection for late-stage cancers and monitoring for recurrence. Research and funding are increasing as companies work to improve methodologies and results, as well as to broaden the market. Pushing development into earlier cancer stages for screening, surveillance and diagnosis has high priority. Attend this session to hear an update on the process as well as presentations of successful examples.

Moderator

Stanley R. Hamilton, MD
Professor and Head of Pathology and Laboratory Medicine
The University of Texas MD Anderson Cancer Center

Dr. Hamilton has been involved in research and clinical applications of the molecular pathology of gastrointestinal neoplasms since 1982. Of his 341 peer-reviewed publications, over 200 address this topic, including two of the earliest evaluations of genomics as prognostic markers in colorectal adenocarcinoma. In addition, Dr. Hamilton has been active in the cooperative oncology group clinical trials setting for 25 years as a member of the Eastern Cooperative Oncology Group, now the ECOG-ACRIN Cancer Research Group in the National Clinical Trials Network (NCTN). He has published correlative studies of molecular biomarkers using specimens from ECOG clinical trials. The clinical laboratories at UTMDACC under his direction provided the pre-analytics and analytics for 2,843 tumors for E5202, the first integral-marker phase III clinical trial in colon cancer in the NCI cooperative group setting, and 5,946 tumors for NCI-MATCH (EAY131). Dr. Hamilton is a member of the ECOG-ACRIN Leadership as Deputy Chair for Laboratory Science.

Speakers

Anirban Maitra, MBBS
Professor of Pathology and Translational Molecular Pathology Scientific Director, Sheikh Ahmed Center for Pancreatic Cancer Research Co-Leader, MD Anderson Pancreatic Cancer Moon Shot™
The University of Texas MD Anderson Cancer Center

Dr. Maitra is Professor of Pathology and Translational Molecular Pathology at UT MD Anderson Cancer Center, and Scientific Director of the Sheikh Ahmed Bin Zayed Center for Pancreatic Cancer Research (since August 1, 2013). Over the past decade, his group has made several seminal observations in the biology and genetics of pancreatic cancer. His laboratory has access to large numbers of well annotated samples of pancreatic adenocarcinomas and precursor lesions, as well as human patient derived xenograft models. He also has extensive expertise with genetically engineered mouse models of pancreatic cancer, and with experimental therapeutics and drug development for this disease.

Victor Ugaz, PhD
Professor, Artie McFerrin Department of Chemical Engineering
Texas A&M University

Victor M. Ugaz, Ph.D. is a Professor and Holder of the Charles D. Holland ’53 Professorship in the Artie McFerrin Department of Chemical Engineering at Texas A&M University. He joined the faculty in January 2003, with research interests focused on microfluidic transport phenomena. His research focuses broadly on harnessing the unique characteristics of transport and flow at the microscale, with specific interests in microfluidic flows (both single-phase and nanoparticle suspensions), microchip gel electrophoresis, PCR thermocycling in novel convective flow devices, and construction of 3D vascular flow networks for biomedical applications. Ugaz earned BS and MS degrees in Aerospace Engineering at The University of Texas at Austin, and a PhD in Chemical Engineering from Northwestern University. He currently serves as Chair of the interdisciplinary Master of Biotechnology (MBIOT) program, Assistant Agency Director for Research Development in the College of Engineering at Texas A&M, and has served as past President of the American Electrophoresis Society (AES).

1:45 – 2:45 PM - CONCURRENT SESSION 2 - PRODUCT DEVELOPMENT RESEARCH

Where: **Glass Oaks** Topic: ***Product Development Research Company Showcase - cont.***

3:00 – 4:45 PM - POSTER SESSION A

Where: **Rio Grande Hall**

3:00 – 4:45 PM - CONCURRENT SESSION - PRODUCT DEVELOPMENT RESEARCH

Where: **Glass Oaks** Topic: ***Product Development Research Company Showcase - cont.***

DETAILED SESSION DESCRIPTIONS AND SPEAKER INFORMATION

TUESDAY, NOVEMBER 14

8:00 – 8:45 AM - OPENING SESSION

Where: **Ballroom A** Topic: ***When Precision Medicine Is Not So Precise***

In the prime of life, an avid runner, Dr. Neil Spector, who trained at the top academic institutions became deathly ill from a mysterious illness. His doctors were baffled and attributed his unusual symptoms to stress, with nothing glaringly abnormal showing up on routine laboratory testing. After four years of fighting to stay alive and convince his doctors there was something medically wrong, a diagnosis was finally made and appropriate treatment administered. Dr. Spector will discuss how he miraculously overcame all the odds, the importance of balancing the science of precision medicine and the "art" of medicine and the lessons that he learned as a physician-scientist who found himself on the other side of a highly complex medical healthcare system.

Neil Spector, MD
Director of the Developmental Therapeutics Program, Duke Cancer Institute
Duke University

Author of "Gone in a Heartbeat: A Physician's Search for True Healing," Neil Spector, MD, is a leader in applying translational research to the clinical development of molecularly targeted personalized cancer therapies. He broke through conventional thinking to bring new treatment options to the arsenal of breast cancer drugs, fought to include rare subtypes in clinical trials, and worked to develop collaborations that helped transform laboratory successes into real therapies for patients. His application of translational research to the preclinical and clinical development of lapatinib remains an example of how precision oncology can transform treatment of cancer patients, and facilitate the development of targeted cancer therapies. Dr. Spector is currently the Sandra Coates Chair in Breast Cancer Research at the Duke University School of Medicine, leader of the Duke Cancer Institute Developmental Therapeutics Program, and he was selected by his peers as a Komen Research Scholar. In addition to his research, Dr. Spector continues to see oncology patients and was recently appointed National Director of Precision Oncology for the VA Healthcare System.

8:45 – 10:00 AM - GENERAL SESSION

Where: **Ballroom A** Topic: ***Diet, Obesity, Lifestyle and Cancer: Risk and Survival***

Moderator

Ross Brownson, PhD
Professor and Director, Prevention Research Center
Brown School and School of Medicine, Washington University in St. Louis

Chair of a CPRIT Prevention Review Panel, Dr. Brownson is the Bernard Becker professor at Washington University in St. Louis, with appointments in the Brown School and the Alvin J. Siteman Cancer Center. He is currently involved in numerous community-level studies designed to understand and reduce modifiable risk factors such as physical inactivity, obesity, and tobacco use. In particular, he is interested in the impacts of environmental and policy interventions on cancer risk factors and he conducts research on dissemination of evidence-based interventions with a focus on policy settings and health departments. Dr. Brownson has authored nine books and more than 450 peer-reviewed articles.

Charles Fuchs, MD, MPH
Director, Yale Cancer Center and Physician-in-Chief of Smilow Cancer Hospital
Yale University

An internationally recognized expert in gastrointestinal cancers and cancer epidemiology, Dr. Fuchs was previously professor of medicine at Harvard Medical School and chief of the gastrointestinal oncology division and the Robert T. and Judith B. Hale Chair in Pancreatic Cancer at Dana-Farber Cancer Institute. Dr. Fuchs conducts research in gastrointestinal cancer epidemiology. In addition to studying the influence of diet and lifestyle, his research team is looking at the influence of such biomarkers as insulin-like growth factors, steroid hormones, and polymorphisms of metabolism enzymes on the risk of these cancers. Dr. Fuchs also conducts research assessing various treatment regimens and new drugs for gastrointestinal cancers.

Graham Colditz, DrPH, MD, MPH
Associate Director Prevention and Control
Alvin J. Siteman Cancer Center, Washington University in St. Louis

As an epidemiologist and public health expert, Dr. Colditz has a longstanding interest in the preventable causes of chronic disease, particularly among women. An internationally recognized leader in cancer prevention, Dr. Colditz is interested in strategies to speed translation of research findings to prevention strategies that work. His past research has focused on the health effects of smoking, weight and weight gain, physical activity, diet, and the adverse effects of medications such as postmenopausal hormone therapy, documenting that current use increases risk of breast cancer.

10:00 – 11:30 AM - POSTER SESSION B

Where: **Rio Grande Hall**

11:30 AM – 12:30 PM - LUNCH

Where: **Ballroom B & Arbor**

12:30 – 1:15 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH

Where: **Ballroom A** Topic: ***Progress on Childhood Cancer Research***

With cancer still serving as the leading cause of death from disease among children and adolescents, researchers are working to make progress in key areas. Join this session to hear about specific research projects to develop more effective treatment for childhood cancer and learn about future research and prevention directions.

Moderator

Stephen X. Skapek, MD
Chief, Division of Pediatric Hematology-Oncology, Department of Pediatrics
The University of Texas Southwestern Medical Center

Dr. Skapek believes that caring for children with cancer requires both clinical and research excellence. He leads one of the larger pediatric cancer programs in the United States, comprising some 25 faculty physicians who all have established and growing expertise in specific areas of childhood cancer and blood disorders. He also leads a research lab that focuses on tumor-suppressor genes in soft-tissue sarcomas. Dr. Skapek holds the UT Southwestern Distinguished Chair in Pediatric Oncology Research. He also serves as Medical Director of the Gill Center for Cancer and Blood Disorders at Children's Medical Center in Dallas. Dr. Skapek serves on several leadership committees for the international Children's Oncology Group, the world's largest clinical research organization focused on childhood cancers. He is also a member of the Association for Research and Vision Ophthalmology, the American Society of Pediatric Oncology, and the American Association of Cancer Research.

Speakers

Abbey Berenson, MD, PhD
Director, Center for Interdisciplinary Research in Women's Health
The University of Texas Medical Branch at Galveston

Dr. Berenson's research interests involve improving women's health from puberty to menopause. She has maintained extramural support for her studies in adolescents and young women since 1994. Currently, she is leading cancer prevention projects aimed at increasing uptake of the human papillomavirus (HPV) vaccine. Her projects include offering the vaccine to young women while they are patients on the postpartum unit, providing one-one counseling on HPV, HPV-related cancers, and the HPV vaccine to mothers of children seen in pediatric clinics, and outreach to young men and women in medically underserved areas of the Golden Triangle. She has published 40 papers in peer-review journals and presented her CPRIT projects at a number of conferences, including those in Lisbon and CapeTown.

Barry Maurer, MD, PhD
Associate Professor
Texas Tech University Health Sciences Center

Dr. Maurer is a board-certified pediatric oncologist and academic developmental cancer researcher conducting basic laboratory investigations and early phase clinical trials. His major interests are the cellular mechanisms, translational development, and clinical testing of the cytotoxic retinoid, fenretinide, as a dihydroceramide-increasing agent, both as a single agent and in combination with other modulators of ceramide pathways in adult and pediatric tumor systems. He currently holds two investigator-initiated, FDA investigational new drug applications related to this research.

Brendan Lee, MD, PhD
Chairman, Molecular and Human Genetics
Baylor College of Medicine

As a pediatrician and geneticist, the overall mission of Dr. Lee's research program is to translate the study of structural birth defects and inborn errors of metabolism into a basic understanding of development, disease and novel therapeutic approaches. His long standing interest has been the study of human inborn errors of metabolism and structural birth defects of the skeleton. In the study of metabolism, he has applied genetic approaches to the study of biochemical genetic disorders (specifically urea cycle disorders) as models of complex disease (those involving nitric oxide dysregulation). In the study of structural birth defects, his research team has discovered paracrine and endocrine signaling pathways that regulate skeletal development including morphogens (TGFb, Wnt and Notch), post-transcriptional regulation by microRNAs, and extracellular matrix protein modifications (e.g., collagen prolyl-hydroxylation), and their contribution to cancers both intrinsic and metastatic to bone.

James Amatruda, MD, PhD
Associate Professor of Pediatrics, Molecular Biology and Internal Medicine
The University of Texas Southwestern Medical Center

A physician-scientist, Dr. Amatruda divides his time between his research laboratory and Children's Medical Center, Dallas, where he specializes in the care of children with cancer and blood disorders. Research in his lab focuses on understanding the genetic causes of childhood cancers, including genitourinary cancers and sarcomas, using zebrafish models and human genomic approaches. At UT Southwestern, Dr. Amatruda is the Associate Division Director for Research in the Division of Pediatric Hematology-Oncology, and Assistant Director of the Medical Scientist Training Program. He also serves as Chair of the Germ Cell Tumor Biology and Rare Tumors Biology committees in the Children's Oncology Group.

Joshua Mendell, MD, PhD
Professor, Department of Molecular Biology and Investigator, Howard Hughes Medical Institute
The University of Texas Southwestern Medical Center

Dr. Mendell has made major contributions to the understanding of the mechanisms that govern gene expression in normal physiology and cancer, and his research group has been at the forefront of dissecting the contributions of microRNAs (miRNAs) and other noncoding RNAs to these processes. Dr. Mendell's laboratory provided one of the first demonstrations that miRNAs function as components of critical oncogenic and tumor suppressor pathways and that miRNAs represent potent and non-toxic anti-cancer therapeutic agents when delivered systemically. More recently, the Mendell laboratory has demonstrated that other types of noncoding RNAs, including long noncoding RNAs, similarly regulate cancer-relevant processes including genomic stability. Dr. Mendell has been the recipient of several awards including the Allan C. Davis Medal for the Outstanding Young Scientist in the State of Maryland in 2007, the AACR Award for Outstanding Achievement in Cancer Research in 2010, and the O'Donnell Award from the Academy of Medicine, Engineering, and Science of Texas in 2016. Dr. Mendell was appointed as an HHMI Early Career Scientist in 2009 and an HHMI Investigator in 2015. In 2011, Dr. Mendell received a Rising Stars Award from the Cancer Prevention and Research Institute of Texas and relocated his laboratory from Johns Hopkins to UT Southwestern Medical Center in Dallas where he is currently a Professor of Molecular Biology and member of the Simmons Cancer Center and Center for Regenerative Science and Medicine.

Peter Houghton, PhD
Professor of Molecular Medicine, Director of Greehey Children's Cancer Research Institute
The University of Texas Health Science Center at San Antonio

Dr. Houghton received his PhD from the Institute for Cancer Research, London University, and joined St. Jude Children's Research Hospital where he became Chair, Department of Molecular Pharmacology, and Co-Leader for the Solid Malignancies Program. In 2009 he became Director, Center for Childhood Cancer and Blood Diseases, at The Research Institute at Nationwide Children's Hospital, Columbus Ohio, and from 2014 has been Director, Greehey Children's Cancer Research Institute, University of Texas Health Science Center, San Antonio. His work in developmental therapeutics, has focused largely on pediatric sarcomas. Specifically, understanding the role of insulin-like growth factors in the genesis of pediatric sarcomas, and developing approaches to inhibiting these signaling pathways. This focus led him to identify rapamycin and other rapalogs as potent inhibitors of sarcoma cell proliferation, and to map the pathway downstream of mTORC1 that is important for tumor cell proliferation. Another major focus of his work has been developing xenograft models of childhood cancers. He initiated preclinical development of the camptothecin drugs, topotecan and irinotecan that are now standard components of many pediatric clinical protocols. Dr. Houghton was the Principal Investigator of the National Cancer Institute (NCI) sponsored Pediatric Preclinical Testing Program (PPTP), and a member of the Pediatric Preclinical Testing Consortium where he conducts new agent evaluation against pediatric sarcoma and kidney cancer models. He is the PI on a large multi-institutional P01 grant entitled Studies of Childhood Sarcomas as well as other NIH funded grants. Dr. Houghton has over 35 years of experience in preclinical testing. Dr. Houghton has both NIH and industry support for studies involving drug combinations with ionizing radiation using human tumor xenograft models of pediatric cancer.

12:30 – 1:15 PM - CONCURRENT SESSION 2 - PREVENTION

Where: **Wedgwood** Topic: ***Dissemination and Implementation Science for Cancer Control: Realizing the Potential of Discoveries***

This session will explore recent advancements in dissemination and implementation science that are relevant to cancer prevention and control. Participants will expand their understanding of how this science can improve their work. In particular, the session will explore the potential of dissemination and implementation science, gaps in the evidence base, and opportunities for practice- and policy-based research. The session objectives are to: describe the underpinnings of implementation research; explore some dissemination research topics and gaps (illustrated with policy research); and describe resources for building D&I capacity.

Ross Brownson, PhD
Professor and Director, Prevention Research Center
Brown School and School of Medicine, Washington University in St. Louis

Chair of a CPRIT Prevention Review Panel, Dr. Brownson is the Bernard Becker professor at Washington University in St. Louis, with appointments in the Brown School and the Alvin J. Siteman Cancer Center. He is currently involved in numerous community-level studies designed to understand and reduce modifiable risk factors such as physical inactivity, obesity, and tobacco use. In particular, he is interested in the impacts of environmental and policy interventions on cancer risk factors and he conducts research on dissemination of evidence-based interventions with a focus on policy settings and health departments. Dr. Brownson has authored nine books and more than 450 peer-reviewed articles.

12:30 – 1:15 PM - CONCURRENT SESSION 3 - PRODUCT DEVELOPMENT RESEARCH

Where: **Glass Oaks** Topic: ***Clinical Trial Design***

The session will cover the general concept of clinical trial design for oncology focused trials. In addition to the basic design concepts that have been in practice for years, the session will focus on newer design elements that allow sponsors to reduce the time and cost of therapeutic products clinical trials. Additionally, the session will focus on specific considerations for testing immuno-oncology products, the latest guidance from the FDA, and novel trends that will shape future trial design.

George Peoples, COL (ret), MD, FACS
Founder and CEO
Cancer Insight, LLC and the Cancer Vaccine Development Program (CVDP), Metis Foundation

After retiring from 30 years of active duty as a military surgeon and research scientist, Dr. Peoples created Cancer Insight, LLC. The clinical research and development organization currently conducts multiple phase I and II trials at 50 plus sites across the United States. He also continues his work with CVDP discovering, developing, and clinical testing of cancer vaccines. Additionally, Dr. Peoples is a professor of surgery at Uniformed Services University of the Health Sciences and an adjunct professor of Surgical Oncology at MD Anderson Cancer Center. He is the past Chair of the Cancer Program, San Antonio Military Medical Center (SAMMC) and the past Deputy Director of the United States Military Cancer Institute. Dr. Peoples served as the Chief of Surgical Oncology at Walter Reed Amy Medical Center and at SAMMC. He has written extensively on the immune response to cancer with more than 350 peer-reviewed manuscripts, abstracts, and book chapters.

1:20 – 2:05 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH

Where: **Ballroom A** Topic: ***Progress on Childhood Cancer Research - cont.***

1:20 – 2:05 PM - CONCURRENT SESSION 2 - PREVENTION

Where: **Wedgwood** Topic: ***Approaches to Community Needs Assessment and Stakeholder Engagement***

This session will focus on community health needs assessment models that are evidenced-based and have been shown to be applicable for use in Texas because they offer practical ways to engage communities in cancer prevention, as well as other public and community health initiatives. Dr. Philips will describe the purpose for and overall approach of useful public health models, with special focus on community stakeholders and how to engage them in collaborative efforts to better prevent and educate about cancer. Dr. Stewart will offer an applied example of how these approaches are being used in a rural area to identify priorities, approaches, and partners that have begun to address local and regional cancer needs. Discussion will follow.

Billy U. Philips, PhD, MPH
Executive Vice President
The F. Marie Hall Institute for Rural and Community Health, Texas Tech University Health Sciences Center

Dr. Philips' work focuses on improving the health and well-being of the communities of Texas using innovative and scholarly research, advanced use of technology, and comprehensive education and outreach. He is also responsible for the direction, implementation, and overall programming of telemedicine for the entire Health Sciences Center including the federally funded TexLa Telehealth Resource Center grant and demonstration projects such as the Telemedicine Wellness Intervention Triage and Referral (TWITR) Project, the Next Generation 9-1-1 Telemedicine Medical Services Pilot Project, and the Frontiers in Telemedicine Training Lab, the only one of its kind in the nation. An established NIH investigator and author of numerous books, peer-reviewed articles, and other scholarly works in community-based research and chronic diseases, Dr. Philips has a long and distinguished career supporting preventive and public health initiatives.

Kenneth Stewart, PhD
Professor/Director of Community Development Initiatives
Angelo State University

Dr. Stewart established ASU's Community Development Initiatives (CDI) in 2007 and continues to serve as its director. CDI conducts community-based research to advance community development projects in San Angelo, the Concho Valley, and West Texas. Dr. Stewart serves as program evaluator for Access to Breast and Cervical Care for West Texas (ABCC4WT), a CPRIT funded breast and cervical cancer prevention program serving a 21-county area in West Texas. He headed the community-based assessment team that conducted The Community Health Needs Assessment of the Poor and Extremely Poor in West Texas. Completed in 2015, the study revealed numerous gaps between health and behavioral health service capacities and the prevalence of chronic diseases found in the populations living below the poverty line in 20 counties of West Texas. A member of the editorial advisory board for the *Rural Health Quarterly*, Dr. Stewart has also published several books, numerous peer-reviewed articles, and other scholarly works on social problems, minority-majority group relations, community development, and public health.

1:20 – 2:05 PM - CONCURRENT SESSION 3 - PRODUCT DEVELOPMENT RESEARCH

Where: **Glass Oaks** Topic: ***High Cancer Drug Prices: Causes, Patient Impact and Potential Solutions***

Over the past 10 years, cancer drug costs have increased in an unprecedented fashion. The rapid escalation in cancer care costs has taken a significant toll on patients and families faced with a cancer diagnosis. During this lecture, Dr. Hagop Kantarjian will detail the historical background of high cancer drug prices, discuss potential causes as well as justifications by the pharmaceutical industry, and elaborate on the harm the rising cost has on patients. The session will examine possible solutions to delivering precision-medicine solutions while maintaining an economically sustainable cancer care system.

Hagop M. Kantarjian, MD
Professor and Chairman, Department of Leukemia
The University of Texas MD Anderson Cancer Center

Dr. Kantarjian leads the nation's largest leukemia practice, known for its extensive participation and leadership in developing new treatments through research and clinical trials. Dr. Kantarjian has developed a number of treatments, including chemotherapy combinations and the single agent clofarabine for acute lymphocytic leukemia (ALL); the hypomethylating agent decitabine, approved by the U.S. Food and Drug Administration (FDA) for myelodysplastic syndromes in 2006; liposomal vincristine, FDA-approved in 2012 for ALL; and ruxolitinib, approved for myelofibrosis in 2011. He has also championed multiple targeted therapies for chronic myeloid leukemia (CML), including imatinib, dasatinib, nilotinib, ponatinib, bosutinib, and omacetaxine, all of which received FDA approvals between 2001 and 2012. He is currently developing monoclonal antibodies in adult ALL. On the MD Anderson faculty since 1983, Kantarjian holds the Kelce Margaret Kana Research Chair and is associate vice president of Global Academic Programs. He was recently appointed as the Baker Institute Scholar in Health Policy.

2:25 – 3:10 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH

Where: **Ballroom A** Topic: ***Update on CPRIT-Funded Core Facility Research***

The goal of this session is to highlight several CPRIT supported core facilities that are developing forward looking strategies to support cancer research in Texas.

Moderator

James K.V. Willson, MD
Chief Scientific Officer
Cancer Prevention and Research Institute of Texas

Dr. Willson leads the Cancer Prevention and Research Institute of Texas (CPRIT) academic research program in supporting innovation in cancer research and recruiting world-class cancer researchers to Texas institutions. He is nationally renowned for his work in the genetics of colorectal cancer, having spent more than three decades in the field. Dr. Willson's research led to the development of cell and animal models for human colon cancer that have been key to identifying genetic factors in disease progression. Dr. Willson joined CPRIT in March 2016 following a distinguished career as director of Simmons Comprehensive Cancer Center and associate dean of oncology programs at The University of Texas Southwestern Medical Center. Under his leadership, Simmons Cancer Center became one of only 45 cancer centers in the U.S. to achieve comprehensive status from the National Cancer Institute (NCI). He helped bring the same prestigious designation to Case Comprehensive Cancer Center in Cleveland, where he served as its director from 1994-2004. A graduate of the University of North Carolina at Chapel Hill, Dr. Willson earned his MD from the University of Alabama in 1976. He completed his residency in internal medicine at Johns Hopkins Hospital in 1981 and received additional training at the NCI.

Speakers

Funda Meric-Bernstam, MD
Chair of the Department of Investigational Cancer Therapeutics -- the Phase I Program, and Professor in the Divisions of Cancer Medicine and Surgery, and The Nellie B. Connally Chair in Breast Cancer
The University of Texas MD Anderson Cancer Center

The Medical Director of the Institute for Personalized Cancer Therapy (IPCT), Dr. Meric-Bernstam has a basic and translational research program that is focused on molecular therapeutics, predominantly on PI3K/Akt/mTOR signaling, to delineate the mechanism of action of each agent targeting this pathway and the molecular alterations useful to prospectively identify patients who will benefit most from each agent, and optimal combination therapies. Her research is focused on identifying molecular markers to predict and monitor drug response and novel biomarker-driven combinations. As the Medical Director of the Institute for Personalized Cancer Therapy at MD Anderson, she has not only led large efforts of genomic testing within the institution, but has a) helped build a framework for rapid assessment of actionability of genomic alterations; b) established a Precision Oncology Decision Support Team who can provide point of care input for actionability; c) launched the public website "www.personalizedcancertherapy.org" providing access to expert curation of information on therapeutic relevance of specific genes/variants; d) created databases and clinical trial alert systems to facilitate accrual to genotype-selected trials across the institution; and e) monitors trial enrollment after genomic testing to identify approaches to obstacles to trial enrollment. She has participated in, as well as led, trials including investigator-initiated trials, cooperative group trials, and industry sponsored trials. These trials have ranged from a window of opportunity trials, neoadjuvant therapy trials, a Phase I and II trials in the advanced cancer setting as well as new surgical techniques, new imaging devices and molecular diagnostics.

Gaudenz Danuser, PhD
Chair of the Lyda Hill Department of Bioinformatics
The University of Texas Southwestern Medical Center

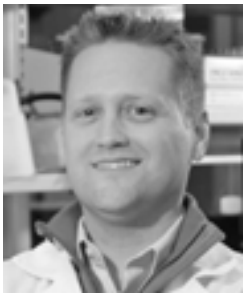
In July 2015 Dr. Danuser was appointed as the inaugural chair of the Lyda Hill Department of Bioinformatics. He also holds the Patrick E. Haggerty Distinguished Chair in Basic Biomedical Science. Before moving to UT Southwestern, Dr. Danuser directed research laboratories at ETH Zurich (2002 – 2003), at The Scripps Research Institute in La Jolla (2003 – 2009), and at Harvard Medical School (2009 – 2014). Trained as an engineer (geodetic and electrical engineering/computer science), he entered the field of cell biology as a postdoctoral fellow in the Program for Architectural Dynamics of Living Cells at the MBL in Woods Hole. Since then, he has focused his research on the question of how chemical and mechanical signals integrate in the regulation of cytoskeleton dynamics and membrane trafficking. He has redirected his efforts towards understanding the implications of mechanical and chemical cell shape regulation in migration and survival of the metastatic cell, including the roles mechanical cues play in conferring what his lab calls 'mechanical drug resistance'. His contributions to cell biology and biophysics have been recognized by several awards and honors.

Martin M. Matzuk, MD, PhD
Stuart A. Wallace Chair, Robert L. Moody, Sr. Chair, and Professor
Baylor College of Medicine and Director of Clinical Chemistry, Ben Taub General Hospital

Dr. Matzuk, Director of the Center for Drug Discovery at Baylor College of Medicine and Director of Clinical Chemistry at Ben Taub General Hospital, is recognized for his elucidation of TGFβ superfamily, germ cell, and hormonal signaling pathways in cancer and reproductive medicine using functional genomics approaches. He has published more than 320 papers (including over 25 papers in *Cell, Nature,* and *Science* journals), generated over 100 mouse models, lectured in excess of 170 symposia in 27 countries, and has been supported continuously by the NIH since 1991. Based on Google Scholar, 100 of his papers have been cited over 100 times, and 25 papers have been cited over 400 times. Dr. Matzuk's other honors include the Richard Weitzman Award from the Endocrine Society, HypoCCS Award from Eli Lilly, Society for the Study of Reproduction Research Award, Pfizer Outstanding Investigator Award from the American Society for Investigative Pathology, Roy Greep Award from The Endocrine Society, International Fundacion IVI Award in Reproductive Medicine, and a MERIT award from the NIH. He in an inventor on a dozen patents and has a highly successful therapeutic on the market. Dr. Matzuk was elected to the

National Academy of Sciences and The Academy of Medicine, Engineering, and Science of Texas in 2014 and was elected as a Fellow in the National Academy of Inventors in 2016. He is the principal investigator on the CPRIT Core Facility Support Award "Preclinical Candidate Discovery Core."

Michael Scheurer, PhD, MPH
Director, Childhood Cancer Epidemiology and Prevention Program Associate Professor, Department of Pediatrics, Section of Hematology/Oncology
Baylor College of Medicine



Dr. Scheurer's research focuses on viruses and immune function as risk factors for cancer development and progression. His laboratory looks for novel ways to identify and catalog molecular markers of viral infection, including host-virus interactions, as risk factors for the development of cancer. He is actively involved with two large international research groups focused on two rare tumors: the Brain Tumor Epidemiology Consortium and the Childhood Leukemia International Consortium. Dr. Scheurer is currently working with other researchers and clinicians at Texas Children's Cancer Center to develop a statewide study to examine risk factors for childhood brain tumors. He also currently has a research project examining Human papillomavirus (HPV)-associated cancers, in particular cervical cancer, including the examination of the HPV vaccine and its effects on cancer incidence. He has an increasing program looking at Human cytomegalovirus (HCMV) and host immune function in relation to pediatric and adult brain tumors, and he also has an interest in the factors that contribute to the poor prognosis and outcome for brain tumor patients, including neurocognitive decline and other therapy-related toxicities.

2:25 – 3:10 PM - CONCURRENT SESSION 2 - PREVENTION

Where: **Wedgwood** Topic: ***Dissemination and Implementation – Strategies and Examples***

One of CPRIT's objectives is to facilitate the dissemination and implementation of successful CPRIT funded projects by supporting the development of resources based on these projects. Four recipients of the Dissemination of CPRIT – Funded Cancer Control Interventions (DI) *award will discuss strategies and processes for the effective adaptation and implementation of their projects as well as showcase resources and products to assist those interested in adapting and implementing their evidence based interventions while maintaining fidelity to the original program.*

Moderator

Rebecca Garcia, PhD
Chief Prevention and Communications Officer
Cancer Prevention and Research Institute of Texas

Dr. Rebecca Garcia leads CPRIT's prevention and communications efforts. Ten percent of CPRIT's total funding is dedicated to evidence-based prevention services. Her responsibilities include directing the prevention program and fostering collaboration among the cancer and disease prevention community to maximize CPRIT's impact. In addition, she is responsible for overseeing CPRIT's strategic communications efforts. Prior to joining CPRIT in August of 2009, she served as Vice President, Continuing Professional Development, for Physicians' Education Resource (PER), a medical education and communications company. Previously, Dr. Garcia was Vice President of Health Sciences for the Susan G. Komen for the Cure where she managed Komen's scientific research grants and education programs. Dr. Garcia attended the University of Texas at Austin and received a bachelor's degree in medical technology from the University of Texas Health Science Center at Dallas. She obtained a master's degree in Biomedical Communications at the University of Texas Health Science Center at Dallas and a doctorate from the Department of Higher Education at the University of North Texas.

Speakers

Jane Bolin, PhD, JD, BSH
Center Director, Health Policy and Management
Texas A&M Health Science Center

Dr. Bolin has served as co-principal investigator on three CPRIT cancer prevention grants on screening for colorectal, breast and cervical cancer in a low-income uninsured population and PI on one dissemination grant from the Cancer Prevention and Research Institute of Texas. She is also the director of the federally funded Southwest Rural Health Research Center at the Texas A&M School of Public Health, conducting policy-relevant research for the benefit of rural and underserved areas of Texas and the nation. As a professor at the Texas A&M School of Public Health, Dr. Bolin's other academic interests include public health law, health disparities, evidence-based interventions, community-based participatory research and chronic disease, particularly diabetes.

Lorraine Reitzel, PhD, FAAHB
Principal Investigator, Department of Psychological, Health & Learning Sciences
University of Houston

Dr. Reitzel's research program focuses on better understanding the social determinants of health and health risk behaviors, as well as the specific biopsychosocial mechanisms that account for disparities in health risk behaviors and health outcomes. Her CPRIT-supported work is focused on the dissemination and implementation of a multi-component tobacco-free workplace program within behavioral health centers across Texas. She co-founded and currently co-directs the HEALTH Research Institute, a hub for the university's community-informed translational research aimed at reducing health disparities and promoting health equity in Houston. She has published more than 110 peer-reviewed empirical articles, is a fellow of the American Academy of Health Behavior, and serves as a Chair of an Institutional Review Board at her academic institution.

Maria Fernandez, PhD
Director, Center for Health Promotion and Prevention Research
The University of Texas Health Science Center at Houston

An internationally known expert in the field of health promotion and cancer control and prevention, Dr. Fernandez has extensive experience in community-based participatory research in cancer control and prevention among underserved populations. She has conducted studies ranging from the description of conceptual models to the development and evaluation of interventions to increase cancer control and prevention. She has also worked to understand and accelerate the use of evidence-based interventions in real-world settings. Dr. Fernandez has received more than $12 million in funding as a principal investigator during the past five years and collaborates as a co-investigator on other studies. Her work is featured in 106 peer-reviewed publications and several book chapters. She also co-authored the book *Planning Health Promotion Programs: An Intervention Mapping Approach*.

Rahkshanda Rahman, MD, FRCS, FACS
Director of the Amarillo Breast Center of Excellence and Professor of Surgery, School of Medicine
Texas Tech University Health Sciences Center

Dr. Rahman leads a CPRIT-funded prevention project, *Access to Breast and Cervical Care for West Texas,* which provides screenings and education for residents in 26 Texas Panhandle counties. She joined the Texas Tech University Health Sciences Center (TTUHSC) in 2009 after serving as the founder and director of the interdisciplinary breast fellowship program at the University of Massachusetts. At TTUHSC, Dr. Rahman spearheaded formation of the first nationally accredited Breast Center of Excellence in the Texas Panhandle. Currently, she is the director of the Amarillo Breast Center of Excellence and professor of surgery for the TTUHSC School of Medicine. Dr. Rahman serves on numerous local and national boards and committees including the American Society of Breast Surgeons and the Amarillo Area Breast Health Coalition. She graduated from the Aga Khan University Medical College in Karachi, Pakistan, where she completed her internship and residency. She then spent several years furthering her studies, completing fellowships in breast and general surgery in 2001 at Aga Khan, followed by another fellowship at the University of Arkansas for the medical sciences division of surgical oncology.

2:25 – 3:10 PM - CONCURRENT SESSION 3 - PRODUCT DEVELOPMENT RESEARCH

Where: **Glass Oaks** Topic: ***Start-up Trials and Tribulations***

Companies engaged in early-stage development often face an uphill battle. Sometimes it is years before a drug, product or service reaches the market, so pre-revenue companies must survive by periodically tapping investors for cash. Then they must navigate the turbulence of clinical trial results that can either make or break them. Clinical trials and the rules that govern them are coming under pressure for an overhaul. With the odds sometimes against them, how do start-up companies manage and secure funding and reach success? Attend this lively panel discussion on start-up trials and tribulations.

Moderator

Matt McManus, MD, PhD
Chief Executive Officer
Asuragen, Inc.

Dr. McManus joined Asuragen in August 2014 with more than 20 years of clinical diagnostic leadership experience, and was previously the CEO and president of PrimeraDx, Inc., a molecular diagnostics company marketing a novel, multiplexed, multi-modal, molecular diagnostics instrument for oncology, infectious disease, and genetic testing. Dr. McManus also served as head of Cleveland Clinic Laboratories and chief operating officer of the Pathology and Laboratory Medicine Institute at the Cleveland Clinic. He received an MD and PhD from the University of Pennsylvania School of Medicine, MBA from Boston College and his bachelor's from the College of the Holy Cross.

Speakers

Fahar Merchant, PhD
Chairman, President, CEO
Medicenna Therapeutics, Inc.

Dr. Merchant is a 25-year biotech veteran, a serial entrepreneur and co-founder of Medicenna. Previously, he was president and CEO of Protox Therapeutics where he established a late clinical stage urology company. At Protox, he raised more than $70 million through multiple PIPEs, including a $35 million investment by Warburg Pincus. In 1992, he co-founded IntelliGene Expressions, Inc., a biologics CDMO, and built it to one of the fastest growing companies in Canada. In 2000, by strategic in-licensing, he co-founded Avicenna Medica, Inc., a clinical stage oncology company that was sold a year later to KS Biomedix (LSE) for $90 million. Dr. Merchant was CTO and Director of KS Biomedix until its acquisition by Xenova. Dr. Merchant has closed several transactions valued at more than $300 million.

Harpreet Singh, PhD
Chief Executive Officer
Immatics US, Inc.

With help from a CPRIT grant, Dr. Singh co-founded Immatics US, Inc. As Immatics Biotechnologies GmbH managing director and chief scientific officer, he is dedicated to the translation of science into highly innovative cancer immunotherapeutics. At Immatics GmbH, Dr. Singh leads a team dedicated to target and TCR discovery, immunology, manufacturing, and translational development. Dr. Singh holds numerous patents and is the co-author of 30 publications in peer-reviewed journals, including *Nature Medicine, Nature Biotechnology, Journal of Experimental Medicine, and Brain and Blood*.

Jon Northup
Chief Executive Officer
Beta Cat Pharmaceuticals, LLC

Currently, Mr. Northup serves as CEO of several translational oncology companies working on novel cancer therapies from bench to bed, as well as CEO of Indigo Clinical Research, a clinical data services company in India. Mr. Northup is a published author with several articles and frequent presentations within the industry as well as two books – *"The Pharmaceutical Industry"* chapter in *The Business of Healthcare Innovation and Prescription Pricing in Chain and Independent Pharmacies*. Mr. Northup worked for Eli Lilly and Company in a variety of executive positions in Corporate Strategy, Business Development, Marketing, and Sales for more than 28 years. During that time, he led 50 collaborations with other pharmaceutical and biotech companies, and participated on the launch team of many Lilly products, including Prozac, Axid, Humatrope, and Humulin.

3:15 – 4:00 PM - CONCURRENT SESSION 1 - ACADEMIC RESEARCH

Where: **Ballroom A** Topic: ***CPRIT Academic Research RFA Funding Mechanisms***

Attend this session to hear about current and future funding opportunities for academic research.

James K.V. Willson, MD
Chief Scientific Officer
Cancer Prevention and Research Institute of Texas

Dr. Willson leads the Cancer Prevention and Research Institute of Texas (CPRIT) academic research program in supporting innovation in cancer research and recruiting world-class cancer researchers to Texas institutions. He is nationally renowned for his work in the genetics of colorectal cancer, having spent more than three decades in the field. Dr. Willson's research led to the development of cell and animal models for human colon cancer that have been key to identifying genetic factors in disease progression. Dr. Willson joined CPRIT in March 2016 following a distinguished career as director of Simmons Comprehensive Cancer Center and associate dean of oncology programs at The University of Texas Southwestern Medical Center. Under his leadership, Simmons Cancer Center became one of only 45 cancer centers in the U.S. to achieve comprehensive status from the National Cancer Institute (NCI). He helped bring the same prestigious designation to Case Comprehensive Cancer Center in Cleveland, where he served as its director from 1994-2004. A graduate of the University of North Carolina at Chapel Hill, Dr. Willson earned his MD from the University of Alabama in 1976. He completed his residency in internal medicine at Johns Hopkins Hospital in 1981 and received additional training at the NCI.

3:15 – 4:00 PM - CONCURRENT SESSION 2 - PREVENTION

Where: **Wedgwood** Topic: ***Dissemination and Implementation – Strategies and Examples (cont'd)***

3:15 – 4:00 PM - CONCURRENT SESSION 3 - PRODUCT DEVELOPMENT RESEARCH

Where: **Glass Oaks** Topic: ***Start-up Trials and Tribulations - cont'd***

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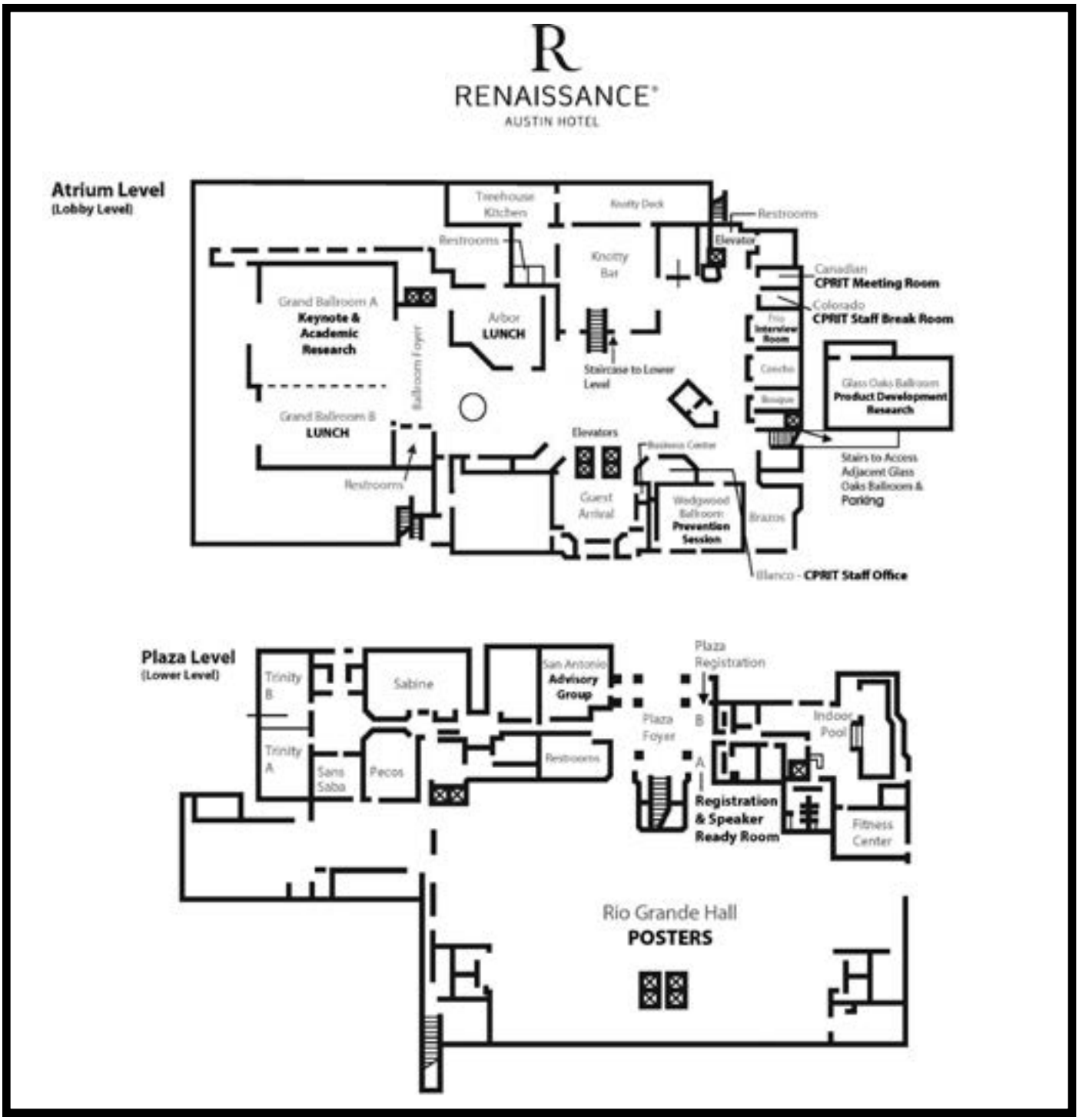

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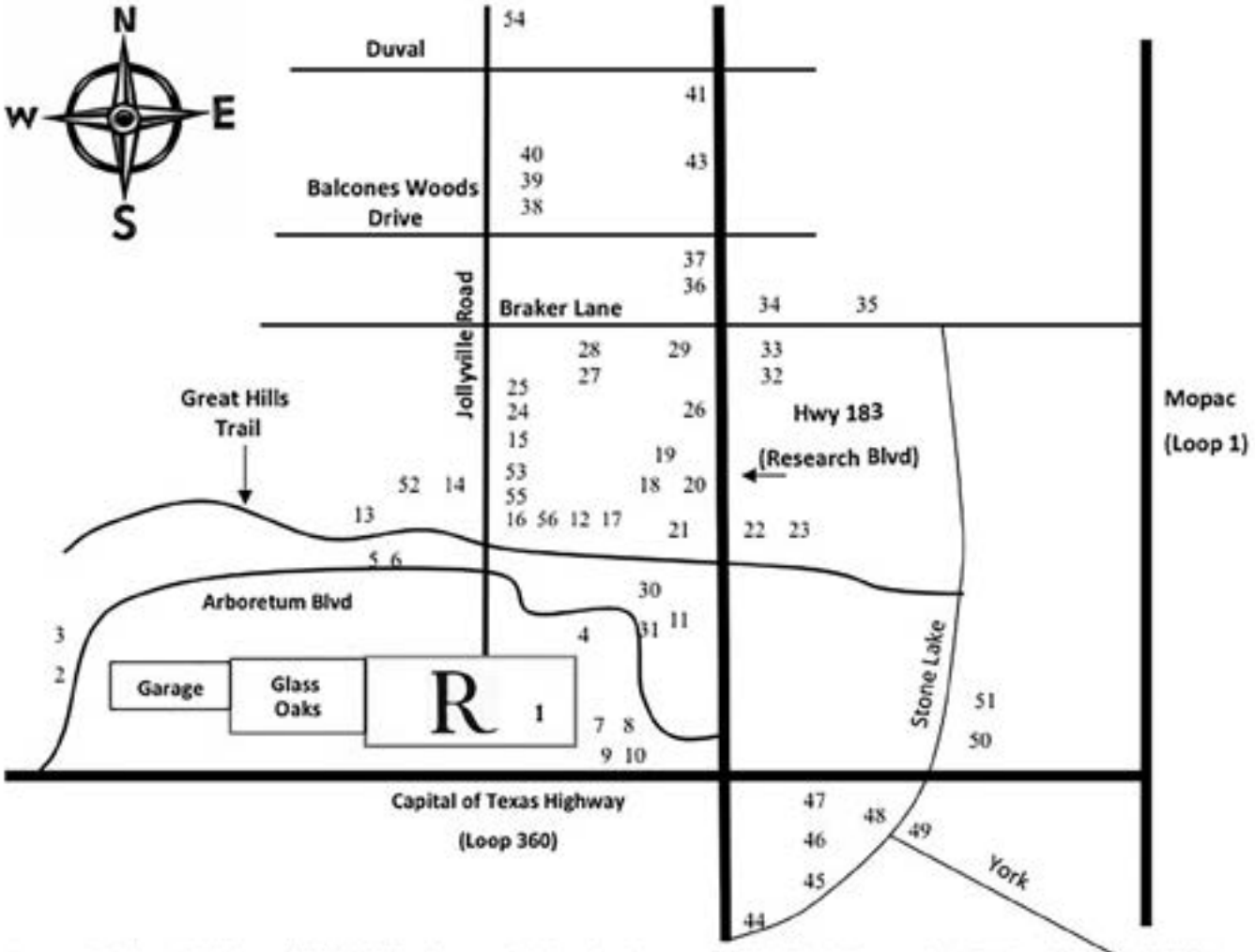

1	***Treehouse Kitchen****	***(512) 795-6100***	20	Salt Grass Steak House	340-0040	39	Carraba's Italian Grill	345-8232
2	Z-Tejas	346-3506	21	Macaroni Grill	795-0460	40	Outback Steak House	343-6333
3	Eddie V's	342-2642	***22***	***Truluck's****	***794-8300***	***41***	***Chuy's****	***342-0011***
4	Zoe's Kitchen	372-9444	23	Jason's Deli	345-9586	43	IHOP	345-7124
5	Noodles & Company	342-8552	24	Brick Over Pizza	345-6181	44	Marie Calender's	349-7151
6	Corner Bakery Cafe	777-4250	25	Fujiyama Habachi	795-8333	45	Manny's	794-0088
7	Five Guys Burgers	338-0300	26	Twin Lion	794-8772	46	Sushi Sake	527-0888
8	Cheesecake Factory	241-0777	27	Subway Subs	345-1050	47	Taco Cabana	338-0345
9	***Amy's Ice Cream****	***345-1006***	28	Taco Bell	338-6033	48	Panera Bread	795-7308
10	Drunken Fish	349-9454	29	McDonalds	346-5440	***49***	***Baby Acapulco's***	***795-9000***
11	***Estancia Churrascaria****	***345-5600***	30	Blue Baker	346-2583	***50***	***North by Northwest****	***231-8157***
12	Bulbritos	356-9607	31	Brios Italian Grill	794-1234	51	Iron Cactus	794-8778
13	Starbucks	795-1965	32	Einstein Brothers Bagels	338-6711	***52***	***Newks****	***795-7507***
14	PF Changs	231-0208	33	Boston Market	346-5222	53	Fire Bowl Café	795-8998
15	***Manuel's****	***345-1042***	34	Chick-Fil-A	343-1989	***54***	***Pour House****	***270-4740***
16	Elevation Burger	608-4054	***35***	***Roaring Fork****	***342-2700***	55	Texadelphia	338-1338
17	Pok-e-Joe's BBQ	338-1990	***36***	***Bone Daddy's****	***346-3025***	56	Tino's Greek Grill	346-3636
18	La Madeline	502-2427	37	Schlotzky's	338-9494			
19	Bombay Bistro	342-2252	***38***	***Rudy's BBQ****	***418-9898***			

Navigator's reccommendation

ABSTRACTS

Academic Research

Product Development Research

Prevention

1 **CPRIT Grantee Poster Session A**

Role of yes-associated protein 1 (YAP1) in human pancreatic ductal adenocarcinoma initiation and progression *Xue Yin, The University of Texas Health Science Center at San Antonio; J. Liu; N. Akanuma; M. Nipper; P. Wang*

Introduction: Understanding the molecular mechanisms underlying pancreatic ductal adenocarcinoma (PDAC) initiation and progression is an urgent need to achieve more effective diagnosis and treatment to this deadly cancer. We have developed a flow cytometry-based, high resolution lineage tracing method and 3D culture system to study PDAC initiation and progression using normal human pancreatic cells. **Methods:** Normal human acinar cells or cells undergoing acinar-to-ductal metaplasia (ADM, AD cells) will be isolated by fluorescence-activated cell sorting (FACS), and cultured in 3D-culture system. Lentivirus carrying YAP1-mCherry will be transduced into acinar cells to study whether YAP1 is sufficient to induce ADM or is required during TGF-beta-induced ADM. Lentivirus carrying either shYAP1-mCherry or shYAP1-KrasG12D-mCherry will be transduced into AD cells to study whether YAP1 is required for AD cell proliferation and Kras-induced prolonged proliferation. ChIP-PCR and genome-wide ChIP-seq will be used to identify the mechanism through which YAP1 promotes PDAC development and progression. Lentivirus carrying inducible shYAP1 will be transduced into cancer producing, engineered AD cells and orthotopically transplanted into SCID mice to investigate whether inhibiting YAP1 could suppress PDAC progression. **Results:** So far, we found that TGF-beta induces YAP1 expression in primary normal human pancreatic cells. However, treating with TGF-beta inhibitor blocks YAP1 induction and ADM, suggesting that YAP1 is downstream of TGF-beta signaling. **Conclusions:** Successful completion of the project will give us a better understanding of how YAP1 functions in human PDAC initiation and progression. It will provide us opportunities to develop new methods for early detection and treatment of PDAC. *Xue Yin is supported by a pre-doctoral fellowship through CPRIT Research Training Award RP 170345 *Jun Liu was supported by a post-doctoral fellowship through CPRIT Research Training Award RP140105. *Pei Wang is CPRIT scholar and funded by First time faculty award.

2 **CPRIT Grantee Poster Session B**

Identification and Characterization of a Novel LncRNA-Derived Chromatin Binding Polypeptide in Breast Cancer *Shrikanth Gadad, The University of Texas Southwestern Medical Center; V. Malladi; C. Camacho; Y. Peng; W. Kraus*

Introduction: Long noncoding RNAs (lncRNAs) play important roles in many cellular processes, such as the regulation of gene expression, cell cycle progression, and cellular identity during embryonic development. LncRNAs have been proposed to act through a variety of molecular mechanisms, although the specific mechanisms are not always clear. Recent studies have indicated that some lncRNAs may engage ribosomes and produce short functional polypeptides. **Methods:** In order to explore the molecular mechanisms of novel lncRNA-derived polypeptides in cancers, we have developed a computational pipeline to scan lncRNAs for short open reading frames (ORFs). We then applied this pipeline to a set of 1,888 lncRNAs expressed in MCF-7 cells, which we identified previously, as well as all previously annotated lncRNAs based on LncRNAdb, Ensembl, Gencode, and the Human Body Map. Furthermore, we used mass spectrometry (MS) to identify small expressed polypeptides isolated from MCF-7 cell extracts. We then overlaid the polypeptide information with the short open reading frames from lncRNAs to identify ORFs that are actually translated into polypeptides. In this way, we have identified expressed polypeptides that match ORFs in expressed lncRNAs in MCF-cells. **Results:** We have focused our analyses on one polypeptide, Tumor-Specific Polypeptide 1 (TSP1), which is expressed from a newly annotated lncRNA. The lncRNA encoding TSP1 is transcribed exclusively in normal testis tissue and cancers. Analysis of the evolutionary conservation across the genomes of sequenced species shows that this lncRNA is conserved only in humans and primates. Analysis of breast cancer samples indicates that amplified expression of the lncRNA encoding TSP1 in breast cancers correlates with clinical outcomes. We have now fully annotated the lncRNA encoding TSP1 (transcription start and stop sites, 5' cap, polyA tail, and exon/intron structure) and cloned the ORF encoding TSP1, which is allowing us to perform functional analyses. We find that TSP1 localizes to the neclei of breast cancer cells and tumors, which suggests that TSP1 is a putative chromatin binding protein. ChIP-seq in MCF-7 cells has generated a comprehensive profile of TSP1 genomic binding sites. Furthermore, immunoprecipitation coupled with mass spectrometry has revealed that TSP1 binds to a number of chromatin-regulating proteins, which may facilitate TSP-1-mediated changes in the chromatin environment at target genomic binding loci. **Conclusions:** Collectively, our preliminary results suggest that TSP1 is a chromatin-associated protein that may be a novel cancer biomarker, as well as a potential therapeutic target.

3 **CPRIT Grantee Poster Session A**

Numb prevents a complete EMT by modulating Notch signaling *Federico Bocci, Rice University; M. Jolly; S. Tripathi; M. Aguilar; S. Hanash; H. Levine; J. Onuchic*

Introduction: Epithelial-Mesenchymal Transition (EMT) plays key roles during embryonic development, wound healing, and cancer metastasis. Cells in a partial EMT or hybrid epithelial/mesenchymal (E/M) phenotype tend to exhibit collective cell migration, forming the clusters of Circulating Tumour Cells - the primary drivers of metastasis. Activation of cell-cell signalling pathways such as Notch fosters a partial or complete EMT, yet the mechanisms enabling cluster formation remain poorly understood. **Methods:** Using an integrated computational-experimental approach, we examine the role of Numb – an inhibitor of Notch intercellular signalling – in mediating EMT and the clusters formation of hybrid E/M cells. We developed mechanism-based mathematical models for investigating the role of Numb in mediating EMT both at an individual cell and at a tissue-level. We also knocked down Numb in H1975 cells that can maintain a stable hybrid E/M phenotype in vitro, and examine the clinical significance of Numb in predicting poor survival across cancer types. **Results:** We observed that knockdown of Numb in H1975 cells that display a stable hybrid E/M state is sufficient to destabilize a hybrid E/M state and push them to a full EMT phenotype. Next, our mathematical model recapitulates this ability of Numb in maintaining a hybrid E/M state, and predicts that Numb can alter the relative frequency of hybrid E/M and mesenchymal cells at a tissue level or in clusters of Circulating Tumor Cells (CTCs) – the primary drivers of metastasis. Finally, we show that across cancer types, Numb correlates with worse patient survival. **Conclusions:** Our results indicate that Numb can behave as a phenotypic stability factor (PSF) for a hybrid E/M phenotype by stabilizing hybrid E/M phenotype. Correlation observed between Numb and poor patient survival reinforces the emerging notion that a hybrid E/M, but not necessarily a completely mesenchymal, phenotype associates with elevated tumor progression.

4 **CPRIT Grantee Poster Session B**

RNA-driven gene fusion in human cancer *Sachin Kumar Gupta, Baylor College of Medicine; L. Luo; L. Yen*

Introduction: One of the hallmarks of cancer is the formation of oncogenic fusion genes as a result of chromosomal translocations. Fusion genes are presumed to occur prior to fusion RNA expression. However, studies have reported the presence of fusion RNAs (such as the BCR-ABL RNA in leukemia) in individuals who were negative for chromosomal translocations. The observation, that fusion RNA could be present prior to fusion gene, raises the possibility that cellular fusion RNA created by trans-splicing could act as a guide RNA to mediate genomic rearrangement by annealing to regions of both chromosomes. A precedent for this mechanism is found in lower organisms such as ciliates. However, RNA-driven genomic rearrangement has not been demonstrated in human cells. **Methods:** We transiently expressed short chimeric RNAs resembling a portion of TMPRSS2 and ERG gene sequence in LNCaP cells and treated them with various concentrations of DHT for 3 days. RT-PCR was designed to specifically amplify endogenous fusion RNA derived from the newly induced TMPRSS2-ERG fusion gene, but not from the short chimeric RNAs exogenously expressed from the plasmids. Long-range genomic PCRs and fluorescence in situ hybridization (FISH) were performed to confirm induced fusion gene and to map the genomic breakpoints. **Results:** Our data provide evidence that expression of a chimeric RNA drives formation of a specified gene fusion via genomic rearrangement in mammalian cells. The process is (1) specified by the sequence of chimeric RNA involved, (2) facilitated by physiological hormone levels, (3) permissible regardless of intra-chromosomal or inter-chromosomal fusion, and (4) can occur in normal cells prior to malignant transformation. Furthermore, we identified an endogenous RNA that acts as the 'initiator' RNA to induce TMPRSS2-ERG fusion. The characterizations of the RNA-driven gene fusion will be presented in further details. **Conclusions:** Our data support a model where the initiator RNA with chimeric sequence invades chromosomal DNA to stabilize a transient RNA/DNA duplex using DNA sequences located in two distant genes. Resolution of such an RNA/DNA duplex by DNA break/repair mechanisms might yield the final gene fusion through recombination in regions prone to DNA breaks. The proposed RNA-driven model may provide a mechanism that can 'specify' gene fusion partners in early disease stages, and could have fundamental implications in the biology of mammalian genome stability, as well as gene editing technology via mechanisms native to mammalian cells. This project has been supported by CPRIT training grant RP160283 and CPRIT HIHRRA RP160795.

5 **CPRIT Grantee Poster Session A**

A phosphotyrosine switch controls antitumor activity of estrogen receptor b *Bin Yuan, The University of Texas Health Science Center at San Antonio; C. Clark; Y. Hu; R. Li; T. Curiel*

Introduction: ERa and ERb, which are encoded by different genes (ESR1 and ESR2), mediate the diverse physiological effects of estrogens. Despite sequence homology and similar transcriptional activity, these two ER subtypes exert distinct and even opposite biological functions in cancer. ERa is well known for its role in supporting estrogen-dependent breast tumor growth, whereas ERb has an antitumor activity in multiple cancer types including breast, prostate, colorectal, ovarian cancers, and melanoma. Furthermore, current literature indicates both tumor-intrinsic and -extrinsic antitumor activity of ERb. The ERb antitumor activity offers a potential target for anticancer therapies. However, it is not clear how ERb antitumor activity can be rallied. In recently published work, we identified a phosphotyrosine residue in human ERb, which is highly conserved in all mammalian ERb orthologs, but not present in ERa (alanine in ERa). Importantly, this phosphotyrosine switch controls ERb tumor-intrinsic activity. **Methods:** We generated a whole-body knock-in (KI) mouse model in which the phosphotyrosine residue of endogenous mouse ERb is mutated to phenylalanine. And we utilized the murine melanoma cell line B16F10, colon cancer cell line MC38 and mammary gland tumor cell line M-Wnt1, implanted subcutaneously into syngeneic WT and KI mice for these experiments. **Results:** We found that multiple tumor types grew more robustly in KI recipient mice than in their WT counterparts. Furthermore, melanoma-bearing KI mice displayed more lung micro-metastases than WT control. These data demonstrate that the phosphotyrosine switch is important for ERb tumor-extrinsic antitumor activity. In mouse bone marrow chimeras, we found that tumor growth was significantly faster in KI>WT chimeras (with KI immune cells) versus WT>WT control, suggesting that KI-derived immune cells poorly deterred tumor growth. Preliminary data suggest less immune cell activation in KI versus WT. **Conclusions:** Taken together, our results uncover a previously unrecognized molecular switch that harnesses ERb antitumor activity in both tumor-intrinsic and -extrinsic manners. The implication of our laboratory findings in boosting efficacy of the current immunotherapy will be discussed.

6 **CPRIT Grantee Poster Session B**

The effect of focal adhesion on the mechanobiology of lung cancer cell during metastasis *Richard Han, Rice University; S. Vetsa; S. Mehta; C. Wanna; D. Gibbons; K. Grande-Allen*

Introduction: A mouse model of human lung adenocarcinoma driven by mutations in K-ras and p-53 genes was adapted to investigate the roles of mechanics and cellular epithelial-to-mesemchymal transition (EMT) potential. We are particularly interested in the focal adhesion pathway, as the mechanical stimuli from ECM could govern the cell adhesion and migration, pivotal steps in EMT and metastasis. Cell-matrix organization resulting from interfering with the formation of focal adhesions was investigated at macro- and ultras-structural levels quantitatively. **Methods:** 344SQ metastatic lung tumor cells, and an integrin beta-1 (ITGB1) knock down variant were encapsulated in collagen gels under incubated static tensions. Collagen gels with 344SQ cells were treated with dasatinib, a Src inhibitor were investigated. The elastic properties of the gels were measured using mechanical tester. Gel pieces were stained with DAPI and phalloidin for confocal imaging, and cell spatial distribution was determined using image analysis. SEM imaging of the gels was used to determine the cell morphology and collagen alignment. **Results:** Interfering with focal adhesions, either by ITGB1 knock down or inhibiting Src resulted in reduced elastic moduli compared to controls. At the ultrastructural level, blocking the focal adhesion pathway reduced the collagen fiber alignment and induced cellular phenotypic changes, with more cell clustering resembled the non-metastatic epithelial cell morphology. Additionally, f-actin was over produced and cellular spatial distribution changed to a more clustered pattern. **Conclusions:** Inhibiting the formation of focal adhesions also prevents cells from aligning collagen fibers in the direction of tension to the extent observed in controls, indicating less modulation of ECM. It also appears to drive more cell-cell adhesion in 3D culture, resulting in clusters of cells that suggest a reversion to a more epithelial phenotype. The cells cluster within a few days, leaving less time for organizing the neotissue, which as a result is less strong.

7 **CPRIT Grantee Poster Session A**

Functional Characterization of Genomic-Glycosylation Aberrations in Tumor Initiation and Progression *Carman K.M. Ip, The University of Texas M.D. Anderson Cancer Center; X. Peng; K. Jeong; K. Scott; G. Mills; P. Ng*

Introduction: Glycosylation, one of the most common post-translational modifications of proteins, plays a central role in regulating protein function. Emerging evidence supports altered glycosylation contributing to tumor progression as well as affecting therapy response. Understanding the rules regulating altered glycosylation in cancer may thus provide new insight for the development and implementation of therapy approaches. N-glycosylation occurs at the motif consists of a consensus sequence Asn-Xaa-Ser/Thr/Cys, where Xaa is not proline. Genomic missense mutations could potentially lead to a loss or gain of N-glycosylation sites due to disruption or creation of consensus sequences. However, whether N-glycosylation site altering aberrations have functional consequences during tumorigenesis has not been systematically evaluated. The aim of this study is to identify patient-derived mutations with the potential to alter N-glycosylation sites in cancer genes and to study their functional consequences. **Methods:** To identify aberrations in N-glycosylation sites, all missense mutations that disrupt or create N-glycosylation consensus sequences in all proteins were computationally identified based on sequence data from The Cancer Genome Atlas (TCGA) and International Cancer Genome Consortium (ICGC). The suite of potential N-glycosylation site aberrations that locate in the extracellular domain of secreted or membrane bound proteins, where N-glycosylation mostly occurs, were put forward for functional characterization based on oncogenic transformation in Ba/F3 and MCF10A cells in the absence of growth factors or cytokines and the effects on motility and invasion in MCF10A. The effects of functional aberrations on the proteome will be assessed using reverse phase protein arrays and drug sensitivity tested experimentally. **Results:** By using computational algorithms, we identified 41011 missense mutations with the potential to disrupt or create N-glycosylation consensus sequences from TCAG and ICGC data sets. Among all potential N-glycosylation site altering mutations, 24882 potential gain and 16156 potential loss of N-glycosylation site mutations locate at the extracellular domain of membrane bound or extracellular proteins. 3144 of the potential loss of N-glycosylation site mutations are experimentally identified or predicted as N-glycosylation sites by the 'NetNGlyc' or the PROSITE pattern predictor based on annotation in UniProtKB/Swissprot. Over 40 potential N-glycosylation site altering mutations in receptor tyrosine kinase and cadherin families were selected and are in the process of testing through the functional pipeline and in migration and invasion assays. **Conclusions:** This study may reveal unexpected roles and mechanisms by which N-glycosylation site altering aberrations contribute to tumor progression and therapy response.

8 **CPRIT Grantee Poster Session B**

Elevated D-2-hydroxyglutarate during colitis drives progression to colorectal cancer *Arianne Theiss, Baylor Research Institute; J. Han; D. Jackson; X. Wang; J. Holm; L. Sweetman*

Introduction: Although the association between inflammatory bowel diseases, predominantly ulcerative colitis (UC) and Crohn's disease, and an increased risk of developing colorectal cancer is well-established, the pathogenesis of colitis-associated cancer (CAC) is poorly understood. D-2-hydroxyglutarate (D2HG) is produced in the tricarboxylic acid cycle and quickly converted to alpha-ketoglutarate by D-2-hydroxyglutarate dehydrogenase (D2HGDH). Levels of D2HG are normally low and accumulation of D2HG has been linked to oncogenesis in glioma and acute myeloid leukemia. **Methods:** We utilized quantitative metabolic profiling to detect molecular pathways involved in disease progression from colitis to cancer. To induce CAC, wild-type C57BL/6 male mice were intraperitoneally injected with 7.6 mg/kg azoxymethane (AOM) followed by 2 cycles of 3% dextran sodium sulfate (DSS; 1 week DSS and 3 weeks recovery). Urine was serially collected at baseline, during DSS (colitis stage), and the day before sacrifice (polyp stage) and metabolites were analyzed using gas chromatography-mass spectrometry. Expression of D2HGDH was measured in AOM-DSS-treated mice and in baseline mucosal biopsies from UC patients who progressed to CAC or UC patients remaining dysplasia-free. A subset of mice treated with AOM-DSS was i.p. injected with 25 mg/kg D2HG or vehicle once daily during DSS administration. Severity of colitis (body weight loss, severity of diarrhea, and presence of blood in the stool) were monitored during DSS and recovery phases. Excised colons were observed for polyp number/size and embedded for dysplasia scoring. **Results:** In the AOM-DSS model of CAC, urine level of D2HG during colitis correlated positively with subsequent polyp counts and severity of dysplasia. Colonic expression of D2HGDH was decreased during DSS colitis and in UC patients at baseline who progressed to cancer. Mice injected with D2HG exhibited delayed recovery from colitis and severe tumorigenesis. **Conclusions:** D2HG enhances the progression of colitis to colon cancer. Urine D2HG and tissue D2HGDH expression are potential novel biomarkers to identify patients at risk of progressing from colitis to cancer. The D2HG/D2HGDH pathway provides potential novel therapeutic targets for the treatment of CAC.

9 **CPRIT Grantee**
Poster Session A

Unraveling the role of RNA secondary structure in promoter-proximal pausing of RNA polymerase II in cancer cells *Yingjie Zhu, The University of Texas Medical Branch at Galveston; D. Baillat; N. Elrod; E. Wagner; M. Rowicka*

Introduction: Eukaryotic transcription from initiation to elongation and termination is known, whereas emerging evidence points to the pausing of transcription, in which RNA polymerase II pauses in proximal of promoter before transitioning into productive elongation. Although RNA polymerase II pausing has been shown to be a key step in transcription regulation as a rate-limiting step, the mechanisms behind this process remain poorly understood. In this study, we propose a possible mechanism in promoter-proximal pausing caused by RNA secondary structure. **Methods:** We predicted the stability of RNA secondary structure around TSS in human genes by testing RNA free energy. Global run-on sequencing (GRO-seq) data detecting nascent RNAs were used to establish pausing possibility in the different gene regions. Then, based on the pausing possibility, we investigated the difference of RNA structural stability between those gene regions. **Results:** We identified a region downstream of the TSS has higher RNA stability in secondary structure in comparison with gene body. By analyzing nascent RNA sequencing data, we found that highly paused genes performed higher stability and significant difference in comparison with lowly paused genes. It suggests pausing was regulated by special RNA secondary structure. Further, we used highly paused genes to characterize secondary structure elements shared among genes impacted by pausing. We found that a short stem-loop structure may contribute to RNA pol II pausing. Using its structure characteristics, we also observed substantial pausing genes in different cancer cell lines and also Drosophila cells but in different patterns. **Conclusions:** Our studies suggest that RNA secondary structure can be a temporary barrier to impede the progress of RNA polymerase II in the vicinity of transcription start sites. The structural characteristics identified in this study will provide for genetic engineering to regulate transcription in cells. Further study on pausing mechanisms will contribute to understanding transcription dysregulation, thus paving the way to exploiting these insights for cancer biology.

10 **CPRIT Grantee**
Poster Session B

Gpr161 functions as a tumor suppressor in medulloblastoma by restricting generation and maintenance of cerebellar granule cell progenitors in a primary-cilium dependent manner *Issei Shimada, The University of Texas Southwestern Medical Center; S. Hwang; B. Somatilaka; S. Mukhopadhyay*

Introduction: Cerebellar granule cell (GC) progenitors proliferate in a sonic hedgehog (Shh)- and primary cilia-dependent manner, while oncogenic Shh signaling promotes medulloblastoma formation. The orphan G-protein-coupled receptor, Gpr161 localizes to primary cilia, and basally suppresses Shh signaling by regulating Gli transcriptional repressor versus activator generation. However, the role of factors basally repressing Shh pathway in generation and maintenance of GC progenitors is unknown. **Methods:** Here, we demonstrate that neural stem cell (NSC)- or GC progenitor-specific Gpr161 knockout mice develop Shh-subtype medulloblastomas, which are molecularly identical to Shh-subtype human tumors. **Results:** Gpr161 depletion increased Shh signaling and proliferation of GC progenitors in the external granule layer (EGL) postnatally, with highest incidence of tumorigenesis upon mid-gestational deletion in NSCs. In particular, both generation and proliferation of GC progenitors in the upper rhombic lip and formative EGL, respectively, were increased in the mid-embryonic cerebellar anlage, along with upregulation of Shh signaling. Furthermore, loss of Gpr161 was accompanied by absence of cerebellar foliation, and varying degrees of dysplasia. Interestingly, concomitant disruption of cilia demonstrated that Gpr161 limits GC progenitor generation and proliferation in a cilia-dependent manner. Notably, reduced expression of GPR161 and that of factors trafficking the receptor to cilia, such as intraflagellar transport complex A subunits and Tubby like protein 3, correlated with poor survival of human SHH-subtype medulloblastoma patients. **Conclusions:** Thus, Gpr161 is a bona fide tumor suppressor in Shh-subtype medulloblastoma.

11 **CPRIT Grantee**
Poster Session A

The possible role of PRMT1-mediated EGFR methylation in EGFR function and cetuximab sensitivity in triple negative breast cancer *Hirohito Yamaguchi, The University of Texas M.D. Anderson Cancer Center; W. Xia; H. Liao; M. Hung*

Introduction: Epidermal growth factor receptor (EGFR) is often overexpressed in triple-negative breast cancer (TNBC). However, patients with TNBC did not respond well to anti-EGFR therapies in clinical trials. Our previous study shows that that the methylation of arginine 198/200 (R198/200) in EGFR is involved in the resistance to EGFR monoclonal antibody cetuximab in colorectal cancer cells. Thus, we further studied the role of the EGFR methylation in the intrinsic resistance to cetuximab in TNBC. **Methods:** We performed immunohistochemical staining of methylated EGFR at R198/200 in TNBC patient tissues. Moreover, to determine the role of PRMT1, which is the enzyme responsible for EGFR R198/200 methylation, we knocked down PRMT1 in MDA-MB-468 TNBC cells, and examine the activation of EGFR and its downstream molecules. Finally, we examined the effects of pan-PRMT inhibitor, AMI-1, on the response to cetuximab by colony formation and soft agar assays. **Results:** We found that EGFR is highly methylated as colorectal cancer, and that methylation and activity were attenuated in PRMT1-knockdown cells compared to the parental cells. We also investigated cell proliferation and sphere formation of the PRMT1-knockdown cells, and found that knockdown of PRMT1 also reduced cell proliferation and sphere formation. We also demonstrated that AMI-1 sensitized MDA-MB-468 cells to cetuximab. **Conclusions:** These results suggest that PRMT1-mediated EGFR methylation plays a role in EGFR function and cetuximab resistance in TNBC. Thus, the combination of cetuximab and PRMT1 inhibitor may be a therapeutic option for patients with methylated EGFR-expressing TNBC.

12 **CPRIT Grantee**
Poster Session B

MoPAC: an online tool for fast and flexible analysis of CRISPR functional screens *Oscar Villarreal, The University of Texas M.D. Anderson Cancer Center; D. Su; X. Shi; H. Xu*

Introduction: High-throughput functional genetic screens based on CRISPR–Cas9 or –dCas9 systems have become increasingly popular in biomedical research studies such as cancer drug discovery. CRISPR screens are diverse in experimental designs, cell types, and conditions of cell selection, making it difficult to analyze the data in “one-click”. Interactive computational tools are in demand for refined analysis and data interpretation through graphic user interfaces. **Methods:** We propose MoPAC (Modular Pipeline for Analysis of CRISPR screens), which consists of a set of optimized computational modules for quality evaluation, normalization, data interpretation, and quantitative comparison among multiple samples. Through an online graphic interface, MoPAC users are allowed to visualize their data in an interactive manner, and to define customized analysis streams that best fit the experiments. **Results:** We demonstrate the application of MoPAC in a CRISPR knockout screen on two KRAS-mutant cancer cell lines treated with MEK inhibitor. MoPAC successfully determined common and cell-specific essential genes in these lines. Moreover, it identified BRAF and FGFR1 as two key genes that are in synthetic lethality with MEK inhibition. **Conclusions:** In summary, MoPAC has shown to be a fast and flexible tool for the analysis of CRISPR functional screens, with great potential in accelerating drug discoveries.

13 **CPRIT Grantee**
Poster Session A

Current progress in creating an ex-vivo 3D cell-culture model from decellularized mice colons to study colorectal cancer *Busola Alabi, The University of Texas Southwestern Medical Center; R. LaRanger; J. Shay; W. Wright*

Introduction: Many of the models to test and develop therapeutics against cancerous cells involve using 2D in vitro assays in which cells are seeded as monolayers on plastic plates. However, these models do not necessarily recapitulate the in vivo tumor micro-environment. For example, in vivo tumors tend to be more densely populated in the center than the periphery resulting in an uneven distribution of oxygen, nutrients and permeability to chemotherapeutic agents throughout the tumor. Furthermore, in vivo cancer cells are not present in isolation but instead interact with stromal cells such as fibroblasts. All these different cell types that make up the tumor niche are attached to the extracellular matrix (ECM) of the tissue. The ECM provides architectural support as well as signaling proteins that direct cellular processes including differentiation. **Methods:** To better model these complex interactions of the cancer niche in vitro, we are developing a 3D ex-vivo model to study human colorectal cancer using ECMs obtained from decellularized mice colons (DMC). **Results:** When we seeded HT29, a colon cancer cell line, onto the DMC with the aid of a bioreactor, a large fraction of the cells either differentiated into mucin-2 producing cells or stayed proliferative and did not invade the basement membrane. When we made these cells into organoids in Matrigel, most the cells continued to proliferate and did not express mucin-2. Expectedly, DLD-1 and HCT116, two non-multipotent colon cancer cell lines were unable to differentiate when seeded onto the DMC. Because the ECM has been noted to undergo various remodeling processes during tumorigenesis, we tested for changes in stiffness using the Young’s Modulus of the DMC after it was reseeded. We found an increase in the stiffness of the DMC after recellularization with cancer cells.

Conclusions: To more completely model the tumor microenvironment, we plan to reconstitute the matrix with human colonic epithelial cells (HCEC), myofibroblasts, endothelial cells and various cancer cell types. Because the decellularization process renders the colon tissue transparent we will be able to follow the activities of these cells, over time, using confocal time lapse microscopy. Finally, we plan to use this ex-vivo system to identify driver genes necessary for progression of colon cancer to a more invasive form by making use of the CRISPR CAS9-powered GECKO screen as well as a panel of isogenically progressed HCEC.

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14 **CPRIT Grantee Poster Session B**

Bacteriophage therapy as an alternative method to treat secondary infections in cancer patients and essential importance to understand biophysical processes of DNA extraction from bacteriophages *Olga Samoylova, The University of Texas Medical Branch at Galveston; B. Pettitt*

Introduction: Cancer patients during and after treatment are often at risk of getting bacterial infections. Some pathogenic bacteria develop resistance to antibiotics, which requires alternative treatment methods. Bacteriophage therapies can be used to treat such bacterial infections. There is the possibility to redesign phages to target specific bacteria strains with drug resistance. Recognition is often through the proteins of the baseplate encoded by the phage. Genetic material of bacteriophages, DNA or RNA, are carried in the protein capsid and released into the bacteria, disrupting metabolism and causing the bacterium to lyse. Sequence dependent mechanical coupling of the DNA to the thermodynamics of packing can change efficiency and possibly inhibit packing of some sequences. Understanding the biophysical basis of the biological process which transfers a viral genome to infect a cell is very important to the cellular machinery and many disease related fields central to the sequence design issue for reprogramming phages for emerging strains. **Methods:** We employ all-atoms molecular dynamics simulations combined with experimental data to model DNA extraction from the bacteriophage. Different concentration of species inside the capsid and in the surrounding environment creates the osmotic pressure difference. We consider the consequences of osmotic pressure on the DNA in terms of stability and the effective interactions between DNA duplexes, salt and the environment. We use molecular dynamics simulations with semipermeable barriers to model the osmotic pressure. **Results:** Preliminary calculations have confirmed our implementation yields the correct osmotic pressure for ionic solutions of sodium chloride and for polyethylene glycol crowders. We performed a set of simulations designed to decompose the contributions of the osmotic pressure from the individual components (DNA, crowders, and salt) separated by semipermeable barriers. Multiple DNA molecules simulated to model DNA-DNA interactions inside the capsid were also performed. Results for the osmotic pressure are reported. **Conclusions:** Our approach can be used to predict the osmotic pressure necessary to confine DNA in the phage, and determine the driving forces acting on genome inside the viral capsid. Truncated (tail region) idealized phage systems packed with various sequences will be simulated to study the mechanical consequences with DNA transferring through the tail-channel under an external driving force. This is an integral area of research which is necessary for the development of genetically modified phages for better bacterial detection purposes or for the therapeutic applications.

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15 **CPRIT Grantee Poster Session A**

PTEN loss confers poly [ADP-ribose] polymerase (PARP) inhibitor resistance in BRCA1-depleted triple-negative breast cancer *Jun Yin, The University of Texas M.D. Anderson Cancer Center; C. Sun; J. Garnett; C. Ip; K. Do; G. Mills; S. Lin*

Introduction: BRCA1-deficient cancers, which share some similarities with TNBC in clinical pathologies and outcomes, have evolved to tolerate loss of BRCA1 function, rendering them vulnerable to PARP inhibition. Interestingly, in our preliminary data, nearly 100% (37/38) of TNBC patients with BRCA1-low-gene expression also have low-level PTEN RNA levels. Patients with both low BRCA1 and PTEN gene expression levels (DBL) account for approximately 27% of the total TNBC cohort, which are associated with a worse prognosis. However, we have previously implied that cell lines with a single loss of either BRCA1 or PTEN are more sensitive to PARPi than those with loss of both, regardless of other mutations (ATM, BRCA2, or TP53). This raises the concern that PARPi in BRCA1-deficient patients won't be effective in those patients whose tumors simultaneously have low PTEN expression, and therefore ultimately should be treated differently. **Methods:** We performed global proteomic profiling (reverse phase protein array - RPPA) of MCF-10A model system before and after irradiation at different time courses, aiming at finding out the key molecules that are dynamically recruited upon double strand breaks (DSBs). Additionally, by integrating transcriptome data from the selected cell lines and patients, we established a unique gene signature that was specific to DBL group, serving as a guide for targeting the pathways that are uniquely associated with DBL group. **Results:** We believe that it is the insufficient early-stage recruitment of chromatin binding 53BP1, and therefore its reduced retention upon double strain breaks that contribute to the HR efficiency in cells with loss of both PTEN and BRCA1. Our preliminary data also hinted that RNF168, which is molecule upstream in the DNA response pathway, is strongly associated with 53BP1 regulation in Brca1-deficient cells. Integrated the unique gene signature of DBL group with its associated pathways analysis, we determined that the S/G2 checkpoint may be defective following DNA damage, indicating checkpoint dysregulation in this group. This observation implies that DBL cells should be sensitized to or Wee1 inhibitors (e.g., MK1775) by their checkpoint defect and we've also further observed that DBL group exhibited significantly better sensitivity than other groups in response to MK1775. **Conclusions:** These data clearly demonstrate that loss of PTEN reverses HRD function in Brca1-depleted cells and this phenotype is strongly associated with the better recruitment of Rad51 foci and less 53BP1 foci upon DSBs for DBL group, and this group can be potentially targeted by Wee1 inhibitors.

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16 **CPRIT Grantee Poster Session B**

Comprehensive identification of bone cancer driver genes by using Li-Fraumeni syndrome iPSCs *Dung-Fang Lee, The University of Texas Health Science Center at Houston; R. Zhou; J. Tu; A. Xu; C. Huff; L. Strong; R. Zhao*

Introduction: Osteosarcoma is one of the most frequent primary malignant tumors in children and adolescents. Despite the fact that the 5-year survival of localized osteosarcoma is only 60-65% and far worse for metastatic disease, treatment strategies for this malignancy remained nearly unchanged during the last four decades. The complexity of osteosarcoma and limited access to tumor samples posed difficulties for better understanding of this disease from the molecular level. Therefore, novel and reliable disease models for osteosarcoma are in urgent need and identifying novel driver genes involved in osteosarcoma initiation and development is of great translational importance. Li-Fraumeni syndrome (LFS) is an autosomal dominant disease caused by germline mutations in the gene TP53, which predispose individuals to a wide range of malignancies, especially osteosarcoma; thus LFS is an ideal model system to study this malignancy. We developed a novel disease model platform by reprograming LFS patients' fibroblasts to induced pluripotent stem cells (iPSCs), and further differentiate these iPSCs into mesenchymal stem cells (MSCs) then to osteoblasts, the cells from which osteosarcoma originate. Interestingly, LFS iPSC-derived osteoblasts recapitulated the osteosarcoma phenotype, creating "a bone tumor in a dish". **Methods:** In this study, we will utilize this novel disease model to identify cancer drivers that contribute to the development of LFS associated osteosarcoma. Succinctly, we will record the genomic changes along differentiation stages by performing whole genome sequencing of LFS samples with different tumorigenic potential (MSCs, osteoblasts, osteoblasts grown in soft agar and in SCID mice). Systematic analyses of whole-genome alterations in these samples will provide "genomic snapshots" depicting the process of how osteosarcomas initiate and develop. **Results:** After LFS patient-derived iPSCs have been successfully differentiated into osteoblasts, soft agar assay for testing tumorigenic ability were performed. LFS patient derived osteoblasts formed more colonies compared to wild-type osteoblasts, confirming in vitro tumorigenicity of LFS derived osteoblasts. **Conclusions:** Further completion of this study should provide a systematic characterization of genome alterations during the initiation and development of osteosarcoma. Identification of critical bone cancer drivers in this study will potentiate the development of novel treatment for osteosarcoma. Successful recapitulation of the osteosarcoma development process using "a bone tumor in a dish" system will also bring new capabilities to the field of cancer modeling. Since iPSCs can differentiate into any human tissues, the LFS iPSCs platform has great potential in modeling other cancers, such as brain tumor and breast cancer, which are also commonly seen in LFS patients.

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17 **CPRIT Grantee Poster Session A**

Down-Regulation of the MKK4/JNK2 Axis in NSCLC Suppresses Tumor Growth and Metastasis *Tamer Kaoud, The University of Texas at Austin; N. Ebelt; S. Van Ravenstein; L. Du; K. Tsai; K. Dalby*

Introduction: Mitogen-activated protein kinase kinase-4 (MKK4) has been reported to either enhance or suppress oncogenesis. Evidences of its pro-oncogenic activities in breast, pancreatic, lung and skin cancer have been reported. Although the mechanism of its possible tumorigenic role is still unclear. Recent studies in glioblastoma and lung carcinoma have suggested important roles for the constitutive activation of its downstream substrate JNK2. **Methods:** JNKs require phosphorylation by both MKK4 and MKK7 to be fully activated. The JNK2 isoform shows a

unique propensity among the JNKs to autophosphorylate in vitro. Here we show that JNK2 autophosphorylation contributes to the proliferation and migration of NSCLC cells under conditions of low serum through an MKK4-dependent mechanism. This suggests a pro-oncogenic role of MKK4 in NSCLC through a JNK2 autophosphorylation-dependent pathway. **Results:** Evidence in several cell lines, including mouse embryonic stem cells lacking MKK4 or MKK7 suggests that autophosphorylation alone activates JNK2 weakly in cells. However, JNK2 autophosphorylates on Thr-183, to create a pool of JNK2 primed for activation by MKK4, which phosphorylates JNK2 on Tyr-185 to activate it. Under conditions of low serum the down-regulation/overexpression of MKK4 or JNK2 but not MKK7 or JNK1 suppresses/promotes proliferation of multiple NSCLC cell lines, through STAT3. Under the same conditions, A549 cell migration is inhibited upon down regulation of either MKK4 or JNK2. Further supporting the notion that active JNK2 results primarily from autophosphorylation of Thr-183, pan-JNK ATP competitive inhibitors (JNK-IN-8 and SP600125) showed a dose-dependent dephosphorylation of JNK2 in NSCLC cell lines and inhibited their proliferation under conditions of low serum. Moreover, the downregulation of MKK4 or inhibition of JNK2 autophosphorylation by SP600125 inhibited nuclear localization of JNK2 in A549 cells cultured in low serum. To further understand the pro-oncogenic role of MKK4 in the A549 cell line, we investigated tumor growth and lung metastasis in A549 Xenografts in which either JNK2 or MKK4 were stably knocked down. Either JNK2 or MKK4 down regulation showed a similar suppression of tumor growth and lung metastasis if compared to cells expressing an shRNA control. Sequencing of MKK4 in the A549 cells revealed no genomic deletion or somatic mutations. **Conclusions:** Taken together, the data suggest that MKK4 may exhibit pro-oncogenic properties in NSCLC by activating Thr-183-autophosphorylated JNK2. Targeting this pathway may reduce or block lung tumor progression and/or metastasis.

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18 **CPRIT Grantee**
Poster Session B

Investigating the role of the Hippo signaling pathway in mouse pancreas *Ming Gao, The University of Texas Health Science Center at San Antonio; J. Liu; F. Sharkey; R. Johnson; P. Wang*

Introduction: Large tumor suppressor kinase 1 and 2 (Lats1&2) are the core kinases of the Hippo signaling pathway, and play critical roles in regulating cell growth and organ size during animal development. Inactivation of the Hippo signaling pathway has been demonstrated to initiate tumor development in certain organs. However, the function of Lats1&2 in the pancreas and pancreatic cancer development is still elusive. **Methods:** To investigate the function of Lats1&2 in the pancreas, we generated mice with adult pancreatic acinar cell–specific deletion of Lats1&2 genes with Rosa26LSL-YFP locus. The tails of pancreata were collected for western blot and Q-PCR examination. **Results:** Interestingly, instead of enlarging of the pancreas or pancreatic tumorigenesis, the deletion of Lats1&2 genes (DKO) in pancreatic acinar cells resulted in severe inflammation and fibrosis of the pancreas. To further examine the mechanisms, we took advantage of a Rosa26 reporter to trace individual Lats1&2 null cells in vivo. We found that the loss of Lats1&2 did not affect cell growth directly but activated pancreatic stellate cells (PSCs). This was followed by immune cell infiltration and acinar-to-ductal metaplasia in Lats1&2 null pancreases. In addition, we detected that several cytokines and chemokine genes, such as ctgf, cxcl12, cxcl16, were unregulated in Lats1&2 null pancreases before immune cell infiltration. Moreover, when we treated DKO mice with anti-ctgf antibody, we found that ctgf blockage partially rescued the pancreatitis phenotype. Finally, we revealed that deletion of Yap1 and Taz, which served as the downstream effectors of Lats1&2, can rescue the pancreatitis phenotype. **Conclusions:** In our present study, we found that deletion of the Lats1&2 genes in acinar cells caused pancreatitis through activation of pancreatic stellate cells. Our study discovered a new mechanism of the inflammatory and fibrotic response initiated by pancreatic epithelial cells and regulated by the Hippo signaling pathway, which is likely to be useful for the identification of new strategies for controlling pancreatic inflammation and fibrosis, as well as prevention of pancreatic cancer. Acknowledgement: *Ming Gao is supported by a pre-doctoral fellowship through CPRIT Research Training Award RP 170345 *Jun Liu was supported by a post-doctoral fellowship through CPRIT Research Training Award RP140105. *Pei Wang is CPRIT scholar and funded by First time faculty award.

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19 **CPRIT Grantee**
Poster Session A

AMP-activated protein kinase links metabolic regulation to epigenome modification in leukemia-initiating-cells *Yajian Jiang, Baylor College of Medicine; A. Kitano; V. Luu; T. Hu; D. Nakada*

Introduction: Metabolic reprogramming impinges on epigenome through metabolites such as acetyl-CoA and alpha-ketoglutarate in cancer. Therefore, disruption of metabolic regulators may lead to an alteration of the epigenome. AMP-activated kinase (AMPK) is a master regulator of energy homeostasis by activating catabolic pathways and suppressing anabolic activities. Previously we found that AMPK is essential for the leukemogenic function of leukemia-initiating-cells (LICs) in MLL-AF9 driven leukemia. Deletion of AMPK induced multiple changes in metabolism including reducing glycolysis activity and attenuating pentose phosphate pathway. However, whether deletion of AMPK results in epigenome modification through the altered metabolism in LICs remains unclear. **Methods:** Mass spectrometry was performed to identify the altered metabolites in glycolysis. Validation of specific metabolites such as acetyl-CoA was performed using fluorometric biochemistry assays. To profile the altered epigenome in AMPK deficient LICs, we used immunoblot and chromatin immunoprecipitation sequencing (ChIP-seq). Perturbation of the intracellular acetyl-CoA pool was performed by either supplementing acetyl-CoA precursor acetate to LIC culture or deleting acetyl-CoA producing enzymes such as Acly and Acss2 through the CRISPR-Cas9 system. Histone acetylation was assessed through immunoblot and cell growth was monitored by cell counting. **Results:** We found that acetyl-CoA levels were reduced in AMPK KO leukemia cells. Both acetylated histone H3 and H4 were decreased in AMPK KO LICs. ChIP-Seq results indicated histone hypoacetylation across the genome as well as at MLL-AF9 targeted genes in AMPK KO LICs. Moreover, gene set enrichment analysis revealed that the MLL-AF9 targeted gene transcripts were less enriched in AMPK KO LICs. Lastly, we found that perturbation of the acetyl-CoA pool affected histone acetylation and cell growth. Specifically, supplementation of acetate to LIC culture increased the intracellular acetyl-CoA and histone acetylation levels as well as promoting cell growth. Deleting Acss2 or Acly suppressed acetyl-CoA, decreased histone acetylation levels and hampered cell growth. **Conclusions:** Together, our work links AMPK to epigenomic modification and suggests that AMPK does not only serve to regulate metabolic activities. Instead, we found that AMPK deficiency decreased acetyl-CoA pool and further reduced histone acetylation in LICs. This resulted in suppression of MLL-AF9 targeted genes and impaired cell growth. This work raises the possibility that metabolic intervention can modify the epigenome and potentially synergize with epigenetic drugs in suppressing leukemia growth.

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20 **CPRIT Grantee**
Poster Session B

Critical Role of NLRP12 in Colorectal Cancer *Hasan Zaki, The University of Texas Southwestern Medical Center; S. Hu; Y. Kwak*

Introduction: NLRP12, a cytosolic pattern recognition receptor in the family of NOD-like receptors, has recently emerged as negative regulator of intestinal inflammation and cancer. We have demonstrated that Nlrp12-/- mice are highly susceptible to azoxymethane (AOM) plus dextran sodium sulfate (DSS)-induced colorectal cancer (CRC), showing increased tumor burden and faster tumor progression. However, the precise mechanism underlying NLRP12-mediated regulation of CRC is unclear. Therefore, here we investigated the molecular mechanism of NLRP12-mediated regulation of colorectal cancer using a chemical injury models (AOM/DSS) and genetic models (APCmin+) model **Methods:** To understand the role of NLRP12 in CRC, we induced colorectal tumorigenesis in wild-type (WT) and Nlrp12-/- mice using AOM plus DSS. Colon tissue collected at day 10 and day 80 following tumor induction was analyzed for the activation of cell signaling pathways and the expression of pro-tumorigenic molecules. In a different approach, we crossed WT and Nlrp12-/- mice with APCmin mice. APCmin and APCminNlrp12-/- mice were examined for the development of intestinal and colonic polyps at 5 months after birth. Tumor burden were counted, cell signaling pathways were analyzed by western blotting, and the expression of tumor promoting factors were measured by real time PCR. **Results:** While we observed increased activation of inflammatory signaling pathways NF-B and ERK in the colons of Nlrp12-/- mice during early time point (day 10), no such effect of NLRP12 on NF-B and ERK was observed in tumors (day 80). In contrast, tumor bearing colons of Nlrp12-/- mice express higher level of tumorigenic factors including cMyc, Axin2, Ccnd1, Cox2, Lgr5, and VEGF as compared to those in WT mice. Interestingly, these genes are downstream of the Wnt/-catenin signaling pathway. Consistently, AOM/DSS-treated Nlrp12-/- mouse colons exhibit significantly elevated levels of -catenin. The role of NLRP12 in the regulation of the Wnt/b-catenin pathway was further evidenced by studies using Apcmin mice. Crossing Nlrp12-/- mice with APCmin mice led to increased adenomatous polyps development in the small and large intestines. We also observed higher expression of tumor promoting genes in Nlrp12-/-APCmin mouse colons as compared to those in APCmin mice. **Conclusions:** Our data suggest that NLRP12 may play a role in regulating CRC via regulation of the Wnt--catenin pathway. This study shed light on a novel mechanism of regulation of Wnt/-catenin by innate pathogen sensor NLRP12 that may help develop better treatment for CRC.

21 **CPRIT Grantee Poster Session A**

Developing therapeutic strategies for lung cancer treatment by targeting mitochondrial function *Sarada Preeta Kalainayakan, The University of Texas at Dallas; P. Ghosh; S. Dey; K. FitzGerald; L. Liu; L. Zhang*

Introduction: Previously, studies focused mainly on the precept that tumors depend on glycolysis for energy and growth (the Warburg effect) and that mitochondria are dysfunctional in cancer cells. However, there is mounting evidence suggesting that some cancer cells exhibit elevated mitochondrial respiration. Recent studies in our lab have demonstrated that non-small cell lung cancer (NSCLC) cells exhibit intensified mitochondrial respiration and oxygen consumption. We further demonstrated that targeting increased mitochondrial respiration with a therapeutic agent that causes enhanced ROS production and mitochondrial fission effectively hampers proliferation of NSCLC cells in vitro. Our study aims to determine whether targeting mitochondrial function affects NSCLC tumor growth and progression in vivo. **Methods:** Luciferase expressing NSCLC cells were implanted in the lungs of NOD/SCID mice to generate orthotopic xenografts. The mice bearing orthotopically implanted NSCLC tumors were treated with an agent that targets mitochondrial function. Tumor growth was monitored by non-invasive bioluminescence imaging (BLI). Immunohistochemistry (IHC) was performed on sections obtained from paraffin embedded lung tissues to discern the mechanisms of action of the agent. **Results:** BLI data demonstrated that there was a considerable reduction in radiance in mice that received the mitochondria-targeting agent. IHC data indicated that there was a reduction in expression of proteins involved in heme transport and degradation and hemoproteins involved in mitochondrial respiration in mice treated with the mitochondria-targeting agent. Further, IHC data indicated reduced levels of a putative heme sensor and heme chaperone necessary for maintaining levels of cellular heme and hemoproteins in mice that received the mitochondria-targeting agent. **Conclusions:** Our results suggest that targeting mitochondria affects proteins involved in heme synthesis and degradation, thereby affecting hemoproteins involved in mitochondrial respiration and significantly inhibiting lung tumor growth. Our results also indicate the possibility that our mitochondria targeting agent acts via regulating levels of a putative heme sensor.

22 **CPRIT Grantee Poster Session B**

Targeting the Epigenetic Vulnerabilities of Myeloid Leukemia *Jian Xu, The University of Texas Southwestern Medical Center; Z. Gu; Y. Liu; H. Cao; M. Chen; Y. Zhang; L. Qi; X. Liu; K. Li; K. Dickerson; F. Cai; W. Chen; M. Ni; R. DeBerardinis*

Introduction: Myeloproliferative neoplasms (MPNs) are clonal, progressive blood cancers characterized by alterations of multiple signaling (e.g. JAK2 and RAS) and epigenetic pathways in hematopoietic stem cells (HSCs). A major challenge is to elucidate the molecular pathways controlling the progression of MPNs from chronic to life-threatening stages. The identification of driver oncogenic mutations in JAK2, CALR or MPL has transformed our knowledge of MPNs; however, patients with non-mutated JAK2, CALR and MPL (so-called 'triple-negative') had the highest incidence of leukemic transformation and the lowest overall survival, indicating that other factors may contribute to MPNs through JAK2-dependent or independent pathways. **Methods:** We have developed new mouse models of MPN by hematopoietic-selective activation of oncogenic Ras (NRasG12D+/-) and inactivation of Ezh1 or Ezh2, the enzymatic subunit of the Polycomb Repressive Complex 2 (PRC2). Working with these genetic models, we seek to better understand the relationship between epigenetics and metabolism in leukemia initiation by focusing on the role of Ezh1 and Ezh2 in the development of myeloid neoplasms. **Results:** While activation of NRasG12D+/- alone led to chronic myeloproliferation, Ezh2 knockout (E2-KO) markedly accentuated disease progression from indolent to highly penetrant lethal MPNs and/or acute leukemia, resulting in marked increases in platelets and neutrophils, severe anemia, extramedullary hematopoiesis, and early lethality. These mice also displayed expansion of hematopoietic stem/progenitor compartments and a skewed differentiation towards megakaryopoiesis at the expense of erythropoiesis in the bone marrow and spleen. More importantly, while no fibrosis was observed in NRasG12D+/- mice, loss of Ezh2 together with NRasG12D+/- (E2-KO) resulted in extensive myelofibrosis, destructive myelodysplasia, and occasional leukemic infiltration in the bone marrow, spleen and liver. Our results provide compelling genetic evidence that Ezh2 insufficiency and oncogenic Ras contribute synergistically to the development of MPNs, particularly myelofibrosis. Strikingly, while loss of Ezh1 alone did not cause any defects in normal hematopoiesis, concurrent inactivation of Ezh1 and Ezh2 (E1E2-KO) completely abolished MPN development and myelofibrosis. **Conclusions:** Our results established an essential role of Ezh1 in the pathogenesis of Ezh2-deficient MPNs, and identified a selective epigenetic vulnerability for MPNs induced by Ezh2 deficiency. The selective vulnerabilities raise the possibility of leveraging Ezh1 as targeted therapies to specifically eradicate Ezh2-mutant LSCs. Hence, our study promises to provide critical insights into developing new therapies to selectively eliminate leukemia-initiating cells harboring alterations of epigenetic pathways.

23 **CPRIT Grantee Poster Session A**

Intratumour Heterogeneity is Associated with Survival of Patients with Stage IA Lung Adenocarcinoma *Kelly Quek, The University of Texas M.D. Anderson Cancer Center; J. Li; J. Fujimoto; J. Zhang; J. Wang; W. Lee; R. Chen; C. Chow; C. Behrens; X. Mao; A. Correa; X. Song; J. Zhang; E. Roarty; R. Thornton; M. Coyle; L. Little; C. Gumbs; M. Antonoff; N. Kalhor; C. Moran; A. Weissferdt; W. William Jr.; S. Swisher; J. Lee; J. Heymach; I. Wistuba; P. Futreal; J. Zhang*

Introduction: Our previous study has suggested that complex genomic intratumour heterogeneity (gITH) was associated with an increased risk of relapse in patients with localized lung adenocarcinomas (LUAD). We have launched a study to investigate genomics profile ITH of Stage IA NSCLC (a patient population with no optimal biomarker to guide postsurgical therapy) to understand the molecular evolution during early carcinogenesis and to identify biomarkers for early detection and intervention. **Methods:** We performed multiregion whole exome sequencing on 30 Stage IA LUAD and matched normal lung tissue to a median sequencing depth of 494x. 15 patients have relapsed within 3 years post-surgery (cases) and 15 patients have not relapsed with a minimum of 5-year postsurgical follow up (controls). Shannon diversity index (SDI) was used to quantify ITH in each individual tumour. Kaplan-Meier method was used to evaluate the relationship between ITH and disease-free survival (DFS) as well as overall survival (OS). **Results:** Consistent with our previous study, 22 of 24 (91.7%) canonical cancer gene mutations were shared events by all regions of individual tumour. Compared to non-relapsed controls, tumours from relapsed cases demonstrated significantly higher degree of ITH (mean average SDI of 1.43 in cases versus 1.21 in controls, $p = 0.03$ and mean maximum pairwise SDI of 1.84 in cases versus 1.62 in controls, $p = 0.008$). Compared to non-relapsed controls, tumors from relapsed cases demonstrated significantly higher degree of ITH (mean average SDI of 1.43 in cases versus 1.21 in controls, $p = 0.03$ and mean maximum pairwise SDI of 1.84 in cases versus 1.62 in controls, $p = 0.008$). Higher degree of gITH was associated with shorter OS ($p = 0.003$) and shorter DFS ($p = 0.004$). Significantly higher mutation burden was observed in tumors from relapsed patients (average 10.4 mutations per Mb versus 6.94 mutations per Mb, $p = 0.03$). The overall mutational spectra showed strong enrichment of signature 4 substitutions (associated with smoking) and a subtle degree of enrichment for signature 1 (associated with age), and signature 13 (associated with APOBEC), reflecting multiple mutational processes contributing to the genetic diversity during cancer development. **Conclusions:** Majority of cancer gene mutations are clonal events during early carcinogenesis of LUAD. Complex gITH may be associated with more aggressive biology and inferior clinical outcome in patients with Stage IA LUAD, therefore, may be evaluated as a potential biomarker.

24 **CPRIT Grantee Poster Session B**

Pancreatic ductal adenocarcinoma can be generated from human acinar cells *Pei Wang, The University of Texas Health Science Center at San Antonio; J. Liu; N. Akanuma*

Introduction: Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadly human malignancies and is characterized by the accumulation of a series of genetic mutations during disease progression. Few models are available to study the molecular mechanisms of the tumorigenesis process of human PDAC. **Methods:** To model human PDAC development, we developed a genetic manipulation system to transduce normal human primary pancreatic exocrine cells (hPECs) with lentiviral vector expressing KRASG12D-mCherry and lentiviral CRISPR targeting CDKN2A/p16, p53 and SMAD4. We have confirmed the efficiency of the p16 CRISPR, p53 CRISPR, and SMAD4 CRISPR constructs in editing the genome to mutate the respective gene loci. We identified the signaling pathway that promotes acinar to ductal metaplasia (ADM) from hPECs. To generate PDAC from hPECs, we sorted acinar cells from hPECs and induced ADM. Two million of the genetic engineered AD cells were transplanted subcutaneously or orthotopically into NOD-SCID mice. **Results:** The xenografts were harvested two months after transplantation. Pathological analysis found that invasive and metastatic PDAC were generated. We confirmed that the xenografts are derived from human cells with anti-human nuclear antigen antibody (anti-HuNu). Anti-Pan cytokeratin staining proved that the lesions were made up of epithelial cells. **Conclusions:** For the first time, we have generated PDAC from human acinar cells, suggesting acinar cells are one of the origins for

PDAC. Further comparison with ductal cell derived tumors is ongoing. Our study will reveal the cellular origins of PDAC and provide insight into human PDAC development.

25 **CPRIT Grantee**
Poster Session A

FGF-WNT cooperativity and the novel role of lncRNAs in translational regulation in breast cancer: a new SINE of the times *Tuan Nguyen, Baylor College of Medicine; J. Rosen; E. Kabotyanski; L. Reineke; Y. Dou; P. Zhang; A. Malovannaya; K. Roarty; Q. Mo; X. Zhang; Y. Chen; Z. Bing; J. Neilson; R. Lloyd; M. Ellis*

Introduction: FGF and WNT signaling are frequently deregulated in human cancer and play critical roles in mammary stem cell self-renewal and expansion. Breast tumors with deregulation of both pathways have the worst prognosis compared with those with deregulation of either pathway alone. Using an inducible system of FGFR1 (iFGFR1), we demonstrated that simultaneous activation of FGF and WNT signaling dramatically reduces tumor latency as compared to activation of each pathway alone. The resulting tumors exhibit increased expression of critical translation machinery components, indicating potential involvement of translational regulation in FGF-WNT induced tumorigenesis. In this study, we investigate the translational mechanisms and propose a novel role of long non-coding RNAs (lncRNAs) in regulation of translation. **Methods:** We employed ribosome profiling (Ribo-Seq) to identify selectively translated RNAs induced by acute iFGFR1 activation in mouse mammary epithelial cells with constitutive WNT hyperactivation. RNA-Seq and mass spectrometry were performed for inter-omic correlation analyses. CRISPR-Cas9 technology was utilized to investigate regulatory roles of lncRNAs in translation. **Results:** Many genes involved in regulation of mitosis and stem cell signaling pathways are translationally upregulated upon iFGFR1 activation while many genes with decreased translation are involved in senescence. Transcripts with enhanced translation are enriched for G-quadruplex and poly-U motifs at the 5' and 3' UTR respectively. Treatment with Silvestrol, an inhibitor of eIF4A, a protein required for unwinding G-quadruplexes to initiate translation, delays FGF-WNT induced tumor progression without affecting mouse weight, suggesting the therapeutic potential of translational inhibitors in FGF-WNT tumorigenesis. In addition to mRNAs, many lncRNAs are associated with ribosomes and have altered affinity for ribosomes in response to iFGFR1 activation, implicating potential roles of lncRNAs in translational regulation. Surprisingly, Malat1, originally thought to be a nuclear-restricted lncRNA that regulates metastasis, has increased affinity for polysomes upon iFGFR1 activation. We demonstrated that Malat1 transcripts localize to the cytoplasm in a cell cycle dependent manner, which can be regulated by iFGFR1 signaling. Through bioinformatics analyses, we identified 123 mRNAs that may base pair with the SINE element, which is about 100 base pairs, on Malat1. Deletion of the SINE element resulted in an inhibition of cell proliferation, G1 arrest, mitotic defects, and more surprisingly decreased global translation. **Conclusions:** Our study revealed a novel mechanism of crosstalk between lncRNAs and translational regulation in FGF-WNT driven cancer progression, specifically how Malat1 regulates protein synthesis.

26 **CPRIT Grantee**
Poster Session B

Structural Study of Regulation of de novo DNA Methyltransferases *Ren Ren, The University of Texas M.D. Anderson Cancer Center; X. Zhang; X. Cheng*

Introduction: DNA methylation is an important epigenetic modification for regulating of gene expression and chromatin organization. De novo DNA methyltransferases Dnmt3a and Dnmt3b, together Dnmt3L, established genomic DNA methylation pattern during embryonic and germ line development, with DNMT3L as an accessory factor. Dnmt3a and Dnmt3b have more than thirty isoforms from alternative splicing or alternative promoter usage. Dnmt3b3 is catalytically inactive and represents the dominant Dnmt3b isoform in somatic cells. Dnmt3b3 is frequently overexpressed in cancer cells. It has recently been shown that Dnmt3b3 appears to be able to stimulate gene body methylation in differentiated cells, analogous to Dnmt3L stimulating Dnmt3a in ES cells. **Methods:** We developed a co-purification scheme of Dnmt3a/Dnmt3b3 or Dnmt3b/Dnmt3b3 complexes. Co-purification of Dnmt3a (or Dnmt3b) and Dnmt3b3 was achieved by mixing Dnmt3a (or Dnmt3b) and Dnmt3b3 cell pellet together during lysis. Dnmt3a (or Dnmt3b) contained an N-terminal His6-SUMO tag, and Dnmt3b3 domain was a glutathione S-transferase (GST) fusion protein. The protein complex was purified with the use of three-column chromatography. The GST and SUMO tags were cleaved by specific proteases. **Results:** Here we show that indeed the catalytic inactive Dnmt3b3 can form stable complex with Dnmt3a and Dnmt3b and influence their enzymatic activity, similar to Dnmt3L. We are characterizing these complexes structurally to understand the mechanism how Dnmt3b3 stimulates the activity of Dnmt3a and Dnmt3b. **Conclusions:** Dnmt3L is expressed poorly if at all in differentiated cell types, whereas Dnmt3a and -3b expression is retained in somatic cells. This raises the question of how de novo DNA methylation is restricted in somatic cells, whether Dnmt3a and -3b enzymatic activities are regulated and (if so) the structural basis for that regulation. Our data lead to a model in which a catalytic inactive Dnmt3b3 recruits Dnmt3a and -3b to regions of chromatin where epigenetic modifications occur.

27 **CPRIT Grantee**
Poster Session A

Xenotransplantation of pediatric low grade gliomas confirms the enrichment of BRAF V600E mutation and preservation of CDKN2A deletion in a novel orthotopic xenograft mouse model of progressive pleomorphic xanthoastrocytoma *Mari Kogiso, Baylor College of Medicine; L. Qi; H. Lindsay; Y. Huang; X. Zhao; Z. Liu; F. Braun; Y. Du; H. Zhang; G. Bae; S. Zhao; S. Injac; M. Sobieski; D. Brunell; V. Mehta; D. Tran; J. Murray; P. Baxter; X. Yuan; J. Su; A. Adesina; L. Perlaky; M. Chintagumpala; D. Parsons; C. Lau; C. Sephan; X. Lu; X. Li*

Introduction: Pediatric low grade gliomas (PLGG) may still recur despite gross total resection. To identify cellular and molecular changes that drive PLGG progression, we analyzed putative cancer stem cells (CSCs) and evaluated key biological changes in a novel and progressive patient-derived orthotopic xenograft (PDOX) mouse model. **Methods:** 36 PLGGs were collected and examined for putative CSC (CD133 and CD15) expression and tumorigenicity in SCID mouse brains. Long-term in vivo evolution was analyzed in a novel PDOX model of pleomorphic xanthoastrocytoma (PXA), named IC-3635PXA. Reproducibility of histological features of original patient tumor, progressive phenotype and normal mouse brain responses were detected by immunohistochemistry. Genetic alterations (BRAF V600E and CDKN2A) were confirmed by pyrosequencing and FISH, respectively. In vitro drug screening for BRAF V600E inhibitors and BRAF inhibitors was performed with xenograft-derived 3635PXA cell line. **Results:** Flow cytometric analysis of 22 PLGGs detected CD133+ (<1.5%) and CD15+ (20.7 ± 28.9 %) cells, and direct intra-cranial implantation of 25 PLGGs led to the development of 1 PDOX model from a grade II PXA. While CSC levels did not correlate with patient tumor progression, neurosphere formation and in vivo tumorigenicity, the PDOX model, IC-3635PXA, reproduced key histological features of the original tumor. Similar to the patient tumor that progressed and recurred, IC-3635PXA also progressed during serial in vivo subtransplantations (4 passages), exhibiting increased tumor take rate, elevated proliferation, loss of mature glial marker (GFAP), accumulation of GFAP-/Vimentin+ cells, enhanced local invasion, distant perivascular migration, and prominent reactive gliosis in normal mouse brains. Molecularly, xenograft cells with homozygous deletion of CDKN2A shifted from disomy chromosome 9 to trisomy chromosome 9; and BRAF V600E mutation allele frequency increased (from 28% in patient tumor to 67% in passage III xenografts). In vitro drug screening identified 2/7 BRAF V600E inhibitors and 2/9 BRAF inhibitors that suppressed cell proliferation. **Conclusions:** In summary, we showed that PLGG tumorigenicity was low despite the presence of putative CSCs, and our data supported GFAP-/Vimentin+ cells, CDKN2A homozygous deletion in trisomy chromosome 9 cells, and BRAF V600E mutation as candidate drivers of tumor progression in the PXA xenografts.

28 **CPRIT Grantee**
Poster Session B

Structural and Functional Study of Transcriptional Repressive Complex of KAP1/Trim28 with KRAB Domain containing Zinc Finger proteins *Suparna Bhattacharya, The University of Texas M.D. Anderson Cancer Center; Z. Zhou; X. Zhang; Z. Wang; X. Cheng*

Introduction: Krüppel-associated box (KRAB) domain containing Cys2–His2 (C2H2) zinc finger (ZF) proteins are the largest and most rapidly diverging family of DNA binding transcription regulators in mammals (1). KRAB-ZF proteins act mostly as transcriptional repressors (2) via KRAB associated recruitment of the corepressor protein KAP1 (3), also known as tripartite motif-containing protein 28 (Trim28) (4). The KAP1/Trim28 associated cofactors include histone deacetylases, histone H3 lysine 9 (H3K9) methyltransferase SETDB1 (SET domain bifurcated 1), heterochromatin protein 1 (HP1), DNA methyltransferases, and several others. Biochemical studies have suggested that the N-terminal fragment of KAP1/Trim28 interacts with KRAB domain of KRAB-ZF proteins (5). **Methods:** We developed a co-expression and co-purification scheme of KAP1/Trim28 proteins in complex with KRAB domains. Co-expression of N-terminal fragment of KAP1/Trim28 and KRAB domain was achieved by the sequential transformation of two plasmids into Escherichia coli strain BL21 (DE3). KAP1/Trim28 contained an N-terminal His6-SUMO tag, and KRAB domain was a glutathione S-transferase (GST) fusion protein. The protein complex was purified with the use of three-column chromatography. The GST and SUMO tags were cleaved by specific proteases during purification. The purified complexes were examined by dynamic and static light scattering and screened by transmission electron

microscopes (TEM) in Baylor. **Results:** Our preliminary negative stained EM images have indicated that the N-terminal fragment of KAP1/TRIM28 forms linear homo-oligomers, whereas adding KRAB domain would induce the homo-oligomers to form a ring like compact stable complex. **Conclusions:** Taken together, our biochemical and structural approaches will provide detailed protein-protein and protein-DNA interactions for KAP1/Trim28-KRAB mediated transcriptional repression. A KRAB–ZF Protein binds target DNA sequence-specifically through its C-terminal array of C2H2 zinc fingers, while the N-terminal KRAB domain recruits the KAP1/Trim28 corepressor to establish histone H3 lysine 9 (H3K9) methylation-dependent silencing.

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29 **CPRIT Grantee**
Poster Session A

Mechanism for KDM5 Histone Lysine Demethylase Inhibition in Breast Cancer Cells *Qin Chen, The University of Texas M.D. Anderson Cancer Center; J. Horton; X. Zhang; X. Cheng*

Introduction: Members of the family of Jumonji C (JmjC) domain-containing histone lysine demethylase 5 (KDM5) are Fe(II) and alpha-ketoglutarate-dependent dioxygenases, whose enzymatic activities are responsible for removing methyl groups from methylated lysine 4 of histone H3 – a chromatin mark that on a genome-wide scale is broadly associated with gene activation. Accumulating recent evidence supports a role for KDM5 family members (A, B, C, and D) either as oncogenic drivers (5B) or tumor repressors (5D). For example, KDM5B is overexpressed in ER-positive (ER+) but downregulated in ER-negative (ER-) breast cancer cells, whereas KDM5D is a suppressor of prostate cancer. Attracted by the recent development of small molecule KDM5 inhibitors and the therapeutic potential of reducing drug-resistant cancer cell growth, we analyzed a few commercially available, cell permeable inhibitors (KDM5-C70, JIB-04, etc) in human embryonic kidney 293 (HEK293) cells, ER+ (MCF-7) and ER- (MDA-MB231) breast cancer cells. KDM5-C70 is a cell-permeable prodrug that is hydrolyzed by an esterase within the cell to generate a potent inhibitor that occupies the binding site of alpha-ketoglutarate. JIB-04 is a pan inhibitor of the Jumonji demethylase superfamily and a promising reagent for targeting taxane-platin-chemoresistant non-small cell lung cancer. **Methods:** Non-malignant HEK293 and two malignant breast cancer cell lines (MCF7 and MDA-MB231) were cultured and treated with different doses of available compounds (including KDM5-C70 and JIB-04). After 36 – 48 hours of treatment, cells were harvested and the total cell lysates were used for Western blot assays using antibodies against KDM5A, -5B, -5C and trimethylated H3 lysine 4 (H3K4me3). **Results:** We showed that the KDM5-C70 compound significantly increases protein levels of KDM5B and KDM5C, but not KDM5A. The increase in protein (demethylase) level appears to be correlated with the potency of inhibition in cells and is accompanied by the increased level of H3K4 methylation (the substrate of the demethylase). **Conclusions:** A possible mechanism of KDM5-C70 stabilizing KDM5 protein will be discussed.

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30 **CPRIT Grantee**
Poster Session B

PPARD genetic deletion inhibits APC mutation-driven-colorectal tumorigenesis *Xiangsheng Zuo, The University of Texas M.D. Anderson Cancer Center; R. Tian; Y. Liu; Y. Deguchi; W. Xu; J. Jaoude; W. Chen; F. Liu; S. Gao; M. Moussalli; I. Shureiqi*

Introduction: Identification of critical molecular events driving colonic tumorigenesis could lead to the development of much-needed novel therapeutics for this commonly fatal disease. Aberrant Wnt/beta-catenin signaling activation due to APC mutations is a very critical common event in colorectal cancer (CRC) tumorigenesis. The peroxisome proliferator-activated receptor-delta/beta (PPARD) modulates many cellular functions critical for health and disease and is a downstream target of aberrant Wnt/B-catenin signaling pathway. Various data suggest that a positive feedback loop exists between PPARD and Wnt/B-catenin to propel CRC tumorigenesis. PPARD is upregulated in human CRC. However the role of PPARD in CRC tumorigenesis is controversial because PPARD has also been reported to inhibit intestinal tumorigenesis in APCmin mice. Data from our published studies with mouse models of intestinally targeted PPARD knockout and intestinally targeted PPARD overexpression showed that PPARD strongly enhanced AOM-induced CRC tumorigenesis. However, our AOM modeling results might be considered insufficient to resolve the controversy regarding PPARD's role in APC mutation-driven CRC because of experimental modeling differences. In this study, we have used intestinally targeted PPARD deletion model to interrupt the interaction between PPARD and Wnt/B-catenin and thus to examine the mechanistic significance of this interaction to CRC tumorigenesis. **Methods:** To clarify the effect of PPARD genetic deletion on Wnt/B-catenin signaling and CRC tumorigenesis, we have developed a novel mouse model by 1) breeding PPARD conditional knockout (CKO) mice with Apc580 CKO to generate Apc580-PPARD-CKO mice, and then 2) breeding Apc580-PPARD-CKO mice with CDX2-Cre mice to generate Apc580mu-PPARD-KO-Gut mice, in which PPARD genetic deletion and APC580 mutation were intestinally targeted via Cre-recombinase expression driven by CDX2 promoter. **Results:** PPARD KO in intestine of Apc580mu-PPARD-KO mice was verified by qRT-PCR and western blot. PPARD deletion significantly reduced tumor numbers in both colon and 1/3 distal small intestine in Apc580mu mice and prolonged survival of the mice with Apc580mu from 158.5 ± 5.61 (mean ± SEM) days for the mice with WT PPARD to 200.00 ±10.45 days for the mice with intestinal PPARD KO. PPARD KO significantly reduced the colonic crypt proliferative zone in Apc580mu mice, as demonstrated by Ki67 immunohistochemistry staining. Furthermore, PPARD KO decreased the levels of active B-catenin and its target gene cyclin D1 in colorectal epithelial cells of Apc580mu mice, as measured by western blot and q-RT-PCR, respectively. **Conclusions:** Our findings demonstrate the mechanistic importance of PPARD to CRC tumorigenesis as driven by APC mutations.

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31 **CPRIT Grantee**
Poster Session A

Dynamic Regulation of Histone Acetylation by Nuclear Proteolysis Controls Cell Cycle Gene Expression and Chromosome Integrity in Multiple Myeloma *Laure Maneix, Baylor College of Medicine; P. Iakova; S. Moree; L. Fletcher; P. Lulla; S. Yellapragada; A. Catic*

Introduction: Transcription factors are generally short-lived proteins that undergo active turnover. The dynamic interaction of transcription factors and co-regulators with promoters and enhancers allows cells to continuously adjust gene expression. Whereas the composition and binding of transcription factors at genomic sites is the focus of a widespread research effort, relatively little is known about how these complexes are being removed by the ubiquitin-proteasome system (UPS). Multiple myeloma (MM), the second most common hematopoietic malignancy, has become a model disease for drugs that interfere with the UPS through either blocking or facilitating protein elimination. The proteasome inhibitor Bortezomib, for instance, is used as first-line treatment in myeloma; yet, the process by which myeloma cells are killed by this drug is ill-defined. Since transcription factors are prime targets of proteasomal degradation, our research is focused on defining how proteolysis regulates transcriptional dynamics in this disease and determining the therapeutic relevance for treatment with proteasome inhibitors. **Methods:** Following proteasome inhibition in multiple myeloma cell lines, we performed chromatin-immunoprecipitation for histone H3 acetylation (K27) and multiple histone deacetylases and used next generation sequencing (ChIP-seq) to identify unique gene clusters that are actively regulated by the proteasome and quantify epigenetic changes in dependence of protein turnover. **Results:** Our findings reveal that cell cycle genes, particularly subsets of genes involved in centromere formation and sister chromatid segregation during mitosis, are associated with nuclear protein turnover and are transcriptionally repressed by proteasome inhibition. Notably, proteasome inhibition increased the recruitment of specific histone deacetylases (HDACs) to the promoters of genes involved in centromere formation. We are investigating the mechanisms for UPS regulation of HDAC abundance at specific genomic locations. Moreover, data analysis of a panel of multiple myeloma patients shows that the expression levels of HDACs correlate with patient survival, specifically when treated with proteasome inhibitors. We are currently exploring how histone modifications and proteasome activity crosstalk in a therapeutically relevant manner in multiple myeloma. **Conclusions:** This research project will contribute to our understanding of epigenetic and transcriptional dynamics in MM. With our focus on the continuously changing abundance of transcription factors and co-regulators at promoters of cell cycle genes, we seek to unlock new pathways for molecular therapy, as well as identify more specific targets for treatment compared to blunt proteasome inhibition. Elucidating the mechanisms of action and resistance to proteasome inhibition will help advance future MM therapy.

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32 **CPRIT Grantee**
Poster Session B

Effects of TLX/NR2E1 ligands on gene expression in Glioblastoma cell line *Aleksandra Cvoro, Houston Methodist; C. Benod; D. Sieglaff; P. Jones; P. Webb; H. Pownall*

Introduction: The nuclear receptor (NR) superfamily consists of transcriptional factors that are highly attractive targets for addressing a range of pathologies including cancer. In addition to the well-characterized ligand-activated NRs, this family comprises a large number of orphan nuclear receptors (ONR) whose ligands remain unknown. TLX, an ONR, is predominantly expressed in the central nervous system. TLX is highly expressed in Glioblastoma Multiforme (GBM) and drives neural stem cells (NSC) and brain tumor stem cells (BTSC) self-renewal; these qualities make TXL a potential therapeutic target for treating GBM. We recently identified multiple TLX ligands that potentiate its repressive activity. Now, we have identified new binding compounds with therapeutic promise.

Understanding how these ligands regulate transcriptional activity is critical to the development of more efficient and selective anti-cancer drugs. **Methods:** We assessed effects of five TLX ligands (published compounds ccrp1, ccrp2, ccrp3 and new compounds IACS-809 and IACS-814) in glioblastoma cell line LN229 using the Illumina BeadArray. Results were verified by qRT-PCR. Pathway Enrichment Analysis was performed using GeneCodis analysis. **Results:** Microarray analysis to compare TLX ligand effects on gene expression profiles versus control LN229 cells revealed that one of our newly acquired compounds, IACS-809, caused changes in the expression of 112 genes, consistent with their roles as a TLX antagonists. By contrast, previously identified compounds, ccrp1-3, elicited little or no major effects on gene expression. qRT-PCR confirmed profound IACS-809-related transcriptional repression of multiple members of S100 family genes (S100A4, S100A1, S100A13). S100 proteins are Ca-binding proteins involved in several human neoplasms. IACS 809 also induced expression of more than 60 genes, including stress-responsive sestrin 2 (SESN2), and nerve growth factor (VGF). Analysis of IACS 809 target genes using Pathway enrichment analysis pointed towards TLX involvement in Aminoacyl-tRNA biosynthesis (5 genes induced: MARS, WARS, CARS, IARS, YARS). Recent studies have revealed non-canonical roles of multiple ARSs pathologically linked to cancers included GBM. IACS-809 did not regulate any tested genes in U87MG GBM cells that do not express TLX. **Conclusions:** We identified IACS-809 as a TLX ligand that modulates TLX transcriptional activity in LN229 cells. Actions of IACS-809 are distinct from those of previously identified TLX agonists, ccrp1-3. IACS-809 action might be particularly relevant in the context of therapeutic applications of this class of compounds in treatment of GBM as well as other cancers.

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33 **CPRIT Grantee**
Poster Session A

The protein arginine methyltransferase 6 (PRMT6) regulates DNA methylation and contributes to global DNA hypomethylation in cancer *Nicolas Veland, The University of Texas M.D. Anderson Cancer Center; Y. Zhong; S. Gayatri; J. Dan; B. Strahl; S. Rothbart; M. Bedford; T. Chen*

Introduction: DNA methylation is aberrant in cancer as global DNA hypomethylation is frequently detected, with unknown causes for this dysregulation. DNA methylation is maintained when DNA methyltransferase-1 (DNMT1) is recruited by UHRF1 (ubiquitin-like PHD and RING finger domain–containing 1), which binds to histone H3 and is impaired by methylation of H3 at arginine 2 (H3R2). Interestingly, PRMT6, which catalyzes H3R2 methylation, is overexpressed in cancer. Based on these observations, we hypothesize that overexpression of PRMT6 could disrupt the binding of UHRF1 to chromatin leading to reduced DNA methylation, and that abnormal H3R2 methylation caused by PRMT6 upregulation contributes to global DNA hypomethylation in cancer. **Methods:** Cells: mouse embryonic stem cells (mESC) and human MCF7 breast cancer cells were used for overexpression and downregulation/ inhibition of PRMT6, respectively. DNA methylation analyses: dot blot was performed with specific antibody. Bioinformatic analyses: PRMT6 expression and DNA methylation data of tumor samples were obtained from TCGA. **Results:** Using mESC and MCF7 cells, we demonstrate that PRMT6 overexpression leads to increased H3R2 methylation and disassociation of UHRF1 from chromatin, which results in loss of DNA methylation. Then, we analyzed DNA methylation level in cancer cells and TCGA samples with different PRMT6 expression levels. Among cell lines, MCF7 and LNCaP, showed the highest levels of PRMT6 expression, which correlates with the lowest levels of DNA methylation. This correlation was confirmed with our TCGA data analysis. Finally, we showed that the effect of PRMT6 in DNA methylation is reversible, as knockdown or inhibition of PRMT6 restored the level of DNA methylation in MCF7 cells. **Conclusions:** Our findings indicate that the recruitment of DNMT1/UHRF1 complex to chromatin is modulated by PRMT6-dependent H3R2 methylation and that upregulation of PRMT6 contributes to global DNA hypomethylation in cancer.

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34 **CPRIT Grantee**
Poster Session B

Tumor cell fragmentation and large vesicle formations in microfluidic capillary bifurcations *Nabiollah Kamyabi, The University of Texas M.D. Anderson Cancer Center*

Introduction: Circulating tumor cells (CTCs) play an important role in cancer metastasis. Cells from the primary tumor detach, intravasate into blood vessels, and are transported by blood flow to distant sites. These circulating tumor cells can pass through or physically trapped in microcapillaries or adhere to the endothelium lining the blood vessels. During this trip, circulating tumor cells in microcirculation undergo significant fragmentation within capillary bifurcations. Thus, flow-induced fragmentation of CTCs to distant organs is an essential event in the multistep process of cancer metastasis. Despite the hematogenous dissemination of a large number of CTCs into the blood stream, less than 0.01% survive to produce metastases. It is shown that physical forces such as cell fragmentation can destroy CTCs along with biological factors, contributing significantly to metastatic inefficiency. **Methods:** To understand the physical mechanisms governing tumor cell fragmentation we used microfluidic devices with parallel bifurcation channels. Also, to quantify cell rupture we defined innovative metrics such as fragmentation time, sizes, and percentage of fragmented cells. We used techniques such as fluorescent/confocal microscopy to illuminate the mechanisms underlying the cell fragmentation. **Results:** We found that cell nucleus never fragments, and cortex does not exist in the vesicles; in other words, vesicles produced after fragmentation are only lipid bilayer packages of cytosolic liquid. Using a library of inhibitor drugs, we found that the cell membrane dominates the dynamics of fragmentation. Also using a high-throughput version of our fragmenting device, we found tumor cells remain viable after days of fragmentation but are incapable to proliferate. We used a library of cell lines such as prostate, breast, lung cancer cells and found cell fragmentation metrics are capable of distinguishing highly and poorly metastatic tumor cells and cells with epithelial and mesenchymal origins. **Conclusions:** In summary, our studies elucidate the important role played by mechanics of tumor cells on poorly understood fragmentation phenomena and metastatic potential of tumor cells in microcirculatory conditions. Moreover, the devices we introduced have the potential to be used clinically in diagnostic and therapy purposes. Future studies can be pursued to understand the molecular mechanisms underlying our findings.

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35 **CPRIT Grantee**
Poster Session A

Discovery of Novel Transcript Variants of Myogenic Regulatory Factors in Rhabdomyosarcoma *Erin Butler, The University of Texas Southwestern Medical Center; Y. Zheng; L. Xu; S. Skapek*

Introduction: Rhabdomyosarcoma, the most common soft tissue sarcoma in children, is composed of skeletal myoblast-like cells in which normal differentiation programs – including an irreversible cell cycle arrest – are seemingly derailed. The molecular basis for the differentiation arrest are not clear in most cases of rhabdomyosarcoma. Given the apparent differentiation arrest, we hypothesized that alternative splicing in the MYOD1 family of muscle regulatory factors genes may contribute to the differentiation defect in rhabdomyosarcoma, providing a selective growth advantage to incipient rhabdomyosarcoma cells. **Methods:** A computational algorithm was used to detect alternative splicing in myogenic regulator factors using RNAseq data from 44 rhabdomyosarcoma specimens. Retroviral vectors were generated to express wild type (WT) and splicing variants, and GFP or RFP markers, in cultured fibroblasts and human rhabdomyosarcoma cells, and the effects were analyzed using a variety of molecular and cell biology approaches. **Results:** Of genes encoding the four MYOD1-related muscle differentiation factors (MYOD1, MYF5, MYOG, MRF4), RNAseq analysis showed evidence for alternative splicing to “skip” exon 2 in only MYOD1 and MYF5 in 34% and 38% of RMS specimens but not in normal human muscle. RTPCR demonstrated the presence the alternatively spliced form of MYOD1, MyoDdelta-exon2, in two rhabdomyosarcoma cell lines. Ectopic expression of WT MyoD, but not MyoDdelta-exon2, induced morphologic changes and muscle gene expression in cultured fibroblasts and Rh18 rhabdomyosarcoma cells. By using GFP and RFP markers, competitive co-culture assays demonstrated a growth advantage to fibroblasts expressing MyoDdelta-exon2. **Conclusions:** Alternative splicing in rhabdomyosarcoma can generate forms of MYOD1 and MYF5 that lack exon 2, rendering them unable to foster muscle differentiation and the accompanying cell proliferation arrest. Exon 2 “skipping” generates a form of MYOD1 that provides a growth advantage over cells expressing WT MYOD1, providing a potential mechanism to impair muscle differentiation and excess proliferation in rhabdomyosarcoma. On-going investigations are addressing whether MyoDdelta-exon2 provides dominant negative activity over WT MYOD1, and using RTPCR to confirm “exon 2 skipping” in archived human rhabdomyosarcoma specimens.

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36 **CPRIT Grantee**
Poster Session B

Mediator Kinase as a transducer and therapeutic target in oncogenic WNT/B-Catenin signaling *Lindsey Barron, The University of Texas Health Science Center at San Antonio; A. Clark; T. Boyer*

Introduction: Colorectal cancer (CRC) remains a major health problem worldwide as it is the second most commonly diagnosed cancer in women and men, respectively. Few effective treatment options exist for advanced stage disease, thus, the development of targeted therapies is crucial for treatment. CRC arises from the maintenance of the progenitor phenotype in intestinal crypts, which is dependent on the expression of genes programmed by the canonical WNT/B-catenin pathway. Accordingly, constitutive pathway activation through mutations in the Adenomatous

Polyposis Coli (APC) tumor suppressor or B-catenin is a driver in >90% of CRCs. B-catenin activates transcription through its direct physical and functional interaction with the MED12 subunit of Mediator. Within Mediator, MED12 nucleates the assembly of a discrete "kinase" module that includes MED13, Cyclin C, and CDK8, an oncoprotein required for B-catenin-dependent gene activation and CRC growth. These findings establish the Mediator kinase module as a key node of oncogenic activation within the WNT/B-catenin pathway, and further identify CDK8 kinase activity as a prospective therapeutic target in WNT-driven CRCs. Mechanistically, B-catenin binds directly to MED12 within the kinase module, triggering MED12-dependent activation of CDK8 through a direct interaction involving MED12 exon 2-encoded sequences and a phylogenetically conserved surface groove on Cyclin C. **Methods:** In this study, the CRISPR/Cas9 system was used to abrogate Mediator kinase activity by genetic disruption of the MED12:Cyclin C interface in the human CRC cell line, HCT116. ChIP-seq for H3K27ac was used to determine superenhancer alterations. Global levels of H3K27ac and H3S10P were assessed by immunoblot. **Results:** Loss of Mediator kinase activity altered the epigenetic deposition of the active superenhancer mark, H3K27ac, and lead to diminished expression of WNT-target genes, reduced cell proliferation and colony formation. Globally, levels of the H3K27ac mark correlate with the H3S10P mark, which has been previously shown to be CDK8-dependent. **Conclusions:** Therefore we conclude that the mediator kinase module plays a role in regulating superenhancer integrity via the deposition of the H3K27ac and H3S10P markings. Since genetic disruption of the MED12:Cyclin C interface reversed the oncogenic properties associated with these markings, we believe that this interface represents an attractive target for the development of targeted molecular therapies for advanced stage CRC. Lindsey Barron is supported by a CPRIT postdoctoral training fellowship, the CPRIT Research Training Award (RP170345).

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37 **CPRIT Grantee**
Poster Session A

Data mining immune repertoires in cancer tissue biopsy *Jared Ostmeyer, The University of Texas Southwestern Medical Center; S. Christley; W. Rounds; I. Toby; B. Greenberg; N. Monson; L. Cowell*

Introduction: Tumor infiltrating lymphocytes (TILs) can be found in tumor biopsies. These important cells, which participate in the natural control of a tumor, are often suppressed by the tumor microenvironment. With the advent of next generation sequencing, it has become possible to sequence several thousand unique immune receptor sequences per tumor biopsy. However, identifying which sequences are important has proven challenging because only a subset of the immune receptors are likely participants in the anti-tumor immune response—the other immune receptors represent irrelevant noise. **Methods:** Immune receptor sequences from cancer biopsies are downloaded from publicly available datasets. Statistical methods we developed are used to identify receptor sequences that may participate in the anti-tumor response. **Results:** We have developed a family of statistical methods to help identify immune receptors that are in response to a specific disease. Every receptor sequence is scored by a detector function, and the scores are aggregated together to predict a sample label. The detector function is found by maximizing the likelihood of predicting the correct sample labels. High scoring sequences are analyzed based on the assumption that they may be participating in a disease specific immune response. Our approach has already proven useful in diagnosing Multiple Sclerosis, achieving a diagnostic accuracy of 73 out of 102 patients on unseen and unused data. We will present our efforts to apply the same methods to colon cancer using a public dataset. Already, we have obtained encouraging results that we are attempting to validate. Finally, we will discuss our ongoing efforts to build models for other cancer types. **Conclusions:** We have developed new methods to help identify tumor infiltrating lymphocytes responding to a cancer. These receptors might serve as the basis for new kinds of therapies.

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38 **CPRIT Grantee**
Poster Session B

Playing at the 'NET' benefits breast cancer metastasis *Arzu Ulu, The University of Texas Health Science Center at Houston; Y. Zuo; W. Oh; J. Frost*

Introduction: Breast cancer is a deadly disease affecting 1 in 8 women in the United States. The 5-year survival in patients with metastatic disease is only 22% despite huge efforts at early detection and improved treatment options. This is mainly due to our limited understanding of underlying mechanisms associated with the metastatic phenotype. Cancer cells need to gain migratory and invasive properties to metastasize to distant sites. Activation of the RhoGTPase, RhoA, is critical for cancer cell migration and invasion, and RhoA is overexpressed in breast cancer. Unfortunately, direct targeting of RhoGTPases is challenging due to its undruggable nucleotide binding site and ubiquitous expression which underscores the necessity of finding different targets that would interfere with the RhoGTPase pathway. **Methods:** For that reason we have used tools of innovation, in particular changing the point of view. Since RhoA has been shown as undruggable, we focused on its unique modulator, the RhoGEF Net1A (neuroepithelial cell transforming gene 1A). We employed immunofluorescence staining, cell migration and invasion assays to elucidate how Net1A controls RhoA activation and cell motility. **Results:** While all other RhoGEFs are exclusively in the cytosolic compartment of cells, Net1A localizes to the nucleus in the absence of stimulation, preventing it from activating RhoA. Upon stimulation of breast cancer cells with EGF (epidermal growth factor), Net1A relocalizes into the cytosol and activates RhoA, which in turn promotes cell migration and invasion. We demonstrate that the MAPK (mitogen activated protein kinases) pathway as well as CRM1 (chromosomal maintenance 1)-mediated nuclear export are involved in EGF-induced cytosolic relocalization of Net1A in breast cancer cells. **Conclusions:** Using an innovative approach by focusing on a unique RhoA modulator, our study identifies a novel mechanism for controlling cell migration and invasion, which subsequently highlights novel anti-cancer targets. Since there are inhibitors for these targets currently in clinical trials, this study will progress fast towards conducting in vivo experiments and more importantly human trials. Acknowledgement: UTHealth Innovation for Cancer Prevention Research Training Program Post-Doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant # RP160015).

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39 **CPRIT Grantee**
Poster Session A

In vivo analysis reveals temporally and spatially distinct homologous recombination pathways and a potential chemotherapeutic target *Rhea Kang, The University of Texas M.D. Anderson Cancer Center; F. Cole; M. Biot*

Introduction: Homologous recombination (HR) faithfully repairs DNA double-strand breaks (DSBs) and contains many semi-redundant pathways, but our knowledge of which HR repair pathways are used under which condition is limited, especially in vivo at endogenous sites. Meiotic recombination is an excellent system to study HR because a large number of programmed DSBs are repaired by HR using the homologous chromosome, which allows us to track natural outcomes at endogenous hotspots. DSB repair by HR produces either crossovers (COs), resulting in exchange of flanking markers, or noncrossovers (NCOs) revealed by short patch-like repair, both of which involve gene conversion (GC) where original sequence has been replaced by the donor sequence. Abrogation of any single HR pathway that contributes to CO and NCO formation is known to result in severe genomic instability and cancer (i.e. Bloom syndrome). COs are much more deleterious than NCOs because COs can lead to loss of heterozygosity. Therefore, interventions that promote CO formation at the expense of NCOs can further sensitize cancers cells. My central working hypothesis is that individual HR pathways will have distinguishing temporal and qualitative features that facilitate or hinder that pathway's ability to compensate for the loss of others. By establishing a novel system that can interrogate the kinetics of HR pathways in vivo in mammals at endogenous sites, we can determine which HR pathways are utilized in the absence of others to identify potential chemotherapeutic targets. **Methods:** Mouse spermatocytes were synchronized using an inhibitor WIN 18,446 followed by retinoic acid injection. Synchronized cells at early, mid-, and late prophase I were isolated by flow cytometry, and the level of synchrony was determined by immunofluorescence. Recombination analysis on synchronized cells was performed by PCR at hotspots. **Results:** My temporal analysis shows that there are two classes of NCOs: distal NCOs away from the hotspot center that are formed during early prophase I, and central NCOs that are formed coincidentally with MLH1/3-dependent COs in the hotspot center during mid-prophase I. To analyze CO formation by structure-selective nucleases (SSNs) and dissolution pathways, I examined recombination in mice lacking meiotic CO resolvase activity. Synchronized spermatocytes revealed a reduction in COs and concomitant increase in long NCOs consistent with dissolution by RecQ helicases. In these mice, dissolution and SSNs do not become apparent until late prophase I. **Conclusions:** By utilizing the system I have established, I will test the impact of small-molecule inhibitors of RecQ helicases by direct in vivo injection.

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40 **CPRIT Grantee**
Poster Session B

Elucidating the molecular pathogenesis of familial glioma *Daniel Jacobs, Baylor College of Medicine; K. Fukumura; M. Bainbridge; G. Armstrong; D. Muzny; B. Melin; J. Huse; M. Bondy*

Introduction: In recent years, the molecular characterization of sporadically arising diffuse gliomas has identified key alterations driving these tumors and delineated molecularly and clinically distinct subclasses of disease. However, less is known about the molecular nature of gliomas that are familial in origin. To address this question, we performed

whole exome sequencing of 18 tumors from unrelated individuals with a family history of glioma collected through the Gliogene International Consortium. **Methods:** FFPE specimens were sectioned and reviewed to localize neoplastic tissue for DNA extraction. Sample QC, library preparation, exome plus targeted capture including the TERT promoter region (TERTp), and paired-end sequencing on the Illumina HiSeq 2000 platform were performed at the Baylor College of Medicine Human Genome Sequencing Center (HGSC). Sequence data were processed using the HGSC Mercury pipeline and mutations were called with respect to blood-derived germline DNA sequencing data for each case using Mutect v1.1.7. Variants were annotated using Oncotator, COSMIC, and dbSNP databases. Copy number profiling was performed using the Illumina HumanOmniExpress BeadChip and analyzed using Illumina GenomeStudio v2.0. **Results:** Exome sequencing was completed at an average read depth of 116X with 97% of targeted bases covered at least 10 times. We observed a median of 50.5 non-silent somatic mutations (range: 14-97) across the 18 tumors profiled. Codeletion of chromosome arms 1p and 19q was observed in two cases, and TERTp hotspot mutations C228T or C250T were observed in eight. All three molecular subtypes of sporadic glioma were observed, including IDH-mutant, 1p/19q codeleted (n=2), IDH-mutant, 1p/19q intact (n=7), and IDH-wildtype tumors (n=9). Characteristic subtype-specific mutations (e.g., TP53 and ATRX mutations among IDH-mutant, 1p/19q intact tumors) were observed in most cases. For two cases with previously reported germline mutations in telomere shelterin complex gene POT1, the first (POT1 E450X) displayed somatic IDH1 mutation, 1p/19q codeletion, and a compound heterozygous POT1 mutation (R117H), while the second (POT1 G95C) displayed somatic IDH1 mutation without 1p/19q codeletion or POT1 loss of heterozygosity. Neither case had acquired TERTp or ATRX mutations. **Conclusions:** This study highlights the role that deleterious germline mutations play in compromising molecular pathways required for gliomagenesis, as exemplified by the absence of typical acquired mutations affecting telomere regulation in cases with germline POT1 mutation. Outside of these select cases, the genomic landscape of gliomas in this study largely recapitulates that which is seen in sporadic glioma.

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41 **CPRIT Grantee**
Poster Session A

Disruption of apicobasal polarity impairs endometrial development and promotes endometrial tumorigenesis *Erin Williams, The University of Texas System; R. Broaddus; A. Gladden*

Introduction: Unlike most cancer types, the incidence and mortality of endometrial cancer is increasing and onset is occurring at younger ages. This underscores the importance of uncovering the basic mechanisms of endometrial tumorigenesis. Disruption of cell polarity is frequently observed in epithelial cancers, but is not well studied in endometrial cancer. The epithelium of the endometrial gland, the primary cell type thought to give rise to endometrial cancer, is shed and re-established after each menstrual cycle. This continual repopulation requires a constant reorganization of the epithelium. We investigated the status of apicobasal polarity in low-grade endometrial cancer to assess the role of polarity in early endometrial tumor development. **Methods:** We utilized human tissue samples and endometrial cancer cell lines to examine the effects of apicobasal polarity on endometrial epithelium. In addition, in order to understand how apicobasal polarity is working within the uterus in vivo, we generated a mouse model. We deleted Merlin (gene: Nf2), an apicobasal polarity regulator, within the uterus (Nf2lox/lox; Wnt7a-cre (Nf2cKO) or Nf2lox/lox; PR-cre Nf2cKOPR). **Results:** We determined that Par3, an apical polarity protein, localizes to the apical region in normal human endometrial glandular epithelium, however in low-grade tumor samples Par3 was mislocalized. Additionally, we found that many endometrial cancer cell lines also show a decrease in Par3 protein levels. Reintroduction of Par3 resulted in decreased proliferation and increases expression of markers associated with differentiation. Since Notch receptor localization was shown to be affected by Merlin, a Par3 regulator, we examined the Notch receptors in endometrial cancer cell lines and found an increase in membrane localization when Par3 was overexpressed. In addition, in human endometrial samples, we determined that Notch receptors localize to the basolateral membrane in normal endometrial glands but are diffuse in low-grade cancer samples. Since Notch receptors must be localized properly to interact with the transmembrane Notch ligands, we examined downstream targets and found multiple downstream targets were decreased in endometrial cancer. In order to understand how polarity affected the endometrium in vivo, we examined our Nf2cKO mice. Merlin-deficient endometrium displays a loss in endometrial gland formation and an aberrant stratification of the luminal epithelium. **Conclusions:** Apicobasal polarity is involved in both endometrial development and tumorigenesis mediated through the regulation of transmembrane receptor signaling that maintains normal proliferation and differentiation.

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42 **CPRIT Grantee**
Poster Session B

Dependency of Radiation Dose Levels on The Treatment Responses in AT1 Prostate Tumors in Rats *Tatsuya Arai, The University of Texas Southwestern Medical Center; T. Chiu; J. Campbell; D. Yang; S. Stojadinovic; R. Mason*

Introduction: Previous studies have shown that, in the prostate tumor (Dunning subline R3327-AT1), larger responses of blood-oxygen-level-dependent (BOLD) and tissue-oxygen-level-dependent (TOLD) MRI to oxygen breathing challenge coincided with longer tumor growth delay following irradiation. The earlier studies employed a total amount of radiation dosage of 30Gy. We hypothesized that the application of greater dosage would neutralize the tumor control effects of oxygen responsiveness demonstrated by BOLD/TOLD MRI. In this preliminary study, various levels of radiation dosages were tested to investigate their tumor control effects. **Methods:** Radiation Treatment: Tumors were irradiated with a single dose using a small animal X-ray irradiator. The dosage levels (ranging from 30 to 80Gy with 10Gy increment) were selected for each tumor in a balanced order. The endpoint of this study was 200 days after irradiation without a sign of tumor regrowth. **Results:** The number of tumors treated with 30, 40, 50, 60, 70, and 80Gy were 1, 3, 3, 3, 4, and 3, respectively. One control tumor did not receive the radiation. Relatively low and high dose groups consist of tumors receiving 30–50Gy and 70–80Gy, respectively. Local Tumor Control: The mean±S.D. of tumor volume among tumors in the low dose group which reached the 200 days endpoint were 0.22±0.02cm-3 (n=3). The volume of the rest of tumors (n=4) in the low dose group which did not reach the endpoint were 0.31±0.11 cm-3. Their survival days were 82±23 days after the treatment. Similarly, the tumor volume in the high dose group that reached the endpoint were 0.39±0.16cm-3 (n=4). The volume and the survival days of the rest of tumors in the high dose group were 0.23±0.08cm-3 and 110±59 days, respectively (n=3). Two of three animals receiving 60 Gy, reached the endpoint and their volume was 0.22±0.02cm-3. The tumor volume and survival days of the remaining one with 60 Gy were 0.35cm-3 and 87 days, respectively. The results from the one control tumor were 0.82 and 31 days. **Conclusions:** The preliminary study showed the tumor control effects of radiation treatment in the AT1 prostate tumor with different dose levels. Our overall goal is to correlate the results with oxygen sensitive MRI data (i.e. Interleave BOLD and TOLD) which were collected. We are going to further investigate the relationship among the tumor control effects, dose levels, and oxygen responsiveness.

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43 **CPRIT Grantee**
Poster Session A

Telomerase Reactivation In The Lgr5+ Cells Rescues Stem Cell Depletion Through Suppressing The ER/UPR Stress Pathway *Deepavali Chakravarti, The University of Texas M.D. Anderson Cancer Center; R. DePinho; B. Hu; A. Wang*

Introduction: Telomere shortening has been correlated with several aging related pathogenesis of the intestine like Crohn's disease and ulcerative colitis. Inflammatory bowel disease has been established as a significant risk factor for developing colon cancer. GWA studies have revealed ER stress related proteins play important role in the initiation of such inflammatory bowel diseases. Late generation (G4) of the telomerase deficient mice exhibit symptoms of inflammatory bowel disease and neoplasia of both the small and the large intestine by 6 months of age compared to the early generation counterpart (G0) and can be an excellent model to study the progression of inflammatory bowel disease to colon cancer development. Closer examination revealed an increase in ER stress protein expression in the stem cell compartment leading to premature differentiation of the stem cells to a more progenitor like population. Telomerase reactivation reverses the phenotype and extends the lifespan of these mice. **Methods:** In order to study the role of telomerase activation in the intestinal compartment we crossed the late generation telomerase deficient LSL-mTert animals to the tamoxifen inducible Lgr5-EGFP CreERT2 model. In this model we could reactivate telomerase at desired time specifically in the intestinal stem cell compartment. We characterized the intestines with immunohistochemical analyses and electron microscopy. With the help of beta galactosidase lineage tracing experiments and BrDU incorporation assay we determined the proliferation rate and the cell turn over rates in these animals. We performed RNAseq and qPCR analysis. We also isolated crypts and performed organoid cultures from early and late generation of the animals. **Results:** Unexpectedly we found that the intestinal crypts from the G4 mice showed neoplastic lesions and crypt degeneration accompanied by high degree of immune infiltrates. Young G4 animals exhibit elevated rate of apoptosis, cell turn over and proliferation in comparison to the G0 mice. RNA-seq indicated upregulation of the ER phagosomal pathway and immune pathways. Increase in ER stress was further confirmed by electron microscopic analysis, IHC and qPCR. Interestingly reactivation

of telomerase specifically in the Lgr5+ stem cells suppressed the ER/UPR pathway and reduced stem cell proliferation and loss through differentiation. This also led to the increased lifespan of these animals. **Conclusions:** In conclusion telomerase reactivation preserves stem cell loss by reducing ER stress and thereby extends lifespan.

44 **CPRIT Grantee**
Poster Session B

Imaging and modeling pro-metastatic pathways *Gaudenz Danuser, The University of Texas Southwestern Medical Center*

Introduction: Metastatic cells stand out with their ability to migrate, adapt, and survive in a wide range of mechanical and chemical micro-environments. While numerous genes and pathways have been identified as promoting these functions, we know still very little about the integrated control of these cell functions at a sub-cellular scale. I moved my lab to UT Southwestern to establish a basic cancer cell biology program with the goal of imaging and mathematically modeling the regulation of prometastatic cell functions. **Methods:** We have invested much of our CPRIT resources into the development of unique live cell imaging approaches. In particular we adopted high-resolution light-sheet microscopy to the task of imaging molecular processes in human single cells and tumor organoids relatively deep inside models of metastatic site tissue and tumor stroma. Related to the live 3D imaging is the development of robust software pipelines that process vast flows of unstructured image data. We have written programs for the segmentation and parameterization of cells shapes, for the analysis cell interactions with the surrounding fibrous extracellular matrix, and for relating these cell architectural variables to the spatiotemporal organization of cytoskeleton and signaling. **Results:** Key findings of our studies thus far using this technology include: 1) Demonstration of a bistable switch between tumorigenic and metastatic cell behavior downstream of the KRASV12 mutant expression level in lung cancer models. 2) Discovery of a mechanism of action for the Rac P29S mutant, which confers an increase in metastasis and drug resistance in melanoma. 3) Identification of blebs and filopodia as morphological motifs that enhance cell survival. 4) Discovery of a new class of macromolecular assemblies that are composed of the molecular components of integrin-mediated adhesions, yet are not in mechanical contact with the extracellular matrix. Possibly, this class of adhesion-like assemblies is competent to generate pro-survival signals and to contribute in conjunction with the morphological motifs described before to the enhanced survival of metastatic cells in different environments. **Conclusions:** We have established a worldwide unique imaging infrastructure to probe pathways conferring the metastatic potential of cancer cells. We are currently widening than diversity of probes and advance the image acquisition technology to allow sub-cellular resolution imaging in xenograft models zebrafish and mouse.

45 **CPRIT Grantee**
Poster Session A

Modeling Hereditary Retinoblastoma-associated Osteosarcoma by Engineered hESCs *Jian Tu, The University of Texas Health Science Center at Houston; Z. Huo; R. Zhao; D. Lee*

Introduction: Osteosarcoma is the most common malignancy bone tumor among children and adolescents. The five-year overall survival of localized osteosarcoma hovers around 60-70%, but dramatically decreases to 20-30% for metastatic patients. Retinoblastoma is the most frequent eye cancer in children. About 1/3 of patients with retinoblastoma harbor the germline RB1mutation, resulting in the development of retinoblastoma. The much higher incidence of osteosarcoma was found in patients with hereditary retinoblastoma than sporadic retinoblastoma. However the underlying mechanisms are still partly understood. **Methods:** (1) We apply CRISPR/Cas9 genome editing to generate RB1 hotspot mutations in human embryonic stem cells (hESCs) to model bone malignancy in hereditary retinoblastoma (RB) patients. (2) We define pluripotent characteristics of the RB1 mutated hESCs by both qRT-PCR and immunostaining.(3) We examine if RB1 mutated hESC-derived osteoblasts phenocopy RB-associated osteosarcoma.(4)We apply RNAseq and CHIP-seq to identify the transcriptome and genome binding alterations in RB-associated osteosarcoma. **Results:** Three hotspot mutations (c.1333C>T, c.1363C>T, andc.1401C>T) of RB1are individually generated in hESC H1 line as H1(RB1/mtRB1) by CRISPR/Cas9 genome editing methodology. All of these clones carrying heterozygous RB1 mutation mimics genetic pattern of RB. RB1 mutation in H1(RB1/mtRB1) is further confirmed by Sanger sequencing and western blot. These H1(RB1/mtRB1) lines express pluripotency factors (NANOG, OCT4 and SOX2), hESC surface markers (TRA-1-81 and SSEA4) as well as alkaline phosphatase, suggesting they are pluripotent stem cells. **Conclusions:** The RB1 mutated hESCs can be created by CRISPR/Cas9 technology. RB-associated osteosarcomagenesis will be modeled and analyzed using H1(RB1/mtRB1)lines. Completion of this study will provide valuable insight into development of a more effective treatment strategy for RB patients with osteosarcoma.

46 **CPRIT Grantee**
Poster Session B

Extracting common and distinctive structures from genomic datasets *Hai Shu, The University of Texas M.D. Anderson Cancer Center; H. Zhu; X. Wang*

Introduction: It often occurs in medical sciences that multiple types of data are measured on a common set of objects. For example, The Cancer Genome Atlas (TCGA) collected genomic data on various platforms for human cancer tumors. A typical model for jointly analyzing two such datasets is to decompose each dataset into three parts: a common structure containing the shared information between datasets, a distinctive structure characterizing the individual information within each single dataset, and residual noise. Existing methods often focus on the orthogonality between the common and distinctive structures, which distracts their attention from the more important orthogonality between distinctive structures. **Methods:** We instead enforce the orthogonality between the two distinctive structures to guarantee that no common structure is retained therein. To this end, we develop a novel decomposition method based on the canonical variables that are the sequentially obtained closest features between two datasets. We carefully define the common and distinctive components for these canonical variables, and then collect them to form the desirable common and distinctive structures of two datasets. **Results:** The proposed method outperforms state-of-the-art methods in both simulated data and the TCGA datasets of human breast cancer. **Conclusions:** The proposed method successfully imposes the orthogonality between the distinctive structures of two datasets to avoid additional common structure being retained therein.

47 **CPRIT Grantee**
Poster Session A

Targeting neuroblastoma cancer stem cells using CRISPR/Cas9 *Julie Tomolonis, Baylor College of Medicine; S. Agarwal; J. Shohet*

Introduction: High-risk neuroblastoma (NB) is an aggressive pediatric tumor of neural crest origin arising within the sympathetic nervous system. NB remains a challenge to treat, with long-term survival rates below 40% and less than 10% in those that suffer with relapse. Disease relapse is known to be fueled by cancer stem cell-like cells (CSCs) in other tumor models. Recently, we identified and characterized a highly tumorigenic, drug resistant, and metastatic subpopulation in NB based on surface expression of granulocyte colony stimulating factor receptor (G-CSFR; CD114). These CD114+ cells represent <1% of total NB cells and can self-renew and form tumors from as few as 10 cells in vivo. Furthermore, we found that cytokine G-CSF treatment increases NB tumor growth and metastasis with an increase in total CD114+ cells in vivo. Here, we utilized the advanced CRISPR/Cas9 mediated genomic editing tools to directly target NB CSC subpopulation. This study will provide better understanding of the role of CD114 in NB tumorigenicity and in CSC maintenance. **Methods:** We designed high specificity sgRNAs flanking exons 8 and 9 of the CSF3R gene. This is a highly-conserved cytokine binding domain that allows for G-CSF receptor activation and dimerization. sgRNA were synthesized using PCR amplification and in vitro transcription. Ribonucleoprotein (RNP) complexes of Cas9 protein and sgRNA were electroporated into NB cell lines (SH-SY5Y & NGP) and a control cell line (BeWo). Potential mutant clones were characterized using PCR for editing efficiency and genotype, RT-PCR for mRNA, Western blot for protein expression, and flow cytometry for CD114 surface expression. **Results:** We designed several sets of sgRNA guide pairs and electroporated the Cas9 RNP mix into BeWo cells, a placental choriocarcinoma cell line with high expression of CD114. Depending on the sgRNA guide pair, we achieved 100% knockout efficiency as determined with PCR genotyping. Furthermore, the genomic knockout efficiency is found to be correlated with reduction in CD114 surface expression as determined with flow cytometry. NB cell lines were electroporated using optimized constructs with about 40% editing efficiency. Promising NB CD114 knockout clones have been isolated and characterized. Further studies to determine the effects of CD114 knockout on NB growth, drug response, and tumorigenicity are ongoing. **Conclusions:** NB cell lines can be efficiently edited by CRISPR/Cas9 based genomic editing method. CSF3R exons 8 and 9 are essential for CD114 function and knockout of these exons leads to the loss of CD114 surface expression.

48 **CPRIT Grantee**
Poster Session B

miR-195 regulates the response of non-small cell lung cancer to microtubule targeting agents by targeting CHEK1 *Xiaojie Yu, The University of Texas Health Science Center at San Antonio; Y. Zhang; D. Cavazos; X. Ma; A. Pertsemlidis*

Introduction: microRNAs (miRNAs) are a family of small non-coding RNAs (18-24 nt) that post-transcriptionally repress gene expression by direct binding to the 3' untranslated regions (UTRs) of their targets. By targeting cancer-related genes, miRNAs have been shown not only to

regulate cancer growth/progression, but also to modulate the response of cancer cells to chemotherapy. Such miRNAs are potential candidates for therapeutic intervention. **Methods:** Aiming to identify functional miRNAs in non-small cell lung cancer (NSCLC), we performed a high-throughput screen and found that miR-195 inhibits the growth of NSCLC cells and sensitizes them to microtubule-targeting agents (MTAs), a family of chemotherapeutic drugs widely used for NSCLC treatment. The function and mechanism of miR-195 in NSCLC were demonstrated both in vitro and in vivo. **Results:** We demonstrated that miR-195 synergizes with both an old-school MTA (paclitaxel) and a new-fangled one (eribulin) to repress the growth of NSCLC cells. Over-expression of miR-195 sensitizes NSCLC cells to paclitaxel and eribulin, while knockout of miR-195 confers resistance to paclitaxel and eribulin. Importantly, lung tumors with miR-195 over-expression are more sensitive to eribulin treatment than control tumors. Induced expression of miR-195 in lung tumors potentiates the efficacy of eribulin to repress tumor growth. Additionally, we showed that miR-195 directly targets CHEK1 to regulate the response of NSCLC cells to paclitaxel and eribulin. The direct and specific binding of miR-195 to the 3'UTR of CHEK1 was confirmed by luciferase reporter assay. Repression of CHEK1 using siRNAs and chemical inhibitor synergizes with paclitaxel and eribulin to repress the growth of NSCLC cells. Over-expression of CHEK1 contributes to the resistance to paclitaxel and eribulin in NSCLC cells. Analysis of TCGA data show that CHEK1 is significantly up-regulated in lung tumors compared to adjacent normal tissues and that its up-regulation is associated with worse recurrence-free and overall survival. **Conclusions:** We report the identification of miR-195 as a sensitizer to microtubule-targeting agents in NSCLC, mediated by its repression of CHEK1. Mouse xenografts with induced or constitutive over-expression of miR-195 show that tumors with high miR-195 expression are more sensitive to drug treatment and that induction of miR-195 potentiates the efficacy of eribulin in repressing tumor growth. These results highlight the possible application of miR-195 expression as a biomarker to predict patient response to MTAs and the potential for delivery of miR-195 mimic as an adjuvant to chemotherapy.

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49 **CPRIT Grantee**
Poster Session A

Biodegradable multilayered nanofilms for cancer cell isolation and recovery *Wei Li, Texas Tech University; Z. Dong*

Introduction: Selective isolation and purification of circulating tumor cells (CTCs) from whole blood is an important capability for both clinical medicine and biological research. Current techniques to perform this task place the isolated cells under excessive stresses that reduce cell viability, and potentially induce phenotype change, therefore losing valuable information about the isolated cells. The goal of our work is to effectively isolate as well as non-inversely recover cancer cells using a microfluidic device coated with a biodegradable multilayered nanofilm. To this end, we have applied layer-by-layer (LbL) assembly to create a library of ultrathin coatings using a broad range of materials through complementary interactions. **Methods:** We systematically studied the effect of various flow conditions and channel geometries on the thickness and surface roughness of the resulting films. We also investigated the biocompatibility and degradation behaviors of a series of enzymatically-degradable films made from naturally derived polymers. By developing an LbL nano-film coating with an affinity-based cell-capture surface that is capable of selectively isolating cancer cells from whole blood, and that can be rapidly degraded on command, we are able to gently isolate cancer cells and recover them without compromising cell viability or proliferative potential. **Results:** This film system has been applied to two capture and release platforms: 1) microfluidic HB chip and 2) hollow glass microspheres. Detailed characterization on the film system was conducted via fluorescent microscopy, AFM, profilometer, TGA, QCM-D, immunofluorescent staining, etc. We show that layer-by-layer (LbL) assembly as an effective method to coat nanometer scale film inside microfluidic devices with complex microstructures. We achieved 80% capture efficiency and 95% release efficiency for spiked prostate cancer cells with heterogeneous levels of expression of the surface antigen EpCAM, as well as CTCs in the blood samples of patients with metastatic lung cancer. The viability of released cells was demonstrated to be ~90%. The CTCs in the patient blood samples were found to range from 3.4 to 4.9 CTCs/mL, while less than 0.5 CTCs/mL was found in control samples. **Conclusions:** Our approach has the capability to overcome practical hurdles and provide viable cancer cells for downstream analyses.

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50 **CPRIT Grantee**
Poster Session B

CliP: Fast subclonal architecture reconstruction from whole-genome sequencing data *Kaixian Yu, The University of Texas M.D. Anderson Cancer Center; S. Shin; H. Zhu; W. Wang*

Introduction: Tumors as well as various human tissues usually consist of different subpopulations (subclones) that are characterized by somatic mutations. The composition of such subpopulations may affect disease prognosis and treatment efficacy. And understanding the subclonal structure helps infer the evolutionary history of cells which can further guide the discovery of driver mutations such as those in cancer studies. Currently most subclonal reconstruction methods are Dirichlet Process (DP) based, requiring expensive computing since MCMC algorithm is commonly adopted to solve the problem, and careful post-processing due to the fact that the number of clusters scales with number of single nucleotide variations (SNVs) in the DP setting. **Methods:** We present CliP (Clonal structure identification through penalizing pairwise difference), a fast and minimum post-processing algorithm for calling subclonal structures using whole-genome sequencing data. CliP deterministically solves a penalized likelihood problem, making execution much faster. **Results:** In a simulated sample with 15,000 SNVs, it takes CliP less than 1 hour to finish the subclonal reconstruction, which is about 100 times faster than other methods. CliP is also capable of handling sequencing data at low coverages (30X-60X). Based on 125 simulated samples, CliP showed comparable prediction performance with DP-based methods. In the application to ICGC whole-genome sequencing data from 2,703 tumor samples from 39 cancer types, CliP provided results within 4 days and was able to analyze the hypermutator (>100,000 SNVs) samples correctly. **Conclusions:** We have proposed CliP, a fast and accurate subclonal reconstruction method that requires minimum post-processing. It is especially suitable for quickly processing large cohorts containing thousands of whole-genome sequencing data to analyze cancer heterogeneity and their evolutionary histories.

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51 **CPRIT Grantee**
Poster Session A

Integrative Network Analysis Reveals Rampant Signaling Cascade Rewiring and Vulnerability in Distinct Breast Cancer Subtypes *Song Yi, The University of Texas M.D. Anderson Cancer Center; D. Mcgrail; S. Lin; N. Sahni*

Introduction: Mutational processes leave genomic 'scars' on the DNA, known as mutational signatures that are thought to be reflective of specific defects in DNA damage response. However, many of these observed signatures remain largely unresolved in their origin as well as ways to therapeutically target them in the way PARP inhibitors are being used to target BRCA1/2 mutant breast and ovarian tumors that have defects in homologous recombination repair. In this work, we deconvolve these mutational signatures from TCGA sequencing data, and integrate this data with transcriptomic and proteomic analysis to give a global view of the global network rewiring that corresponds with these genomic scars. This integrated analysis revealed multiple differentially regulated pathways both at the gene and protein level. For instance, in one mutation signature enriched in basal breast cancer, we find that it corresponds with enrichment for purine metabolism at the gene level as well as proteins known to suppress BRCA1 expression. **Methods:** Molecular profiling of tumors RNAseq, DNA mutations (WXS), and protein expression (mass spectrometry) were acquired through TCGA; drug sensitivitiy data was acquired from CTRPv2. Mutations signatures were determined by deconvolution of tri-nucleotide mutational frequencies. Pathway enrichment was determined using GSEA. **Results:** Globally, comparing protein and gene expression levels shows that 51% of genes positively correlate with protein levels, predominately genes involved in cell cycle and immune signaling. Differential analysis between basal and luminal breast cancers shows enrichment of 177 Reactome pathways based on total protein levels, compared to only 87 pathways from matched gene expression data. Further analysis of phospho-protein levels revealed 157 enriched pathways, for a total of 260 pathways from proteomic data of which 206 are unique and not predicted through gene expression analysis. Investigating these newly discovered pathway enrichments within basal breast cancers, we find significant up-regulation of proteins involved in gene expression and mRNA processing at both the total and phosphorylated protein level. We validated this finding with a CLICK chemistry based assay to quantify RNA synthesis rates in breast cancer cell lines, revealing nearly a 2-fold increase in basal breast cancer RNA synthesis rates. Moreover, we find that basal breast cancer cell lines show increased sensitivity to inhibitors of RNA synthesis relative to their luminal counterparts. **Conclusions:** This work demonstrates novel network-level proteomic differences between luminal and basal breast cancer subtypes which are verified by in vitro experiments. It helps identify novel therapeutic avenues for basal breast cancer which currently lacks targeted treatments.

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52 **CPRIT Grantee**
Poster Session B

Preventing Twist1 expression inhibits the partial EMT plasticity, basal-like lineage reprograming, intravasation and metastasis of breast tumor cells in mice *Dong-Kee Lee, Baylor College of Medicine; Y. Xu; Z. Feng; Y. Xu; W. Bu; Y. Li; L. Liao; J. Xu*

Introduction: Epithelial-mesenchymal transition (EMT) occurs during embryonic development, wound healing, carcinogenesis and certain other circumstances. Since the migration and invasion capability of cancer cells usually associates with their metastatic potential, EMT has been considered crucial for cancer metastasis. Twist1 is a basic helix-loop-helix domain-containing transcription factor (TF) expressed in multiple types of cancer cells. In breast cancer cells, Twist1 expression induces EMT, stemness, migration, invasion and metastasis. However, the intrinsic role of Twist1 has not been well defined during the entire process of a spontaneous breast tumor initiation, progression and metastasis in vivo. **Methods:** We developed two genetic mouse models of breast cancer in which Twist1 is either wild type (WT) or specifically deleted in the oncogene-induced tumor cells (Twist1^{TKO}). Using Immunohistochemical analysis, we examined the expression patterns of epithelial/mesenchymal markers and EMT inducing TFs, as well as quantitatively analyzing circulating tumor cells (CTCs) and lung metastasis in these two mouse models. **Results:** Twist1 KO showed no effects on tumor initiation and growth. In both group early tumor cells, Twist1 and mesenchymal markers were not expressed, and lung metastasis was absent. Twist1 expression was detected in ~6% of the advanced WT tumor cells. Most of these Twist1+ cells co-expressed several other EMT-inducing TFs (Snail, Slug, Zeb2), lost ERa and luminal marker K8, acquired basal cell markers (K5, p63) and exhibited a partial EMT plasticity (E-cadherin+/vimentin+). In advanced tumor cells, Twist1 KO largely diminished the expression of the aforementioned EMT-inducing TFs and basal and mesenchymal markers but maintained the expression of the luminal markers. CTCs were detected in mice with advanced WT tumors but not in Twist1^{TKO} tumors. Nearly all WT CTCs co-expressed Twist1 with other EMT-inducing TFs and both epithelial and mesenchymal markers. Mice with advanced WT tumors developed extensive lung. Mice with advanced Twist1^{TKO} tumors developed very little lung metastasis. Therefore, Twist1 is required for the expression of other EMT inducing TFs in a small subset of tumor cells. Together, they induce partial EMT, basal-like tumor progression, intravasation and metastasis. **Conclusions:** This study showed that Twist1 expression is commonly associated with the expression of other EMT inducing TFs in a small number of primary breast tumor cells and CTCs, programming a partial EMT and a basal-like tumor cell phenotype to drive these cells disseminate into the circulation and metastasize to the lung. Twist1 may be a potential target for controlling breast cancer metastasis.

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53 **CPRIT Grantee**
Poster Session A

Nuclear Receptor NR4A1 is a Tumor Suppressor Down-regulated in Triple-negative Breast Cancer *Jianming Xu, Baylor College of Medicine; H. Wu; J. Bi; Y. Peng; L. Huo; X. Yu; Y. Zhou; L. Qin; Y. Xie*

Introduction: The nuclear receptor (NR) superfamily contains hormone-inducible transcription factors that regulate many physiological and pathological processes through regulating gene expression. NR4A1 is an NR family member that still does not have an identified endogenous ligand, and its role in cancer is also currently unclear and controversial. In this study, we aimed to define the expression profiles and specific role of NR4A1 in the highly malignant triple-negative breast cancer (TNBC), which still lacks available targeted therapies. **Methods:** Age-matched normal mouse mammary glands and mammary gland tumors were prepared from female wild type and K14-cre;p53(loxP/loxP);Brca1(loxP/loxP) mice, respectively. Paraffin sections prepared from 60 human non-cancer breast tissues and 148 TNBC were provided by University of Texas (UT) Southwestern Medical Center, UT MD Anderson Cancer Center and Sun Yat-Sen University. Immunohistochemistry was performed to determine the expression levels of NR4A1 in both mouse and human breast tissues and tumors. Patients' TNBC relapse-free survival was calculated using the Kaplan-Meier method and compared using the Gehan-Breslow-Wilcoxon test. Cell lines with either NR4A1 overexpression or knockdown were generated to assess the role of NR4A1 in TNBC cells. Immunoblotting, cell proliferation, cell migration, cell invasion, qPCR and xenograft mouse tumor models were performed by following commonly used protocols. **Results:** Bioinformatic analysis revealed a decrease of NR4A1 mRNA expression in human TNBC samples. Semi-quantitative analysis of NR4A1 protein expression by immunohistochemistry also identified a progressive NR4A1 reduction during the development of mouse basal-like mammary tumors and a significant NR4A1 downregulation in human TNBC samples. Furthermore, the expression levels of NR4A1 in human TNBC were negatively associated with tumor stage, lymph node metastasis and disease recurrence. Moreover, ectopic expression of NR4A1 in MDA-MB-231, a TNBC cell line with little endogenous NR4A1, inhibited the proliferation, viability, migration and invasion of these cells, and these inhibitions were associated with an attenuated JNK1–AP-1–cyclin D1 pathway. NR4A1 expression also largely suppressed the growth and metastasis of these cell-derived tumors in mice. **Conclusions:** These results demonstrate that NR4A1 is downregulated in TNBC and restoration of NR4A1 expression inhibits TNBC growth and metastasis, suggesting that NR4A1 is a tumor suppressor in TNBC.

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54 **CPRIT Grantee**
Poster Session B

TREX2 inhibitors treat breakpoint cluster region/abelson-induced cancers *Mi Young Son, The University of Texas Health Science Center at San Antonio; Q. Zhou; J. Ko; P. Hasty*

Introduction: Breakpoint cluster region-abelson (BCR/ABL) is a fusion protein generated from a chromosomal translocation. BCR/ABL is a constitutively active tyrosine kinase that influences cell cycle and DNA damage responses to increase the risk of cancer like chronic myelogenous leukemia and acute lymphoblastic leukemia. Tyrosine kinase inhibitors (TKIs) effectively treat these cancers but resistance is a big problem. Genomic instability (GI) contributes to TKI resistance. We hypothesize that BCR/ABL impairs homologous recombination (HR) permitting the faulty use of DNA damage tolerance (DDT) to cause GI that leads to cancer progression and drug resistance. I propose that a member of DDT, TREX2 (Three prime repair exonuclease 2), causes most of the GI in BCR/ABL-induced cancers and that TREX2 inhibitors will reduce GI and resistance. **Methods:** Mouse embryonic stem cells were cultured. iPOND was used to purified proteins on replication fork (RF). Two-color fluorescent in situ hybridization was to detect chromosomal abnormalities. A dose-response curve was used to determine the level of drug sensitivity. Loss of heterozygosity (LOH) of miniHPRT was performed as selecting 6-thioguinine resistant colonies. **Results:** BCR/ABL-phosphorylated RAD51 pY315 purified to the RF with increasing levels of hydroxyurea (HU), a RF blocker. In addition, expression of RAD51^{Y315F} (defective for BCR/ABL-phosphorylation) caused spontaneous and HU-induced GI. Thus, BCR/ABL phosphorylates RAD51 Y315 in response to stalled RF and it could cause GI. Deletion of TREX2 that is involved in DDT pathway reduced dramatically LOH in RAD51-mutant cells compared to RAD51-wild type cells. The small molecules, TREX2 inhibitors also reduced LOH in RAD51-mutant cells. In addition, TREX2-null cells enhanced sensitivity of RAD51-defective cells to camptothecin that is a topoisomerase I inhibitor and one of cancer treatment. **Conclusions:** TREX2 inhibitors is an obvious possibility in treating cancers that express BCR/ABL. TREX2 inhibitors could enhance cell killing of chemotherapeutic agents in cancer cells while protecting the patient from mutations to reduce the risk of therapy-related disease.

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55 **CPRIT Grantee**
Poster Session A

Pre-existence of polyresistant cancer stem cells in high-grade ovarian cancer *Wa Xian, The University of Texas Health Science Center at Houston; B. Wang; F. McKeon*

Introduction: High-grade ovarian cancer (HGOC) shows excellent responses to standard-of-care surgery and paclitaxel/carboplatin therapy only to relapse 6-24 months later with typically resistant disease. While the origin of this recurrent, resistant disease is unclear, most believe it is acquired by the action of chemotherapeutics. Using novel stem cell technology that enables the cloning of cancer stem cells (CSCs) from epithelial cancers, we have generated large libraries of CSCs from multiple cases of HGOC. And while the vast majority of these CSC clones are killed by standard-of-care chemotherapeutic drugs, a minor fraction shows profound resistance not only to paclitaxel/carboplatin but to a wide range of structurally unrelated chemotherapeutic drugs to which these cells had no prior exposure. We describe screens for drugs that selectively target this resistant CSC population. **Methods:** Libraries of 10- to 100,000 CSC clones were generated from individual, therapy naïve, HGOC resections using technology we developed for cloning so-called "adult" stem cells from normal columnar epithelia (Wang et al., 2015) **Results:** Paclitaxel/carboplatin resistant CSCs were identified in CSC libraries derived from therapy naïve tumors at ratios of 1:50 to 1:300. By copy number variation, these resistant variant clones proved distinct from the bulk of CSCs, and by gene expression analysis varied from sensitive clones by more than 700 differentially expressed genes. Independent resistant clones from the same library clustered with other resistant clones by both copy number variation and gene expression profiles, suggesting the possibility that resistance within a single tumor is dominated by a single type of resistant CSCs. Clones resistant to paclitaxel/carboplatin were screened in a 384-well format against a wide range of experimental drug-like molecules. These pre-existing resistant clones also proved to be profoundly resistant to a large number of structurally unrelated chemotherapeutic drugs. This same screening program identified drugs that act alone or in combination with paclitaxel to eliminate these resistant clones, suggesting a route to personalized medicine for addressing the problem of recurrent disease in HGOC. **Conclusions:** Tumors from patients with HGOC possess clonogenic CSCs including variants that are resistant to a broad spectrum of chemotherapeutics to which they have not been exposed. It is likely that such CSCs would survive standard-of-care chemotherapy and contribute to the recurrent disease seen in HGOC. We have identified known and experimental drugs that specifically eliminate these resistant variants and the overall platform represents a potential strategy to addressing the problem of recurrent disease in these patients.

56 **CPRIT Grantee Poster Session B**

Phosphorylation of ASCL1 to disrupt oncogenic activity in SCLC *Demetra Kelenis, The University of Texas Southwestern Medical Center; S. Earnest; M. Cobb; J. Johnson*

Introduction: Small cell lung cancer (SCLC) is an aggressive neuroendocrine cancer that accounts for approximately 16% of new lung cancer diagnoses. Though SCLC is initially responsive to chemotherapy, resistance quickly develops, with 5-year survival rates below 7%, a prognosis that has not improved over the past 30 years. ASCL1 is present in a majority of human-derived SCLC cell lines and, where tested, is required for tumor cell growth. This proneural basic helix-loop-helix (bHLH) transcription factor normally regulates neuronal differentiation during embryonic development. Its requirement in SCLC suggests that strategies to inhibit the function of ASCl1 may represent a novel, targeted SCLC therapy. Proneural bHLH transcription factors, including ASCL1, have a defined lifetime during embryonic development. It has been proposed that proneural bHLH transcription factors are regulated by phosphorylation of a serine residue at a conserved position within the bHLH domain. Phosphorylation at this site, S155 in human ASCL1, has been suggested to function as a switch that rapidly inactivates ASCL1, overcoming an autoregulatory, positive feedback loop that sustains the proliferative capacity of ASCL1-expressing cells. We hypothesize that the phosphorylation of ASCL1 on S155 can be induced to inactivate this oncogenic driver in the context of SCLC. **Methods:** We generated a series of rat ASCL1_S152 (hS155) mutants and assessed their transcriptional activity using an ASCL1-responsive luciferase reporter assay. To characterize the phosphorylation state of ASCL1_S155 in SCLC, we used mass spectrometry of immunoprecipitated ASCL1 protein from the human $ASCL1^{Hi}$ SCLC cell line H889. **Results:** We found that phosphomimetic mutation of S152 results in a transcriptionally inactive protein, as measured by absent reporter activity, whereas unphosphorylatable mutants retain transcriptional activity. While previously reported phosphorylation sites in ASCL1 were detected in our analysis of ASCL1 phosphorylation sites in H889 SCLC cells, phosphorylation of ASCL1_S155 was not found. **Conclusions:** Our findings suggest that strategies to induce ASCL1_S155 phosphorylation may represent a way to inactivate this transcription factor in SCLC, disrupting the growth of ASCL1-dependent SCLC cells. Future work will include assessing the effect of phosphorylation at this site on the transcriptional activity, DNA binding, and heterodimerization capacity of human ASCL1. We will also test whether phosphorylation of ASCL1 at this site can be invoked in SCLC to inhibit tumor growth by replacing wild-type ASCL1 with phosphomimetic variants both in vitro and in vivo. These experiments have the potential to identify a novel, mechanism-based therapy for this treatment resistant cancer.

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Investigations on the interactions of Mre11, Sae2/CtIP, Wss1/Spartan and the proteasome in a novel pathway to repair topoisomerase 1-DNA conjugates *Yizhi Yin, The University of Texas at Austin; T. Paull*

Introduction: Topoisomerase 1 (Top1) is an enzyme that releases topological stress during DNA metabolism by cutting DNA strand via forming a Top1-DNA conjugate, followed by re-ligation of the DNA. If the re-ligation step is inhibited by topoisomerase poisons like camptothecin (CPT), the Top1-DNA conjugate becomes irreversible and leads to lethal DNA breaks, especially, in replicating cells. Topoisomerase poisons are widely used as chemotherapeutics to selectively target cancers. A better understanding in the repair of DNA breaks with Top1-DNA conjugates can help to identify more specific targets for chemotherapy and to reduce the frequency of chemotherapeutic resistance. The classical pathway to remove Top1-DNA conjugates requires an enzyme called Tdp1. Tdp1 cleaves the linkage between Top1 and DNA after proteasome-dependent degradation of Top1. Despite its critical function, mutations in Tdp1 gene in human patients do not cause a predisposition to cancer; this suggests alternative pathways exist to repair Top1-DNA conjugates. The deficiencies of DNA damage repair proteins, including the Mre11 and Sae2/CtIP (yeast/mammalian) endonucleases, cause the sensitivity to CPT in many organisms. However, it remains unclear what roles Mre11 and Sae2/CtIP play in this process, and if a proteolytic degradation of Top1 is required for these pathways. Wss1/Spartan (yeast/mammalian), has been recently identified as a novel protease that degrades Top1 during replication. Nevertheless, it is unclear if Wss1/Spartan interacts with Tdp1 or other proteins in this process. Here I propose a novel pathway of the removal of Top1-DNA conjugates that involves the Mre11 and Sae2/CtIP endonucleases, and the Wss1/Spartan or the proteasome proteolytic components. **Methods:** I will create single and combinations of genetic deficiencies of Wss1/Spartan, the proteasome, Tdp1, Mre11 and Sae2/CtIP in both yeast and human cancer cells to measure the cell growth, sensitivity to CPT, and Top1-DNA conjugate levels in these genetic backgrounds. **Results:** Our preliminary data show that in yeast Wss1 acts in the same pathway as Sae2 and Mre11 in response to CPT. Human cells depleted of CtIP accumulate Top1-DNA conjugates upon CPT treatment. Further depletion of CtIP in Spartan-/- knock-out human cells causes severe growth defects, and accumulation of spontaneous Top1-DNA conjugates. **Conclusions:** Preliminary results in yeast support that Wss1 work in the same pathway as Sae2 and Mre11 in the repair of CPT-induced damage; however, in human cells Spartan seems to act in a different pathway from CtIP. Further investigations are still in process to examine the specific roles of the aforementioned genes in the repair of Top1-DNA conjugates.

58 **CPRIT Grantee Poster Session B**

Investigation of DIS3L2 functions in Perlman syndrome and Wilms tumor *Ryan Hunter, The University of Texas Southwestern Medical Center; Y. Liu; A. Acharya; H. Manjunath; H. Ramalingam; B. Chen; V. Schmid; R. Hammer; T. Carroll; Y. Xie; J. Mendell*

Introduction: Wilms tumor is the most common kidney cancer in children, yet its etiology is incompletely understood. Several recent studies have uncovered a role for loss of let-7 in its pathogenesis. One crucial mechanism through which let-7 expression is controlled is via the activity of the RNA-binding protein LIN28, which binds the precursor of let-7 and triggers the addition of a series of uridines to the 3□ end. This oligouridylated pre-let-7 is then degraded by the exoribonuclease DIS3L2. Poorly characterized until very recently, the DIS3L2 gene has been shown to harbor loss-of-function mutations in patients with Perlman syndrome, an overgrowth syndrome characterized by high neonatal mortality and, interestingly, a strong predisposition to Wilms tumor. Moreover, DIS3L2 has been shown to be deleted or mutated in some cases of sporadic Wilms tumor. The importance of let-7 in Wilms tumor and a purported role for DIS3L2 in the LIN28/let-7 pathway have led to speculation that aberrant expression of let-7 underlies Wilms tumor susceptibility in Perlman syndrome patients. **Methods:** To investigate the regulation of let-7 by DIS3L2 we used TALENs to knockout DIS3L2 in a panel of cell lines with various levels of LIN28 expression. Additionally, to examine the role of DIS3L2 in let-7 regulation within the context of kidney development and to investigate its involvement in Wilms tumor pathogenesis, we used CRISPR-Cas9 to generate Dis3l2-mutant mice. From these mice we isolated embryonic kidney progenitor cells thought to represent a cell of origin for Wilms tumor. In both these progenitor cells and the DIS3L2 knockout cell lines we performed let-7 qRT-PCR. **Results:** Germline Dis3l2 knockout recapitulated some aspects of Perlman syndrome, including neonatal mortality and genitourinary abnormalities, yet neither overgrowth nor renal tumors were observed. Contrary to the prevailing model, loss of DIS3L2 had no effect on mature let-7 expression in the cell lines nor in embryonic kidney primary cultures. **Conclusions:** DIS3L2 is important for proper development and survival beyond birth. Although its role as a tumor suppressor has been established, our data strongly suggest that DIS3L2 tumor suppressor properties are not attributable to its regulation of mature let-7 levels. Ongoing studies aim to identify how dysregulation of other DIS3L2 targets in the developing kidney could contribute to Wilms tumor pathogenesis.

59 **CPRIT Grantee Poster Session A**

High-throughput sequencing of paired T cell receptor alpha and beta in human donors using custom made flow-focusing device *Hidetaka Tanno, The University of Texas at Austin; R. Durrett; J. McDaniel; J. Gollihar; D. Park; A. Pothukuchy; J. Ellefson; W. Voss; G. Ippolito; A. Ellington; J. Goronzy; G. Georgiou*

Introduction: The adoptive transfer of T cells engineered to express tumor-reactive T cell receptor (TCR) has shown promising results. However, the discovery of such TCRs has been difficult so far because determining the sequence of these highly diverse heterodimer proteins requires sequencing of component TCRα and TCRβ at the single cell level. Current methods for single-cell sequencing are costly and have relatively low throughput (a few hundreds of single-cells / run). Because tumor-reactive TCR is extremely rare, a high-throughput single-cell sequencing technology is essential to discover tumor-reactive TCRs. **Methods:** We have developed a simple, low-cost technology for simultaneously sequencing both TCRα and TCRβ from more than $2x10^6$ individual T cells per experiment. A flow-focusing device compartmentalizes the mRNA from a single-T cell mRNA into a small lipid droplet. A RT-PCR reaction within the droplet physically links TCRα and TCRβ mRNA of single-cells. Subsequent high-throughput sequencing of TCRαβ linked cDNA produces paired TCRαβ sequences of single-cells. The whole procedure can be performed within 12 hours. **Results:** From 10^6 peripheral T cells, we obtained >30,000 TCRα:TCRβ clonally distinct sequence pairs on average. TCRα and TCRβ of single-cells were correctly paired at more than 92% precision. **Conclusions:** Our

TCR$\alpha\beta$ sequencing technology is accurate and can find 100-fold more TCR$\alpha\beta$ sequences than conventional technologies. This technology allows identifying tumor-reactive TCRs more quickly and accurately, and thus accelerates immunotherapy using the tumor-reactive TCRs. Acknowledgement: This study was supported by UTHealth Innovation for Cancer Prevention Research Training Program Post-Doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant # RP160015), Defense Threat Reduction Agency under Award Number HDTRA1-12-C-0105, and Dell Medical School's Texas Health Catalyst program. Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the sponsors.

60 **CPRIT Grantee Poster Session B**

The Y537S ESR1 mutation is a dominant driver of distant ER-positive breast cancer metastasis *Guowei Gu, Baylor College of Medicine; L. Tian; D. Dustin; M. Gao; L. Gelsomino; A. Corona-Rodriguez; X. Zhang; S. Fuqua*

Introduction: Estrogen receptor (ESR1) mutations occur at a high frequency in metastatic breast tumors in patients treated with hormonal therapy in the metastatic setting. We do not know if these mutations are involved in metastasis. **Methods:** We generated ESR1 Y537S homozygous mutations using CRISPR Casp-9 technology. Treatment synergy was evaluated using Compusyn. Athymic mice were used in tumor xenograft studies. ChIP-Seq and transcriptome analyses were performed. **Results:** We generated CRISPR ESR1 Y537S mutation homozygous knock-in clones and lentiviral stable pools in MCF-7 cells. Transcriptome profiling revealed elevated expression of Hallmark pathways, including epithelial mesenchymal transition (EMT) and estrogen-regulated gene expression. Mutant cell growth was resistant to tamoxifen, but responsive to fulvestrant treatment. CRISPR Y537S mutant knock-in cells grown in the mammary fat-pad of athymic mice spontaneously metastasized to distant organs including the lung, intestine, and kidneys. In the presence of estrogen, there was no difference in the frequency of distant macrometastases between parental wild-type ER and CRISPR Y537S mutant ER mice. However, in the absence of estrogen, mimicking aromatase inhibitor treatment, 80% of CRISPR Y537S mutant ER mice displayed overt distant macrometastases, but none were observed in parental wild-type ER mice (p=0.04). Interestingly, although CRISPR Y537S mutant ER tumors grown in the mammary fat-pad were unresponsive to tamoxifen treatment, tamoxifen significantly inhibited the growth of mutant tumors at the distant microenvironment (8-fold). Distant tumors retained ER expression and hormone sensitivity. Comparison of residual tamoxifen-treated metastatic tumors with tumors grown at the primary mammary fat-pad site using immunoblot analysis demonstrated significant reduction in estrogen-regulated gene expression, but no effect on the expression of biomarkers associated with EMT, suggesting a disconnect between EMT and distant metastasis in mutant cells. EMT genes were also identified as direct binding site targets in Y537S mutant cells compared with wide-type ER using ChIPSeq. A Y537S ER mutant-specific gene expression signature predicted poor disease-free survival of ER-positive patients using the METABRIC database, and lung-specific metastasis-free survival in a Memorial Sloan Kettering dataset. **Conclusions:** The Y537S ER mutation is a driver of distant metastasis in ER-positive breast cancer cells. Although tamoxifen treatment was ineffective at reducing the growth of mutant cells grown at the primary site, it was effective at reducing distant metastasis. A Y537S ER mutant-specific gene expression signature predicted poor disease-free, and distant lung metastasis in ER-positive patients. Mutation status is a potential new predictive factor for hormone therapy of metastatic breast cancer patients on maintenance hormonal therapy.

61 **CPRIT Grantee Poster Session A**

Intra-tumor heterogeneity analysis of immune response in early stage of non-small cell lung carcinoma using multiplex immunofluorescence and image analysis approaches: methodology and preliminary results *Alejandro Francisco-Cruz, The University of Texas M.D. Anderson Cancer Center; E. Parra; J. Fujimoto; C. Chow; J. Rodriguez-Canales; C. Behrens; N. Kalhor; A. Weissferdt; J. Heymach; S. Swisher; B. Sepesi; J. Lee; C. Moran; P. Futreal; J. Zhang; I. Wistuba*

Introduction: Tumors are composed by subpopulations of cells with distinct genetic, epigenetic and phenotypic features known as intra-tumor heterogeneity (ITH). The development and progression of non-small cell lung carcinomas (NSCLCs) is associated with the interaction between carcinoma cells (CCs), carcinoma stromal (CS) cells and tumor-associated immune-cells (TAICs) such as T-cell lymphocytes (TCLs) and tumor-associated macrophages (TAMs). The aim of this study was to characterize the ITH and immune contexture of NSCLC at early stages using image analysis and multiplex immunofluorescence (mIF) approaches. **Methods:** Forty-eight formalin-fixed, paraffin-embedded (FFPE) lung tumor-tissues from resected NSCLCs were obtained. Two panels for immune profiling were validated, panel 1: AE1/AE3 pancytokeratin, PD-L1, PD-1, CD3, CD8, and CD68; panel 2: AE1/AE3, CD3, CD8, Granzyme-B (GB), CD45RO, and FOXP3. Three not adjacent, intra-tumor regions (3mm^2 each) per case were randomly selected after gridding the whole tumor area. For this report, a total of 15 regions were scanned by Vectra multispectral-microscope (PerkinElmer) and analyzed using InForm-software (PerkinElmer). TAICs were evaluated into CCs and CS compartments. **Results:** Five cases of stage I surgically resected NSCLCs with history of early recurrence (3 adenocarcinomas, ADCs; and 2 squamous-cell carcinomas, SCCs) were selected for preliminary analysis. The median densities of TCLs and TAMs from five cases were 79.3 cells/mm^2 and 91 cells/mm^2, respectively, without significant differences between cases or histologic subtypes. One case of ADC and one case of SCC showed significant higher densities of CCs versus TCLs or TAMs; however, all cases presented higher densities of TCLs and TAMs into CS compartment that CCs compartment. Non-significant differences of TAICs densities into the different regions per tumor were observed. Sixteen phenotypes of TCLs, TAMs and CCs were observed. Significant and positive correlations between the percentages of these phenotypes into the different regions per tumor were observed. Inactive cytotoxic T-cells (CTCs), CTC-PD-1$^+$ and TCL-PD-1$^+$, were the most frequent phenotypes of TCLs observed (97%, 39%, and 44%, respectively) as into CCs as into CS compartments). The percentages of five TCLs phenotypes showed significant differences in 9 regions of ADCs analyzed. **Conclusions:** Preliminary multi-regional analysis of early stages NSCLC showed that the most important intra-tumor phenotypes of TCLs detected are co-inhibited or inactive phenotypes. The phenotypic ITH of TCLs observed in ADCs could represent a signature that differentiates from the SCC histology. Ongoing studies of a larger cohort of cases and correlation with clinical and pathological characteristics, including patients' outcome are warranted.

62 **CPRIT Grantee Poster Session B**

Constitutive Activation of ATM in Neuroblastoma cell lines with the Alternative Lengthening of Telomeres (ALT) Phenotype Induces Resistance to DNA Damaging Agents *Balakrishna Koneru, Texas Tech University Health Sciences Center; T. Nguyen; A. Farooqi; A. Hindle; C. Reynolds*

Introduction: Telomere maintenance is required for cancer growth. A non-telomerase mechanism, alternative lengthening of telomeres (ALT), is a hallmark of some cancers; 10-20% of high-risk neuroblastomas (NB) manifest ALT which is associated with a poor prognosis. There has been a paucity of patient-derived models of ALT cancers. Of 104 human NB cell lines and 32 patent-derived xenografts (PDX) we identified 5 NB cell lines and 4 PDXs with ALT: low TERT mRNA expression (confirmed by TRAP assay), positive for c-circles (extrachromosomal telomeric DNA), and long/heterogeneous telomeres by FISH. **Methods:** Cytotoxicity was assessed using DIMSCAN, gene expression by qRT-PCR, c-circle content by qPCR, DNA damage by immunostaining (53BP1 foci), telomere damage by IF-FISH, ATM knockdown and TRF2ΔBΔM expression by lentiviral shRNA transduction. **Results:** The 5 ALT NB cell lines had a significantly higher mean IC90 ($P<0.001$) for topoisomerase inhibitors relative to 79 comparator TERT+ NB cell lines and demonstrated higher expression of multiple DNA damage response (DDR) genes (29 of 59 genes analyzed, $p<0.05$) relative to 9 multidrug-resistant TERT+ NB cell lines. Numerous baseline DNA damage foci (> 80% co-localized to telomeres) were observed in the nuclei of ALT NB cell lines. We assessed activation of both ATM/ATR kinases (which are involved in DNA damage signaling at telomeres) and observed a marked increase in phosphorylation of ATM kinase and its downstream target CHK2 in ALT NB cell lines but not in TERT+ NB cell lines. Knockdown of ATM in 2 ALT NB cell lines significantly ($p<.05$), reduced DNA damage foci, C-circle (ALT marker) content, expression of 13 of 25 DDR genes that are commonly induced by genotoxic stress, and sensitized ALT NB cells to topoisomerase inhibitors. Transduction of TRF2ΔBΔM (dominant-negative TRF2 , a shelterin protein that blocks ATM at telomeres) activated ATM at telomeres in 2 TERT+ p53 non-functional NB cell lines and induced high resistance to topoisomerase inhibitors. The ATM kinase inhibitor KU60019 sensitized ALT NB cell lines to topoisomerase inhibitors and significantly reduced C-circle content ($P<0.05$) in 3 ALT NB cell lines. **Conclusions:** Telomeres in ALT NB constitutively activate ATM kinase which may be necessary for the ALT phenotype. Our data suggest that activation of ATM kinase in ALT NB contributes to DNA damaging agent resistance by upregulating DDR expression. ATM kinase is potentially a molecular therapeutic target in ALT NB.

63 **CPRIT Grantee Poster Session A**

Mechanisms of resistance towards a rational combined tyrosine kinase inhibitor therapy in triple-negative breast cancer *Hsiang-Ching Chung, Baylor College of Medicine; T. Sun; A. Nair; S. Kurley; N. Neill; S. Tyagi; M. Orellana; R. Dominguez-Vidana; D. Chan; K. Sheng; L. Dobrolecki; R. Mao; C. Nagi; T. Wang; R. Schiff; C. Gutierrez; M. Rimawi; S. Hilsenbeck; C. Shaw; C. Zong; A. Malovannaya; B. Zhang; M. Ellis; C. Osborne; M. Lewis; T. Westbrook*

Introduction: Triple-negative breast cancer (TNBC) is a common subtype of breast cancer that confers a poor prognosis; median survival for metastatic TNBC patients is only 13 months. Currently, there is no effective targeted therapy available for TNBC due to our lack of understanding of the molecular drivers of the disease. Using a forward genetic screen, we recently identified the tyrosine phosphatase PTPN12 as a novel tumor suppressor that is frequently compromised in TNBC (Sun, Cell 2012). Mechanistically, PTPN12 serves as a feedback inhibitor to select oncogenic RTKs. Loss of PTPN12 results in chronic activation of these RTKs and a co-dependency on these receptors in primary and metastatic TNBC. Based on these mechanistic insights, we rationalized a combination tyrosine kinase inhibitor(TKi) therapy by identifying PTPN12-regulated RTK substrates (Nair, Nat Med, accepted). Notably, combined inhibition of these RTKs confers regression of many independent patient-derived xenograft (PDX) models of TNBC in vivo. However, as with targeted therapies in other cancers, drug response is heterogeneous. Identifying genetic or epigenetic determinants of resistance may enable us not only to predict response to this novel therapeutic regimen in TNBC patients, but also overcome drug resistance to enable durable response. **Methods:** To better understand the molecular determinants of drug response, we performed unbiased genetic RNAi screens in multiple TNBC models to identify genes regulating tumor survival and proliferation in the context of combined TKi therapy. We further assessed cellular responses upon drug treatment by multiple unbiased proteogenomic approaches. **Results:** By integrating data from genomic, proteomic, and transcriptomic profiling, we have identified cellular processes that are selectively activated in an adaptive response to this combination TKi therapy that support resistance in these TNBC models. **Conclusions:** We are currently exploring if these pathways can be utilized to enhance efficacy of our rational combined TKi therapy in TNBC patients.

64 **CPRIT Grantee Poster Session B**

Identification of infrequently mutated cancer driver genes through SNV impact prediction in a pathway-based framework *Amanda Koire, Baylor College of Medicine; T. Hsu; P. Katsonis; C. Pickering; J. Myers; M. Frederick; O. Lichtarge*

Introduction: Attempts to identify driver genes of cancer and other complex diseases have traditionally focused on high mutation frequency as a signal of positive selection. As a result, limited statistical detection has left most of the "long-tail" of infrequently mutated genes understudied, as well as many of the pathways they belong to. Using Pathway-EA, we address both problems jointly by detecting pathways that contain groups of genes under collective mutational positive selection. We hypothesize that if multiple genes are capable of disrupting a function when mutated, functionally related genes may be mutated at a low frequency individually but a high frequency overall. Consequently, rare driver genes may operate in pathways together and be collectively biased toward impactful mutations, indicating positive selection. This approach is novel in that it represents integration of the EA equation over pathways and is a fundamentally new representation of evolutionary processes via the language of calculus. **Methods:** For 12 cancer types, somatic missense mutations were obtained through TCGA and annotated with Annovar and Evolutionary Action (EA). Significant (q-value < 0.1) single gene results were identified by comparing the distribution of each gene's EA impact scores to the EA profile of the cancer as a whole and were excluded from further analysis. In order to identify additional cancer drivers for each cancer, the remaining genes were considered on the pathway level using pathways curated by the Reactome database. Each pathway was optimized by leave-one-out analysis to identify the subset of genes in the pathway that maximized bias toward high action mutations. Optimized gene subsets significant after FDR correction and also more significant than at least 95% of the modules obtained from randomly simulated pathways of the same size were considered to contain candidate drivers. **Results:** Computational validation revealed that our candidates were enriched for cancer-related genes, showed independent markers of positive selection in cancer, and were under negative selection in healthy germline exomes. In addition, we experimentally tested 78 of the top novel predictions for head and neck cancer (HNSC) using shRNA screens performed on both HPV+ and HPV- cell lines. In both cell lines, predicted drivers had rankings consistent with their role as drivers and were significantly overrepresented amongst hits from the screen. **Conclusions:** Pathway-EA can identify positive selection acting on groups of genes and can discover novel drivers of phenotype.

65 **CPRIT Grantee Poster Session A**

Modeling LFS-associated Osteosarcoma with TALEN-engineered Mutant TP53 hESCs *An Xu, The University of Texas Health Science Center at Houston; D. Lee*

Introduction: Li-Fraumeni syndrome (LFS, prevalence 1:20,000) is a rare familial cancer predisposition disorder caused by germline mutations in the TP53 tumor suppressor gene. LFS patients have increased incidence of osteosarcoma, one of the most frequent primary non-hematological malignant tumor and the second leading cause of cancer mortality in childhood and adolescence, which provides a perfect model system to study osteosarcoma. Importantly, somatic mutations in TP53 are one of the most frequent alterations in human cancers. **Methods:** (1) We apply TALEN-mediated precise gene editing approach to generate LFS-associated hotspot TP53 mutations in human embryonic stem cell (hESC) H1 line. (2) We differentiate WT and mutant TP53 hESCs into mesenchymal stem cells and then osteoblasts. (3) We perform RNA-seq and ChIP-seq assay to study global gene regulation and p53 genome target genes in WT and TP53 mutant osteoblasts. (4) We utilize bioinformatics approaches to integrate these transcriptomes and ChIP targets datasets to identify the central pathological mechanisms contributing to osteosarcoma development. **Results:** We have engineered multiple hESC H1 clones harboring heterozygous TP53 hotspot mutations, including R175H, G245D, R248W, G249S, R273H, and G282W. All these heterozygous mutations were verified by the genomic DNA sequencing, while the specificities of the TALEN-mediated editing sites were demonstrated by Southern blotting. With these hESC clones, we will differentiate them into osteoblasts and explore the roles of WT and mutant p53 in osteoblastic differentiation and osteosarcoma development. **Conclusions:** The heterozygous mutant TP53 hESC clones can be created by TALEN-mediated precise gene editing methodology. These engineered hESC-derived osteoblasts may provide a comprehensive model for LFS-associated osteosarcoma development. Completion of this study will not only broaden our understanding of pathological mechanism of osteosarcoma, but also set a good example for utilizing hESC in cancer research.

66 **CPRIT Grantee Poster Session B**

SRC-2-mediated Coactivation of Anti-tumorigenic Target Genes Suppresses MYC-induced Liver Cancer *Shruthy Suresh, The University of Texas Southwestern Medical Center; D. Durakoglugil; X. Zhou; B. Zhu; S. Comerford; C. Xing; X. Xie; B. York; K. O'Donnell*

Introduction: Hepatocellular carcinoma (HCC) is the fifth most common solid tumor in the world and the third leading cause of cancer-associated deaths. A transposon mutagenesis screen previously performed in our lab identified mutations that cooperate with MYC to accelerate liver tumorigenesis. This revealed a tumor suppressor role for Steroid Receptor Coactivator 2/Nuclear Receptor Coactivator 2 (Src-2/Ncoa2) in liver cancer. In contrast, SRC-2 was recently shown to promote survival and metastasis in prostate cancer cells, suggesting a tissue-specific and context-dependent role for SRC-2 in tumorigenesis. **Methods:** To definitively test the tumor suppressor activity of SRC-2 in MYC-induced liver cancer in vivo and to further investigate the mechanism(s) through which this coactivator inhibits liver tumorigenesis, we examined the consequences of genetic deletion of Src-2 in a MYC-induced liver cancer model. RNA sequencing, in vivo chromatin immunoprecipitation (ChIP), and functional experiments were performed to identify direct targets that contribute to SRC-2-mediated tumor suppression. **Results:** Src-$2^{-/-}$ mice exhibited a significant enhancement of liver tumor burden compared to Src-$2^{+/+}$ animals. RNA sequencing of liver tumors and in vivo ChIP assays further revealed a set of direct target genes that are bound by SRC-2 and exhibit downregulated expression in Src-$2^{-/-}$ liver tumors. Inhibition of SRC-2 or select SRC-2 target genes including SHP (Small Heterodimer Partner), DKK4 (Dickkopf-4), and CADM4 (Cell Adhesion Molecule 4) accelerated proliferation of human liver cancer cells in vitro and tumorigenesis in vivo, while overexpression of SRC-2 targets, or SRC-2 itself, resulted in tumor suppressive effects. **Conclusions:** Our study demonstrates that genetic inactivation of Src-2 is sufficient to accelerate MYC-mediated liver tumorigenesis. These data suggest that SRC-2 may exhibit oncogenic or tumor suppressor activity depending on the target genes and nuclear receptors that are expressed in distinct tissues and illuminate the mechanisms of tumor suppression by SRC-2 in liver. Moreover, our findings illustrate how combining unbiased forward genetic approaches with cancer genomics and mouse modeling enables functional annotation of genes in human malignancies.

67 **CPRIT Grantee Poster Session A**

Harnessing mitochondrial dysfunction as target for cancer therapy *Natasha Kirienko, Rice University*

Introduction: Under normal conditions, mitochondria undergo constant fusion and fission events that facilitate turnover of damaged material via autophagic degradation (commonly called mitophagy). This process is disrupted in many cancers, leading to an intricate balance. Low-level mitophagic activity decreases ROS and provides raw material for cell division, which can promote tumor survival. Excess mitophagy becomes detrimental and can trigger cell death. Recently, we and others have begun to discover that certain cancers show increased sensitivity to mitophagic activity. For example, sodium selenite (a mitophagic activator) effectively and specifically kills glioblastoma cells in vitro. Recently, we identified two cell lines (MCF7 and LNCaP) that also show sensitivity to mitophagic activation. We're focusing on identifying drugs that activate mitophagy and developing a genetic profile for cancers likely to be susceptible to them. **Methods:** We developed a robust, high-throughput, fragment-based screen to identify small-molecule activators of mitophagy using C. elegans. In parallel, a bioinformatic approach was used to generate a network of genes whose mutation confers sensitivity to mitophagic activation. Hits and the genetic profile will be validated in cancer cell lines. **Results:** Using a high-throughput assay, we screened ~50,000 compounds for novel small molecules that efficiently and specifically activate mitophagy. The screen yielded approximately 150 primary hits. Many belonged to structurally-related clusters. Initial characterization and prioritization of hits is underway. Using C. elegans, we looked for genetic markers indicative of increased sensitivity to mitophagic activators. We assembled a set of ~300 C. elegans genes orthologous to known pro-oncogenes and tumor suppressors (e.g., lin-35/Retinoblastona, cep-1/p53, cul-1/Cullin1, etc.) and genes frequently mutated in cancers (e.g., dpy-6/MUC16/MUC4, unc-68/RYR2, F42H10.3/NEB, etc.). A subset of these genes, when mutated, caused precocious mitophagic activation and increased sensitivity to multiple mitotoxic chemotherapeutics. Importantly, RNAi knockdown of most of these genes did not adversely impact lifespan in the absence of drugs. These genes were used as a seeding set to build and expand a network that provides a mutational signature predicting sensitivity to mitotoxic drugs. **Conclusions:** We are using a multifaceted approach to develop a new kind of cancer treatment. We are building a genetic signature that predicts the sensitivity of patients' cancers to mitophagic activators. We are also optimizing novel mitophagy-inducing chemotherapeutics. Treatments and the genetic signature will be validated and optimized in a panel of cancer cell lines.

68 **CPRIT Grantee Poster Session B**

Targeted deletion of the Aryl Hydrocarbon Receptor in the colonic epithelium promotes the development of aberrant crypt foci in mice fed a high fat diet. *Erika Garcia-Villatoro, Texas A&M University; L. Davidson; E. Callaway; K. Allred; M. Hensel; R. Menon; A. Jayaraman; S. Safe; R. Chapkin; C. Allred*

Introduction: Colorectal cancer is the third leading cause of cancer mortality in the United States. As indicated by a growing body of epidemiological data, obesity and consumption of a high fat diet (HFD) have been strongly associated with an increased risk of colon cancer, as well as an increase in the number and function of intestinal stem cells and loss of tumor suppressor capacity, leading to the formation of colon tumors. Furthermore, regulation of gastrointestinal function and toxicant metabolism is mediated by the aryl hydrocarbon receptor (AhR). AhR is a ligand-activated transcription factor widely expressed in the intestinal epithelium where components of the diet and microbial metabolites can mediate its expression and activation. Studies employing whole animal knockout of AhR have reported an enhanced onset of sporadic colorectal tumors and intestinal inflammation, whereas treatment with AhR-agonists reversed this process. Hence, we hypothesized that the localized loss of AhR exclusively in the intestinal epithelia would enhance the formation of premalignant lesions in the presence of a high-fat diet. **Methods:** Intestinal epithelia-specific AhR knockout mice were fed a HFD (60% kcal from fat) for 23 weeks. Sporadic colon carcinogenesis was induced by six injections of azoxymethane (AOM). Risk of colon cancer was assessed by quantification of premalignant lesions (aberrant crypt foci-ACF) in the colon 17 weeks post AOM treatment. Differential expression of AhR-dependent targets genes and markers known to be involved in obesity and colonic carcinogenesis were measured via RNA-Seq analysis, and proliferation and apoptosis indices were evaluated at the tissue level. Additionally, fecal samples were collected before and after the intervention for targeted metatranscriptomics analysis. **Results:** Lack of AhR in the colonic epithelia significantly increased the number and multiplicity of ACFs compared to wild type control ($P < 0.05$). Proliferation rates were also significantly higher in the AhR knockout group compared to the control ($P < 0.05$). Targeted metabolomics revealed significant differences of known microbial-produced AhR metabolites between genotypes. **Conclusions:** Collectively, these data demonstrate the protective role of AhR against pre-malignant lesions in response to a high fat diet.

69 **CPRIT Grantee Poster Session A**

KLF4 Represses DYRK2 inhibition of Self-renewal and Survival in Leukemia Stem Cells *Chun Shik Park, Baylor College of Medicine; Y. Shen; A. Lewis; T. Chen; D. Lacorazza; M. Puppi*

Introduction: Pharmacological inhibition of BCR-ABL in patients with chronic myeloid leukemia (CML) induces remission but fails to efficiently eradicate self-renewing leukemic stem cells (LSCs). Although CML can be successfully managed with targeted therapy by suppressing BCR-ABL kinase activity with tyrosine kinase inhibitors (TKI), most patients must remain on therapy indefinitely and TKI discontinuation is still considered experimental. Further studies are needed to eradicate the LSC population, a 'CML reservoir' that escapes TKI therapy by developing BCR-ABL-independent mechanisms of self-renewal and survival. Thus, a better understanding of leukemic self-renewal is needed to develop LSC-specific drugs to prevent reactivation during discontinuation of chemotherapy or emergence of chemoresistance. **Methods:** We used loss-of-function mouse model and samples from patients with CML to study the role of KLF4 in CML pathogenesis. **Results:** We discovered that KLF4 differentially regulates self-renewal in normal and leukemic stem cells and uncovered a novel mechanism that could be targeted for therapy. Deletion of the Klf4 gene severely abrogated progression of BCR-ABL(p210)-induced CML by impairing survival and self-renewal of LSCs. Mechanistically, loss-of-KLF4 resulted in elevated DYRK2 levels associated with p53-mediated apoptosis and inhibition of self-renewal through depletion of c-Myc protein by proteasome degradation. Supporting this model, stabilization of DYRK2 protein, by inhibition of the ubiquitin E3 ligase SIAH2 with vitamin K3, induced apoptosis in CML cell lines and primary cells from CML patients. In contrast to $CD34^+$ bone marrow cells from healthy individuals, vitamin K3 inhibited the capacity of $CD34^+$ bone marrow cells from CML patients to generate colonies in methylcellulose. **Conclusions:** Our results suggest that DYRK2 is a dual regulator of self-renewal and survival in CML LSCs and a potential new target for therapy. This work was funded by CPRIT (RP140179).

70 **CPRIT Grantee Poster Session B**

PepQuery enables fast, accurate, and convenient cancer proteogenomic analysis *Bo Wen, Baylor College of Medicine; X. Wang; B. Zhang*

Introduction: Cancer genomics studies have identified a large number of genomic alterations that may lead to novel, cancer-specific protein sequences. Proteins resulted from these genomic alterations are attractive candidates for cancer biomarkers, therapeutic targets, and neoantigens. The leading approach to proteomic validation of genomic alterations is to analyze tandem mass spectrometry (MS/MS) data using customized proteomics databases created from genomics data. Such analysis is time-consuming and requires thorough training and detailed knowledge in proteomics data analysis, leading to a gap between MS/MS data and the cancer genomics community. Here, we present a new search engine PepQuery, which does not require customized databases and allows quick and easy proteomic validation of genomic alterations. **Methods:** PepQuery takes as input a novel peptide, protein, or DNA sequence, or novel genomic features in the VCF, BED, or GTF file format, and the workflow includes five major steps: target peptide sequence preparation and initial filtering, candidate spectra retrieval and peptide-spectrum match scoring, competitive filtering based on reference sequences, statistical evaluation, and competitive filtering based on unrestricted modification searching. **Results:** We demonstrated high sensitivity and specificity of PepQuery in validating completely novel proteins, novel splice junctions, and single amino acid variants. We also showed that PepQuery is effective in removing false identifications reported by previous proteogenomics studies. PepQuery is available as a standalone application as well as a web-application (http://www.pepquery.org) in which the three published Clinical Proteomic Tumor Analysis Consortium datasets on colorectal, breast, and ovarian cancers are directly available. Searching one peptide against about 10 million MS/MS spectra took less than 30 seconds on a computer with 16 threads. **Conclusions:** We have developed PepQuery, a peptide-centric search engine for novel peptide identification and validation. We demonstrated the sensitivity and specificity of PepQuery. We anticipate that PepQuery will significantly increase the usage of MS proteomics data in the genomics community.

71 **CPRIT Grantee Poster Session A**

Codon-level co-occurrences of germline and somatic variants in cancer often lead to incorrect variant annotation and underestimated impact prediction *Young Won Kim, Baylor College of Medicine; A. Koire; J. Wang; P. Katsonis; H. Jin; O. Lichtarge*

Introduction: Cancer cells explore a broad mutational landscape, bringing the possibility that tumor-specific somatic mutations could fall in the same codons as germline single nucleotide variants (SNVs) and leverage their presence to produce substitutions with a larger impact on protein function. While multiple, temporally consecutive mutations to the same codon have in the past been detected in the germline, this phenomenon has not yet been explored in the context of germline-somatic variant co-occurrences during cancer development. When these events occur, current methods for somatic variant calling ignore the germline context and can potentially annotate the resultant amino acid change incorrectly. Since multiple changes to a codon are more likely to result in a stopgain or non-conservative amino acid change, such incorrect annotations are likely to underestimate the true impact of the variants on protein fitness. In this way, tumor-specific variants could be leveraging existing germline variants to produce mutations with larger effects on phenotype. **Methods:** To assess the prevalence and impact of these events, and to identify whether these events undergo positive selection during tumorigenesis, we examined germline context at somatic mutation sites for 1395 patients across four tumor types (breast, skin, colon, and head and neck) representative of different points along the somatic mutation rate spectrum. For each patient, we compared their somatic and germline variant call files and identified in cis somatic variants that were within two nucleotides of a germline variant and predicted to affect the same amino acid as the germline variant in cancer genes. Variant impact was predicted using the Evolutionary Action (EA) method, which predicts impact of missense SNVs on protein fitness resulting from the amino acid substitution. **Results:** We found 392 codon-level co-occurrences between germline and somatic variants, including over a dozen in well-known cancer genes. We found that while these events do not appear to be under obvious positive selection during tumorigenesis, the somatic variant call was not an accurate representation of the protein site in the majority of cases where these events occurred. When the germline contexts of the somatic variants were considered, the amino acid changes and their predicted impacts on protein fitness were significantly larger. **Conclusions:** We conclude that these events often lead to imprecise annotation of somatic variants and underestimated impact prediction on protein fitness.

72 **CPRIT Grantee Poster Session B**

Dissecting the role of PCDH7, an oncogenic cell surface receptor, in non-small cell lung cancer *Kathryn O'Donnell, The University of Texas Southwestern Medical Center; X. Zhou; B. Evers; J. Richardson; R. Hammer*

Introduction: Given the promise of membrane proteins as therapeutic targets in human malignancies, we examined cell-surface receptors that may act as drivers of lung tumorigenesis. We recently reported that PROTOCADHERIN 7 (PCDH7), a transmembrane receptor and member of the Cadherin superfamily, is frequently overexpressed in NSCLC tumors where this event is associated with poor clinical outcome. In human bronchial epithelial cells and NSCLC cell lines, PCDH7 overexpression synergizes with KRAS and EGFR to induce MAPK signaling and tumorigenesis. Conversely, PCDH7 depletion suppresses ERK activation, sensitizes cells to MEK inhibitors, and reduces growth of NSCLC xenografts. These oncogenic effects are associated with the ability of PCDH7 to bind to Protein Phosphatase 2A (PP2A), which directly de-phosphorylates ERK1/2, and the SET oncoprotein, a potent inhibitor of PP2A, thereby suppressing PP2A activity. **Methods:** To further evaluate the role of PCDH7 in lung tumorigenesis in vivo, we generated a Cre-inducible PCDH7 transgenic mouse model. We bred $PCDH7^{LSL}$ mice with $Kras^{LSL\text{-}G12D}$ mice and infected animals with Adeno-Cre to determine whether PCDH7 is sufficient to accelerate $Kras^{LSL\text{-}G12D}$-driven lung tumorigenesis. Animals were sacrificed and analyzed for evidence of larger or more numerous adenomas or development of adenocarcinomas. Conversely, to determine if Pcdh7 is required for lung tumorigenesis in $Kras^{LSL\text{-}G12D}$;Tp53 fl/fl mice, we employed a recently described in vivo somatic genome editing approach to rapidly interrogate PCDH7 function in $Kras^{LSL\text{-}G12D}$;Tp53 fl/fl mice. **Results:** We demonstrated that PCDH7 increases phospho-ERK1/2 and accelerates mutant Kras-mediated tumorigenesis in an autochthonous mouse model. Moreover, inhibition of PCDH7 function using somatic gene editing reduced lung tumor burden and prolonged survival of $Kras^{LSL\text{-}G12D}$; Tp53 fl/fl mice. We also observed a significant decrease in phospho-ERK1/2 in Pcdh7 knockout tumors. **Conclusions:** These findings establish a critical oncogenic function for PCDH7 in vivo and demonstrate that PCDH7 is an actionable therapeutic target in NSCLC. Moreover, this work uncovers a new mechanism through which PCDH7 leads to hyperactivation of the MAPK pathway, a critical driver of lung tumorigenesis. Future studies will examine the extent to which PCDH7 inhibition modulates therapeutic responses in NSCLC cells and animal models.

73 **CPRIT Grantee Poster Session A**

Targeting Protein Deglycosylation as a Novel Anticancer Approach *Victor Lin, University of North Texas Health Science Center at Fort Worth; A. Zolekar; Y. Wang*

Introduction: Proteostasis is an intricate balance between the synthesis and degradation of proteins and is a tightly regulated process in all eukaryotic cells. Interestingly, proteasome inhibitors like bortezomib and carfilzomib have shown that targeting protein quality control and homeostasis is a useful approach to eliminate cancer cells. This suggests that proteasome-mediated protein degradation, one of the well-known molecular components involved in proteostasis, is crucial for cancer cells to sustain their viability and oncogenic signaling. Our group has extended our initial developmental biology studies of a genetic disease to studying the same gene involvement in cancer, and have discovered how this novel target, a glycosidase involved in proteasome-mediated protein degradation, may play a role in cancer formation and progression. **Methods:** Initially, global gene expression studies were performed to identify differentially expressed genes amongst several sets of cancer cell lines and their normal cell type counterparts. Utilizing Western Blotting we explored the expression of a differentially expressed protein in a multitude of cancer cell types, including pancreatic cancer, breast cancer, and melanoma, then evaluated its role in cancer biology for those cancer types using several molecular approaches like short hairpin RNAs (shRNA) to knockdown the gene, Western Blotting to determine signaling pathways, and flow cytometry and MTT cell proliferation assays to assess the enzyme's role in cell proliferation and cell death. **Results:** From global gene expression studies and protein analyses, we identified that there is a dramatic difference in expression patterns of this glycosidase gene and protein between normal cells and their cancer counterparts in pancreatic cancer, breast cancer, and melanoma. With focus on melanoma, short hairpin RNA knockdown studies have shown a significant increase in apoptosis for multiple melanoma cell lines, regardless of mutations in RAS or BRAF, while having a negligible effect on normal cells (e.g. human fibroblasts and melanocytes). From our data, we have learned that apoptosis triggered by targeting this particular glycosidase in melanoma cells is mediated by pleiotropic anticancer responses. **Conclusions:** In future studies, as we continue to study the association between this glycosidase and the death or survival of different types of cancer cells, we will pursue the design and synthesis of small molecules against this enzyme, then further test this protein deglycosylation route as a promising target for cancer therapy.

74 **CPRIT Grantee Poster Session B**

Nuclear relocalization of mutant NPM1 induces downregulation of HOX/MEIS1, terminal differentiation, and cell cycle arrest *Michael Gundry, Baylor College of Medicine; L. Brunetti; H. Sheppard; A. Guzman; M. Goodell*

Introduction: NPM1 mutated acute myeloid leukemia (AML) is a distinct entity in the WHO classification of hematopoietic cancers. It displays a specific phenotype characterized by favorable prognosis and upregulation of HOX cluster genes. NPM1 is a multifunctional nucleolar chaperone. All the mutations in NPM1 described so far in result in cytoplasmic protein localization (NPM1c) through the acquisition of a nuclear export signal (NES) at the C-terminus. The role of NPM1 in leukemogenesis is still a matter of debate and there is no direct proof that cytoplasmic localization of mutant NPM1 is necessary for maintenance of leukemia. **Methods:** We recently developed a CRISPR-Cas protocol for highly efficient gene editing in hematopoietic cells. Using an sgRNA spanning the insertion site (NPM1c sgRNA), we aimed to specifically introduce indels adjacent to the mutation, alter the reading frame and disrupt the C-terminal NES. We transfected NPM1 mutA cells with NPM1c sgRNA and assessed molecular and cellular phenotypes. **Results:** After transfection of two NPM1 mutated cell lines (OCI-AML3 and IMS-M2) with NPM1c sgRNA, we found that the NPM1mutA allele was edited in 70-90% of cells, resulting in nuclear re-localization of the mutant protein. Nuclear re-localization was followed by significant impairment of cell growth (3.7-4 fold decrease), colony forming ability (16-20 fold reduction in colonies) and engraftment in xenograft models (significant loss of indels at NPM1mutA allele in engrafted cells). The observed immunophenotype and growth defects were preceded by significant downregulation (5 fold) of HOXA genes, HOXB genes and MEIS1. Chromatin profiling revealed that the

mechanism of downregulation appeared to involve loss of active promoters and enhancers, rather than the deposition of repressive chromatin marks. Precise editing of NPM1 mutant cell lines using HDR revealed that cell growth and differentiation levels were inversely proportional to the mutant NPM1 nuclear/cytoplasmic ratio. We reasoned that the dependency of NPM1-mutated cells on the cytoplasmic localization of NPM1c would sensitize them to nuclear export inhibitors. Indeed, treatment of OCI-AML3 cells with 50nM Selinexor (KPT-330) induced both morphologic and immunophenotypic differentiation beginning as early as day 5. Furthermore, the transcriptional and chromatin changes phenocopied those observed with CRISPR-targeting of the mutant allele. **Conclusions:** By achieving nuclear re-localization of mutant NPM1, we demonstrated that cytoplasmic localization of NPM1 is necessary for maintenance of the leukemic phenotype. Drugs promoting mutant NPM1 nuclear localization are attractive candidates for clinical success in NPM1-mutated AML.

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75 **CPRIT Grantee**
Poster Session A

TRIM44 in quiescent multiple myeloma cells stabilizes HIF-1a via deubiquitination for niche control *Nami McCarty, The University of Texas Health Science Center at Houston; Z. Chen; T. Lin*

Introduction: Multiple myeloma (MM) is an incurable B cell malignancy characterized by the proliferation of plasma cells within the bone marrow (BM) microenvironment. Despite progress in the treatment of MM, including the use of high-dose chemotherapy and autologous stem cell transplantation, a considerable proportion of patients are refractory to all therapies. This resistance is related to the molecular genetic heterogeneity in the MM cells as well as to the contributions of the BM, which is one of the key determinants for treatment outcome. **Methods:** Our previous studies using PKH67 fluorescent tracers showed that MM heterogeneity is correlated with the presence of stem-like cancer cells (Chen et al., Blood, cover). This study was the first to demonstrate a quiescent MM cell niche and the effects of functional interactions between quiescent MM cells and the microenvironment on MM growth and progression. To delineate the molecular pathways involved in PKH+ MM cell functions, we performed gene profiling analyses. DNA profiling analyses of the PKH+ and PKH-CD138+ cells revealed a novel gene called the tripartite motif containing 44 (TRIM44). **Results:** A search of the integrated cancer microarray database (Oncomine) further revealed that TRIM44 gene expression was significantly upregulated in MM compared to normal or monoclonal gammopathy of undetermined significance (MGUS, a precursor stage of MM), suggesting that TRIM44 expression may play an oncogenic role, contributing to MM progression. TRIM44 silencing, using CRISPR-CAS9 led to MM cell death, indicating the critical role of TRIM44 in MM cell survival. TRIM44 up-regulation, using lentivirus-mediated targeting, rendered MM cells to be maintained in a quiescent status. This proliferative status was reversible when TRIM44 was down-regulated. TRIM44 over-expressing ($TRIM44^{OE}$) MM cells were better equipped to compete with HSCs for niche support, which further increased their localization to the BM. Increased $TRIM44^{OE}$ MM cell targeting suppressed HSC differentiation into leukocytes. Despite its role in promoting quiescence, TRIM44 up-regulation in MM increased bone destruction in xenograft mice, which resembles the human MM pathology. TRIM44-induced MM cell survival within the BM was partly due to hypoxia-inducible factor-1a (HIF-1a) stabilization by TRIM44, which decreases HIF-1a polyubiquitination and degradation by its deubiquitinase activity. **Conclusions:** Our data unveil novel roles of quiescent MM cells in MM pathology and its relation to MM survival within a hypoxic niche. In addition, our data further support that TRIM44 plays a unique role in promoting the survival of quiescent MM cells in the BM by stabilizing HIF-1a.

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76 **CPRIT Grantee**
Poster Session B

Enhancer invasion shapes MYCN dependent transcriptional amplification in neuroblastoma *Charles Lin, Baylor College of Medicine*

Introduction: Amplification of the oncogenic basic helix-loop-helix transcription factor MYCN is a defining genetic feature of high-risk neuroblastoma. Despite clear functional information defining the oncogenic role of MYCN in this disease, the effect of MYCN on genome structure and function remains incompletely understood. **Methods:** To first profile MYCN downregulation from oncogenic levels, we experimentally selected a panel of human neuroblastoma cell lines with and without MYCN amplification that express varying levels of MYCN, and employed the well-characterized tet-off MYCN SHEP-21N cell line model. Additionally, we explored the consequences of MYCN induction by engineering a tet-on MYCN model in the parental SHEP neuroblastoma cell line grown for multiple passages in a low MYCN state. Across MYCN-amplified neuroblastoma lines, we used chromatin immunoprecipitation coupled to high-throughput sequencing (ChIP-seq) to generate a consensus genome-wide map of ~10,000 regions that exhibit strong and consistent MYCN occupancy. **Results:** We find that at oncogenic levels, MYCN associates with E-box (CANNTG) binding motifs in an affinity dependent manner, binding to canonical (CACGTG) E-boxes at promoters and invading abundant weaker clustered motifs at enhancers. Such enhancer invasion by MYCN shapes transcriptional amplification, notably at the most highly occupied MYCN target genes which are most sensitive to perturbation and are linked to poor patient survival. At invaded enhancers, we identify the enhancer-specifying transcription factor TWIST1 as an oncogenic collaborator and dependency to MYCN in neuroblastoma. Loss of MYCN globally collapses chromatin acetylation and transcription, consistent with prior descriptions of the related MYC oncoprotein as an amplifier of gene expression. **Conclusions:** These data argue a central role for enhancers in predicating the often highly tumor specific "MYC target gene signatures" and identify disruption of the MYCN enhancer regulatory axis as a promising therapeutic strategy to counteract oncogenic transcription.

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77 **CPRIT Grantee**
Poster Session A

Genome-wide mapping of DNA double-strand breaks in Escherichia coli *Devon Fitzgerald, Baylor College of Medicine; S. Rosenberg*

Introduction: Cancer is an evolutionary process fueled by genome instability. DNA double strand breaks (DSBs) are highly toxic to all organisms, and inaccurate repair of DSBs can lead to a variety of genome alterations. In Escherichia coli, starvation stress triggers transient genome instability by decreasing the fidelity of DNA double-strand break (DSB) repair. Importantly, stress-induced mutagenic break repair (MBR) generates point mutations and gross-chromosomal rearrangements near repaired DSBs and can generate clusters of closely-spaced mutations. Similar MBR mechanisms have been reported in many cell types, including human cancer cells. Kataegis (localized mutation "storms") in cancer genomes, and other clustered mutations are proposed to originate from MBR-like mechanisms, and probably occur close to the original DSB location. Thus, the genomic distribution of spontaneous DSBs may drive local mutation rates and alter the repertoire of mutations from which novel phenotypes can emerge. However, mechanistic drivers of spontaneous DSB formation in cells and their possible localization in genomes are poorly understood. **Methods:** We have developed and validated a method to map the genomic distribution of DSBs. We are using ChIP-seq to map the genome-wide binding profile of Gam, a specific DSB-binding protein from bacteriophage Mu. We call this novel technique Gam-seq. **Results:** First, we show that Gam-seq enriches for DNA flanking an endonuclease-induced DSB. Next, we used Gam-seq to detect spontaneous DSBs in the E. coli genome. We find substantial regional differences in the relative frequency of spontaneous DSBs—DSB signal varies approximately 10-fold between different genomic regions, with relative hot- and cold-spots ranging in size from a few hundred to a few thousand basepairs. DSB signal correlates with gene orientation and transcription level. **Conclusions:** Preliminary results suggest that spontaneous DSBs are non-randomly distributed within the E. coli genome. We are currently using Gam-seq to identify mechanisms of DSB formation and localization in E. coli, as a model for similar processes in cancer cells.

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78 **CPRIT Grantee**
Poster Session A

Structures of human double-stranded DNA break repair complexes *David Taylor, The University of Texas at Austin; Y. Zhou; A. Davis; T. Paull*

Introduction: Genomes provide the blueprint for cells to function. The cell has evolved elegant pathways to repair damaged genomic DNA, and defects in these DNA-repair machines lead to genomic instability and cancer. Double-stranded breaks are the most deleterious types of DNA damage. These breaks occur frequently during DNA replication and can be promoted by exogenous DNA-damage inducing factors. These lesions can be repaired via non-homologous end joining or homologous recombination. The Mre11–Rad50–Nbs1 (MRN) complex is central to eukaryotic double-stranded break repair. MRN senses these breaks by binding DNA ends with high affinity. MRN then activates the DNA damage response. Ku70/80 competes for DNA ends with MRN and recruits the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to sites of damage for non-homologous end joining (NHEJ). Defects in MRN and end joining repair pathway components are linked to cancers of the breast, lung, colon, and skin. Uncovering the molecular mechanism of double-strand break repair is necessary to understand the biology of cancer and to discover new paradigms for cancer therapies. **Methods:** We used cryo-electron microscopy to directly visualize intermediate states in DNA double-stranded break repair in humans. **Results:** We have performed negative stain EM on MRN and shown it exists in a 'closed' state. Additionally, Initial class averages show MRN is stabilized by DNA binding and contain additional density for the Nbs1 protein. Excitingly, we have obtained class averages of a DNA-PKcs-Ku70/80 complex that clearly

show both the DNA-PKcs and Ku components. **Conclusions:** We are currently in the first-year of our work funded by a CPRIT Scholar award to David Taylor. These initial results suggest that high-resolution structural information will be obtained for these two complexes. Structures of these intermediates will provide insights into MRN architecture and site-specific recognition of double-stranded breaks. Our studies on the dynamics of how DNA-PKcs-Ku70/80 removes MRN and how these complexes can undergo concerted structural rearrangements to bridge the two DNA ends for repair. These structural snapshots will provide the mechanistic basis for NHEJ.

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79 **CPRIT Grantee**
Poster Session A

Dominant-negative SMARCA4 (BRG1) mutations induce convergent effects on the enhancer accessibility landscape *H. Courtney Hodges, Baylor College of Medicine*

Introduction: Mutation of SMARCA4 (BRG1), the ATPase of BAF (mSWI/SNF) and PBAF complexes, contributes to a range of malignancies and neurologic disorders. Here we investigated the effects of dominant-negative SMARCA4 disease mutations on BAF complex dynamics and genome-wide accessibility. **Methods:** We used integrative techniques, including bioinformatic analysis of tumor sequencing studies, structural biology, epigenomics, and live-cell imaging to interrogate the altered mechanisms induced by heterozygous missense mutations of SMARCA4. **Results:** By constructing a homology model of SMARCA4 based on crystal structures of related Snf2-like ATPases, we discovered that cancer mutations target conserved, functionally important surfaces and disrupt key steps in the mechanochemical cycle of remodeling. Despite distinct modes of inactivation, heterozygous expression of mutants led to convergent changes of the open chromatin landscape at thousands of sites across the genome in mESCs. To our surprise, loss of accessibility did not occur at sites that accumulated PRC1, but was enriched at active enhancers, where it coincided with loss of H3K27ac but not H3K4me1. Heterozygous SMARCA4 mutation altered accessibility at hundreds of sites identified as superenhancers in many different tissue types. Losses were especially enriched in transcriptionally active "A compartments." Analysis of gene expression using RNA-seq showed increased expression of Myc and its target genes. **Conclusions:** Together, our data suggest that disruption of enhancer accessibility is likely to be a key source of altered function in SMARCA4-mutated disorders in a wide variety of tissues.

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80 **CPRIT Grantee**
Poster Session B

Evaluating transcription factor networks as targets for the treatment of neuroendocrine tumors *Karine Pozo, The University of Texas Southwestern Medical Center; R. Kollipara; J. Minna; A. Gazdar; J. Johnson*

Introduction: Achaete-scute homolog 1 (ASCL1) is a transcription factor that is highly expressed in neuroendocrine tumors (NETs) including, gastrointestinal carcinoids, medullary thyroid carcinoma and neuroendocrine prostate cancer. It is expressed in most but not all small cell lung cancer (SCLC) tumors and cell lines. ASCL1 expression is particularly critical for the proliferation of some gastrointestinal carcinoids and SCLCs. Inhibiting ASCL1 transcriptional activity may thus be a valid therapeutic strategy for these NETs. However transcription factors (TFs) have been historically difficult to target. Given that TFs belong to complex regulatory networks, we propose to identify and target multiple components within an ASCL1-transcriptional network rather than ASCL1 alone. We have previously detected ASCL1-bound genomic regions associated with the active chromatin epigenetic mark, H3K27Ac in SCLC cells. Here we report the identification of an ASCL1-containing transcriptional network in SCLC cells and evaluate its targeting by the transcriptional inhibitor, mithramycin. **Methods:** Chromatin immunoprecipitation followed by high-throughput sequencing (ChIP-seq) were conducted by immunoprecipitating chromatin from NCI-H2107 and NCI-H69 SCLCs ($5X10^7$ cells) with10 mg H3K27Ac antibodies (Abcam-Ab4729). ChIP-seq libraries were sequenced on an Illumina High-Seq2000. siRNA transfections, immunoblotting and MTS-cell proliferation assays were conducted using standard procedures. **Results:** 82 overlapping TF genes, including lineage-specific TF genes for, ASCL1, Forkhead box protein A2 (FOXA2) and Nuclear factor 1 B-type (NFIB), were found associated with the active chromatin epigenetic marks H3K27Ac in SCLC cell lines. This suggests ASCL1, FOXA2 and NFIB may belong to the same transcriptional network. siRNA-mediated knock-down of ASCL1 leads to decreased FOXA2 levels but it has no effect on NFIB levels, implicating ASCL1 as a transcriptional regulator of FOXA2 but not NFIB. Mithramycin stops cell proliferation and reduces ASCL1, FOXA2 but not NFIB protein levels. **Conclusions:** Our studies identify the beginning of a transcriptional network necessary for SCLC proliferation in which ASCL1 regulates FOXA2. Targeting multiple TFs within a network with mithramycin can stop cell proliferation and as such suggests a therapeutic strategy for NETs. Because of the importance of NFIB in mediating metastatic behavior of SCLC, these data indicate approaches other than targeting ASCL1 and use of mithramycin will be needed to target NFIB.

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81 **CPRIT Grantee**
Poster Session A

Therapy-induced apoptosis stimulates cancer cell proliferation via WNT-containing apoptotic bodies *Stephen Wallin, The University of Texas M.D. Anderson Cancer Center; G. Eisenhoffer; A. Brown*

Introduction: The ability to prevent tumor repopulation after anticancer treatments has been a significant barrier to reducing morbidity and mortality of malignant tumors. Standard chemotherapeutic agents induce the death of rapidly dividing cells. Dying cells can provide instructive cues that influence the behaviors of surrounding cells, yet the mechanism for this communication between apoptotic and neighboring cells is not well understood. Here we show that treatment with chemotherapeutics promotes caspase-dependent production of WNT-containing apoptotic bodies that stimulate cancer cell proliferation. **Methods:** We used live imaging and fixed tissue analysis to characterize apoptosis of MDA-MB231 breast cancer cells after exposure to different chemotherapeutics. Transcript levels for WNT pathway members were analyzed by quantitative real time PCR. Protein levels and localization within the apoptotic cells were determined by immunofluorescence confocal microscopy. Breast cancer-derived apoptotic bodies were isolated by differential ultracentrifugation and confirmed using flow cytometry and transmission electron microscopy. Time lapse microscopy was used to follow fluorescently labeled apoptotic bodies after addition to healthy cultures. **Results:** Time lapse microscopy of human breast cancer cells after treatment different chemotherapeutic agents revealed highly regulated, distinct morphological processes during apoptosis and the subsequent production of apoptotic bodies. We identified specific WNT molecules induced in dying cells that become enriched in the apoptotic bodies. Purification and addition of the breast cancer–derived apoptotic bodies to healthy cultures stimulated proliferation. Further, live imaging revealed cancer cells that engulf the apoptotic bodies go on to divide. Inhibition of either apoptosis or WNT signaling eliminated the apoptosis-induced cell division. **Conclusions:** This study presents a novel mechanism by which dying cancer cells communicate with their healthy neighbors after chemotherapy treatment. We have identified unique mitogenic proteins induced by damage in apoptotic cells, and characterized a novel mechanism by which apoptotic cells transfer signaling molecules and induce localized proliferation in neighboring cells. Thus, apoptotic-body mediated regrowth may provide a possible mechanism for tumor repopulation and treatment resistance.

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82 **CPRIT Grantee**
Poster Session B

Chemical induction of Krüppel-Like Factor 4 shows anti-leukemic properties in Acute Myeloid Leukemia *Andrew Lewis, Baylor College of Medicine; C. Park; A. Cooper; X. Peng; D. Lacorazza*

Introduction: Acute Myeloid Leukemia (AML) continues to evade effective therapeutic advances indicated by the lack of novel treatment approaches over the past 30 years. Transcript level repression of KLF4 in AML patients across subtype classifications and genetic abnormalities suggests potential tumor suppressor function. Our group has also demonstrated the importance of this gene in restraining cell cycle progression of leukemic T-cells by preventing the activation of kinase pathways. We hypothesized that KLF4 inhibits cell cycle progression and survival in human AML cells. **Methods:** Using human AML cell lines, we determined KLF4 protein, then by genetic and chemical methods examined the effect of restoring KLF4 expression. **Results:** In order to test this hypothesis, we began by detecting basal KLF4 protein levels in a panel of 6 AML cell lines. NB4, MonoMac-6, SKM1, and NOMO-1 cells had non-detectable KLF4 protein levels when compared to lymphoblastoid cells used as non-leukemic controls. In order to study pharmacological activation of KLF4, we utilized the chemical compound APTO-253, which had previously been reported to induce KLF4 expression in human colon cancer cells. Immunoblot analysis confirmed induction of KLF4 in 3 AML cell lines following treatment with this compound, but not in K562 cells. In the panel of AML cell lines, APTO-253 treatment resulted in apoptosis in 5 out of 6 AML cell lines with IC_{50} values ranging from 1 to 5 μM at 24 hours, while treatment did not significantly induce apoptosis in non-AML control cell line K562 at doses up to 40 μM. Analysis of DNA content by propidium iodide staining revealed G1 cell cycle arrest and Annexin V staining revealed induction of apoptosis. In order to account for potential effects which were not the result of KLF4 induction, we transduced NB4 cells with a retroviral vector driving ectopic expression of KLF4 or a control empty retroviral vector. KLF4 overexpressing cells exhibited drastic apoptosis and G1 cell cycle arrest, similar to results observed in the presence of APTO-253. To test whether KLF4 expression might cooperate with chemotherapy agents via its known regulation of apoptotic pathways, we treated cells

with a combination of APTO-253 and the chemotherapeutic compound daunorubicin. Treatment with APTO-253, however, did not enhance cytotoxicity of daunorubicin in tested AML cell lines. **Conclusions:** Altogether, chemical and genetic restoration of KLF4 expression results in selective cytotoxicity, apoptosis, and cell cycle arrest in AML cells. This finding supports the possibility of therapeutic approaches for AML involving KLF4 induction.

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83 **CPRIT Grantee Poster Session A**

Optimization of Gene Editing Technology for Generation of DEAR1 Knockout in Human Breast Cancer Cells *Nanyue Chen, The University of Texas M.D. Anderson Cancer Center; Z. Huang; U. Le; S. Balasenthil; C. Evers; D. Duose; A. Killary*

Introduction: Ductal carcinoma in situ (DCIS) is an early, preinvasive form of breast cancer which, if untreated, progresses to invasive ductal carcinoma (IDC) in approximately 40% of cases. Predictive and prognostic markers are critically needed to stratify DCIS with a heightened risk of progression to IDC for which more aggressive surveillance and treatment might be warranted, as well as individuals with favorable prognosis, who might be spared rigorous therapeutic regimens. Our laboratory has discovered a novel tumor suppressor DEAR1 (Ductal Epithelium Associated Ring Chromosome 1, annotated as TRIM62). DEAR1 is mutated and homozygously deleted in breast cancer and is downregulated in DCIS. We recently found that DEAR1 functions as a negative regulator of TGFbeta signal transduction by binding to and ubiquitinating SMAD3, the major effector of TGFbeta-mediated Epithelial-Mesenchymal Transition (EMT). Therefore, the mutation or loss of function of DEAR1 may play an important role in DCIS to IDC progression. To investigate if loss of DEAR1 contributes to progression from DCIS to IDC, we developed a strategy for gene editing to knockout or edit mutations in DEAR1 in two different breast model systems. **Methods:** Two gene editing technologies, i.e. TALENS and CRISPR-mediated (Cas) systems were developed to knockout (KO) DEAR1 alleles in the breast cancer cell line DCIS.COM and in the immortalized human mammary cell line 76N-E6. **Results:** Exhaustive studies were performed to develop DEAR1 KO clones in DCIS.COM and 76N-E6 cells using both CRISPR and Talens technology. We further validated these KO clones at the DNA and RNA level. At the DNA level, genotyping verified editing and digital droplet PCR confirmed that there is no wild type (WT) DEAR1 sequence in tested KO clone. At the mRNA level: we performed regular RT-PCR, TA cloning and Sanger sequencing and verified the INDEL of most KO clones. Furthermore, we performed RACE-Smart technique and excluded any trace of WT sequence in RNA of KO clones. However, DEAR1 protein expression was still present by westerns despite convincing data at the genotypic and RNA level. We are using 2D-DIGE and mass-spectrometry assays to identify proteins of similar size as DEAR1 that might be recognized by our antibody as well as we are generating a monoclonal antibody for DEAR1. **Conclusions:** Extensive characterization of DEAR1 KO at the DNA and RNA confirm that we have successfully knocked out DEAR1. Experiments are underway to definitively determine whether the DEAR1 antibody recognizes additional proteins besides DEAR1.

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84 **CPRIT Grantee Poster Session B**

Hyperspectral expansion microscopy using SERS nanoparticles *Camille Artur, University of Houston; T. Womack; F. Zhao; J. Eriksen; D. Mayerich; W. Shih*

Introduction: Newly developed expansion microscopy techniques offer a dramatically different approach to super-resolution biomedical imaging by physically expanding tissue such that spatial features smaller than the diffraction limit can be resolved on a conventional fluorescence microscope. With minimal changes to well established immunostaining protocols, tissue sections go through an isotropic three-dimensional expansion which preserves their structural information. This technique nevertheless suffers from significant signal loss caused by a reduced number of labels per focal volume, and is inherently limited in terms of multiplexing. We propose the use of functionalized gold Raman tags with a well-defined spectral signature as a remedy to these limitations, allowing hence fast, bright, and spectrally resolved expansion microscopy imaging. **Methods:** Conjugated extrinsic SERS labels consist of 10nm-13nm gold nanorods labeled with a monolayer of Raman active near-infrared dyes, protected by a passivation layer and further conjugated with streptavidin. 10μm mouse brain sections are stained against the NeuN antibody, biotinylated secondary and the SERS labels. Slices are embedded in a polyelectrolytes hydrogel which can swell by a factor of 5 upon addition of water. Tissue sections are imaged pre- and post-expansion on a dark-field microscope then on a home built line-scan Raman microspectrometer with 785 nm excitation. **Results:** The SERS tags prove their effectiveness and specificity in labelling NeuN antigens on the brain sections pre- and post-expansion. Unlike traditional fluorophores, the staining of neurons is visible on conventional microscopes. Pre-expansion, the stained structures are purple in brightfield and yellow-red under darkfield conditions. After tissue expansion, the gels are transparent but the SERS particles and the structures they label are clearly visible in darkfield. Hyperspectral images are obtained by mapping the intensity of the signature Raman peaks of the labels. Due to the plasmonic resonance of the gold nanoparticles, the Raman intensity of the adsorbed dyes is greatly enhanced. It allows very short integration times and yields high contrast with no fluorescence background. Furthermore, the SERS labels are totally immune to photobleaching and the staining is stable for months. **Conclusions:** This technique suggests that expansion microscopy can theoretically accommodate hyperspectral techniques, opening the door to super-multiplex imaging, which recent research suggests can achieve upwards of 20 simultaneous molecular components.

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85 **CPRIT Grantee Poster Session A**

The role of Ductal Epithelium Associated Ring Chromosome 1 (DEAR1) in the regulation of stem/progenitor cell properties *Mimi Le, The University of Texas M.D. Anderson Cancer Center; N. Chen; S. Balasenthil; A. Killary*

Introduction: Breast cancer is the most commonly diagnosed cancer and second-leading cause of cancer-related deaths in women in America. A quarter of lesions diagnosed annually are ductal carcinoma in situ (DCIS), one of the earliest pre-invasive forms of invasive ductal carcinoma (IDC). Without therapeutic intervention, 30-40% of DCIS cases can progress to IDC. Understanding the mechanisms regulating progression from DCIS to IDC would help identify biomarkers to stratify DCIS patients at higher risk of progression or recurrence. Cumulative literature suggests the earliest phase of dissemination from the primary tumor is driven by the epithelial-mesenchymal transition (EMT) program. DEAR1 is a tumor suppressor gene which is mutated, undergoes loss of heterozygosity in breast cancer, and is downregulated in DCIS lesions. DEAR1 also regulates acinar morphogenesis and cell polarity, and is a negative regulator of TGF-beta-driven EMT by binding to and ubiquitinating SMAD3, thereby limiting the amount of SMAD3 available to activate an EMT signature. Overexpression of EMT master regulators, or exposure to TGF-beta in immortalized human mammary epithelial cells (HMECs), results in mammosphere formation and breast stem cell markers, thus linking the EMT process to acquisition of stem cell characteristics. **Methods:** Stable lentiviral shRNA knockdown, in vitro mammosphere assay, cytospin, immunofluorescence, western blot analysis, and real-time quantitative PCR were performed. **Results:** DEAR1 knockdown in immortal HMECs resulted in a significant enhancement of primary mammosphere formation and growth compared to controls, suggesting that DEAR1 may regulate stem/progenitor cell properties; this effect was greater when cells were exposed to TGF-beta. To determine if DEAR1 regulates stem cell properties through regulation of SMAD3 levels, DEAR1-SMAD3 double knockdown clones were examined for mammosphere formation. Results indicated fewer mammospheres in double knockdown clones, but only in the presence of TGF-beta, suggesting that the mammosphere phenotype is partially dependent on the TGF-beta-SMAD3 pathway. HMEC mammospheres express higher levels of stem cell marker aldehyde dehydrogenase (ALDH1), and co-express luminal and basal cytokeratins, suggesting bipotential capacity. We also observed upregulation of SNAI2 and ZEB1, master EMT and stem cell regulators, in DEAR1 knockdown HMECs. **Conclusions:** Loss of the tumor suppressor/polarity regulator DEAR1 promotes stem cell properties in part through the DEAR1-TGF-beta-SMAD3 axis. These mechanisms governing acquisition of the stem cell properties may contribute to understanding how DCIS progress to IDC.

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86 **Poster Session B**

Role of the perinuclear protein translation in cancer cell chemo-resistance *Tattym Shaiken, Peri-Nuc Labs LLC*

Introduction: Life of eukaryotic cells is associated with compartmentalization of essential functions. One compartment about which little is known is the perinuclear region or perinucleus. The perinuclear region is surrounded by a wall composed of intermediate filaments that encompasses the nucleus forming the perinucleus. The perinucleus contains ribosomes and regulators of protein biosynthesis. Most protein biosynthesis takes place in the cytoplasm and involves “floating”- and ER-bound ribosomes. Nuclear membrane-bound ribosomes located in the perinuclear space are considered as cytoplasmic ribosomes. **Methods:** We have isolated perinuclear ribosomes and investigated regulation of perinuclear protein translation. **Results:** Eukaryotic initiation factor 4E3 (eIF4E3) cap binding protein that does not bind to 4E binding proteins (4E-BP proteins), initiates perinuclear protein synthesis when eIF4E1-dependent protein synthesis is inhibited. Inhibition of eIF4E1-dependent protein translation by mechanistic Target of Rapamycin (mTOR) kinase inhibitor increased the level of eIF4E3 in the cytoplasm producing a slow-

moving band of eIF4E3 that appeared in the perinucleus. Perinuclear protein translation primarily involves light polysomes for protein synthesis. Perinuclear protein translation correlated with the ribosome assembly in the nucleolus that was manifested as nucleolar hypertrophy. Suppression of other cytoplasmic signaling pathways also result in upregulated perinuclear protein synthesis, translational reprogramming and nucleolar hypertrophy. Perinuclear ribosomes appear to be separate from the cytoplasmic translational machinery as the keratin-plectin cytoarchitecture holds them in the proximity of the nucleus. **Conclusions:** Our results indicate that nutrient sensing protein synthesis and cell survival protein translation can be separated and it is mTOR-independent. Perinuclear protein translation is essential for ribosome biogenesis in stress. This newly recognized secondary pathway, perinuclear protein translation, thus makes cancer cells less dependent on the cytoplasmic signaling pathways and can support sustained proteome imbalance. Many chemotherapy agents directly or indirectly are designed to downregulate protein synthesis. In stressful conditions, cells utilize perinuclear protein synthesis which remains active even when cytoplasmic protein synthesis is reduced or inhibited. Cancer cells can also use glycolysis as their primary energy source for the perinuclear protein translation (the Warburg effect). Suppression of the perinuclear protein translation is a new target that eliminates an escape mechanism that allows cancer cells to become resistant to important chemotherapy agents.

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87 **Poster Session A**

Structural and molecular mechanisms of Ca2+-mediated activation of estrogen receptor-alpha by calmodulin *Yonghong Zhang, The University of Texas Rio Grande Valley; D. Sacks; J. Ames*

Introduction: Estrogen receptor alpha (ER-a) is a nuclear hormone receptor that controls selected genes, regulates proliferation and differentiation of target tissues (e.g. breast) implicated in breast cancer. Binding of estrogen hormone to ER-a induces receptor homodimerization and activates its transcriptional function. Calcium-dependent activation of ER-a is also mediated by calmodulin (CaM) via the ubiquitin-proteasome pathway. The Ca2+-induced binding of CaM to ER-a has important implications for breast cancer. Despite a wealth of information for both ER-a and CaM, the detailed molecular mechanisms underlying this regulation remain to be elucidated. A clear molecular picture of calcium-dependent ER-a signaling is required to develop better therapeutic modalities. **Methods:** This work takes a multi-disciplinary approach incorporating NMR structural biology techniques for 3D structure determination of ER-a/CaM (2:1) complex, in parallel with the detailed analysis of ER-a transcriptional activity in human cells transfected with separate lobes of CaM to provide in vivo evidence that bolsters the structure. **Results:** The structure of Ca2+/CaM bound to two molecules of ER-a (residue 287-305) has been determined by NMR. The two lobes of CaM bind to the same site on two separate ER-a molecules (residues 292, 296, 299, 302, and 303) to form a 1:2 complex and stabilizes ER-a dimerization. The formation of salt bridge between exposed glutamate residues in CaM and key lysine residues in ER-a (Lys-299, Lys-302, and Lys-303) is likely to prevent ubiquitination at these sites and inhibits degradation of ER-a. Transfection of cells with full-length CaM slightly increased the ability of estrogen to enhance transcriptional activation by ER-a of endogenous estrogen-responsive genes. By contrast, expression of either the N- or C-lobe of CaM abrogated estrogen-stimulated transcription of the estrogen responsive genes pS2 and progesterone receptor. **Conclusions:** Ca2+/CaM-induced dimerization of ER-a is required for estrogen-stimulated transcriptional activation by the receptor. In light of the critical role of ER-a in breast carcinoma, binding of CaM with ER-a may represent a novel potential therapy of breast carcinoma. The data suggest that small molecules that selectively disrupt the interaction of ER-a with CaM may be useful in the therapy of breast carcinoma.

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88 **Poster Session B**

Metabolic phenotypes reveal novel therapeutic targets in KRAS/LKB1 mutant non-small cell lung cancer *Ralph DeBerardinis, The University of Texas Southwestern Medical Center; J. Kim; K. Li; K. Huffman; E. Choi; D. Castrillon; B. Chen; J. Kim; J. Xu; J. Minna*

Introduction: Genetic heterogeneity in cancer generates genotype-specific metabolic preferences which may be exploited to kill malignant cells. In non-small cell lung cancer (NSCLC), concomitant oncogenic mutations in KRAS and loss of the tumor suppressor LKB1 specify an aggressive tumor phenotype in both mice and humans. Because KRAS and LKB1 independently regulate metabolism in cancer cells, we studied whether new metabolic phenotypes and vulnerabilities would emerge when both mutations occurred together. **Methods:** We performed metabolomics in cell lines and tumors with mutations in KRAS alone (K) or both KRAS and LKB1 together (KL) to identify emergent metabolic properties. Transcriptome analysis was used to identify mechanisms to explain metabolic dysregulation in KL cells, and loss of function studies were used to assess candidate liabilities in cell lines and xenografted tumors. **Results:** Metabolomics in human cell lines and tumors from both mice and humans revealed that the KL genotype is associated with widespread alterations in nitrogenous metabolites, particularly amino acids and nucleotides. Expression studies revealed that human KL cell lines and tumors express high levels of the urea cycle enzyme, carbamoylphosphate synthease-1 (CPS1), which condenses ammonia and bicarbonate in the mitochondria to produce carbamoylphosphate (CP). Although genetic silencing of CPS1 enhanced ammonia levels and acutely induced cell death in culture and in vivo, the mechanism of toxicity was unrelated to CPS1's conventional function in the urea cycle. Rather, KL cells use CPS1 as a supplementary source of CP to feed pyrimidine biosynthesis. CPS1 silencing caused cell cycle arrest, DNA polymerase stalling and double-stranded DNA breaks. Supplementing CPS1-silenced KL cells with exogenous pyrimidines normalized DNA polymerase processivity and prevented DNA damage and growth suppression. Thus, CPS1 is required to maintain nucleotide homeostasis in NSCLC cells with the KL oncogenotype. **Conclusions:** We discovered a new form of oncogene addiction/synthetic lethality in NSCLC. The KL oncogenotype induces dependence on an unconventional pathway of pyrimidine biosynthesis, and blocking this pathway leads to pyrimidine depletion, DNA damage and cell death. CPS1 and related pathway components represent new, metabolism based, therapeutic targets in this aggressive subset of NSCLC. Ongoing work is uncovering additional liabilities related to nitrogen metabolism in KL cells and tumors.

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89 **Poster Session A**

The role of tumor-associated adipose cells in cancer aggressiveness *Mikhail Kolonin, The University of Texas Health Science Center at Houston; F. Su*

Introduction: Many types of carcinoma eventually tend to develop metastases and resistance to chemotherapy, resulting in lethality. Expansion of white adipose tissue (WAT), and in particular of peritumoral WAT, in obesity has been linked with aggressiveness and mortality of many adenocarcinomas. WAT cell populations linked with cancer progression are adipocytes (the lipid-storing cells) and adipose stromal cells (ASCs, the adipocyte progenitors). Recently, EMT and resistance to therapy has also been linked with the activation of lipid metabolism and epithelial-mesenchymal transition (EMT) in cancer cells. **Methods:** Here, we have investigated the mechanism of human adipose cell interaction with cancer in co-culture models. **Results:** Our data indicate that both WAT-derived cell populations promote EMT. We also show that that adipocytes and ASCs conferring cancer cells chemoresistance. Finally, we provide evidence that adipocytes play a unique role in cancer aggressiveness by serving as a source of long-chain fatty acids for cancer cells. **Conclusions:** This study lays the foundation for subsequent efforts to improve chemotherapy efficacy by combination treatments including those previously developed by our group to target ASC and adipocytes.

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90 **Poster Session B**

Hepatocyte Nuclear Factor 1alpha (HNF1alpha): A possible Oncogene in Pancreatic Cancer *Ramadevi Subramani, Texas Tech University Health Science Center at El Paso; J. Medel; K. Flores; S. Rivera; M. Terres; A. Clift; D. Pedroza; A. Galvez; J. Dodderer; R. Lakshmanaswamy*

Introduction: We have demonstrated that silencing of IGF-1R leads to inhibition of pancreatic cancer. HNF1alpha is one of the transcription factors that was significantly altered in IGF-1R silenced pancreatic cancer cells. Studies have shown that HNF1alpha might play a role in metastasis. However, the mechanism underlying the role of HNF1alpha in pancreatic cancer growth and metastasis is poorly understood. Hence in this study, we attempted to investigate the role of HNF1alpha in pancreatic cancer. **Methods:** HNF1alpha was silenced using siRNA in AsPC-1 pancreatic cancer cells. It was overexpressed in MIAPaCa-2 pancreatic cancer cells. Cell viability was determined using MTS assay. We studied the role of HNF1alpha silencing on pancreatic cancer metastasis using migration, invasion, and colony formation assays. We also examined the key molecular players involved in proliferation, EMT, and apoptosis using Western blot analysis. **Results:** On screening a panel of non-cancerous and cancerous pancreatic cell lines, we observed that the cancer cells express higher levels of HNF1alpha compared to normal pancreatic cells. Even among the cancer cell lines there was a wide range of expression of HNF1alpha. Interestingly, the expression of HNF1alpha was very high in AsPC-1 cells while MIAPaCa-2 had lower expression. Overexpression of HNF1alpha significantly increased the cell viability, while the opposite was observed when it was silenced. In addition, we also observed that HNF1alpha significantly altered the metastatic potential of pancreatic cancer cells. The dysregulated expression profile of key molecule players of proliferation, EMT, and apoptosis (pPI3K, pAKT, Notch, Slug, Vimentin, Bak, Bcl-2, cleaved Caspases-3, 8, etc.,) suggest the oncogenic role

of HNF1alpha in pancreatic cancer. **Conclusions:** We conclude that HNF1alpha is an oncogenic transcription factor and could serve as a potential therapeutic target to treat pancreatic cancer.

91 **Poster Session A**

Deregulated PRAJA1-TGF-beta signaling pathway in Beckwith-Wiedemann syndrome-associated liver tumorigenesis *Jian Chen, The University of Texas M.D. Anderson Cancer Center; M. Hung; X. Su; B. Fang; J. Stroehlein; R. Zhao; D. Lee*

Introduction: Beckwith-Wiedemann syndrome (BWS) is a congenital stem cell disorder characterized by a defective developmental program resulting in enlarged organs. BWS is associated with an 800-fold increased risk of childhood neoplasms, including Wilms tumor, hepatoblastoma, and other childhood cancers. The molecular etiology of BWS is complex and poorly understood. In particular, the molecular mechanisms by which specific pathways drive BWS-associated liver tumorigenesis are unclear. Sptbn1+/-/Smad3+/- mice (Sptbn1, a key adaptor for TGF-beta/Smad3 pathway) with defective TGF-beta signaling develop multiple tumors that are phenotypically similar to those in BWS, suggesting that disrupted TGF-beta signaling may be responsible for driving BWS and BWS-associated malignancies. Therefore, restoring TGF-beta tumor suppressor function would be a potentially effective therapy and a new research direction for BWS-associated cancers. We further sought to determine detailed mechanism by which a defective TGF-beta pathway triggers liver cancer development. **Methods:** (1) We performed the genetic and genome-wide analyses using The Cancer Genome Atlas (TCGA) liver cancer database. (2) Patient-derived induced pluripotent stem cells (iPSCs) were generated from BWS patients. (3) Immunochemistry analyses were performed on BWS-associated tumors (4) TGF-beta induced E3 ligase PRAJA1 phosphorylation assays were performed in hapatoblastoma cells. **Results:** (1) Whole-transcriptome RNA sequencing of liver cancer samples from TCGA display that the defective TGF-beta signaling is associated with poor survival. The TGF-beta pathway-related E3 ubiquitin ligases, PRAJA1, WWP1/WWP2, deubiquitinases (DUBs), and UCHL5 are the most commonly altered genes in liver cancer patients. (2) The levels of PRAJA1 are negatively correlated with Sptbn1, Smad3 or CTCF in BWS-associated tumors. (3) PRAJA1 is increased in liver cancers and dramatically induces liver stem cells to develop into liver tumor–initiating cells. (4) Inhibition of PRAJA1 leads to high levels of apoptosis and reduction of liver cancer tumorigenesis. (5) TGF-beta induces PRAJA1 tyrosine/serine phosphorylation and PRAJA1 may have a negative-feedback role on the TGF-beta pathway. **Conclusions:** Based on our current preliminary data, we demonstrated the critical tumor suppressor role of the TGF-beta pathway in BWS-associated liver tumorigenesis. We focus on targeting defective TGF-beta signaling in liver cancer development and deeply investigate the detailed mechanisms by which PRAJA1 negatively regulates TGF-beta signaling in liver cancers. Completion of this study should provide valuable insight into the development of more effective targeted treatment for BWS-associated liver cancer patients.

92 **Poster Session B**

Telomerase Substrate Precursor 6-Thio-2'-Deoxyguanosine Overcomes Non-Small Cell Lung Cancer First Line Targeted Therapy Resistance and Multi-drug Chemotherapy Resistance *Ilgen Mender, The University of Texas Southwestern Medical Center; R. LaRanger; J. Minna; J. Shay; K. Batten; K. Luitel; M. Peyton; M. Dalvi; M. Ramirez; E. Martinez*

Introduction: Lung cancer patients with advanced disease are treated with standard chemotherapies and/or targeted therapies as first- and second-line therapies. However, these therapies almost universally fail due to tumor heterogeneity leading to intrinsic or acquired drug resistance. Therefore, it is important to seek new approaches to target multi-drug resistance. Since ~90% of primary human tumors express the ribonucleoprotein enzyme telomerase, but not most somatic tissues, telomerase is a highly attractive, almost universal, target for anticancer therapy. Recently, we reported that the nucleoside, 6-thio-2'-deoxyguanosine (6-thio-dG), is very effective in rapidly killing telomerase positive cancer cells in vitro and in vivo, but not normal telomerase silent cells, with minimal cytotoxic side effect to normal tissues. In this study, we tested the effects of 6-thio-dG, in immunocompetent syngeneic xenograft and genetically engineered mouse models of lung cancer and on a large series of human non-small cell lung cancer cell lines including those selected for multi-drug resistance. **Methods:** Colony formation assay, cell viability assay, RNA sequencing, xenograft mouse model, syngeneic mouse model, genetically engineered mouse model **Results:** We found that erlotinib, paclitaxel:carboplatin and gemcitabine:cisplatin resistant cells were sensitive to 6-thio-dG in vitro and/or in vivo. In addition, we tested the anticancer effect of 6-thio-dG in a syngeneic immunocompetent xenograft mouse model and showed that the addition of 6-thio-dG to gemcitabine and cisplatin combination therapy caused more tumor shrinkage compared to doublet therapy alone without increasing toxicities. We used a genetically engineered mouse model of lung cancer (K-RAS LA1) to test the effect of 6-thio-dG and found that tumors in one year old immunocompetent K-RAS LA1 mouse were significantly smaller with just two weeks of treatment with 6-thio-dG. In addition, we tested 6-thio-dG on a large panel of well characterized non-small lung cancer cell lines and observed 73 out of 77 NSCLCs were sensitive. We further demonstrated that the 4 resistant NSCLC lines clustered together (RNAseq), providing a molecular signature for patients that may not respond to 6-thio-dG. **Conclusions:** 6-thio-dG is a novel and highly effective approach to prolong disease control of therapy-resistant tumors in almost all lung cancer patients.

93 **Poster Session A**

Characterizing the efficacy of anticancer drug treatment using mathematical models *Hope Murphy, Texas Christian University; E. Sizemore; A. Naumov; H. Dobrovolny*

Introduction: In order to determine correct dosage of chemotherapy drugs, the effect of the drug must be properly quantified. There are two important values that characterize the effect of the drug: Emax is the maximum possible effect from a drug, and IC50 is the drug concentration where the effect diminishes by half. Currently, the technique used to measure these quantities gives estimates of the values that depend on the time at which the measurement is made. We use mathematical modeling to test a new method for measuring Emax and IC50 that gives estimates independent of measurement time. **Methods:** We used data from Trebunova et. al. for 0 nM, 200 nM, 500 nM, 1000 nM of doxorubicin in MCF-7 cells as a sample data set to test our new method. We fit the data using a mathematical model of tumor growth and examined two assumptions for the effect of doxorubicin: first assuming that doxorubicin reduces growth rate, and second assuming that it reduces the maximum number of cells. **Results:** Our method produced IC50 estimates similar to estimates derived using current techniques. Our calculations show that the Emax for doxorubicin in MCF-7 cells under the assumption of reduced growth rate, is 0.500, and the IC50 is 210 nM. Under the assumption that doxorubicin reduces the maximum number of cells, we found an Emax of 92% and an IC50 of 190 nM. **Conclusions:** We determined values for Emax and IC50 using mathematical models under two assumptions: that the drug reduces growth rate, or maximum number of cells. The IC50 was similar in both cases, but for doxorubicin it seems to be better at reducing the maximum number of cells as opposed to reducing the growth rate. This work is intended to characterize the efficacy of anticancer drug treatments and determine the correct doses before trying those in patients to get the most effective therapeutic treatment.

94 **Poster Session B**

TC-PTP deficiency in mouse epidermis promotes UVB-induced keratinocyte cell survival through the regulation of VEGFR2 signaling *Dae Kim, The University of Texas Rio Grande Valley; M. Baek; M. Kim; J. Lim; L. Morales; A. Tsin*

Introduction: Ultraviolet B radiation (UVB) exposure can contribute to the development of skin cancer by modulating protein tyrosine kinase (PTK) signaling. It has been suggested that UVB radiation increases the ligand-dependent activation of PTKs and induces PTP inactivation. Our recent studies have shown that T cell protein tyrosine phosphatase (TC-PTP) attenuates skin carcinogenesis induced by chemical regimens, which indicates its critical role in the prevention of chemically-induced skin cancer. In the current work, we report that activation of TC-PTP in vitro leads to increased keratinocyte susceptibility to UVB-induced apoptosis via the downregulation of vascular endothelial growth factor receptor 2 (VEGFR2) signaling. **Methods:** We generated immortalized TC-PTP-deficient (TC-PTP KO) keratinocytes from epidermal-specific TC-PTP KO mice. **Results:** Immortalized TC-PTP-deficient (TC-PTP KO) keratinocytes showed increased cell survival against UVB-induced apoptosis which was concomitant with a UVB-mediated increase in the level of VEGFR2 phosphorylation. Treatment of TC-PTP KO keratinocytes with the VEGFR2 inhibitors, SU5416 and ZD6474, reversed this effect and significantly increased cell death after UVB irradiation in comparison with untreated TC-PTP KO keratinocytes. Immunoprecipitation analysis using the TC-PTP substrate-trapping mutant TCPTP-D182A indicated that TC-PTP directly interacts with VEGFR2 to dephosphorylate it and their interaction was stimulated by UVB irradiation. Following UVB-mediated VEGFR2 activation, the level of c-Jun N-terminal kinase (JNK) phosphorylation was also significantly increased in TC-PTP KO keratinocytes compared to control keratinocytes. Similar to our results with VEGFR2, treatment of TC-PTP KO keratinocytes with the JNK inhibitor SP600125 significantly increased apoptosis after UVB irradiation, confirming that the effect of TC-PTP on UVB-mediated apoptosis is regulated by VEGFR2/JNK signaling. **Conclusions:** Our results suggest that TC-PTP plays a protective role against UVB-induced keratinocyte cell damage by negatively regulating VEGFR2-dependent cell survival signaling.

95 **Poster Session A**

Tgf beta-dependent, transcriptional regulation of ARF in human cancer cells *Yen-Ting Liu, The University of Texas Southwestern Medical Center; Y. Zheng; L. Xu; S. Skapek*

Introduction: Disruption of the CDKN2A locus at chromosome 9p21 is one of the most common events in human cancer. Two proteins, p16Ink4a and p14ARF (p19Arf in the mouse), are encoded in this locus and function independently as tumor suppressors. The INK4A and ARF genes are usually deleted or silenced concurrently due to their close proximity at 9p21, but in some settings, their transcriptional control can be uncoupled. Study of their differential regulation, therefore, is important to understand disparate pathways in specific cancerous transformation events. Our laboratory team previously unveiled a new pathway in which Tgf beta induces Arf, but not Ink4a, during mouse eye development. This is intriguing because Tgf beta signaling pathways are often derailed in during cancer development or progression. Numerous effectors have been proposed in the Tgf beta-driven cancer suppression. Here, we are exploring the Tgf beta-ARF pathway human cancer lines. **Methods:** We utilized computational approaches in secondary analyses of public ChIP-seq databases to identify human cell lines with intact ARF gene and open chromatin to allow basal RNA Polymerase II binding at the promoter. We directly studied regulation of ARF expression in response to Tgf beta under different conditions through qRT-PCR and Western blotting. We used molecular biology tools to investigate how transcription factor and RNA polymerase II occupancy at the ARF promoter is influenced by Tgf beta in human cancer cell lines. **Results:** Our studies revealed Tgf beta-dependent induction of ARF transcription in HeLa cells, and the induction slowed proliferation in vitro. The induction of ARF was dependent on SMAD4 and p38MAPK activation in HeLa cells. Following exposure to Tgf beta, SMAD4 and SP1 were recruited to the ARF promoter. However, Tgf beta-induction did not further recruit RNA polymerase II to the promoter region, which appeared to be pre-loaded at the transcription start site in HeLa cells, in contrast to early passage mouse embryo fibroblasts. Even though p53 function is impaired in HeLa cells, p53 inactivation did not account for differential RNA Polymerase II dynamics because the polymerase can be recruited to the mouse Arf promoter p53-/- fibroblasts. **Conclusions:** We report a previously unrecognized ability for Tgf beta to induce the expression of the ARF tumor suppressor in human cancer cell line, and we define mechanism by which Tgf beta engages the transcription machinery at ARF promoter. Ongoing experiments using CRISPR/Cas9-mediated genome editing are further defining enhancer elements that are critical in this process.

96 **Poster Session B**

Stromal Hedgehog pathway activation suppresses growth and metastasis of lung adenocarcinoma *Sahba Kasiri, The University of Texas Southwestern Medical Center; B. Chen; A. Wilson; U. Barrie; U. Marriam; Z. Zeng; J. Kim*

Introduction: Aberrant activation of the Hedgehog (Hh) signaling pathway, a crucial developmental pathway, drives the tumor growth of Gorlin-type cancers. However, recent data suggest that paracrine activation of the pathway is tumor suppressive rather than oncogenic in sporadic epithelial cancers. The role of the pathway in non-small lung cancer is poorly understood. Thus, we explored the role of stromal Hh pathway activation in growth of lung tumor epithelia. **Methods:** Human lung adenocarcinoma cell lines were used to probe SHH mRNA and protein expression. Co-culture of high SHH expressing cell lines with murine embryonic and lung fibroblasts were used to confirm and probe the role of paracrine SHH expression on the growth of lung cancer cells. The in vivo role of paracrine SHH was tested using autochthonous lung cancer models with conditional KRASG12Dactivation, p53 loss, and SHH loss compared to wild-type SHH. **Results:** In human lung adenocarcinoma patients, higher expression of SHH mRNA in lung adenocarcinoma correlated with poor overall and progression free survival. A scan of 35 human lung adenocarcinoma cell lines revealed heterogeneous expression of SHH and IHH with high expression found predominantly in mutant K-Ras lines. Co-culture of high SHH expressing tumor epithelial cells and Shh-Light2 reporter cell lines demonstrated that SHH activated the fibroblast reporter in a paracrine manner, rather than an autocrine effect on cancer cells. Treatment with the SMO inhibitor, KAAD-cyclopamine, also inhibited the growth of tumor epithelial cells in co-culture with NIH-3T3 fibroblast cells but the effect was decreased when co-cultured with lung fibroblasts. Genetic loss of SHH in an autochthonous mouse model, LSL-KrasG12D/+;Trp53fl/fl; Shhfl/f (KPS) did not affect overall survival compared to LSL-KrasG12D/+;Trp53fl/fl (KP) mice However, early inhibition of the Hh pathway by anti-SHH/IHH antibody, 5E1, on KP mice resulted in significantly worse survival rates with increased metastatic burden compared to IgG treatment. Analysis of KP tumors revealed unexpected high levels of IHH mRNA by in situ hybridization that may account for the survival differences seen between genetic ablation and pharmaceutical inhibition of the Hh ligands. **Conclusions:** The signaling pathway acts upon lung stromal cells in a paracrine fashion. Inhibition of Hh activity in vivo worsened mortality rate due to increase in tumor growth and metastases. Furthermore, mutant Kras lung cancers express high levels of IHH that dominates the tumor suppressive effect of our mouse models.

97 **Poster Session A**

New role for histone deacetylase SIRT1 in progression to castrate resistance *Shih-Bo Huang, The University of Texas Health Science Center at San Antonio; D. Thapa; S. Hussain; R. Bedolla; R. Srivastav; R. Reddick; Z. Lai; H. Chen; Y. Chen; R. Ghosh; A. Kumar*

Introduction: SIRT1, a NAD+-dependent deacetylase, is a member of multigene family of Sirtuins. SIRT1 is involved in regulating histone and non-histone proteins and thus affecting regulation of diverse biological activities including cellular stress resistance, genomic stability, energy metabolism and tumorigenesis. Disruption of SIRT1 in the prostate results in the formation of prostatic intraepithelial neoplasia (PIN) lesion, a precursor lesion of prostate cancer (PCA). In contrast, overexpression of SIRT1 leads to development of micro-invasive prostate carcinoma. Furthermore, human prostate tumors show significantly elevated levels of SIRT1. This controversy suggests that SIRT1 may have varied functions in the different stages of PCA and that any changes to SIRT1 could potentially change the transcriptome of the prostate epithelial cells including in response to castration. **Methods:** To address these paradoxical findings, we examined the role of SIRT1 in prostate pathogenesis using stably silenced for SIRT1 in PCA cell lines. **Results:** Our results show that SIRT1 levels are significantly elevated in castrate resistant AR-positive (22Rv1) and AR-negative androgen independent cells (DU145) relative to androgen responsive, LNCaP cells. Silencing SIRT1 resulted in (i) morphological changes indicative of clustering and epithelial mesenchymal transition (EMT); (ii) decreased transformation ability evidenced by reduced growth on soft agar depending on the cell type. Notably, genes involved in nuclear receptor (PXR/RXR/FXR/PPAR) and kinase (AMPK, MSP-RON, and RhoA) signaling are significantly altered as evidenced by RNA-seq analysis. Remarkably, silencing SIRT1 in LNCaP cells reduced AR signaling as evidenced by decreased levels and expression of AR target genes (PSA, TMPRSS2, FKBP5) and secreted levels of PSA. Interestingly, SIRT1 KD reduced PSA reporter activity under both normal physiological and androgen deprivation growth conditions with no significant effect on nuclear or cytosolic levels of AR. More importantly, silencing SIRT1 increased sensitivity to growth under androgen deprivation conditions. However, knockdown of SIRT1 in 22Rv1 cells has no significant impact on AR signaling as well as expression of AR variants, but leads to morphological changes in part through modulation of EMT program. **Conclusions:** Taken together, these data indicate that SIRT1 plays a regulatory role in PCA progression to castrate resistance by altering AR transcriptional network, independent of classical AR signaling. Thus, our study identifies previously uncharacterized role for SIRT1 in promoting castrate resistance and sustaining cell survival, providing opportunities to develop anticancer therapeutic approaches for treatment of patients with advanced stage PCA. Supported by CPRIT RP 150166 (APK).

98 **Poster Session B**

The role of exosome subpopulations in glioblastoma progression *Amanda Haltom, The University of Texas M.D. Anderson Cancer Center; J. Kim; R. Kalluri*

Introduction: Exosomes (Exos) are heterogeneous, naturally arising cell-derived nanovesicles that are proposed to play a role in intercellular communication to maintain homeostasis and response to stress. This may be achieved through the complex heterogeneity of these nano-sized vesicles, which can be demonstrated by the presence of tetraspanin (TSPNs) on the Exo surface. Exos are rich in various TSPNs but predominantly contain CD9, CD63 and CD81. These TSPNs are frequently used to define the presence of Exos, but other studies and our preliminary data have shown that Exos from different sources contain highly variable amounts of each TSPN. Our preliminary data suggests that Exos from a glioblastoma cell line contain much less CD81 than Exos from other cell lines, and CD81 is frequently silenced in glioblastoma patients. Therefore, TSPNs may define functional Exo subpopulations. However, studies examining the presence of different Exo subpopulations defined by TSPNs and their corresponding role in cancer progression remain minimal. We hypothesize that exosomal subpopulations can be defined by their tetraspanin profiles, and that CD81+ Exos play a different role in cancer progression than other Exos. **Methods:** We are using nude mouse models of orthotopically-implanted glioblastoma cells with modified TSPN expression to begin addressing our hypothesis. We first overexpressed CD9 and CD81 in glioblastoma cells and implanted them to nude mice, then we silenced CD9 and CD81 in the same cells and implanted them to nude mice. **Results:** We have found that overexpression of these tetraspanins decreases the survival of tumor bearing mice, and silencing the tetraspanins increases the survival of tumor bearing mice.

Furthermore, overexpression of these tetraspanins leads to an increase of the tetraspanin on the exosome surface. **Conclusions:** This shows that levels of CD9 and CD81 affect glioblastoma progression in nude mice. We are currently determining the mechanism of this effect and whether the presence of CD9 and CD81 on exosomes is causing the change in survival. We will then characterize these exosomes to further determine the reason for the change in survival.

99 **Poster Session A**

MicroRNA miR-34c function in tumorigenesis and metastasis of osteosarcoma *Huan-Chang Zeng, Baylor College of Medicine; Y. Bae; B. Dawson; E. Munivez; L. Wang; L. Kurenbekova; J. Yustein; F. Gannon; B. Lee*

Introduction: MiR-34 family is one of tumor suppressive miRNAs, which is directly regulated by p53 in response to DNA damage and oncogenic stress. In osteosarcoma (OS), expression of miR-34c was decreased as observed in other types of cancer. In our previous study, osteoblast-specific gain of function (GOF) miR-34c mice (Col1a1 2.3 kb-miR34c) showed a critical role of miR-34c in bone homeostasis by regulating Notch signaling. We also found that pathological gain of Notch in committed osteoblastic cells can proliferate immature osteoblasts leading to spontaneous OS. Furthermore, Notch signaling was upregulated in human OS samples. **Methods:** Tumor suppressive role of miR-34c was accessed by monitoring tumor formation and progression by crossing Col1a1 2.3kb-miR34c mice with Col1a1 2.3kb Cre/+; p53 $^{f/f}$. Xenograft was performed to examine the effect of miR-34c on metastasis. Also, Luc reporter murine OS cell lines and syngeneic mouse model (C3H) were used. We assessed the expression of putative miR-34c targets in different human OS cell lines. **Results:** We have found that GOF miR-34c mice showed increased survival compared to Col1a1 2.3kb Cre/+; p53 $^{f/f}$ with a trend of less incidence of lung metastasis. We also found miR-34c is significantly decreased in highly metastatic 143B cells compared to other OS cell lines. Furthermore, xenograft studies using 143B-34c (stably expressing miR-34c) showed regression of tumor growth. Based on transcriptome and bioinformatics analysis, we identified several potential targets of miR-34c in OS metastasis. CD2AP and TLK1 are relatively highly expressed in 143B cells compared to non-metastatic cells. The transcript level of these targets was significantly decreased by overexpression of miR-34c mimic in 143B cells. Recently, we have developed Luc reporter murine metastatic OS cell line (Dunn-Luc and LM8-Luc) and assessed tumorigenesis and metastasis property of this cell line using immunocompetent C3H mice. This in vivo mouse model will help us to understand the functional interaction of miR-34c and these targets in lung metastasis. **Conclusions:** Our study suggests that miR-34c plays a tumor suppressive role in OS and also inhibits metastasis by regulating multiple targets. The molecular function of the inhibitory role of miR-34c in OS metastasis via targeting CD2AP and TLK1 is under way.

100 **Poster Session B**

Optimizing RNA Biosynthetic Tagging Through Selective Genome Editing *Sarah Almasri, The University of Texas Health Science Center at San Antonio; X. Yu; Y. Zhang; A. Pertsemlidis*

Introduction: Uracil phosphoribosyltransferase (UPRT) is a pyrimidine salvage pathway enzyme that converts uracil to uridine monophosphate (UMP). Introducing this enzyme into mammalian cells allows them to biosynthetically label newly synthesized RNA when grown in the presence of 4-thiouracil (4TU). 4TU is converted into 4-thiouridine monophosphate (4TUMP) and then incorporated into RNA. Since mammalian cells do not exhibit UPRT activity and nucleic acids do not innately contain thio-substituted nucleotides, this method allows for cell-specific expression of UPRT. As efficiency of 4TUMP incorporation into RNA is critical to the success of such labeling, we aim to eliminate other pathways capable of yielding UMP, directly or indirectly. Uridine monophosphate synthetase (UMPS) is a bifunctional enzyme. One subunit, orotidine-5'-phosphate decarboxylase (ODCase or OMP decarboxylase), catalyzes the formation of UMP. We hypothesize that reducing levels of this enzyme could improve 4TUMP incorporation into RNA and therefore RNA labeling efficiency in UPRT-expressing cells. **Methods:** We obtained a construct encoding the UPRT cDNA from the University of Oregon and pairs of murine cancer cell lines that differ in their ability to metastasize from MD Anderson Cancer Center and Tel Aviv University. UPRT expression of the transfected cells was validated by qRT-PCR and by western blot, with accuracy of detection confirmed using an siRNA designed against UPRT. Cells were grown in the presence of 4TU with one group treated with siRNAs to knock down UMPS and the other group treated with a control oligo. We isolated RNA, biotinylated it, pulled down labeled RNA with streptavidin, and assessed the efficiency of labeling as a function of UMPS knockdown. **Results:** We confirmed that labeling of RNA is limited to cells expressing UPRT with 4TU present. We knocked down UMPS levels by siRNA, confirmed decreased mRNA and protein levels of UMPS by qRT-PCR and western blot, and established that knock-down does not significantly affect cell growth. We are currently identifying the 4TU concentration and treatment time needed for optimal labeling. **Conclusions:** Experiments are ongoing, but we predict that decreasing UMPS levels will increase the reported ~10% efficiency of 4TU labeling of RNA. The ability to efficiently and selectively label RNA will allow us to distinguish RNAs of tumor and host origin and identify RNA species that are biomarkers of cancer initiation or progression and potential targets for therapeutic intervention. Acknowledgments: The William and Ella Owens Medical Research Foundation.

101 **Poster Session A**

HER3 and the long non-coding RNA LINC00052 interplay promotes tumor growth in breast cancer *Ahmed Salameh, The University of Texas Health Science Center at Houston; X. Fan; N. Zhang; Z. An*

Introduction: Human epidermal growth factor receptor 3 (HER3) is overexpressed and activated in a number of cancer types under the conditions of acquired resistance to other HER family therapeutic interventions. Better understanding of the complex regulation of HER3 and establishment of biomarkers will improve the strategies to target HER3 for cancer therapy. HER3 studies in our group have included demonstration that HER3 regulation is a key sensor in the regulation of signaling in HER2 expressing cancer cells; the HECT family E3 ligase NEDD4 regulates HER3 signaling and is a biomarker for efficacies of anti-HER3 antibody therapies; and Parkinson Protein 7 (PARK7/DJ-1) association with HER3 potentiates HER3 activation and signaling in cancer. Studies have shown that, besides proteins, long non-coding RNAs (lncRNAs) have essential roles in tumorigenesis and occupy a critical space in cancer progression and metastasis. **Methods:** We analyzed gene expression profiles in breast cancer cells stably transduced with HER3-shRNA, small hairpin RNA for HER3 silencing. We established the correlation of expression of an lncRNA, LINC00052, with HER3 levels in breast cancer cells. We then investigated the relationship between LINC00052 expression and HER3 phosphorylation. Next, we tested whether LINC00052 expression promotes growth of breast cancer cells in a high HER3 context and whether LINC00052 plays a role in the regulation of HER3 expression in breast cancer cells. To this end, we altered LINC00052 expression in cells of two breast cancer cell lines by knockdown of LINC00052 using shRNA-silencing or by ectopically expressing full non-spliced RNA LINC00052. To interrogate the function of LINC00052 in xenograft tumor models, we implanted breast cancer cells stably expressing LINC00052-shRNA, LINC00052-ectopic, or control constructs in nude mice. **Results:** Profiling analysis showed that LINC00052 expression level changed significantly in response to HER3 knockdown. Gene silencing of LINC00052 diminished both LINC00052 and HER3 expression and reduced cancer cell growth in vitro and in vivo. LINC00052 overexpression promoted cancer cell growth in vitro and in vivo and increased HER3-mediated downstream signaling. Importantly, neutralization of HER3 signaling with HER3 targeting monoclonal antibodies (mAbs) blocked LINC00052 mediated cancer cell proliferation in vitro and tumor growth in vivo, suggesting LINC00052 promotes cancer growth through HER3 signaling. **Conclusions:** Taken together, our results indicate that high LINC00052 levels predict activation of HER3-mediated signaling, and LINC00052 expression level may serve as a potential biomarker for HER3 targeted antibody cancer therapies.

102 **Poster Session B**

The systematic analysis of protein-coding and long non-coding RNAs in diverse astrocyte populations and their correlates in glioma *Raquel Cuevas Diaz Duran, The University of Texas Health Science Center at Houston; Y. You; X. Dong; B. Deneen; J. Wu*

Introduction: Glioma is the most common and aggressive malignant tumor of the central nervous system with high recurrence and mortality rate. Over the past two decades, the majority of brain tumor drugs entering clinical trial evaluation failed, highlighting the need of finding new therapeutic targets. Recent research identified subpopulations of astrocytes in the mouse brain and their correlates in glioma with distinct cellular, molecular, and functional properties. We hypothesize that mouse glioma samples expressing specific astrocyte subpopulation markers can be used for studying subtypes of human glioma. Furthermore, evidences have shown that long non-coding RNAs (lncRNAs) can regulate oncogenes and tumor suppressor genes affecting the proliferation, apoptosis, invasion, migration, and metastasis of tumor cells. Therefore, by investigating lncRNAs with disrupted gene expression in both human and mouse glioma, we can find conserved regulatory mechanisms representing potential therapeutic targets. **Methods:** We performed a comprehensive transcriptomic analysis of protein-coding genes and lncRNAs in different subtypes of human gliomas as well as healthy human brain samples. We found differentially expressed genes using the following pairwise group comparisons: glioma vs healthy brain, anaplastic vs non-anaplastic, secondary vs primary, astrocytoma vs oligodendroglioma, and recurrent vs non-recurrent. We compared the gene expression profiles of human glioma and mouse glioma samples

expressing specific astrocyte subpopulation markers in homologous genomic regions. To understand the possible cis-regulatory functions of homologous differentially expressed lncRNAs, we implemented a systematic correlation analysis of lncRNAs and their neighboring protein-coding genes. **Results:** We found protein-coding genes and lncRNAs with aberrant expression in the different subtypes of human glioma samples. Interestingly, many of the differentially expressed genes in mouse glioma samples with specific astrocyte subpopulation markers had homologous regions with altered gene expression in human glioma samples. We found some differentially expressed lncRNAs highly correlated with the expression of protein-coding genes in the close vicinity, similar to their human homologs, indicating possible conserved regulatory mechanisms in cis. **Conclusions:** Different subtypes of glioma may arise from specific subpopulations of astrocytes. Our results demonstrate that RNA-seq data from glioma mouse samples bearing astrocyte subpopulation markers may be used to find potential biomarkers for glioma grade and subtype classification. We are generating a catalogue of differentially expressed lncRNAs with human homologs that are potentially involved in the regulation of glioma. These lncRNAs may represent a novel class of therapeutic targets.

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103 **Poster Session A**

NPSD4: a new player in the DNA damage response *Erin Atkinson, The University of Texas M.D. Anderson Cancer Center; B. Wang*

Introduction: The DNA damage response (DDR) refers to the mechanisms that are activated upon DNA damage to ensure that DNA is repaired correctly. Improper repair can lead to mutations, oncogene activation, and genomic instability. The DDR involves a series of signaling cascades, potentiated by many different types of post-translational modifications, including SUMOylation. Through proteomic analysis of proteins involved in DDR SUMOylation, we have identified an uncharacterized protein that is recruited to sites of DNA damage that we have named New Player in SUMO dependent DNA damage repair 4 (NPSD4). NPSD4 is recruited to DNA damage tracts and has two SUMO interacting motifs (SIMs), making it a candidate SUMO-regulated DDR protein. Additionally, NPSD4 localizes to the heavily SUMOylated promyelocytic leukemia nuclear bodies (PML NBs) in a SIM-dependent manner. In telomerase negative cancers, PML NBs contain telomeric DNA and are thought to be the location of telomere recombination and elongation through the telomere maintenance mechanism termed Alternative Lengthening of Telomeres (ALT). We hypothesize that NPSD4 functions in SUMO regulated DNA repair, replication and ALT telomere maintenance. **Methods:** We performed GST pulldown assays, mass spectrometry, and immunoprecipitation to identify NPSD4 interacting partners. We created point mutations in the SIMs to abrogate SUMO interaction. We used live cell imaging to analyze NPSD4 recruitment to DNA damage sites and NPSD4 localization was evaluated by immunofluorescence. We generated NPSD4 knockdown cells and performed a DNA fiber assay to evaluate the effect of replication stress. Sister chromatid exchange was analyzed by metaphase spread. ALT activity in NPSD4 knockdown cells was analyzed by c-circle assay. **Results:** NPSD4 preferentially interacts with SUMO2/3 in a SIM dependent manner. NPSD4 forms nuclear foci that colocalize with ALT associated PML NBs. NPSD4 nuclear foci formation is SIM dependent. However, recruitment to DNA damage laser tracts is not. NPSD4 knockdown cells exhibit a decrease in replication rate and ALT activity. Knockdown of NPSD4 increases sister chromatid exchange. We have confirmed NPSD4 interaction with proteins involved in DDR and replication. **Conclusions:** These results indicate that NPSD4 is likely important for genomic stability and ALT telomere maintenance. As genomic instability contributes heavily to tumor development, characterization of novel DDR proteins can lead to better understanding of tumorigenesis. Additionally, elucidating the ALT mechanism may lead to development of novel therapies for ALT cancers, many of which currently have poor prognoses. Further study is needed to identify the mechanism by which NPSD4 functions.

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104 **Poster Session B**

Promyelocytic Leukemia Protein (PML) Supports Mutant KRAS-Driven Lung Cancer *Smita Rindhe, The University of Texas Southwestern Medical Center; M. Padanad; M. Melegari; J. Rodriguez-Canales; I. Wistuba; P. Scaglioni; R. DeBerardinis; J. Minna*

Introduction: PML, a central component of nuclear bodies (NBs), is a well-established tumor suppressor. However, recent studies revealed that PML supports breast cancer and leukemia progression by modulating lipid metabolism. Depending upon the cellular context, PML interacts with different partner proteins in NB and thus regulates different cellular networks, which could explain the paradoxical role of PML in cancer. Activating mutations of proto-oncogene KRAS (mutant KRAS) is associated with aggressive, therapy-resistant non-small cell lung cancer (NSCLC). Since mutant KRAS is still a challenging therapeutic target, there has been an intense clinical interest in identification of downstream player of mutant KRAS. Here, we investigate the role of PML in KRAS driven lung cancer. **Methods:** To understand the role of PML in lung cancer growth, we studied CCSP-rtTA/Tet-op-K-RasG12D ; Pml-/- mice. To further investigate the role of PML in human NSCLC cell proliferation, we depleted PML was in 16 NSCLC cells lines using shRNAs. Moreover, we used CRISPER/Cas9 technology to knockout PML. To obtain functional and mechanistic data, we used the Seahorse XF-24-3 Extracellular Flux Analyzer to measure cellular respiration and immunoblot, RT-PCR and mass spectrometry to assess mitochondrial metabolism of NSCLC cell lines depleted of PML. **Results:** We demonstrated that PML is selectively important for cell proliferation in NSCLC cells harboring mutant KRAS but not wild type KRAS. We also found that PML is essential for the ability of mutant KRAS human NSCLC cells to form colonies in soft agar. Knockdown of PML abrogates ATP production and causes a marked increase in reactive oxygen species (ROS) production in NSCLC cell lines as well as in Pml-/- MEFs compared to wild type MEFs. Silencing of PML shows marked induction of AMP-activated protein kinase (AMPK) phosphorylation at Thr172. Loss of PML results in reduced mitochondrial respiration. Depletion of PML cause down regulation of genes involved mitochondrial metabolism. In addition, in vivo experiment showed reduced tumor burden in KRASG12D; Pml-/- mice compared to wild type mice. Altogether, our data suggests that loss of PML results in dysfunctional mitochondria which translated into energy crisis and NSCLC growth arrest. **Conclusions:** Our study suggests that PML cooperates with mutant KRAS to support the rapidly proliferating lung cancer cells via metabolic reprogramming. Taken together our data support the conclusion that PML is involved in important aspects of energy reprogramming and proliferation of lung cancer cells which could provide a potential therapeutic strategy for targeting KRAS driven lung cancer.

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105 **Poster Session A**

Fast Deconvolution Tool for Separating Subtype Specific Signals from Mixed Tumor Genomic Data *Liuqing Yang, The University of Texas M.D. Anderson Cancer Center; J. Marron; W. Wang; H. Zhu*

Introduction: With the advance of deep sequencing techniques, the heterogeneity within a tumor tissue, referred as intra-tumor heterogeneity, becomes a prevalent confounding factor to tumor genomic studies. Analysis on genomic profilings from heterogeneous tumor samples can potentially lead to false positive differential expression conclusions, and even influence patients' clinical outcomes and therapeutic responses. **Methods:** To address the intra-tumor heterogeneity issue, we developed a Fast Tumor Deconvolution (FasTD) tool to separate the pure tumor signals from tumor-nontumor mixtures in an efficient way. Assuming a linear combination of the abundance of the mixing components and availability of some reference information for the non-tumor part, our semi-parametric regression-based model can quickly provide estimates for the tumor proportion in a mixture, as well as output the tumor specific genomic profile. **Results:** We demonstrate FasTD is a competitive tumor deconvolution tool for both simulated data and The Cancer Genome Atlas (TCGA) RNA-seq datasets. In particular, our method is computationally more than a thousand times faster than several current probabilistic models, while taking the whole genomic profiles as an input (with no requirement for pre-selected signature genes). **Conclusions:** The effort to extract the pure tumor signals in heterogeneous tumor samples is greatly reduced by our method.

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106 **Poster Session B**

Incompatibility of Bmal1 and Hnf4a in hepatocellular carcinoma *Baharan Fekry, The University of Texas Health Science Center at Houston; A. Ribas-Latre; C. Baumgartner; C. Kwok; P. Patel; L. Fu; S. Yoo; F. Sladek; K. Eckel-Mahan*

Introduction: Hepatocellular carcinoma (HCC) is the most common liver cancer worldwide and is often deadly. Recently studies have revealed that environmental (for example, night shift work) or genetic disruption of the 24-hr circadian clock increases the incidence of HCC, though the mechanisms are not known. Present in all cells of the body, circadian rhythms are driven in part by the ubiquitously-expressed transcriptional regulator, Bmal1. Disruption of hepatic Bmal1 produces spontaneous HCC in mice. This study examines the circadian activity of the hepatocyte nuclear receptor 4 alpha (HNF4α) protein in HCC, and suggests that one of its isoforms provides a key link between circadian disruption and HCC via its regulation of Bmal1. **Methods:** Spontaneous human and mouse HCC specimens as well as HCC cell lines were analyzed for HNF4α isoform expression as well as clock function. Circadian rhythmicity of HNF4α target genes as well as its relationship to the core circadian clock was observed in normal and transformed cells following circadian synchronization of cells in vitro. Chromatin immunoprecipitation and reporter assays were used to test Bmal1 suppression by specific HNF4α isoforms. Antagonism between HNF4α and Bmal1 was tested at the level of migration and invasion of HCC cells, 3D organoid growth, and tumor growth in immune compromised mice. In vivo bioluminescence was used

to track HNF4α-positive HCC growth with or without manipulation of the Bmal1 protein. **Results:** These data reveal that HNF4α, generally thought to have tumor suppressor activities, is heterogeneously expressed in HCC, where it competes for expression with the core circadian protein Bmal1. HNF4α provides isoform-specific circadian restraint at target cyclin and EMT-related genes. The P2 isoform of HNF4α is unique to HCC cells and downregulates Bmal1. The data reveal that the P2 isoform of HNF4α is primarily responsible for the incompatibility with Bmal1, providing direct transcriptional repression of the Bmal1 gene. Forced expression of Bmal1 in HNF4α-positive HCC inhibits viability and migration as well as the growth and progression of tumors in vivo. **Conclusions:** This study provide the first evidence that the circadian clock is downregulated at the level of Bmal1 by a specific HNF4α nuclear receptor isoform only in the context of HCC and that forcing tumors to re-introduce BMAL1 expression results in cell death. These data suggest that targeting the circadian clock by upregulation of the circadian protein, Bmal1 in HNF4α-positive tumors may provide a new way to inhibit tumor progression.

107 **Poster Session A**

The Chicken Egg Chorioallantoic Membrane Model: A Swiss army knife for generating PDX, deriving vascularized 3D tumors, and developing novel bioassays *Mariana Villanueva, Baylor College of Medicine; R. Pathak; H. Liu; J. Patel; L. Dobrolecki; M. Lewis; R. San Martin; D. Rowley; S. Woodfield; S. Vasudevan; C. Filgueira; F. Ferraro; A. Grattoni; A. Sikora*

Introduction: The chick chorioallantoic membrane (CAM) model is a highly vascularized extra-embryonic membrane connected to the embryo through a continuous circulatory system, and easily accessible for experimental manipulation. It has been widely used to study angiogenesis and provides a uniquely supportive environment to model biological processes. We have developed various biologically relevant models including Patient Derived Xenografts (PDX), 3D vascularized tumors from cell lines and bioassays for metastasis and radiosensitivity using a novel CAM-based platform technology. **Methods:** PDX and 3-D Tumors: Patient tumors and cancer cell lines are grafted on the chorioallatoic membrane (CAM) of 5-7 day SPF certified fertilized chicken eggs (white longhorn) along with optimized grafting matrix comprised of laminin, collagen, entactin, and a mix of growth factors. Tumors are allowed to grow for 5-7 days before being harvested. Bone Metastasis Assay: 3-D organoids comprising prostate cancer cells/human adult mesenchymal stem cells (VCaP/MSC) cells were co-implanted with humanized bovine bone chips onto the CAM, to track the metastatic potential of the prostate cancer cells. Metastatic colonization was confirmed with hematoxylin and eosin (H&E) staining and IHC. **Results:** We have established 103 CAM-PDX lines from 34 patients across 7 different cancer types with an average take rate of 75-80%. Additionally, 14 CAM-PDX lines have been derived from previously established primary patient-derived breast cancer PDX lines maintained in immunodeficient mice, and from cryopreserved tumor specimens. Our CAM-based platform can also derive highly vascularized 3-D tumors recapitulating the phenotypic hallmarks of the original tumors from multiple cancer cell lines including breast, pancreas and prostate. Using the CAM-based platform we have successfully modeled the interactions between reactive endosteum on trabecular bone and metastatic cancer cells. This novel in ovo xenograft system was used to demonstrate the ability of Tenacin-C coated trabecular bone cubes to recruit CAM blood vessels in order to colonize VCaP cells. The system can be extended to other cancer types to study mechanisms of metastasis. A major advantage of our models is the easy access to the tumor graft/plaque, which can be exploited to administer various drugs/anti-cancer compounds and make real-time assessments of tumor response using imaging methods like MRI and IVIS. **Conclusions:** In conclusion, we have developed a rapid, scalable, and cost-efficient novel chicken egg-based platform technology with a potential to accelerate cancer research and discovery.

108 **Poster Session B**

Ceramide Synthase-6 alters sensitivity of Acute Lymphoblastic Leukemia cells to ABT-737, a pan-BCL-2 family of Protein inhibitor and Dexamethasone *Dattesh Verlekar, Texas Tech University Health Sciences Center; H. Cho; S. Wei; M. Kang*

Introduction: Ceramides, key intermediators in the biosynthesis of complex sphingolipids, are synthesized by the enzyme ceramide synthase (CERS). Six different isoforms of ceramide synthase (CERS1-CERS6) with varying substrate specificity generate ceramides of diverse chain lengths. Ceramides play a role in the regulation of cell growth, differentiation, apoptosis and senescence. In normal tissues, CERS2, an enzyme synthesizing ceramides with C24 acyl chain (C_{24}-Cer), is highly expressed and has the widest tissue distribution while CerS6 generates C_{16}-Cer with low and tissue-specific distribution. Our preliminary data showed that CERS6 levels were significantly higher in acute lymphoblastic leukemia (ALL) cells in comparison to Peripheral Blood mononuclear cells and T-Lymphocytes derived from healthy human volunteers. The purpose of this study is to investigate the role of CERS6 in chemo-resistance in ALL models. **Methods:** C_{16}-Cer levels were measured by HPLC/MS/MS. Protein levels of CERS6, PARP, Caspase 3 and Caspase 8 were determined by western blotting and apoptosis was assessed by Annexin-V using flow cytometry. Stable overexpression and knock-down of CERS6 was achieved by lentiviral vector system. Statistical comparisons were carried out using unpaired student's t-test with Welch's correction. Cytotoxicity of conventional and investigational anti-leukemia agents was evaluated in T-cell ALL cells with CERS6 knocked-down and overexpressed. **Results:** CERS6 knockdown significantly decreased C_{16}-Cer by four-fold ($p<0.01$) while CERS6 overexpression increased C_{16}-Cer by two-fold ($p<0.05$). CERS6 knockdown in CCRF-CEM cells increased their sensitivity to a pan BCL-2 inhibitor ABT-737 as well as glucocorticoid (dexamethasone). The percent survival at 72h in ABT-737 (100nM) or dexamethasone (100nM) treated CCRF-CEM cells transduced with shCERS6 was 5% ($p<0.001$) and 2% ($p<0.001$) with a significant increase in apoptotic cells compared with the percent survival of 87% and 33%, for non-targeted shRNA-transduced cells. CERS6 overexpression in CCRF-CEM cells conferred resistance to ABT-737 and dexamethasone. The percent survival in cells with exogenous CERS6 treated with ABT-737 (300nM) or dexamethasone (100nM) for 72h was 39% ($p<0.001$) and 40% ($p<0.001$) relative to 2% and 1% for vector control. Higher cleaved PARP, cleaved Caspase 3 and cleaved Caspase 8 were observed in CCRF-CEM cells with CERS6 knockdown, which was reversed by overexpression of CERS6, suggesting that CERS6 alters ALL cell sensitivity to anti-leukemia drugs via extrinsic pathway of apoptosis. **Conclusions:** Altered CERS6 expression significantly affected the sensitivity to ABT-737 and dexamethasone in ALL cells via extrinsic apoptotic pathway. Understanding the mechanism by which CERS6 interferes with apoptosis, could enable discovery of novel targets for ALL treatment.

109 **Poster Session A**

LinkedOmics: analyzing multi-omics data within and across 32 cancer types *Bing Zhang, Baylor College of Medicine; S. Vasaikar; S. Peter; J. Wang*

Introduction: The Cancer Genome Atlas (TCGA) project has performed molecular profiling of human tumors using genomic, epigenomic, transcriptomic, and proteomic platforms, and each tumor is comprehensively characterized by around 100,000 molecular attributes in addition to typical clinical attributes. To make these data directly available to the entire cancer research community, several data portals have been developed. However, none of the existing data portals allow systematic exploration and interpretation of the complex relationships between the vast amount of clinical and molecular attributes. **Methods:** We developed LinkedOmics (http://www.linkedomics.org), a web platform that focuses on the discovery and interpretation of associations between clinical and molecular attributes. LinkedOmics includes three data analysis modules. The LinkFinder module allows flexible exploration of associations between a molecular or clinical attribute of interest and all other attributes, providing the opportunity to analyze and visualize associations between billions of attribute pairs for each cancer cohort. The LinkCompare module enables easy comparison of the associations identified by LinkFinder, which is particularly useful in multi-omics and pan-cancer analyses. The LinkInterpreter module transforms identified associations into biological understanding through the pathway and network analysis. All modules provide user-friendly data visualization. **Results:** The current version of LinkedOmics contains multi-omics data and clinical data for 32 cancer types and a total of 11,158 patients from the TCGA project. It is also the first multi-omics database that integrates mass spectrometry (MS)-based global proteomics data generated by the Clinical Proteomic Tumor Analysis Consortium (CPTAC) on selected TCGA tumor samples. In total, LinkedOmics has more than a billion data points. We used several case studies to demonstrate the utility of LinkedOmics in revealing functional impact of somatic mutation or copy number alteration on mRNA or protein expression, in deriving multi-omics based protein signature for poor prognosis, in performing pan-cancer analysis to identify survival-associated gene expression signature, and in connecting novel pan-cancer poor prognosis markers to tumor invasiveness and aggressiveness. **Conclusions:** LinkedOmics provides a unique platform for biologists and clinicians to access, analyze and compare cancer multi-omics data within and across tumor types.

110 **Poster Session B**

Cyclic Mechanical Strain Regulates Cancer Drug Resistance and Metastatic Potential *Adrianne Spencer, The University of Texas at Austin; J. Lee; D. Chavarria; D. Choksi; A. Baker*

Introduction: Drug resistance and metastasis are two major barriers to the effective treatment of cancer. A major limitation in the discovery and development of drugs that overcome drug resistance or prevent the

spread of cancer is a lack of high throughput in vitro assays that accurately recreate the cell-cell interactions and mechanical forces that occur during cancer progression and metastasis. **Methods:** To investigate the role of cyclic mechanical strain in the regulation of drug resistance, we used a high throughput biaxial oscillating stretch system (HT-BOSS) to mechanically strain cancer cells at a range of percent strains. Cells were plated in custom-made well plates with flexible silicone membrane bottoms. MDA-MB-231 breast cancer cells were mechanically strained for 24 hours at strains ranging from 0 – 17.5% strain. RNA sequencing, immunostaining, cell adhesion, and drug resistance studies were conducted to assess drug resistance and metastatic potential after cells were conditioned with mechanical strain. Cancer cell adhesion to endothelial cells in the presence of fluid flow was used as one metric to evaluate metastatic potential in cells. Breast cancer cells were conditioned with mechanical strain at a range of strains and then an adhesion assay was performed in the presence of shear stress. **Results:** Conditioning with mechanical strain resulted in a decrease in proliferation of MDA-MB-231 breast cancer cells compared to unstrained cells. RNA sequencing identified increased expression of genes associated with drug metabolism, cell adhesion, and proliferation in breast cancer cells mechanically strained at 7.5 and 15% strain for 24 hours. An assay investigating cell survival in response to chemotherapeutic drug treatment found that strained cells were less effected by the drug treatment. Additionally, mechanically strained cells appear to be significantly less proliferative while being strained. Mechanical strain at strains ranging from 2.5 – 17.5% increased adhesion of breast cancer cells to endothelial cells in the presence of fluid flow. Meanwhile, treatment of breast cancer cells with integrin inhibitors while being strained attenuated the increased adhesion to activated endothelial cells. **Conclusions:** Our findings indicate that cyclic mechanical strain regulates drug resistance, proliferation, and cell adhesion in the presence of flow in MDA-MB-231 breast cancer cells as demonstrated through gene expression, protein expression, and functional assays.

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111 **Poster Session A**

NELF-mediated RNA polymerase II pausing contributes to BRCA1-associated breast cancer development and progression *Chi Zhang, The University of Texas Health Science Center at San Antonio; X. Zhang; H. Chiang; B. Yuan; Y. Hu; R. Li*

Introduction: Negative elongation factor (NELF), a four-subunit protein complex (NELFA, B, C/D and E), is well known for its function in mediating RNA polymerase II pausing at the promoter-proximal region. Published work indicates that NELF plays physiological roles in tissue development and homeostasis. Notably, recently published work from our laboratory demonstrates that tissue-specific deletion of NELFB in mouse mammary gland results in severely developmental defects. However, the role of NELF in cancer development and progression remains unclear. Previous study of our lab found that NELFB/COBRA1 directly interacts with BRCA1, thus offering a potential link between NELF and the tumor-suppressing activity of BRCA1. **Methods:** To investigate NELF's function in the initiation of BRCA1-associated breast cancer, we generated mammary epithelium-specific BRCA1 and COBRA1 double knockout mice. We compared normal mammary development and tumor development in BRCA1/NELF single and double knockout mice. To study NELF's function in breast cancer progression, we manipulated NELF expression levels in breast cancer cells and assessed the impact of NELF depletion and overexpression using in vitro and in vivo tumor assays. To determine the clinical relevance, we also analyzed the expression levels of the four NELF subunits in various breast cancer subtypes using public datasets. **Results:** We found that BRCA1 and NELF double knockout mice exhibited significantly lower mammary tumor incidence than BRCA1 single knockout mice. Ablating NELFE in MDA-MB-436 cells resulted in reduced colony formation. Moreover, bioinformatics analyses using public datasets revealed that mRNA levels of NELFE were increased in all subtypes of breast cancer compared to normal tissue, with the highest in triple negative breast cancer. Furthermore, high expression levels of NELFE in patients are associated with poor survival rate. **Conclusions:** Taken together, our results suggest that NELF not only promotes BRCA1-associated mammary tumourigenesis but also facilitates breast cancer progression. Molecular and genomic characterization of NELF functions in BRCA1-associated tumorigenesis will be presented.

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112 **Poster Session B**

Deconvolution of colorectal cancer omics data *Chen Huang, Baylor College of Medicine; E. Lurie; A. Milosavljevic; R. Slebos; D. Liebler; B. Zhang*

Introduction: Tumor is a complex tissue containing not only cancer epithelial cells but also many other cell types, including fibroblasts, endothelial cells, and immune cells. Dissecting cell-specific physiology from the whole bulk tumor is necessary to understand intra-tumor functional interaction and provide additional clues for immune therapy development. Compared with traditional flow cytometry- or laser capture microdissection (LCM)-based cell isolation, in silico data deconvolution provides a fast and non-invasive way to investigate the tumor composition and cell type-specific gene expression. **Methods:** In this project, we used EDec to deconvolve the colorectal cancer (CRC) RNA and protein expression data, which are from TCGA and CPTAG datasets, respectively. During the deconvolution, CRC is assumed to be comprised of four cell types: cancer epithelial, normal epithelial, stromal and immune cells. There are two steps in EDec deconvolution pipeline. In the first step, EDec uses whole genome DNA methylation as the input and generates constituent cell proportions for each sample. By using this cell proportion information, EDec then takes the combined gene expression from whole bulk tumors as the input, and outputs the cell type-specific gene expression in the second step. **Results:** By using the EDec pipepline, we obtained the relative ratio of constituent cell types and their specific gene expression. Our preliminary deconvolution of colorectal cancer successfully recapitulated the cell composition difference across cancer subtypes. It also discovered cell-specific markers for each constituent cell types. Furthermore, the cell type-specific protein expression resulted from deconvolution was well-supported by an independent proteomic dataset from LCM-based cell isolation. Most of the protein expression patterns were also consistent with those reported by the Human Protein Atlas (HPA). As a proof of concept, we showed that functional analysis based on cell-type specific gene expression could identify novel enrich pathways, which would be otherwise masked in the heterogenous bulk tumor expression datasets. Finally, we identified several significant cell-type specific protein markers whose expression are associated with distinct clinical outcomes, highlighting the value of deconvolution in identifying prognostic factors. **Conclusions:** Cell type-specific expression of colorectal cancer generated by in silico data deconvolution provides deeper insights into functional analysis and clinical prediction.

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113 **Poster Session A**

Change in expression of drug resistance-associated genes after chronic drug treatment in a model of Kaposi Sarcoma *Nooshin Mirza Nasiri, University of North Texas; R. Robey; F. Ali-Rahmani; M. Gottesman*

Introduction: AIDS-related Kaposi sarcoma (KS) is a type of cancer that occurs commonly in AIDS patients. It develops from the cells that line lymph or blood vessels in patients with seriously compromised immune systems. AIDS-related KS is commonly treated with protease inhibitors (PIs) such as atazanavir, darunavir, ritonavir, lopinavir and nelfinavir. Chemotherapy, such as adriamycin and taxol, is also used to treat KS when antivirals do not control the disease. Members of the ATP-binding cassette (ABC) protein family of drug efflux transporters including ABCB1, ABCC1, ABCG2 are the main cause of multi-drug resistance (MDR) in cancer cell lines and transport a wide variety of agents out of the cell against a concentration gradient. PIs are known to be both substrates for and inhibitors of ABC transporters. A previous study from our lab reported upregulation of ABCB1 in the SLK Kaposi sarcoma cell line after chronic treatment with doxorubicin in the presence of antivirals. However, this cell line was found to actually be a renal cell line CAKI-1, leading us to repeat the experiments with the L1T2 cell line derived. We treated the L1T2 cell line with taxol and/or protease inhibitors, and examined gene expression changes. **Methods:** To study gene changes in the L1T2 cell line, cells were treated for 4 weeks with protease Inhibitors and/or taxol after which RNA was isolated and gene expression was measured with a custom TaqMan low-density array (TLDA). To determine whether L1T2 cells express functional P-gp, first cell membrane expression was measured by flow cytometry in untreated L1T2 cells and treated cells, then efflux of the fluorescent substrate rhodamine 123, and three-day cytotoxicity assays were performed on L1T2 cells or L1T2 treated cells. **Results:** Results showed taxol treatment led to higher expression of ABCB1 expression, ritonavir led to higher expression of ABCG2, and nelfinavir treatment increase both ABCB1 and ABCG2 expression. While darunavir treatment led to decreased ABCB1 expression. We focused on P-glycoprotein (P-gp), the product of the ABCB1 gene expression. Valspodar led to an increase in intracellular rhodamine fluorescence due to inhibition of P-gp activity. Lopinavir, nelfinavir, ritonavir and atazanavir also appeared to inhibit P-gp activity. **Conclusions:** Combination of taxol or doxorubicin with protease inhibitors as treatment for L1T2 cells leads to increased efficacy via inhibition of P-gp activity; however, treatment of L1T2 cells with taxol alone or individual protease inhibitors leads to changes in expression of ABC transporter proteins.

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114 **Poster Session B**

Role of plasmacytoma variant translocation-1 in promoting osteosarcoma metastasis *Susan Tsang, Baylor College of Medicine; L. Kurenbekova; M. Nomura; N. Rainusso; J. Yustein*

Introduction: Osteosarcoma is the most prevalent bone cancer in pediatric and adolescent patients. Patients who present only primary lesions have an approximately 60% chance of survival, while those who

develop secondary lesions have a 20% survival rate. Because current treatments are not as beneficial to patients with metastatic disease, our project is focused on understanding genes which enhance primary lesions ability to adopt a more aggressive behavior. Our institute and other research groups have shown that patients with 8q24 amplification have a worse prognosis compared to those who have chromosomal balance of this same region. Besides c-Myc, this region harbors a long non-protein coding RNA called plasmacytoma variant translocation-1 (PVT-1). The aim of our study is to characterize the phenotypic and mechanistic role of PVT-1 in osteosarcoma. **Methods:** The phenotypic role of PVT-1 is done by using an osteosarcoma cell line, HOS, which has either stable overexpression of PVT-1 or the corresponding blank control. We used these cell lines to perform proliferation, migration, and invasion assays. In addition, In Vivo studies are currently being conducted to identify if the In Vitro results could be recapitulated in a whole organism. Secondly, we will elucidate the mechanism which PVT-1 uses to promote these tumorigenic behaviors. The mechanism(s) will be identified by determining PVT-1 direct binding partners and this will be done by using Chromatin Isolation by RNA Purification followed by mass spectrometry/ sequencing. To determine potential signaling pathways dependent or downstream of PVT-1, we will perform Reverse Phase Protein Array and Gene Expression Array. Subsequently we will perform In Vitro and In Vivo studies to verify the existence of these pathways. **Results:** PVT-1 is overexpressed in a significant subset of human osteosarcoma sample tumors. In Vitro studies demonstrate that overexpression of PVT-1 enhances proliferation, migration, and invasion phenotypes. In addition, In Vivo experiments are ongoing. **Conclusions:** PVT-1 ability to promote multiple tumorigenic behaviors could mean that PVT-1 plays an important role in tumor progression. Experiments are currently being performed to determine the mechanism(s) by which PVT-1 is able to induce these phenotypes.

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115 **Poster Session A**

Structural and functional characterization of LEDGF/p75 in complex with cellular and pathogenic binding partners *Katerina Cermakova, Baylor College of Medicine; H. Hodges*

Introduction: Lens Epithelium Derived Growth Factor (LEDGF, p75, or PSIP1) is a chromatin tethering factor that binds H3K36me2/3 marks through its PWWP domain and recruits other regulators to actively transcribed genes. At gene bodies, LEDGF/p75 recruits diverse proteins through its integrase binding domain (IBD), including MLL1-containing COMPASS complexes. The interaction of MLL1 with LEDGF/p75 is essential for cellular transformation in mixed lineage leukemia, and we have recently validated this interaction as a target for therapeutic intervention. Furthermore, LEDGF/p75 plays important roles in other disease settings, such as HIV/AIDS. Here, the LEDGF/p75 chromatin tethering function is hijacked by human immunodeficiency virus 1 (HIV1) to guide viral integration into active chromatin. Formation of the HIV1 integrase-LEDGF/p75 complex is a crucial step in viral replication, making LEDGF/p75 an attractive therapeutic target for two diseases with significant impacts on human health. Unfortunately, the structural basis for its diverse physiological roles has remained poorly understood because binding lifetimes are transient and short-lived. **Methods:** We performed a structural investigation of LEDGF/p75 and its binding partners using protein NMR on free proteins and protein chimeras. Specifically, we mapped the interaction interfaces and resolved the structures of LEDGF/p75 in complex with known binding partners, including MLL1, the Myc-interacting factor JPO2 (CDCA7L), and the Zinc-finger protein POGZ. **Results:** We find that interaction of LEDGF/p75 with these factors arises through a conserved short linear motif (SLIM) that adopts a characteristic structure upon binding. Moreover, we identified and validated IWS1 and MED1 as two novel LEDGF/p75 interaction partners, implicating LEDGF/p75 as a component of a key transcriptional regulatory network. **Conclusions:** By revealing the structural basis for the LEDGF/p75 network, our results provide important insight for ongoing drug discovery efforts.

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116 **Poster Session B**

NOTCH1 activation inhibits head and neck squamous cell carcinoma growth *Chenfei Huang, Baylor College of Medicine; S. Moorthy; Q. Li; R. Saade; J. Wang; X. Rao; N. Tanaka; J. Zhang; L. Tang; C. Pickering; P. Zweidler-McKay; A. Osman; T. Xie; E. Shinbrot; L. Xi; D. Wheeler; A. El-Naggar; J. Wang; J. Myers; M. Frederick*

Introduction: NOTCH signaling is known to have a critical role in cell fate decisions, and in cancer the NOTCH1 gene can function as either an oncogene or tumor suppressor depending upon the tumor type. Our group previously discovered NOTCH1 is one of the most frequently altered genes, with a pattern of inactivating mutations suggesting NOTCH1 is a tumor suppressor in in this cancer type. However, recent work by others suggests NOTCH1 signaling possibly promote a more aggressive phenotype or cancer stem cell properties in HNSCCs. Our present study is aimed to systematically compare the phenotypic consequences of NOTCH1 signaling in HNSCC to fully understand its role during HNSCC development, and identify the downstream targets modulated by NOTCH1 signaling. **Methods:** Established HNSCC cell lines wild type for NOTCH1 (PJ34, FADU) or harboring an inactivating mutation (UMSCC22A) were engineered to express activated cleaved NOTCH1 under control of a doxycycline-inducible promoter. Cell growth in two-dimensional cultures was measured with clonogenic assays. Stem-like properties were measured by orosphere formation capacity and anoikis resistance. Aldehyde dehydrogenase activity (ALDH) and CD44 expression were used as stem cell markers for HNSCC, which were tested by flow cytometry. NOTCH1-regulated downstream gene expression changes were examined using RNA-seq and qRT-PCR. **Results:** Activation of NOTCH1 signaling inhibits clonogenic growth of all three cell lines. This growth inhibition is frequently accompanied by spontaneous formation of spheroid-like structures, which shows stem cell appearance. We also find activated NOTCH1 in UM22A and FADU cells promotes orosphere formation and anoikis resistance, conveying some stem-like properties. However, classical stem cell markers including ALDH activity and CD44 expression were not affected by NOTCH1 activation. Furthermore, RNA-seq data demonstrated that NOTCH1 regulated critical cancer associated pathways, including proliferation, differentiation, and migration. Of particular interest, NOTCH1 activation downregulated gene expression of ITGA3, ITGA4, ITGB1, ITGB6, and LAMC2, which are key adhesion molecules that human basal keratinocytes use for attachment to the basement membrane and maintenance in the stem cell compartment. Additionally, NOTCH1 activation downregulates the proto-oncogene AXL and a-catulin. Diminished expression of AXL and a-catulin leads to a loss of HNSCC cell growth capacity. Concomitantly, NOTCH1 activation increased the basal/superbasasl marker SOX2, but also the early differentiation markers KRT4 and KRT13. **Conclusions:** NOTCH1 functions as a tumor suppressor in HNSCC by downregulation of AXL kinase and a-catulin. Stem cell like properties associated with NOTCH1 activation in HNSCC may be a consequence of pathways that recapitulate early differentiation, rather than stem cell maintenance.

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117 **Poster Session A**

Ornithine aminotransferase (OAT) and Adenosylmethionine decarboxylase 1 (AMD1) as novel genes associated with health disparity of prostate cancer *Hamdy Ali, Texas A&M University System Health Science Center; S. Gad; A. Sholl; H. Ali; Z. Abd Elmageed*

Introduction: Prostate cancer (PCa) is the second cause of death in elder men. The incidence and mortality rates of PCa are twice higher in African American (AA) than in Caucasian American (CA) men. The molecular changes associated with this disparity among AA men still unknown. We aim to compare the expression of OAT and AMD1 and identify their underlying molecular mechanisms involving in promoting the disproportionate of PCa among AA men. **Methods:** The expression of OAT and AMD1 in AA men was carried out by Real-Time PCR, Western blot and Immunohistochemical (IHC) analyses in PCa cells derived from AA and CA men. Validation of these genes was performed on forty Paraffin-embedded PCa tissue sections and their expression was correlated with clinical outcomes of PCa patients. **Results:** Upregulation of OAT and AMD1 ($p<0.05$) was identified in PCa cells derived from AA compared to CA men. Overexpression of OAT, AMD1 in AA cell lines was further confirmed by Western blot analysis. IHC studies revealed that these two proteins were differentially expressed in AA PCa tissues and were positively correlated with tumor stage and biochemical recurrence-free survival in PCa patients. **Conclusions:** The differential gene expression of OAT and AMD1 in PCa anticipates that dysregulation of these transcripts in AA compared to CA men may underlie the genetic factors contribute to health disparity of PCa. These data provide new insights into development of reliable diagnostic and prognostic markers of aggressive PCa among AA men.

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118 **Poster Session B**

Investigating the role of neutrophil elastase in breast cancer growth and metastasis *Taylor Chrisikos, The University of Texas M.D. Anderson Cancer Center; H. Li; S. Akli; K. Keyomarsi; S. Watowich*

Introduction: Breast cancer is the most common cancer among women, with metastatic disease causing the majority of breast cancer-related mortalities. Nonetheless, treatment options for metastasis remain limited. Previous studies have indicated that immune cells within the tumor microenvironment and the pre-metastatic niche play a large role in regulating metastasis. For example, in a spontaneous model of breast cancer (PyMT), neutrophils have been implicated in promoting lung metastasis. However, in neutrophil elastase knockout PyMT mice, lung metastasis is greatly reduced. Determining the mechanisms by

which neutrophil elastase contributes to metastasis could lead to novel therapeutic interventions for treatment of metastatic breast cancer. **Methods:** Flow cytometry was used to evaluate immune cells in organs and tumors. Multiplex assays were used to measure serum cytokines. FACS was used to purify cell subsets from tumors and RNA expression was assessed by qRT-PCR. Mice: FVB/N-Tg(MMTV-PyVT)634Mul/J; B6.129X1-Elane^{tm1Sds}/J; C57BL6/J Cell lines: Polyclonal PyMT tumor cell line derived from PyMT+ C57BL6/J mouse, acquired from DG DeNardo (Department of Pathology & Immunology, Washington University School of Medicine in St. Louis). **Results:** PyMT tumors drove the expansion and mobilization of myeloid populations from the bone marrow. Deletion of neutrophil elastase had no effect on the development or distribution of neutrophils in steady state conditions; however, in PyMT+ tumor-bearing mice, removal of neutrophil elastase reduced the frequency of specific myeloid populations, including neutrophils and macrophages, in the lungs and liver. Serum cytokine analyses revealed that PyMT+ mice lacking neutrophil elastase had reduced levels of G-CSF, CCL2, CCL7 and CXCL1, compared to tumor bearing mice with neutrophil elastase. In mice orthotopically injected with a PyMT tumor cell line, tumor volume was reduced two-fold in mice without neutrophil elastase. RNA expression analyses of purified populations isolated from the tumor microenvironment revealed that PyMT tumor cells and the non-immune stroma produced G-CSF. In contrast, CCL2, CCL7 and CXCL1 were produced by the immune infiltrate within the tumors. **Conclusions:** Neutrophil elastase promotes tumor growth and is correlated with increased levels of myeloid growth factors and chemoattractants that can be produced in the tumor microenvironment. Elevated expression of these factors may influence the abundance and infiltration of myeloid populations in the lungs and other organs of tumor-bearing mice. Future studies will determine the specific roles of neutrophil elastase in promoting these immune populations and how they contribute to tumor growth and metastasis.

119 **Poster Session A**

Kinetics of small molecule interactions with membrane proteins in single cells measured with mechanical amplification *Yan Guan, Arizona State University*

Introduction: Advances in structural biology have led to an exponential growth in the number of membrane proteins with determined three-dimensional (3D) structures. However, to understand the cellular functions of membrane proteins, it is also necessary to determine the interaction kinetics of the membrane proteins with various molecules. This is because cells perform many functions, including communication, through the interactions of their membrane proteins with molecules in the extracellular medium. However, measuring the interactions of molecules with membrane proteins in the natural lipid environment has been a difficult task. **Methods:** The mechanical deformation is expected because the law of thermodynamics predicts that when molecules bind to a surface, the surface tension changes, leading to amechanical response in the cell membrane. According to thermodynamics, the surface concentration of molecules bound on the membrane surface is proportional to the derivative of surface tension and to the chemical potential of the molecules. At the same time, the chemical potential is related to the bulk concentration. Therefore, the molecular binding is directly proportional to the surface tension change, and thus, the molecular interactions with the membrane proteins can be determined by measuring the mechanical deformation in the membrane. **Results:** We report an observation of mechanical deformation of cells upon interactions of the cellular membrane proteins with molecules in the extracellular medium, and demonstrate a real-time analysis of the interactions in single cells by analyzing the mechanical deformation with subnanometer resolution. Our measurement is based on a differential detection method that provides subnanometer accuracy to monitor cell edge deformation. Using this capability, we have monitored the kinetics of both large and small molecule interactions with membrane proteins, including glycoproteins and ion channels in intact cells (fixed or living), and obtained the binding kinetic constants. For large molecules, the kinetic constants agree with those obtained with a plasmonic imaging technique. For small molecules, the present method represents the first kinetic measurement, and direct comparison with other techniques is not possible, but the equilibrium constants extracted from the present method are consistent with those obtained with end-point radioactive labeling assays. The imaging capability allowed us to reveal cell-to-cell variability and region-to-region variability within the same cell. **Conclusions:** This new strategy provides mechanical amplification of small binding signals, making it possible to detect small molecule interactions with membrane proteins. This capability, together with spatial resolution, also allows the study of the heterogeneous nature of cells by analyzing the interaction kinetics variability between different cells and between different regions of a single cell.

120 **Poster Session B**

Metabolomic profiling provides insight into human disease *Katarzyna Broniowska, Metabolon, Inc.; T. Everingham; J. Kinchen; K. Beebe*

Introduction: Although cancer is well recognized as a genetic disease, there is an emerging awareness that the host of mutations driving it converge to promote an established hallmark of tumor cells – reprogramming of metabolic potential to support unrestricted growth. In addition to this role, recent work has extended the relevance of metabolism to the host immune response, as well as interplay with the environment (e.g. the role of the microbiome) in response to therapies. Metabolomic technology therefore have become an important focus for oncology (as well as being a useful tool for phenotypic profiling in other research areas). Metabolon is a world leader in the metabolomic analyses – illustrating this premise, we will highlight our unique portfolio of technologies, and how this technology can be applied to advance cancer research. **Methods:** Our primary platform, DiscoveryHD4, provides whole-metabolome coverage across all major metabolite classes, with the option of additional complex lipid coverage. This unparalleled profiling technologies quickly and accurately identify and quantify metabolites and map molecule pathways to identify diseases, discover biomarkers and better understand complex biological processes. The details of our technology will be discussed during the presentation. **Results:** Metabolomic technology has become an important focus for oncology. Specific case studies and examples will be detailed in the discussion. **Conclusions:** Metabolomic profiling can provide mechanistic insight into human disease, or biomarkers for clinical studies.

121 **CPRIT Grantee Poster Session B**

Development of DNA-compatible Suzuki-Miyaura Reaction in Aqueous Media *Jian-Yuan Li, Baylor College of Medicine; H. Huang*

Introduction: DNA-encoded chemical library (DEL) is a cost-effective technology for discovery of novel chemical probes and drug candidates. Combining the benefits of combinatorial chemistry and next-generation DNA sequencing, DEL enables exploration of greater chemical space than conventional high throughput screening and allows simultaneously screening of hundreds of millions of compounds. A major limiting factor in assembling productive DELs is the availability of DNA-compatible chemical reactions in aqueous media. **Methods:** In an effort to increase the chemical and structural diversity of small molecules displayed by the DEL, we have developed a robust Suzuki reaction that is compatible to the DNA structures. Suzuki coupling is a time-tested method for the synthesis of pharmaceuticals and bioactive molecules. **Results:** By employing a water soluble Pd-precatalyst, we have developed conditions that allow efficient coupling of aryl bromides/chlorides and a wide variety of boronic acids including heteroaromatic boronic acids. In addition, we have applied this Suzuki reaction to the DNA bifunctional scaffold with heteroaryl bromide and amine that could be further functionalized. **Conclusions:** The novel Suzuki reaction with a broad substrate scope enables synthesis of drug-like molecules in aqueous media. The compatibility of the developed method to the synthesis of DEL will also be discussed.

122 **CPRIT Grantee Poster Session B**

DNA Compatible Nitro Reduction and Benzimidazole Synthesis *Huang-Chi Du, Baylor College of Medicine; H. Huang*

Introduction: DNA-encoded Library (DEL) has emerged as a cost-effective alternative technology for hit generation that addresses the limitations and economic shortcomings of high-throughput screening (HTS). DEL enables the exploration of chemical spaces four to five orders of magnitude greater than is achievable by traditional HTS methods, resulting in the direct discovery of high-affinity ligands to disease targets. The key to the success of DEL is the structural diversity of the small molecules displayed by the library. But it is often limited to DNA compatible chemical reactions in aqueous media. **Methods:** In order to increase the library structure diversity, we developed a facile sodium dithionite–mediated nitro reduction in water and subsequent synthesis of benzimidazoles on DNA. **Results:** By employing sodium dithionite, we have established an efficient protocol for reducing nitro group. The new protocol offers easy operation and circumvents pyrophoric potential of the conventional method (Raney Ni). The utility of this method is also demonstrated in versatile synthesis of benzimidazoles on DNA. **Conclusions:** In summary, we have developed a facile and versatile method to reduce DNA-conjugated aryl nitro compounds to corresponding amines in aqueous media. The utility of this methodology was demonstrated in one-pot synthesis of various benzimidazoles on DNA. With a broad substrate scope and simple operation, the newly developed chemistry is expected to find wide use in the preparation of diverse DELs.

123 **CPRIT Grantee Poster Session B**

Cryo-EM structural refinement of cancer targets at near-atomic resolution *Fengyun Ni, Baylor College of Medicine; T. Ma; T. Zang; J. Ma; Q. Wang*

Introduction: Cryo-electron microscopy (Cryo-EM) has emerged as a promising technique for understanding molecular mechanisms of carcinogenesis and progression. Hardware advances in recent years have allowed atomic-resolution single-particle Cryo-EM reconstruction for macromolecular assemblies with high symmetry. However, this atomic resolution is still beyond the reach for many biomolecular assemblies of lower or no symmetry. Thus, there is an urgent need for advanced computational methods to aid in Cryo-EM reconstruction at near-atomic resolution. Our lab recently developed a powerful Parallel Continuous Simulated Tempering (PCST) algorithm that is highly efficient in accelerating barrier crossing and finding native structures than a conventional simulated annealing method. In this study, we introduce the PCST algorithm to refine Cryo-EM structures of three cancer targets at near-atomic resolution. **Methods:** To benchmark the application of PCST algorithm to Cryo-EM structural refinement, we choose three cancer targets: 20S proteasome (6.8 Å), AAA ATPase p97 (6.9 Å), and group II chaperonin Mm-cpn (8.0 Å). The initial model will be used to prepare a structural-based force field to guide configurational search by PCST algorithm. Plausible models are selected from resulting trajectory by statistical potential and further fitted into Cryo-EM densities. The models will be further analyzed in three aspects: 1) to examine the model quality by calculating geometry statistics; 2) to convert root mean square fluctuation of the system to atomic B-factors that will be compared with resolution distribution of experimental map; and 3) to identify the potential functional motions of the system through structural ensemble analysis of the trajectory. **Results:** By examining the quality of refined structures from our studies and comparing with corresponding high-resolution crystal structures if available, these test cases will demonstrate the applicability of PCST algorithm to Cryo-EM structural refinement at near-atomic resolution. The enhanced sampling efficiency of PCST algorithm generates better conformations for fitting into Cryo-EM map. Investigation of atomic fluctuations in structural model will provide a more valid description of Cryo-EM map quality. Structural ensemble analysis of the PCST trajectory will shed new light on dynamic properties intrinsic to a given system. **Conclusions:** With the combination of structural-based modeling and enhanced sampling by PCST, our strategy not only improves Cryo-EM structures at near-atomic resolution, but also better interprets experimental map quality. This method is expected to help solve Cryo-EM structure of Polycomb repressive complex 2, a master epigenetic regulator.

124 **CPRIT Grantee Poster Session B**

Efficient acylation of DNA-conjugated carboxylic acids with amines in aqueous media *Mee-Kyung Chung, Baylor College of Medicine; H. Huang*

Introduction: DNA-encoded chemical library (DEL) has emerged as a cost effective platform for hit generation. The chemical and structural diversity of the small molecules displayed by the DEL is critical to successful discovery of novel drug-like chemical matters. Thus, the availability of efficient synthetic methods that enable facile derivatization and are compatible with structurally diverse building blocks is key to the preparation of productive DELs. Due to the easy access to large and diverse sets of carboxylic acids and amines, amide bond formation, i.e., acylation is one of the key reactions for DEL synthesis. While the majority of the reported acylation involve reactions between DNA-conjugated amines and carboxylic acids, there are few examples of acylation between DNA-conjugated carboxylic acids and amines. In addition, the existing methods are limited in substrate scope and are not effective with sterically hindered carboxylic acids. **Methods:** We developed a facile and versatile PyAop mediated amide coupling between DNA-conjugated carboxylic acids and amines. The reactions were optimized by systematically changing various parameters (temperature, buffers, pH and concentration) and the optimized conditions were then applied to a wide range of amines and acids. DEL synthesis compatibility was also investigated using DNA tag ligation. In addition, the mechanism of activation of acid in water was also investigated by PyAop stability tests. **Results:** The PyAop mediated acylation was optimized by temperature, buffer media and the sequence of adding reagents. The reaction offered a broad substrate scope in terms of both acids and amines. DNA-conjugated sterically hindered carboxylic acids efficiently coupled with a wide variety of amines. Successful DNA tag ligation showed that the PyAop mediated acylation is compatible with DNA structure. **Conclusions:** Facile and versatile PyAop mediated amide coupling between DNA-conjugated acids and amines in aqueous media was successfully developed. The new protocol demonstrated a broad substrate scope. The reaction conditions were compatible with the DNA structure and were amenable to DEL synthesis.

125 **CPRIT Grantee Poster Session B**

Center for Innovative Drug Discovery: Enhancement of a Shared Cancer Resource for South Texas *Stanton McHardy, The University of Texas at San Antonio; M. Hart*

Introduction: This presentation will outline the enhancement and growth of the existing Center for Innovative Drug Discovery (CIDD), a truly first of its kind resource of core facilities and capabilities in South Texas, to better support the discovery and development of new cancer therapeutics. **Methods:** The CIDD, which is comprised of two integrated core facilities for Medicinal Chemistry at UTSA and High Throughput Screening (HTS) at UTHSCSA, has been providing researchers in San Antonio and South Texas access to coordinated technologies, services and expertise that advance drug discovery and development for the last 5 years. The two core facilities provide research collaborations and services that support multiple stages of early, pre-clinical cancer therapeutic development. **Results:** Through multidisciplinary and multi-institutional collaborations, the CIDD has worked on >40 cancer related programs at multiple stages of the pre-clinical drug discovery process and had significant impact in program development and strengthening extramural funding opportunities for researchers. **Conclusions:** The overriding goal of this CPRIT supported core facility is to further enhance and grow the capacity of the CIDD to create the most comprehensive and innovative pre-clinical drug discovery and development facility in South Texas to support the discovery of new cancer therapeutics. This presentation will provide an overview of the CIDD, capabilities and resources, as well as specific program examples.

126 **CPRIT Grantee Poster Session B**

Enantioselective Synthesis of CIDD-0072424; A PKC epsilon Inhibitor to Reduce Alcohol and Nicotine Consumption for Cancer Prevention *Hua-Yu Wang, The University of Texas at San Antonio; R. Messing; J. Wang; S. McHardy*

Introduction: One-fifth of the world's population uses tobacco products, and in the US approximately 50% of all cancer deaths are attributable to smoking. Tobacco use increases risk of cancer of the lung, mouth, larynx, pharynx, esophagus, stomach, colon, rectum, liver, pancreas, kidney, bladder, uterine cervix, and ovary, and possibly breast, and of myeloid leukemia. Almost 40% of the world's population consumes alcoholic beverages and 15% of adults and teenagers over 15 years of age engage in heavy episodic drinking. Recent estimates attribute approximately 5.5% of all cancer deaths worldwide to heavy alcohol use. Therefore, there is considerable need for the development of new therapeutic agents to treat these disorders. Current evidence indicates that protein kinase C epsilon (PKCe) is a good target for development of drugs to treat alcohol and nicotine use disorders, based partially on studies using gene-targeted mice that lack this enzyme (Prkce-/- mice). Preliminary animal studies also show PKCe inhibitors provide robust activity in ethanol and nicotine administration models, as well as various pain models. Through a collaboration with the UT Austin Waggoner Center, the goal of our work is to develop novel, selective, and highly effective PKCe drugs to treat alcohol and nicotine use disorders. **Methods:** With good CNS active lead PKCe inhibitors identified, there was a major unmet research need to improve the current synthesis of these lead compounds and provide a robust synthesis route that is enantioselective, scalable and efficient in order to easily access the structural diversity for 3-point structure-activity relationship (SAR) studies. To this end, we utilized an asymmetric Nitro-Mannich reaction as the key step in building the desired chiral diamine moiety present in lead PKCe compounds. **Results:** After screening several organocatalysts and conditions, the key Nitro-Mannich reaction sequence was achieved in 98% yield and 95% enantiomeric excess. The overall synthesis provided the desired compound in 8 steps and 35% overall yield. **Conclusions:** The new and improved enantioselective synthesis of CIDD-0072424 provides the desired compound in high yield and high optical purity, as well as allows for rapid, 3-piont SAR studies. This presentation will highlight the new enantioselective synthesis of CIDD-0072424 and PKCe SAR studies, as well as key ADME data on this lead compound.

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Development of an informatics platform for the analysis of DNA-encoded library screens to enable small molecule drug discovery *Kevin Riehle, Baylor College of Medicine; J. Faver*

Introduction: DNA-encoded library (DEL) screening is a modern small molecule drug discovery strategy which combines the strengths of combinatorial chemical synthesis and high-throughput next-generation DNA sequencing. Such libraries (which typically contain millions to billions of unique molecules) are assayed for binding affinity as a complex mixture, and the identities of potential hit compounds are determined via DNA sequencing. Compared to other drug discovery platforms, successful DEL screening has unique requirements for informatics support which may not be as standardized as methods for high-throughput screening (HTS). To enable DEL screening at Baylor College of Medicine, we have heavily customized our registration environment (Dotmatics software) to allow scientists to manage information about libraries, selection experiments, and sequencing runs in addition to using common features like inventory and electronic lab notebooks (ELNs). **Methods:** This project is supported by a computational cluster and series of virtual machines (VMs) deployed to manage each aspect of the project. The computational cluster allows for the scheduling of many parallel jobs, which decreases the turnaround time and better optimizes the cluster usage by running a series of jobs that have specific hardware requirements. Sequence output (Illumina MiSeq, NextSeq, and HiSeq) resulting from the DEL screen is uploaded via FTP and data files are subsequently accessible on each server / VM, allowing for seamless access to data from any machine within our customized platform. Uploaded sequence files are then linked to their corresponding experiments, which triggers the automated pipeline to decode the results of the selection by querying the registration system for all necessary input. **Results:** We have developed a semi-automated informatics pipeline that decodes the results of DEL screens, leveraging the information (library design, experimental conditions, analysis settings, and amplicon structure) stored in our customized registration environment. **Conclusions:** Customized environments can enable alternative drug discovery platforms via integration with in-house pipelines which provide new functionalities on top of the built-in features (commercially available and open source solutions) to aid in automation and analysis of DEL screens.

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Bioinformatics Core Facility at UT Southwestern Medical Center *Gaudenz Danuser, The University of Texas Southwestern Medical Center; B. Cantarel; Y. Xie; M. Kim*

Introduction: For the past two years we have been building a core facility that serves the cancer community at UT Southwestern in solving bioinformatics tasks. The facility is being established in parallel to the launch of the Lyda Hill Department of Bioinformatics, which grows an academic program in scholarly research and student training in bioinformatics. **Methods:** The Bioinformatics Core Facility (BICF) serves the community in two categories: 1) Foundational services include a help desk, which answers bioinformatics-related questions on the spot or in short-term fee-for-service projects. The help desk also triages complex tasks into one of four top-tier services (see below). Foundational services also include nanocourses, which are two-day courses covering theory and practice of bioinformatics methods; and provision of software pipelines and curated databases that give the cancer researcher with limited bioinformatics expertise convenient access to state-of-the-art data analytical tools. 2) Top-tier services include a 'bioinformaticist-on-demand' program, where a project director can hire a BICF staff member to work on a particular project. The value of this program for the campus is that BICF offers a standing pool of bioinformatics talent, which dramatically shortens recruitment times and retains know-how beyond the sunset of a particular project. Top-tier services also include support with program development, and flagship projects, where BICF leads the development of bioinformatic infrastructure for cancer research (see results). The most unique top-tier service is the fellows program. Trainees and research staff can sign up for a research phase in the BICF quarters, where they get trained and supervised by experienced staff and via peer-to-peer interactions with other fellows. Prior to BICF, these researchers worked in isolation in labs with no tools for quality control in data analytics. The fellows program is conceived after the matrix organization in industry. A fellow works at the intersection between topical guidance by a cancer researcher and technical guidance by BICF staff. **Results:** BICF is staffed by 12 Ph.D. level research associates. We have handled ~100 help desk calls per year, we have accommodated 10 - 15 'bioinformaticist-on-demand' projects, and we have launched 4 major flagship projects. Most importantly, one flagship project contributed all analytics to a CLIA-certified genomic cancer screening pipeline that is now offered at UT Southwestern. **Conclusions:** The launch of BICF has fundamentally changed the quality and accessibility of bioinformatics for cancer research and clinical work at UT Southwestern.

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The CPRIT Therapeutic Antibody Core *Zhiqang An, The University of Texas Health Science Center at Houston; N. Zhang; G. Salazar*

Introduction: Anti-cancer antibodies represent one of the most significant advances in cancer therapy. During the last 25 years, therapeutic antibodies have become a major drug modality for cancer with more than 40 therapies in clinical use and hundreds more in development. This emerging trend is largely due to their desirable safety profile, high target specificity, and efficacy. Despite the success, there is an urgent need for novel antibody cancer targets for all cancer types, especially those of unmet medical needs. Almost all academic researchers engaged in cancer drug target discovery employ antibodies as reagents in both in vitro and in vivo studies. Some of the reagent antibodies exhibit significant efficacy in animal disease models and offer potential for drug development. However, most of the promising antibodies are never advanced further as cancer therapies due to the lack of access to key technologies in therapeutic antibody discovery and development. **Methods:** The CPRIT Therapeutic Antibody Core is a state-of-the-art platform for cancer therapeutic antibody lead optimization and development, which provide state-wide support and service to advance lead antibodies from academic laboratories to the stage of preclinical development. Therapeutic antibody lead optimization is a complex and technologically demanding process. The core facility offers four major functional modules: 1) Lead identification; 2) Lead optimization; 3) Lead construction; and 4) Antibody production. The CPRIT antibody core facility is available to independently funded researchers engaged in antibody drug discovery in Texas-based institutions. By optimizing lead antibody candidates with "drug-like" properties, researchers will gain competitively for attracting alternative funding(s) to continue development of the optimized antibodies for cancer therapies. **Results:** In its first two years, the Therapeutic Antibody Core established a scientific advisory board, established a high throughput antibody discovery and characterization platform, initiated 10 major and 20 minor antibody drug discovery programs, constructed a phage-displayed human antibody library, established an antibody-drug conjugates platform, filed multiple patent applications on cancer antibody drug candidates, publication of peer-reviewed papers, completed two licensing agreements, and

hosted a symposium to showcase successful core supported projects. **Conclusions:** We will continue most of the Core projects initiated during the first couple years into subsequent years. In addition, we will add additional new projects. We anticipate significant outcome from some of the Core projects in the coming years in terms of patent filings, licensing agreements, publications and funded grant proposals.

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Collaborating with the Center for Drug Discovery at Baylor College of Medicine Using DNA-Encoded Chemical Libraries *Hongbing Huang, Baylor College of Medicine; J. Anglin; M. Bangs; K. Bohren; J. Campbell; S. Chamakuri; Y. Chen; M. Chung; M. Corsello; S. Dilliard; H. Du; J. Faver; S. Guduru; P. Jain; Z. Jin; J. Li; G. Miklossy; O. Monty; P. Nyshadham; M. Palaniappan; K. Riehle; P. Rosner; C. Santini; N. Simmons; S. Trivedi; N. Ucisik; Y. Wang; D. Young; Z. Yu; M. Matzuk*

Introduction: Screening DNA-encoded chemical libraries (DELs) is a cost-effective alternative technology for hit generation that addresses the limitations and economic shortcomings of high-throughput screening (HTS). DELs are collections of organic compounds in which each structure is tagged with a DNA identification barcode. In analogy to phage-display technology, the DNA-tag facilitates the synthesis and allows the simultaneous screening of very large sets of compounds. The screening process typically involves affinity selection of libraries against a protein target similar to phage display. The advent of increasingly efficient next-generation sequencing technology for high-throughput DNA sequencing allows simultaneous interrogation of hundreds of millions of compounds at a fraction of the cost for conventional HTS. **Methods:** Employing combinatorial chemistry, we have established a novel DNA-encoded Chemistry Technology (DEC-Tec) platform that leverages the encoding power of DNA to create large collections of small molecules for hit identification. DEC-Tec enables the exploration of greater chemical space than is achievable by traditional HTS methods, resulting in the direct discovery of high-affinity ligands to disease targets. **Results:** Applying novel reaction methods and chemistry schemes, we have built diverse DNA-encoded chemical libraries that consist of more than 1.5 billion of unique drug-like small molecules. Successful selections have been conducted on a diverse set of protein classes including enzymes, binding proteins and transcription factors. High affinity binders have been confirmed in biochemical and biophysical assays. We also obtained co-crystal structures of lead compounds bound to target proteins, which will aid structure-based drug design. **Conclusions:** To serve the biomedical research community in Texas, we have established a straightforward process for collaboration. This collaborative approach will expedite the discovery of novel chemical probes and drug candidates for cancer treatment.

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North Texas Clinical Pharmacology Cancer Core *Trey Putnam, Texas Tech University Health Science Center at Dallas; I. Subramaniyan*

Introduction: The North Texas Clinical Pharmacology Cancer Core (NTCPCC) was established to facilitate translation of basic cancer research into improved care for cancer patients. In order to accomplish this goal, a state-of-the-art analytical/bioanalytical facility was established to help basic cancer researchers and physicians better understand the pharmacokinetics, pharmacodynamics and metabolism of current and potential cancer therapeutics. **Methods:** Overall, the NTCPCC uses its expertise and advanced instrumentation in collaborations with cancer investigators to design and execute studies to understand (1) the optimal way to administer the therapeutic, (2) the action of the therapeutic in the body, and (3) the metabolism of the therapeutic. These aspects are studied in order to maximize efficacy and decrease unwanted side effects. **Results:** A discussion of the current instrumentation and capabilities of the NTCPCC will be presented. Additionally, a summary of current projects will be provided. **Conclusions:** The NTCPCC has been successful in establishing a core facility with the expertise and instrumentation to achieve its specific aims. The NTCPCC has also established active collaborations with cancer investigators and has been successful in conducting several clinical pharmacology focused studies. These collaborations and studies demonstrate that the NTCPCC is achieving its overall goal to help facilitate translation of basic cancer research into improved care for cancer patients.

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Precision oncology decision support core – a high quality, comprehensive clinical research support system *Vijaykumar Holla, The University of Texas M.D. Anderson Cancer Center; J. Zeng; A. Bailey; A. Johnson; N. Sanchez; Y. Khotskaya; B. Litzenburger; M. Shufean; A. Simpson; M. Routbort; J. Rodon; T. Yap; E. Bernstam; G. Mills; J. Mendelsohn; K. Mills Shaw; F. Meric-Bernstam*

Introduction: Cancer is a heterogeneous disease driven by mutations in patient's germline and somatic DNA. Next-generation sequencing (NGS) offers tailored approaches to treating patients based on their tumor genomic profiles. NGS has yielded vast amounts of mutational data, hindering interpretation of the role individual mutations play in tumorigenesis by oncologists without the help of bioinformatic infrastructure. Precision Oncology Decision Support (PODS) core was established to provide point-of-care support locally and across Texas. Herein, we discuss the CPRIT funded PODS core recent progress. **Methods:** PODS core has continued to develop a computational infrastructure that streamlines the annotation process of variants, drugs, and clinical trials. Genomic alterations, therapeutic agents, and clinical trials were annotated using a combination of manual and built-in literature retrieval tools. The functional significance of each variant was assessed and linked to appropriate targeted agents and clinical trials. Annotations were aggregated in a dynamic fashion to facilitate the generation of patient reports, which included a list of matching clinical trials. **Results:** PODS core has built an oncology-centric knowledgebase that is continuously updated. In addition, we increased the breadth of PODS knowledgebase with annotation of drugs (total of 2,354) and clinical trials (total of 4,488). Consequently, PODS generates patient reports that contain variant actionability along with a customized list of matching clinical trials. In addition, we have also implemented an online portal to allow for annotation request submission. To date, PODS has delivered 3,379 total patient reports, covering 14,071 mutations (6,972 unique), to 169 physicians at MD Anderson. Proactive trial alerts were implemented to alleviate physicians' need to keep up-to-date on available clinical trials. To date, 764 proactive trial alerts on 31 genes were sent to 204 physicians. Based on these efforts, enrollment on genotype-selected or relevant trial at MD Anderson has been slowly increasing. To capture whether individual reports are acted upon, a clinical decision follow-up questionnaire is sent to all annotation requestors. Finally, many annotations are available via https://pct.mdanderson.org/ that provides information on 652 functionally or therapeutically significant alterations across 33 genes. **Conclusions:** The development of the PODS core has enhanced the awareness of targeted therapies matched to each patient's molecular profile, increased accrual to genotype-selected trials. We have begun to explore the collaboration with The University of Texas Southwestern Medical Center (UTSW) to help annotate variants from UTSW patients and generate clinical reports.

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Development of a cheminformatics platform for DNA-encoded library screening *John Faver, Baylor College of Medicine; K. Riehle*

Introduction: DNA-encoded library (DEL) screening has become a powerful strategy for hit identification in drug discovery by combining the strengths of combinatorial chemistry and next generation DNA sequencing. In this discovery platform, DEL libraries (which typically contain millions to billions of unique molecules) are screened for binding affinity to biological targets as a complex mixture. The identities of potential hit compounds are then determined via DNA sequencing and statistical analysis. Compared to other drug discovery platforms, successful DEL screening has unique requirements for informatics support which are not as standardized as methods for traditional high-throughput screening (HTS). To enable DEL screening at Baylor College of Medicine, we have developed custom software and data pipelines which handle a broad range of activities from simple data entry to automated analysis of large and complex data sets. **Methods:** Our overall informatics infrastructure is built around three key components: the Dotmatics informatics suite, an automated DNA decode pipeline, and a custom cheminformatics server. Both the DNA decode pipeline and the cheminformatics server were developed in-house to provide functionality specific to DEL library screening, and are closely linked to the commercially available Dotmatics informatics system. **Results:** Our informatics infrastructure allows scientists to manage information about DELs, DEL screens, sequencing experiments, and analyses in addition to standard items like inventory and electronic laboratory notebooks. We have enhanced the utility of the Vortex data analysis software by developing custom scripts which interact with the in-house cheminformatics server to enable DEL related tasks. **Conclusions:** Custom data pipelines and in-house application servers in combination with standard informatics software can be used to enable alternative drug discovery platforms by providing novel functionalities to supplement those commonly available in commercial informatics suites. This work was supported by the Core Facility Support Award RP160805 from the Cancer Prevention Research Institute of Texas (CPRIT).

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Epigenetic deregulation and cellular heterogeneity of the gap junction communicome in endometrial cancer and endometriosis *Nameer Kirma, The University of Texas Health Science Center at San Antonio; S. Polusani; C. Wang; N. Lucio; Y. Zhou; V. Jin; B. Nicholson; T. Huang*

Introduction: Endometrial cancer is the most common malignancy in the reproductive track. Risk is increased with age, with diagnosis at an average of 60 years, but also obesity-associated endometrial cancer is on the rise in a younger age group (around 40 years). In this project, we tested the hypothesis that disruption of genes controlling cell-cell communication, including gap junction and tight junction genes, referred to here as the communicome, may lead to the development of endometrial cancer and endometriosis lesions. **Methods:** DNA Methylation screening and pyrosequencing analysis of primary endometrial tumors were undertaken to assess epigenetic differences between subgroups of non-obese and obese endometrial cancer patients. Cell-cell communication assays and biophysical characterization by atomic force microscopy were used to assess differences in functional cellular interactions affected by demethylating agents and exposure to altered paracrine environments. Single-cell transcriptomics analysis was used to assess endometrial cell heterogeneity in the endometrium, which may lead to the development of endometriosis lesions. **Results:** DNA methylation of candidate communicome loci involved in regulation of gap junction channel communication was significantly ($p<0.01$) more prevalent in endometrial tumors from obese and morbidly obese patients. Treatment of endometrial cancer cells with demethylating agents restored gap junction activity and cellular interactions. Adipose stromal cell paracrine actions affected the expression of the communicome gene expression profile, leading to the suppression of key modulators of gap junction activity. On the other hand, peritoneal mesothelial paracrine actions resulted in in enhancing endometrial cell gap junction communication associated with endometriosis lesion invasiveness into the peritoneum. A progressive alteration in endometrial single-cell heterogeneity expression profile was associated with more severe endometriosis. **Conclusions:** Epigenetic silencing of intercellular communication may be a factor in endometrial cancer development. On the other hand, during active heterotypic invasive processes, such as endometriosis lesion establishment into the peritoneal mesothelial cell lining, reactivation of intercellular communication may be an essential component for cellular invasiveness.

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Poster Session B

Design and production of piperazine-2-acetic acid esters as tools for drug discovery using systematic chemical diversity *Shiva Guduru, Baylor College of Medicine; D. Young; K. MacKenzie; P. Jain; I. Raji; S. Chamakuri; C. Santini*

Introduction: The hunt for new drugs to treat cancer generally involves two important steps: 1. The identification and isolation of biochemical targets implicated in both the initiation and sustenance of the cancerous condition. 2. Exposure of the target to groups of experimental compounds that can interact with it and produce effects that inhibit or reverse the cancerous process. Design of experimental compounds uses principles formulated by clinical experience. Production of experimental compounds is accomplished using synthetic organic chemistry. **Methods:** Among the strategies used to design and create compound collections ("libraries") used for drug discovery, two in particular are being pursued by our laboratories: 1. Fragment Based Ligand Discovery (FBLD) 2. DNA Encoded Compound Technology (DEC-Tech) Application of both of these strategies begins with chemical synthesis. **Results:** Compound libraries are often synthesized by introducing a variety of chemical modifications onto a central molecular structural platform ("scaffold"). Our work goes beyond the basic library synthesis method and involves the production of a scaffold family, i.e. a group of molecular platforms that share a common overall architecture but differ from each other incrementally. **Conclusions:** This poster describes the design and execution of synthesis methodology for the preparation of all possible versions of substituted piperazine-2-acetic acid esters derived from amino acids. Our methodology produces a scaffold family that is suitable as a starting point for compound library production both in FBLD and DEC-Tech, which are described in our accompanying posters. We call this strategy Systematic Chemical Diversity.

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Poster Session B

Construction of a piperazine based small molecule fragment library for fragment based drug discovery *Srinivas Chamakuri, Baylor College of Medicine; K. Tran; S. Guduru; P. Jain; I. Raji; D. Young; C. Santini*

Introduction: Effective cancer treatment remains a major therapeutic challenge. Despite years of research we still do not have effective drugs for many malignancies. However, we have gained much insight into the underlying biology that fuels cancerous processes, in particular the biochemical targets we need to engage to discover better cancer drugs. **Methods:** Over the past decade, fragment-based drug discovery (FBDD) has emerged in both the pharmaceutical industry and in academics as a powerful alternative and complement to traditional high-throughput screening (HTS) approaches for drug lead identification. Fragment based methods are capable of rapidly identifying starting points for structure-based drug design from relatively small libraries of low molecular weight compounds (typically 120-300 Da). FBDD techniques have been successfully applied to identify selective inhibitors for a number of cancer targets including Aurora kinase, PDK1, Bcl-2, Hsp90, CDK, BRAF kinase and some others **Results:** We are interested in constructing a small molecule fragment library to find solutions for the remaining challenges in cancer therapy. In particular we are interested in a Piperazine based small molecule fragment library. The piperazine motif is found in many FDA approved drugs and other reported biologically active compounds; however, functionalization has been primarily confined to derivatization on the nitrogen atoms. We viewed the four carbon atoms that are often unused in the piperazine motif as opportunities for creating new scaffold families for library generation. Our initial foray into the piperazine scaffold area involved producing a three-branch family of optically active disubstituted piperazine-2-acetic acid esters derived from amino acids. The accompanying poster on piperazine-2-acetic acid esters describes our work in both developing the methodology and reducing to practice the production of such scaffolds. The depicted scaffolds are the starting point for our library construction **Conclusions:** This poster will describe the process by which we convert our scaffolds to a fragment library suitable for screening against biochemical targets. The process includes the parameters of library design, the workflow that was developed to insure success in synthesizing multiple compounds simultaneously by parallel synthesis and the technology used to assure purity and quality control for all the members of the fragment library.

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Poster Session B

Exploration of drug-like chemical space and biological activity using piperazine based compound libraries *Prashi Jain, Baylor College of Medicine; S. Chamakuri; E. Samuel; S. Guduru; I. Raji; C. Santini; D. Young*

Introduction: "Chemical space" is the term used to denote the micro-environment that exists around drug-like compounds. Collections ("libraries") of such compounds that incrementally differ from each other are an effective way of exploring the relationship between chemical space and biological relevance ("SAR"; Structure Activity Relationship). Elucidating the details of SAR is at the very heart of cancer drug discovery. Most chemical leads that result in new medications are generated via costly high-throughput biochemical screening (HTS) using large (~106 member) libraries of fully elaborated drug analogs. Even with such large compound libraries the attrition rate of chemical leads is very high and is a major problem in early stage drug discovery. New strategies for lead identification have therefore been developed. **Methods:** One such strategy is Fragment Based Lead Discovery (FBLD). Fully elaborated drug molecules can be considered as a combination of smaller, simpler and more weakly active molecular fragments. Such fragments can be produced by parallel synthesis as shown on an accompanying poster. Because fragments are smaller and simpler than fully elaborated drug molecules, fragment chemical space is much smaller than drug-like chemical space. Fragment screening requires fewer compounds (102-103) compared to HTS. Screening of these fragments, followed by chemical modification, can afford new clinical agents. FBLD is now recognized as a cost-effective way to identify high quality leads in the quest for new therapeutics. Another strategy for lead identification is DNA encoded compound libraries (DEC). DEC is predicated on a more extensive coverage of chemical space. An accompanying poster describes DEC in detail. **Results:** Our research involves the synthesis and screening of piperazine based compound libraries derived using both strategies. Our piperazine scaffolds contain the elements that lend themselves to facile creation of molecular diversity with the goal of improving chemical space coverage and consequently, chances for success. **Conclusions:** This poster will describe our target selection process, how we use our compounds for lead identification via cost-effective biophysical methods and how we can convert chemical leads into clinical agents.

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Poster Session B

Construction of a diverse human antibody phage display library *Robbie Schultz, The University of Texas Health Science Center at Houston; G. Salazar; N. Zhang; Z. An*

Introduction: Phage display technology is a powerful tool for rapidly and efficiently generating fully human monoclonal antibodies. Libraries of phage-displayed antibodies can then be used to isolate antibody fragments against specific antigens using a process of affinity selection called panning. Funded in part by the CPRIT Therapeutic Monoclonal Antibody Lead Optimization and Development Core grant (RP150551), we have constructed a highly diverse human antibody library using phage-display technology. **Methods:** To maximize size and overall complexity, we

created the library using memory B cells isolated from enriched peripheral blood mononuclear cells from multiple healthy donors. Variable regions of both heavy and light chain immunoglobulin genes were isolated using a large primer set. After amplification, the antibody genes were cloned and joined using a flexible linker to generate single-chain variable fragments in a phagemid vector system. The antibody fragments were then displayed on the surface of M13 phage to create a library with a diversity exceeding 10e11 single-chain antibody fragments. **Results:** Sequence analysis showed that variable region gene usage reflects natural abundance within the human antibody repertoire. To date, the library has been used to isolate antibodies against multiple targets, including eight proteins and one peptide. **Conclusions:** In conclusion, we have created an antibody library using phage display technology that has successfully been used to isolate fully human monoclonal antibodies against a variety of targets. Due to its large size and complexity, our library is an ideal tool for selecting antibodies for multiple downstream applications, including potential therapeutic use.

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Poster Session B

TRPM7 kinase domain rather than the channel regulates breast cancer cell migration and tumor metastasis *SoJung Uhm, The University of Texas at Austin; T. Kaoud; X. Xie; R. Mangieri; J. Park; C. Tavares; N. Ebelt; S. Van Ravenstein; J. Yum; M. Cano; S. Mitra; M. Radwan; R. Morrisett; C. Bartholomeusz; K. Dalby*

Introduction: The channel-kinase TRPM7 (transient receptor potential melastatin 7) is a bifunctional protein consisting of a cation channel that is permeable to Mg^{2+}, Ca^{2+} and Mn^{2+} ions fused to a C-terminal kinase domain. A growing number of studies with clinical significance suggest that TRPM7 is linked to adhesion and migration of breast cancer cells and promotes breast tumor metastasis. While the channel properties of TRPM7 have been studied extensively, little is known about the function of its kinase activity. **Methods:** To understand the functions of the kinase domain we identified the first cell-permeable inhibitor of the kinase domain (TRPM7-IN-1) and developed MDA-MB-231 breast cancer cell lines in which TRPM7 is knocked out by CRISPR/Cas9 (KO), and in which various forms of TRPM7 were stably re-expressed. These were wild type TRPM7 (WT), a kinase-inactive mutant of TRPM7 (KD), and TRPM7 containing a truncated kinase domain (KT). **Results:** Knock out of TRPM7 significantly inhibited MDA-MB-231 cell migration. Only expression of the wild type TRPM7 (WT) rescued the migration phenotype, supporting a role for the kinase domain in the regulation of cell migration. Magnesium deprivation, which promotes TRPM7 kinase activity, induces phosphorylation of eEF2, presumably to impede protein synthesis. Treatment of magnesium-deprived HEK293 cells with TRPM7-IN-1 decreased eEF2 phosphorylation, consistent with suppression of TRPM7 kinase activity in-cells. TRPM7-IN-1 decreased the binding of Myosin IIB to TRPM7 in HEK293 and MDA-MB-231 cells. And when MDA-MB-231 cells were treated with increasing doses of TRPM7-IN-1, TRPM7 phosphorylation of Ser-1569 and its downstream substrate myosin IIa (Ser1943) were completely abrogated at a concentration of 5 μM. TRPM7-IN-1 inhibited MDA-MB-231 cell migration and invasion, while treatment of the KO cells with TRPM7-IN-1 showed no further inhibition of migration. Electrophysiological assessment of the TRPM7 channel revealed that the inhibitor did not affect the channel function in MD-MB-231 cells, supporting the notion that the inhibitor affects the migration exclusively through the inhibition of the TRPM7 kinase domain. Finally, in an experimental metastasis model, TRPM7-IN-1 significantly impeded metastasis to the lung. **Conclusions:** Inhibition of TRPM7 kinase activity may reduce or block breast tumor progression and/or metastasis.

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Poster Session B

Identification of ENL YEATS domain inhibitors using a robust and cost-effective AlphaScreen assay *John Veloria, The University of Texas at Austin; A. Devkota; E. Cho; K. Dalby*

Introduction: The chromatin reading domain ENL YEATS has been identified as a critical component in leukemia cell growth and proliferation, using genetic and biochemical studies. However, no known pharmacological inhibitors exist to inhibit the activity of ENL YEATS. Here, we describe the development and optimization of a new high-throughput screen based on the AlphaScreen (Amplified Luminescent Proximity Homogeneous Assay Screen) detection platform, to identify novel molecules that disrupt ENL YEATS binding. **Methods:** To investigate a cost-effective AlphaScreen strategy, 6-histidine (HIS6-Nickel chelate) detection kit from Perkin Elmer with His-tagged ENL YEATS and biotin-H3K9Ac was employed as a model system. The binding assay of ENL YEATS (target protein) and H3K9Ac (substrate peptide) was initially established. In detail, the assays were performed in an assay buffer [50 mM HEPES pH 7.4, 100 mM NaCl, 1.0 mg/ml BSA, and 0.05% CHAPS] using 100 nM His-tagged ENL YEATS and 30 nM biotin-H3K9Ac. Assays were performed in 20 μL volume in white 384-well Optiplates. The assay was read on an Envision plate reader equipped with a high-throughput AlphaScreen laser. All reactions were performed in subdued light conditions (<100 lux) and at ambient temperature. **Results:** We have determined that the concentration of Alphabeads can be reduced by 4-fold from 10 μg/mL to 2.5 μg/mL, and the concentration of peptide can be reduced by 3-fold without negatively affecting assay quality. Additionally, we observed that this new method does not alter the activity of the compounds used during screening, as evidenced by a high correlation of compound inhibition between the two platforms. Furthermore, we have performed a primary screen of approximately 70,000 small molecules and have determined that the assay was robust, and produced z', S/B, and S/N of 0.83 ± 0.08, 66.29 ± 23.19, and 22.45 ± 8.45, respectively. The screen identified 3 compounds with nanomolar potency that are good leads for further pharmacological development. **Conclusions:** This new cost-effective, robust screening platform will be useful for identifying new inhibitors that interfere with chromatin reading proteins, and may help with the subsequent development of anti-cancer drugs targeting oncogenic gene expression

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Poster Session B

CPRIT Core for RNA Therapeutics and Research at Houston Methodist *Ivone Bruno, Houston Methodist; R. Sukhovershin; A. Balog; J. Cooke*

Introduction: The RNAcore at the Houston Methodist Research Institute is supported by the Cancer Prevention Research Institute of Texas (CPRIT) to synergistically work with Texas-based cancer biologists and clinical investigators, to enable the development of novel RNA constructs for basic studies, as well as RNA-based cancer immunotherapies. We develop and synthesize RNA constructs for cancer research, including modified mRNA, long noncoding RNA, siRNA and labeled RNA constructs. We have generated over 100 different constructs for investigators, including RNA encoding transcriptional factors, epigenetic modifiers, chimeric antigen receptors, and genome editing tools. **Methods:** In addition to generating research grade RNA, the RNAcore generates clinical grade RNA using GLP and GMP guidelines to develop Standard Operating Procedures (SOPs) for in vitro transcription, HPLC purification, and analytical testing for the characterization and evaluation of mRNA constructs. We implemented a controlled process that ensures that 1) all manufacturing steps abide by established SOP and batch records, 2) all data is appropriately recorded and documented, 3) all materials comply with appropriate quality standards, 4) all constructs meet well-defined acceptance criteria as assessed using in process tests for intermediate and final products, and 5) operators take corrective/preventative actions when processes fall outside acceptance criteria or deviations from protocol occur. **Results:** We have developed unique methods and processes that allow us to provide: 1) sequence and vector generation for a broad range of cancer biology tools and therapeutics, including RNA encoding vaccine and chimeric antigen receptors, cytokines, proteins involved in proliferation, cellular and signaling pathways; as well as non-coding RNAs, 2) optimization and characterization of mRNA molecules, 3) qualification and analytical testing of purity and integrity for IND enabling studies, 4) consultation regarding quality testing for RNA molecules, protocols and procedures for cellular or systemic delivery of RNA constructs, and methodologies for mRNA generation and purification, and 5) cGMP grade RNA molecules for Phase I/II clinical trials, RNA for pre-clinical GLP studies, or Pre-IND studies. **Conclusions:** The RNAcore is a flexible foundry for generating research tools for cancer biology, as well as RNA therapeutics and RNA-modified cell immunotherapies. The RNAcore supports our Texas cancer biologists and industry clients in discovery and development of RNA constructs and RNA therapeutics, and supports IND enabling studies with RNA analytical tools. Our unique workforce has technical expertise in manufacturing RNA molecules and cell therapies that will continue to support our increasing users group and develop our own novel mRNA based cancer therapeutics.

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Discovery of a Covalent Inhibitor of ERK Docking-Interactions that Inhibits A375 Melanoma Tumor Growth *Sabrina Van Ravenstein, The University of Texas at Austin; T. Kaoud; R. Ghose; P. Ren; W. Johnson; N. Ebelt; M. Cano; M. Warthaka; R. Sammons; A. Piserchio; Q. Wang; K. Tsai*

Introduction: Acquired drug resistance, especially mechanisms associated with the reactivation of the MAPK (RAF/MEK/ERK) pathway represent a major challenge to current treatments of melanoma. Recently, targeting ERK has evolved as a potentially attractive strategy to overcome this resistance. Several ERK inhibitors have already entered clinical trials. Rationale: Most of the available ERK inhibitors are reversible inhibitors that either act through an allosteric mechanism, or by targeting the ATP binding site. Taking advantage of our understanding of ERK-

docking interactions we set out to discover an irreversible substrate-selective inhibitor that targets the protein-binding site of ERK. **Methods:** Biochemical, cell biology and in vivo studies have been employed to characterize the mechanism of action of the first covalent inhibitor of ERK docking interactions. **Results:** Protein NMR, Mass spectroscopy, mutagenesis and molecular docking studies indicate a covalent interaction of the inhibitor with a conserved cysteine residue, Cys-159. Extensive biochemical studies provide an estimate of its kinetic parameters and its kinase-selectivity profile. The new ERK inhibitor inhibits ERK activation, as well as its ability to phosphorylate downstream substrates (e.g. p90RSK and Elk-1) in HEK293T and A375 melanoma cells. The targeting of ERK in HEK293T cells was confirmed using a chemical-genetic approach where the ERK2 C159A mutant was used to rescue the effects of this compound on ERK2 signaling and cell proliferation. Finally, the compound suppressed the growth of melanoma tumor in A375 melanoma cancer xenografts model when administered daily (10 mg/Kg) for 16 days. **Conclusions:** This covalent inhibitor represents a potentially valuable lead molecule whose development may result in a novel class of pharmacologically useful ERK inhibitors for targeting resistant forms of melanoma.

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The Adolescent and Childhood Cancer Epidemiology and Susceptibility Service (ACCESS) for Texas *Michael Scheurer, Baylor College of Medicine; V. Marshall; J. Amatruda; A. Sorrell-Taylor; L. Hartman; M. Al-Rahawan; J. Murray; J. Bernini; R. Erana; U. Ramamurthy*

Introduction: More than 15,000 children and adolescents are diagnosed with cancer in the United States each year, with over 10% of cases diagnosed in Texas. The vast majority of these cancers occur with no recognizable cause; only 5% can be attributed to known genetic predisposition syndromes. Therefore, the need to elucidate the etiological factors contributing to these cancers is paramount. The Adolescent and Childhood Cancer Epidemiology and Susceptibility Service for Texas (ACCESS-Texas) Core Facility will support the conduct of research to identify novel genetic risk factors and gene-environment interactions important in understanding cancer susceptibility among children and adolescents, particularly among the diverse patient population in Texas. **Methods:** Key services are: (1) Enrollment of a diverse population of childhood and adolescent cancer cases, and their parents, from major treatment centers across Texas; (2) Banking of biospecimens for family-based studies of genetic risk factors, gene-environment interaction studies, and biomarker discovery for cancer control; (3) Systematic collection of harmonized risk-factor questionnaire data; and (4) Systematic prospective collection of key clinical and follow-up data. **Results:** The first year of operations for ACCESS has been dedicated to expanding the collection protocol to the other clinics across Texas, to expanding laboratory capabilities, and developing the central data management system. During this time, patient enrollment at Texas Children's Cancer Center continued, and 198 pediatric cancer patients were enrolled. With the expanded enrollment expected at Texas Children's and across the other institutions, we anticipate enrolling approximately 800 cases per year moving forward. Several newly funded grants will leverage ACCESS to conduct exciting new research in childhood and adolescent cancers. One project funded by St. Baldrick's Foundation (PI: Philip Lupo) will use ACCESS as a backbone to examine ethnic differences in acute leukemia risk and outcomes. The KidsCanSeq Study funded by NHGRI (PI: Sharon Plon and Will Parsons) will leverage the clinical network of ACCESS in their efforts to evaluate the utility and improve implementation of genomic sequencing for pediatric cancer patients. A newly funded CPRIT Core facility (INPACT, PI: Carl Allen) will complement the risk factor data and germline samples collected in ACCESS with tumor cell lines that can be used to examine tumor biology and potentially identify novel therapeutic targets. **Conclusions:** ACCESS is a tremendous resource for epidemiological and translational research focused on childhood and adolescent cancers in Texas. Investigators across the state can apply to utilize the resources for individual projects.

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Development of a lipidomics platform for cancer metabolism research *Philip Lorenzi, The University of Texas M.D. Anderson Cancer Center; L. Tan; L. Du; Y. Chiu; L. Martin; J. Weinstein*

Introduction: The field of metabolomics continues to evolve at a rapid pace. Given recent discoveries of new classes of metabolites that are not present in current databases, the human metabolome is now estimated to consist of potentially up to 100,000 metabolites. Measuring that many molecules in a single biological sample, however, is inconceivable. Lipidomics is a sub-field that aims to measure over 80 major classes of lipids, 300 sub-classes, and thousands of individual lipid species including isomeric and isobaric molecular ions. That degree of complexity is more manageable than the entire metabolome, but molecular weight searches alone are not sufficient to identify most lipids in biological samples analyzed by mass spectrometry (MS). Here, we summarize our development of a workflow using higher-energy collisional dissociation (HCD) MS^2 and collision-induced dissociation (CID) MS^3 for characterization and quantitation of lipids from most lipid sub-classes. **Methods:** To optimize a lipid extraction protocol, we tested methanol, chloroform, methyl tert-butyl ether (MTBE), acetone, and isopropanol as extraction solvents against the OVCAR-8 ovarian cancer cell line, and lipids were profiled using a Thermo Orbitrap Fusion Tribrid mass spectrometer with Vanquish UHPLC system. The lipids in each sample were separated on a C30 reversed-phase LC column. The mass spectrometer was operated in electrospray positive and negative modes at resolution 240,000. LipidSearch software was used for lipid identification and quantitation. **Results:** Lipid extraction by MTBE/methanol greatly simplified sample handling relative to the other solvents tested, and the corresponding recovery of lipid species from almost all major classes was the same as, or better than, that with other extraction protocols. Using that method, we were able to report and quantitate approximately 1,000 annotated lipid molecules from the OVCAR-8 cells. **Conclusions:** We optimized a workflow for Orbitrap-based lipid profiling that facilitates identification and quantitation of a wide range of lipids. The workflow is optimized for cancer cell lines and adaptable to more complex samples such as plasma, whole blood, and tissues. Together with a whole blood microsampling procedure developed by our group, the current method may also facilitate longitudinal lipid profiling studies in animals.

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Structure-Based Drug Discovery in a Web Portal: DrugDiscovery@TACC *William Allen, The University of Texas at Austin; S. Mock; J. Fonner; R. Dooley; M. Vaughn; S. Watowich*

Introduction: Computational chemistry methods, including structure-based virtual screening, save time and resources in the drug discovery pipeline. Large databases of commercially-available compounds can be pre-screened and enriched for compounds predicted to bind to a drug target. Tractable numbers of compounds can then be purchased for experimental validation. While successful virtual screening has compelling advantages over purely experimental methods, it requires high-performance computational resources, software licenses, and technical expertise, which may be unattainable for small academic labs. UTMB Galveston has partnered with the Texas Advanced Computing Center (TACC) to provide an accessible and free virtual screening service called DrugDiscovery@TACC to investigators across the state of Texas and around the world. **Methods:** The DrugDiscovery@TACC virtual screening portal was developed atop TACC's science-as-a-service platform Agave (http://agaveapi.co/), an application programing interface that enables interaction between the end user, public and private cloud resources, and the petascale computational resources of TACC. A front-end web portal allows users to upload protein structures and select between several ZINC small molecule libraries for screening. On the back-end, the widely-used virtual screening program AutoDock Vina performs molecular docking calculations on the University of Texas Research Cyberinfrastructure resource Lonestar5 (1252 Cray XC40 nodes, 30,048 compute cores). AutoDock Vina uses empirical shape and chemical complementarity metrics to assess and rank each molecule, returning the results to the user in the portal. **Results:** Our large library containing 642,759 small molecules requires approximately 18.5 hours real time to screen across 24 nodes. This equates to >10,000 hours of CPU time, but results are typically returned to the user within 24 hours of submission. Additional ZINC screening libraries have been prepared including a smaller subset of ~47,000 compounds, and a library of ~194,000 natural products. To date, over 150 users have submitted thousands of virtual screens amounting to nearly 14 million compute hours through the DrugDiscovery@TACC portal. These efforts have led to dozens of documented drug candidate hits. **Conclusions:** The DrugDiscovery@TACC portal provides a valuable and no-cost virtual screening service to Texas researchers. We plan to incorporate new ZINC libraries, new screening methods and programs, and enable lead refinement, all within the web portal. In the long term, we plan to incorporate the portal in to a Texas-based center for oncology research which, in partnership with medicinal chemists and experimental biologists, will help develop leads identified in the early stages of drug discovery and accelerate drug development. The portal is available at https://drugdiscovery.tacc.utexas.edu/.

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Castration resistance transcriptome in prostate cancer revealed by single-cell RNA-seq *Chun-Liang Chen, The University of Texas Health Science Center at San Antonio; A. Horning; Y. Wang; C. Lin; B. Lieberman; D. Mahalingam; C. Wang; M. Gao; P. Wang; Z. Liu; J. Ruan; M. Liss; V. Jin; T. Huang*

Introduction: Fatal metastatic castration-resistant prostate cancer (mCRPC) remains without sensitive early detection biomarkers and effective therapeutic targets. Each year, about 30% of ~30,000 newly diagnosed prostate cancer patients who will develop mCRPC while the other 70% may remain indolent not needing treatment. However, the PSA and other biomarkers are limited in distinguishing the aggressive mRCPC from the slow growing prostate cancer. Among 2.5 million prostate cancer patients, the majority will face a dilemma, to treat or not to treat, at a point as cancer progresses. Early intervention using androgen deprivation showed promise in treating metastatic prostate cancer patients. Biomarkers for mRCPC at an early stage represent an unmet need. With early identification, clinicians could design new treatment strategies can be designed to reduce metastasis-related morbidity and to extend survival of patients. **Methods:** In this study, we deployed single-cell RNA-seq on prostate cancer cells (LNCaP, ABL and PC3) to determine the transcriptomic systems in androgen independency and castration resistance of prostate cancer. **Results:** We identified potential 336 androgen-independence specific genes and 2396 castration resistance specific genes in ABL and PC3 cells respectively, while only 136 genes were shared in both cells. These genes, mostly upregulated were enriched in 43 and 166 signaling pathways that implicated the complexity of the castration resistance transcriptomic systems and networks. The signaling pathways are involved in advanced and metastatic malignancies including WNT, TGFB, ITGAB, STAT, EPHB, focal adhesion, adherens junction, regulation of actin cytoskeleton, gap junction, tight junction and EMT. Malignant potencies of ~ 40 pathways were validated by in silico analysis of the RNA-seq data from the prostate cancer cohort of The Cancer Genomic Atlas (TCGA) using Kaplan-Meier disease free and survival curve analyses. The transcriptomic regulation of these genes was further validated and correlated with GRO-seq and ATAC-seq data. In order to further verify the functions of those signaling pathways in castration resistance, 9 major signaling pathways were evaluated using small molecule inhibitors. Castration resistant prostate cancer cells showed significant defective cell proliferation, migration, invasion and sphere formation in the presence of inhibitors, whereas LNCaP and ABL cells displayed limited or non-significant changes. Interestingly, five small molecule inhibitors showed significant suppression on the growth of circulating tumor cells that were derived from clinical blood samples of prostate cancer patients. **Conclusions:** Our data suggest that those castration resistance specific genes and signaling pathways revealed by single-cell RNA-seq may serve as potential markers and therapeutic targets.

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Progesterone receptor regulation of mTOR signaling in pre-invasive breast cancer *Sean Hartig, Baylor College of Medicine; S. Grimm; N. Chernis; H. Villanueva; C. Callaway; A. Contreras; K. Rajapakshe; S. Huang; C. Coarfa; D. Edwards*

Introduction: Clinical and epidemiological data have established progesterone (P4) is a risk factor for invasive breast carcinoma (IBC). Ductal carcinoma in situ (DCIS) is a precursor to IBC that retains estrogen receptor (ER) and progesterone receptor (PR) expression. Despite the fact that the majority of DCIS are ER and PR positive, whether and how P4/PR influences the progression of DCIS to IBC are unknowns. **Methods:** To address these questions we developed an experimental system by stable expression of ER and PR in a human comedo DCIS cell line. A combination of proteomics, gene expression profiling, and respirometry were used to explore the influence of P4 on molecular pathways and cellular processes in DCIS in vitro. **Results:** DCIS.COM cell lines expressing ER/PR were highly responsive to P4 exhibiting robust regulation of known PR target genes and an inhibition of proliferation. Microarray expression profiling and bioinformatics analysis of publically available data sets revealed gene signatures of ER/PR DCIS cell lines similar to that of luminal breast cancer, indicating the physiological relevance of our cell lines. Using a targeted reverse phase protein array (RPPA) proteomics platform, mTORC1 was identified as a predominant signaling pathway regulated by P4 that is of high interest because of its central role as an integrator of nutrient and growth signals that can enable high rates of protein synthesis required for survival of cancer cells. Additionally, constitutive activation of mTORC1 in DCIS and IBC is often reflected by a combination of PI3KCA mutations and aberrant growth factor signaling. P4 mediated activation of mTORC1 was validated by immunoblotting of downstream protein targets that reflect enhanced protein translation and higher glycolytic activity. We determined that P4 activation of mTORC1 occurs by transrepression of DEPTOR, a member of the mTOR complex that acts as an inhibitor of mTORC1 activity. By chromatin immune-precipitation (ChIP) assay we identified intronic PR binding sites in the DEPTOR gene and demonstrated that repression of DEPTOR and activation of mTORC1 signaling corresponds with P4 induced PR-DNA binding. Inhibition of mTORC1 activity with rapamycin amplified the growth inhibitory effects of P4 in DCIS cells, suggesting PR may collaborate with therapeutic vulnerabilities associated with PI3KCA mutations and activated mTOR in breast cancer. **Conclusions:** Targeting PR together with mTOR inhibitors may represent a new therapeutic avenue for prevention and management of breast cancer progression of pre-invasive to IBC.

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The Gulf Coast Consortium Center for Advanced Microscopy and Image Informatics *Michael Mancini, Baylor College of Medicine; P. Davies; F. Stossi; A. Rao; L. Vergara*

Introduction: The Center for Advanced Microscopy and Image Informatics (CAMII) is a multi-institutional, multi-disciplinary core facility designed to provide investigators from the Gulf Coast Consortium for Chemical Genomics (GCC) access to customized, project-driven, quantitative imaging-based solutions that support both basic and translational cancer research. CAMII builds upon the recent success of a collaboration between the Texas A&M Institute for Biosciences and Technology (Houston campus) and Baylor College of Medicine to create a productive and efficient imaging program in the Texas Medical Center utilizing the sophisticated microscopy resources at both institutions. This successful collaboration has resulted in high impact publications and supported outstanding translational drug discovery research projects in GCC institutions; when combined with an overall increased interest in quantitative microscopy, the CAMII was designed to maximize support for outstanding cancer-related research projects. By providing imaging resources to both established and junior investigators, CAMII will support projects that are at the forefront of contemporary cancer research. In partnership with the GCC drug discovery CFSA programs, CAMII will also augment a drug discovery pipeline supporting promising lead drugs and antibodies from in vitro testing, to in vivo validation and pre-clinical development. **Methods:** The Specific Goals include: 1) supporting meritorious projects by providing researchers with access to infrastructure and technical expertise to facilitate answering the most challenging questions of cancer biology and drug discovery; 2) facilitate development of new technologies and improvement of existing platforms to advance the field of imaging-based cancer research; and, 3) familiarize cancer researchers with the application of advanced imaging-based research technologies to projects that address the causes, prevention, and/or treatment of cancer. **Results:** Results from Center goals/projects will be achieved through the assembled support of a multi-disciplinary team of experts in imaging and imaging informatics operating a state-of-the-art core facility. CAMII is developing focused imaging platforms and informatics to support long-term live cell imaging studies, high resolution single cell analytics and high throughput/high resolution microscopy. As a component of the Gulf Coast Consortium for Chemical Genomics, CAMII will join the GCC network of core facilities supporting cancer-related basic science and drug discovery research in the Texas Medical Center. **Conclusions:** CAMII is committed to having a transformative impact on cancer research in Texas and will contribute to CPRIT's goal of supporting innovation in cancer research and promoting breakthroughs in the search for both cancer prevention and cancer cures.

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Next-Generation Sequencing (NGS) Facility Core at MD Anderson Cancer Center Science Park *Jianjun Shen, The University of Texas M.D. Anderson Cancer Center; M. MacLeod; Y. Lu*

Introduction: The development of NGS over the past eleven years has created a paradigmatic shift in our ability to probe the molecular details of cancer. These technologies allow much more complete analysis of the transcriptome and its regulation, the detection of rare "driver" mutations in cancer genomes, and the ability to quickly and comprehensively define features of the epigenome. **Methods:** With CPRIT funding in 2012, we established a regional NGS Facility Core with HiSeq 2500 and MiSeq instruments at MD Anderson Science Park, dedicated primarily to supporting cancer research in central Texas. We conducted extensive protocol development, quickly established all essential NGS protocols, and prepared and/or sequenced nearly 6000 libraries for 37 current and former User Group members. Our bioinformaticians developed and/or further improved pipelines for both data analysis and checking NGS data quality. To communicate our services and receive feedback on how to best enhance User research, we have provided two formal workshops per year, along with other formal and informal interactions. **Results:** As a result, over the last five years, data from our Core helped generate 44 publications and supported the acquisition of 25 new grants, which were awarded to 16 User Group members, and totaled $25.1M. The publications included 14 in high impact journals: 1 in Cell, 2 in Molecular Cell, 5 in Nature Communications, 1 in Nature Chemical Biology, 2 in Genes & Development, 1 in Journal of Clinical Investigation, and 2 in PNAS. In addition, 10 manuscripts are in review or will be submitted shortly. **Conclusions:** The renewal of our CPRIT grant in 2016, allowed

us to upgrade our sequencing equipment with HiSeq 3000 and NextSeq 500 instruments to better serve our clients. We will continue to provide timely, high quality NGS services using our established protocols, and will continue to develop new protocols as new NGS methods and technologies are developed. Our enhanced bioinformatics analysis team will help central Texas cancer researchers analyze data, develop new pipelines, and draw meaningful conclusions from their experiments. We will continue to provide two workshops per year creating a forum for communication between the Core and User Group members. Ultimately, the Science Park NGS Facility Core will support cancer research that defines the basic mechanisms of gene expression, maintenance of genetic integrity, and the epigenetic changes that are important in normal cells and altered in cancer cells.

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Comparison of ChIPSeq data prepared with different techniques and very low levels of input DNA *Melissa Simper, The University of Texas M.D. Anderson Cancer Center; L. Della Coletta; M. Walker; K. Lin; M. Estecio; M. MacLeod; Y. Lu; J. Shen*

Introduction: ChIPSeq is now the most prevalent method of studying protein interactions with the genome. However, obtaining reliable ChIPSeq data is challenging due to the variability of the immunoprecipitation step, which occasionally yields very limited amounts of DNA. Several companies have developed kits for creating ChIPSeq libraries making it important to determine the kit that will produce the best data from limited amounts of DNA. **Methods:** We evaluated the performance of ChIPSeq kits from four suppliers (Bioo, Diagenode, KAPA and NEB) at nanogram (ng) (10, 5 and 1 ng) and sub-ng [500, 250, 100 picogram (pg)] levels by performing ChIP in LNCaP cells with antibodies against H3K4me3 (a marker of transcriptionally active chromatin that displays sharp peaks), H3K27me3 (a marker of transcriptionally repressed chromatin with broad enrichment domains) and CTCF (a transcription factor) . Total H3 and Input were used as controls for histones and the transcription factor, respectively. **Results:** Diagenode, KAPA and NEB kits maintained high library complexity that decreased at the 100 pg level, while libraries prepared by the Bioo kit exhibited lower library complexity than the others at all concentrations. For H3K4me3, all kits performed fairly well at each concentration, with the majority of samples having >75% of peaks called in promoter regions and about 50% of known promoters marked by sharp peaks. For H3K27me3, each library showed the expected broad enrichment domains except for the Bioo and KAPA kits at 100 pg. The peak intensity of each library negatively correlated with gene expression, with the Bioo kit having the highest and Diagenode and KAPA kits having the lowest correlation. For CTCF, the Diagenode and KAPA kits had better performance than the Bioo and NEB kits, with a higher number of peaks called, a similar percentage of peaks identified with the CTCF motif, and a closer distance between the CTCF motif and the peak summit. **Conclusions:** Our preliminary results suggest the performance of ChIP-Seq kits depends on which proteins are being studied but that none are sufficient for working with ≤100 pg DNA. Nonetheless, all of the kits we evaluated can be used when studying active histone modification such as H3K4me3 in sharp peaks. However, the Bioo kit is best when looking at repressive histone modification with broad enrichment domains, while either Diagenode or KAPA kits are best for transcription factors.

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Initiative for single-cell omics *Chiou-Miin Wang, The University of Texas Health Science Center at San Antonio; N. Lucio; C. Chen; T. Huang; N. Kirma*

Introduction: Recent advances in genomic, epigenomic and biophysical analyses at the single cell level have greatly improved our understanding of intra-tumor heterogeneity and characterization of exfoliated and circulating cancer cells. We have undertaken an initiative to provide cutting-edge single-cell omics technologies for advancing the discovery of biomarkers and therapeutic targets of various tumor types. **Methods:** Single-cell isolation and omics studies were performed using combinations of the following platforms: Combined immunofluorescence-micromanuipulator workstations (CIM) for targeted cell picking; the DEPArray for targeted cell sorting; microfluidic C1 single-cell sorting and processing for single-cell RNA-seq (C1-scRNA-seq), identification of global chromatin accessibility (C1-scATAC-seq) and the C1-Biomark pipeline for single-cell microfluidic targeted expression RT-PCR. In addition, Atomic Force Microscopy (AFM) was used for examining biophysical/mechanical features of individual cells and cell-cell interactions. Analysis and integration of data generated by these platforms were developed by the single-cell informatics and statistics team. **Results:** We have successfully characterized single-cell omics from liquid and tissue biopsies or cell lines of various tumor cells. Here we show some representative data using our single-cell pipelines: CIM and DEPArray were used to isolate rare exfoliated tumor cells from blood and urine. Copy number variation, RNA expression and biophysical characterization of prostate cancer single-cells differentiated castration-resistant patients from castration-sensitive patients, providing novel prognostic biomarkers for prostate cancer, including enhanced cell cycle-related transcription and attenuated androgen response. C1-scATAC-seq identified epigenetic heterogeneity and restricted chromatin accessibility at genomic loci that were highly susceptible to DNA methylation in CTC primary cultures of breast cancer patients. C1-BioMark was used to analyze primary endometrial stromal or epithelial cells isolated from endometriosis patients with different stages of invasive endometriotic lesions. This analysis, using a 48 gene panel, revealed that endometrial stromal cells expressed diminished gap junction gene expression in more advanced stages. The loss of gap junction expression and heterogeneity may relate with enhanced invasiveness of endometriotic lesions outside the uterus. **Conclusions:** We have successfully developed pipelines for single-cell isolation and omics analysis over a spectrum of tumor types. Our single-cell omics initiative has the capacity to detect and characterize cellular subpopulations and rare cells in translational samples, providing powerful tools to understand cancer biology and develop clinically relevant tools to manage deadly diseases. Our data highlight the potential for high resolution single-cell omics and biophysical characterization to identify novel prognostic biomarkers, cellular heterogeneity involved in lesion invasiveness, and epigenomics underlying metastatic cancer.

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Cancer Proteomics and Metabolomics Core Facility *Dean Edwards, Baylor College of Medicine; A. Sreekumar; S. Huang; A. Malovannaya; C. Coarfa; K. Rajapakshe; N. Putluri; S. Jung*

Introduction: Cancer development and progression involves not only alterations in genes, but also protein signaling pathways and metabolism that collectively drive the cancer phenotype. The goal of the combined Proteomics and Metabolomics Core Facility is to assist cancer researchers with discovery of molecular pathways that contribute to cancer progression in various experimental model systems and the identification of novel diagnostic biomarkers and therapeutic targets. **Methods:** The main technology platforms of the Core Facility include 1) mass spectrometry-based metabolomics, 2) mass spectrometry-based proteomics, 3) targeted proteomics by antibody-based reverse phase protein array (RPPA) and 4) multi-omics integrative data analysis and bioinformatics. The core continually strives to advance cutting-edge technologies. Metabolomics has developed targeted assays for steady-state quantification of 650 known metabolites, isotopomer-based flux assays to trace activities of major metabolic pathways in cells, lipidomics for up to 300-400 molecules, and MS-2 unbiased metabolomic profiling. Mass spectrometry-based proteomics includes IP-MS analysis of protein complexes, a label-free quantitative method for unbiased profiling up to 8,000 proteins and profiling different classes of proteins including the kinome, phospho-proteome and transcription factors. The RPPA platform provides highly sensitive robust quantification of 220 proteins representative of major oncogenic signaling pathways. Bioinformatics tools includes workflow pipelines for management and analysis of large omics data sets and for integration of data sets across different omics platforms. **Results:** Over the first five years of operation the Core Facility supported 256 projects for cancer researchers, and 76 publications, many in high impact journals such as Science, Nature, Cell, Cancer Cell and J. Clin. Investigation. The economic impact of the Core Facility includes awarding of 45 grants ($49M total) to users with preliminary data generated by the Core and/or specific aims requiring Core support. Scientific discoveries resulting from Core supported research projects includes identification of drivers of initiation and progression of different cancer subtypes, uncovering mechanisms of resistance to therapies, and identification of potential diagnostic biomarkers and therapeutic targets. Some projects that identified new therapeutic targets have moved forward to the drug development stage. **Conclusions:** This is a well-established and highly productive Core Facility that supports high quality basic cancer research projects for a broad range of Investigators. Future goals are to continue to develop innovative technologies to advance the proteomics and metabolomics fields and to optimize procedures with patient specimens and increase throughput for clinical validation studies.

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The Gulf Coast Consortium's Combinatorial Drug Discovery Program *Peter Davies, Texas A&M University Health Science Center Institute of Biosciences and Technology; C. Stephan; T. Cohen; M. Mancini; A. Rao*

Introduction: Drug repurposing and combinatorial repurposing are cancer therapeutics strategies of great interest to clinical cancer researchers. Repurposing is important for cancer patients because it

has the potential of identifying new therapies that can be “fast tracked” into clinical use without the long delays associated with getting “new” drugs approved for clinical use. High throughput library screening technologies, testing the activity of large numbers of combinations of clinically relevant drugs against the target cancer has the potential to accelerate the discovery of novel therapies for hard to treat cancers. To take advantage of this strategy investigators need access to the sophisticated resources required to support combinatorial drug discovery research including: 1) a core facility that provides the complex technologic infrastructure to conduct high throughput cell-based screening research and 2) a multi-disciplinary team of experts in high throughput drug discovery, imaging-based screening, image analysis and informatics. The Gulf Coast Consortium’s Combinatorial Drug Discovery Program (CDDP), a CFSA-supported multi-institutional core facility is providing researchers with access to these key resources. **Methods:** Combinatorial drug discovery research requires a core facility providing the complex infrastructure necessary to conduct high throughput cell-based screening. The CDDP is fully equipped to run in vitro screens from simple biochemical end points to live cell imaging using fully automated platforms. The core maintains a multi-disciplinary team of experts in the fields of high throughput drug discovery, imaging-based screening, image analysis and data informatics. **Results:** The CDDP’s is providing cancer researchers with access to compound/drug libraries, laboratory automation, specialized cell culture capabilities and imaging platforms, technical expertise and the informatics necessary for library-screening studies using advanced cellular models of cancer, and ”fit for purpose” high throughput cell-based screening technologies to support the discovery of novel therapies for cancer. **Conclusions:** The CDDP’s value is reflected in the large demand for its services. Core collaborators are incorporating many new advanced cellular cancer models into their drug discovery projects with promising combinations can then be rapidly advanced to animal testing and subsequent clinical evaluation.

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mRNA therapy for improved adoptive T-cell transfer *Sahana Suresh Babu, Houston Methodist; J. Liu; F. Mo; M. Mamonkin; J. Thonhoff; S. Appel; K. Chen; M. Brenner; I. Bruno; J. Cooke*

Introduction: Cancer immunotherapy is a promising therapy for a wide variety of malignancies. An exciting approach of cancer immunotherapy is adoptive T-cell therapy, wherein the natural ability of T-lymphocytes to recognize tumor antigens and kill target cells is augmented. In normal human T-lymphocytes, extensive proliferation leads to replicative senescence; a constraint in the number of times that cells can divide. Replicative senescence is characterized by a reduction in telomerase (hTERT) activity and shortening of telomeres. This is an obstacle for T-cells engineered to express chimeric antigen receptors (CAR-T) therapies because the ex-vivo clonal expansion required to achieve therapeutic doses of the CAR-T cells involves a stage of high proliferation. In this regard, an adoptive immunotherapy trial observed that telomere length of transferred lymphocytes correlated with in-vivo T-cell persistence following treatment, suggesting that telomere length and the proliferative potential of the transferred T-cells may play a significant role in avoiding replicative senescence and thereby mediating a successful clinical response. **Methods:** Peripheral Blood Mononuclear Cells (PBMC) were isolated from the human donor blood followed by activation with CD3 and CD28 antibodies to selectively enrich T-cells in culture. High-performance liquid chromatography (HPLC)-grade therapeutic hTERT mRNA was produced in collaboration with the RNAcore production team. Nucleofection technology was employed to transfect the HPLC-grade hTERT and other mRNA into T-cells. Viability and T-cells population were analyzed using flow cytometry following 24hr and 48hr of mRNA transfection. **Results:** We have generated the first preclinical evidence that transfection of hTERT mRNA increases T-cell replicative capacity in vitro, and improves efficacy of CAR-T approach against a murine model of human B-cell malignancy. We have further introduced hTERT to CAR-T cells directed against disialoganglioside (GD2), a surface molecule expressed in neuroblastoma and neuroectoderm-derived neoplasms. Our preliminary data indicate that hTERT mRNA transfected GD2-CAR T cells show an increased cell number and also telomere length compared to controls. **Conclusions:** Our studies demonstrate that hTERT mRNA has great potential to improve the therapeutic benefits of CAR-T therapy. In collaboration with our bioinformatics team, we have also developed optimal codon algorithm for mRNA stabilization in human T-cells. We further aim to develop a novel codon-optimized RNA-based reagent for delivery of therapeutic mRNAs including hTERT that will improve immunotherapies by enhancing the proliferation capacity of CAR-T cells, an approach which can be applied to other somatic cell therapies.

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Poster Session B

Targeted therapeutic drug discovery program (TTP) for integrated, collaborative, high-throughput drug development *Eun Jeong Cho, The University of Texas at Austin; A. Devkota; J. Veloria; R. Edupugant; J. Lee; C. Zhang; P. Ren; K. Dalby*

Introduction: With an increasing understanding of the molecular pathways underlying cancers, translational & clinical investigators are identifying molecular targets at an increasing rate. The challenge for these investigators is having access to the specialized resources and experiences that are necessary to support robust drug development efforts, especially those focused on the early development phase encompassing the validation of good molecular targets and the design & development of chemical probes that effectively “hit” those targets for pre-clinical studies. This is the critical gap that the Targeted Therapeutic Drug Discovery & Development Program (TTP) has been designed to fill, which provides a holistic drug discovery and development stream to help investigators identify potential new drugs. **Methods:** We offer four highly integrated modules to realize a fully cohesive platform for advancing new molecules from ‘discovery’ to animal testing. These are i) a compound screening module, which supports assay design and implementation, to identify molecules for potential lead optimization, as well as data management and follow up mechanistic support. ii) a chemistry module which supports structure-guided synthesis of new analogs, as well as the scale up of lead synthesis. iii) a chemoinformatics & modeling module which a) supports the development of preliminary Structure Activity Relationships (SAR) for hit compounds, as well as the identification of structurally similar commercially available analogs via structure-based docking or pharmacophore searching and b) supports advanced in silico modeling and early prediction of ADMET properties. iv) a lead characterization module which provides access to structural biology facilities and pharmacokinetic expertise. **Results:** We have developed an integrated pipeline to provide translational scientists with collaborative support for the development of new drugs to treat cancer. Projects benefit by collaborating with TTP at various stages within the pipeline. **Conclusions:** We believe our integrated drug discovery platform will increase the number of new compounds in Texas reaching the stage of pre-clinical testing that possess the potency, selectivity and pharmacokinetic parameters needed to engage and inhibit oncogenic targets in tumors. With the decline in drug development in pharmaceutical companies, TTP assumes significant responsibility by serving as a preeminent incubator for the design and advancement of promising therapies.

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Poster Session B

Gulf Coast Consortium for Chemical Genomics: a multi-institutional network of core facilities to support cancer-related drug discovery and development *Suzanne Tomlinson, Gulf Coast Consortia for Quantitative Biomedical Science; C. Stephan; K. Dalby; Z. An; M. Mancini; M. Matzuk; D. Liang; S. Watowich; P. Davies*

Introduction: Since 2001, the Gulf Coast Consortia for Quantitative Biomedical Sciences (GCC) has been a very successful multi-institutional academic collaborative network composed of research and clinical faculty from seven member academic institutions in the Houston/Galveston area. One of these consortia, the John S. Dunn GCC Consortium for Chemical Genomics (GCC CG) is focused on the development of research infrastructure and core facilities to support and promote cancer-related drug and therapeutics discovery research. The program now includes five CPRIT-funded CFSA Core Facilities with complementary expertise and research technologies that are collaborating to provide a network of research resources that can be deployed to accelerate the discovery and development of new cancer therapeutics. The basic concept is that by seamlessly sharing access to critical resources across institutional boundaries without constraint, the network can provide the most efficient and effective support for the development of new cancer therapies. **Methods:** Harnessing original momentum generated through the award of a CPRIT-funded multi-institutional Multi-Investigator Research Award (MIRA; the Texas Screening Alliance for Cancer Therapeutics), the GCC CG has now developed 1) an extensive state-wide network of academic and clinical cancer researchers with projects spanning the entire drug development pipeline; 2) a web-based application and project tracking portal, 3) rigorous review and communication processes; 4) exceptional educational workshops and conferences focused on cancer therapeutics discovery and development, and 5) new collaborative partnerships to develop currently unavailable core resources. **Results:** Leveraging the GCC’s expertise in supporting multi-institutional collaborative research programs, the GCC CG’s network of drug discovery core facilities (the Preclinical Candidate Discovery Core, the Targeted Therapeutic Drug Discovery and Development Program, the Combinatorial Drug Discovery

Program, the Therapeutic Monoclonal Antibody Lead Optimization and Development Core, and most recently the GCC Center for Advanced Microscopy and Image Informatics) are working together to promote and support cancer-related therapeutics research. Three new GCC core facilities, GCC Center for Comprehensive PK/PD and Formulation, the Center for Computer-Accelerated Therapeutics, and the High Throughput Immunosensitizer discovery Core are under development to expand the ability of the network to support drug development projects, extending the pipeline of support to move the most promising therapeutic candidates to preclinical and clinical testing. **Conclusions:** By developing new core resources that "fill" existing "gaps" and networking new and existing therapeutics discovery and development resources into a "cancer resource core network," GCC CG continues to advance CPRIT's goal to move discoveries through development and ultimately to the bedside.

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Risk prediction for Barrett's esophagus and esophageal adenocarcinoma: incorporation of epidemiologic risk factors and 23 confirmed genetic loci *Jing Dong, Baylor College of Medicine; M. Buas; T. Vaughan; S. Zhao; A. Thrift*

Introduction: We developed comprehensive risk prediction models for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) that incorporate a polygenic risk score (PRS) and non-genetic factors. **Methods:** We used pooled data from 3,288 BE, 2,511 EAC, and 2,177 controls from BEACON, the United Kingdom Barrett's Esophagus Gene Study, and United Kingdom Stomach and Oesophageal Cancer Study. A PRS was created from 23 BE/EAC risk loci. We developed and compared risk models with various combinations of non-genetics factors and the PRS. We assessed their predictive accuracy using the area under the receiver operating characteristic curve (AUC). **Results:** Individuals in the highest quartile of the PRS had 2-fold higher risks of BE (odds ratio [OR], 2.22; 95% confidence interval [CI], 1.89-2.60) and EAC (OR, 2.46; 95% CI, 2.07-2.92) compared to those in the lowest quartile of the PRS. Risk models including only demographic/lifestyle factors (age, sex, smoking, body mass index, and nonsteroidal anti-inflammatory drugs) or only gastroesophageal reflux disease (GERD) symptoms had AUCs ranging from 0.637 to 0.667. The AUCs for models adding demographic/lifestyle factors to GERD symptoms were 0.793 and 0.745 for BE and EAC, respectively. Small but significant improvement in AUCs for each model was observed when including the PRS in the model (AUCs range, 0.656-0.799; all $P < 0.001$). Including the PRS in the model of non-genetic factors provided 3.0% and 5.6% improvement in the net reclassification index for BE and EAC, respectively. **Conclusions:** Risk prediction models that combine non-genetic and genetic information may be useful in identifying high-risk populations of BE and EAC for targeted cancer prevention.

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Multi-Objective Optimization based Biomarker Discovery *Zhandong Liu, Baylor College of Medicine; Y. Wan; H. Jin; M. Anderson; C. Mach*

Introduction: Discovering molecular pathways determining patient response to treatment is a critical step towards developing effective cancer therapies. To this end, huge databases of genomic, molecular, and clinical data from large cohorts of cancer patients continue to be assembled by major national and international projects. Multiple measures of disease response often exist, but yet do not provide equivalent insight. Unfortunately, only a small fraction of the information available in the majority of high throughput databases has been effectively used. **Methods:** To combine multiple types of clinical variables and protein-protein interaction networks, we formulated the MPA model through the multi-task learning framework. The first part of the objective function of MPA is a weighted sum of log-likelihood functions on each clinical variable. The first variable is typically treated as binary and hence will be modeled using logistic regression with binomial link. In contrast, duration of survival is a continuous variable with censorship, hence we will use the cox proportional hazards model, which only has a partial likelihood function. A normalization factor is used to ensure that the log-likelihood functions are balanced. The group L2 norm penalty requires the solution for each clinical variable to be similar, but not identical, hence reduces the solution space converging to the same pathway. The L1 norm penalty enforces model sparsity, namely only a small set of genes will be selected and the rest will be set to zero. The network smoothness penalty enforces the solution to be connected on the protein-protein interaction network. **Results:** To evaluate the performance of MPA and identify pathways predictive of patient response to treatment, we applied our method to the Level 3 TCGA ovarian cancer dataset. MPA identified predictive sub-networks to both chemotherapy and overall survival. Anaplastic lymphoma kinase (ALK) is the hub gene in the largest sub-network. Using the identified ALK sub-network by our model, we were able to separate patients into chemo-sensitive and chemo-resistant groups. These two groups demonstrate significant survival differences. We transfected OVCAR3 cells with either an shRNA targeting ALK or a non-targeting control. Our results clearly indicate that knockdown of ALK expression sensitizes OVCAR3 cells to platinum chemotherapy, reflected by a 2-fold decrease in the IC50 for cisplatin. **Conclusions:** These results demonstrate that MPA can effectively combine multiple types of clinical variables and protein-protein interaction networks to identify key pathways most important for driving the growth and progression of cancer.

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Functional Hallmarks of Acute Myeloid Leukemia from Cellular Images *Cecilia Lantos, Rice University; S. Kornblau; A. Qutub*

Introduction: Acute myeloid leukemia (AML) is a devastating blood cancer, with only a 25% patient survival rate. Characterizing AML is a challenge because no single gene or sets of genes define the disease. To address this heterogeneity, proteomic screening of AML cells has supplemented genomics, enabling a new class of molecules to be identified as potential therapies and helping improve clinical trial design. However, translating the proteomic work to the clinic is a long-term endeavor requiring the use of new screening methods. Here we introduce work towards a novel, computational approach to map common histological screening to the AML patients' underlying proteomics signatures. **Methods:** Prior research in our lab has identified key protein signatures predictive of AML patient response to chemotherapy, overall survival and remission duration. However, proteomic screens are expensive and non-standard. AML diagnosis and therapy are currently based on morphological classification of patients' bone marrow cells, and genetic abnormalities. The goal of this study is to apply the prognostics of the proteomic data to the clinic near-term, by developing methods to computationally map the proteomic signatures to a common clinical measure: histological analysis. The proposed project optimizes techniques that recognize cellular phenotypes from bone marrow histology slides and mathematically defines how protein signatures relate to cellular morphology. **Results:** Using pattern recognition techniques, machine leaning and deep learning modeling approach, the morphological cellular data of AML histology image or series of histology images and underlying genetic **Conclusions:** Results of this work will speed up the diagnosis of AML and advance personalized therapy for the heterogeneous blood cancer. The methods developed during this study can be applied directly to routine clinical biopsies for AML to rapidly support personalized, precise therapy, and potentially uncover new pathways for drug targeting.

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Risk of Hepatocellular Cancer in Patients with Non-alcoholic Fatty Liver Disease in Texas *Jennifer Kramer, Baylor College of Medicine; F. Kanwal; S. Mapakshi; Y. Natarajan; M. Chayanupatkul; P. Richardson; L. Li; R. Desiderio; A. Thrift; H. El-Serag*

Introduction: Non-alcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease including hepatocellular carcinoma (HCC) in the U.S. Texas has the highest age-adjusted HCC rates nationwide. However, there are limited data on the risk of HCC in NAFLD in Texas. **Methods:** This was a retrospective cohort study from patients seen at a facility in the Veterans Health Administration located in Texas. Veterans with NAFLD diagnosed between 1/1/2004 and 12/31/2008 were included and followed until HCC diagnosis, death or 12/31/2015. We defined NAFLD as evidence of ≥ 2 elevated ALT values >6 months apart, with no evidence of HBV and HCV or alcohol abuse. We also identified a gender and age-matched control cohort without NAFLD or other risk factors for liver disease. We ascertained all new HCC cases in both cohorts from the Cancer Case Registry and manual chart reviews. We calculated the annual incidence rates for HCC by NAFLD status as well as in subgroups of NAFLD patients. We used a proportional hazard model adjusting for competing risk of death to examine the effect of NAFLD on risk of HCC while adjusting for other confounders. **Results:** We compared 31,815 NAFLD patients from Texas with 31,815 controls. NAFLD patients were significantly more likely to be Hispanic (15.3% vs 4.2%), obese (53.8% vs 35.2%), have diabetes (27.3% vs 19%), hypertension (66.9% vs 55.8%), dyslipidemia (66.0% vs 53.1%), and cirrhosis diagnosis (2.7% vs 0.4%) than controls. During 255,550 person-years (PY) of follow-up, 81 NAFLD patients developed HCC for an incidence rate of 0.32/1000 PY. This rate was significantly higher than controls (0.03/1000 PY) and NAFLD patients from the US overall (0.19/1000 PY). The risk of developing HCC was 8.8-fold higher in NAFLD than controls (hazard ratio=8.84, 95% confidence interval=4.22-18.52). Among patients with NAFLD, those with cirrhosis had the highest annual incidence of HCC (9.6 vs. 0.10/1000 PY in patients without cirrhosis). Male and Hispanic NAFLD patients also had a higher HCC incidence rate (Male: 0.34/1000 PY and Hispanic: 0.43/1000 PY). **Conclusions:** Risk of HCC was higher in NAFLD patients from Texas than that observed in general clinical population and NAFLD patients from US overall. The absolute risk of HCC was higher than the accepted thresholds for HCC surveillance for patients with NAFLD cirrhosis.

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Oxygenation Response to Hypoxic Gas Breathing in Rat Breast Tumor *Ralph Mason, The University of Texas Southwestern Medical Center; T. Arai; J. Campbell; J. Gerberich; H. Zhou; D. Yang*

Introduction: Hypoxic sites in breast tumors are the targets of new therapeutic strategies using hypoxia activated prodrugs. A prerequisite for evaluating this therapy is to establish breast tumor animal models with alterable degrees of hypoxia. Herein, we use oxygenation-sensitive MRI to investigate the changes in hypoxia profile in rat 13762NF tumors during respiratory challenges. **Methods:** Subcutaneously implanted 13762NF tumors (n = 15) were given hypoxic (16% O2) and hyperoxic

(100% O2) respiratory challenges, during which MRI measurements (R1, R2, dynamic R2* and T1-weighted) were conducted at 4.7 T. Histology (H&E and pimonidazole staining) was collected for selected tumors. MRI parameters were analyzed voxel-by-voxel in the tumor and adjacent thigh muscle. Voxel-wise R2* temporal variation relative to baseline (air breathing) was used to categorize the tumor response to a given respiratory challenge. Combined blood-tissue oxygenation profile was derived for all tumors according to the tumor size and responses. **Results:** R1 and R2 maps revealed a structural pattern of 13762NF tumors (viable tissue in the periphery with necrosis at the core), which was verified by histology. Analysis of R2* temporal dynamics differentiated responsive and less responsive regions in the tumor, which were colocalized with viable tissue and necrosis, respectively. The volume fraction of responsive tumor regions decreased with increasing tumor size ($P < 0.05$). In responsive tumor regions, R2* increased by 4.3 ± 1.5 s-1 upon 16% O2 breathing and decreased by 3.3 ± 2.8 s-1 upon 100% O2 breathing, indicating sensitive BOLD (blood oxygen level dependent) effect. T1-weighted signal increased by 5.3 ± 3.1% upon 100% O2 breathing (tissue oxygen level dependent, TOLD, effect), but showed binary response (1.1 ± 1.5% decrease in small tumors vs. 0.5 ± 1.1% increase in large tumors) upon 16% O2 breathing (counteracting BOLD and TOLD effects). Combined blood-tissue oxygenation profile illustrated the differentiated degrees of oxygenation alterations upon hypoxic and hyperoxic respiratory challenges. **Conclusions:** BOLD and TOLD MRI with respiratory challenges (hyperoxic and hypoxic) reveals intratumoral and intertumoral oxygenation heterogeneity in the subcutaneous model of 13762NF tumors. The binary response in tumor oxygenation, which occurred only in the hypoxic respiratory challenge, provided an imaging marker to study the relation between tumor hypoxia level and the efficacy of hypoxia activated prodrugs.

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Poster Session B

Conducting multi-center clinical observational studies using "common data model": A case study for the bladder cancer risk of pioglitazone use *Xiao Dong, The University of Texas Health Science Center at Houston; Y. Wu; H. Xu*

Introduction: It is the common practice to centralize data from multiple sources in multi-center clinical observational studies to increase statistical power and improve generalizability of the study results. However, the major challenge is that the data formats vary across sources. Additionally, some investigators may be reluctant to send their data to the principal study investigator, limiting data sharing and research collaboration across institutional boundaries. In this study, we proposed an innovative approach to conduct multi-center clinical observational studies using "common data model" (CDM) which does not require data centralization. **Methods:** In the "common data model", clinical data from multiple participating study sites are converted to a common format locally. The principal study investigator will develop an analysis pipeline for a specific research question and post the analysis pipeline online, and participating investigators in other study sites can conduct the same study simultaneously on their own data using the analysis pipeline without sending the original data to the principle study investigator. In a case study for the bladder cancer risk of pioglitazone use, we employed the OMOP (Observational Medical Outcomes Partnership) common data model as the common data format, and developed an analysis pipeline to conduct a propensity score matching prospective cohort study. **Results:** A total of 292,212,707 de-identified medical records from 49,826,219 patients across the U.S. between 2005 and 2013 in the Cerner Health Facts® database were successfully converted to the OMOP common data model using Python and open source ETL (Extract, Transform, Load) tools. In the case study, Oracle SQL and R were used to develop the analysis pipeline to analyze bladder cancer risk associated with pioglitazone use. We will upload our analysis pipeline on Github (a computational code sharing website) and we anticipate that five to six other study sites will run our analysis pipeline on their own data locally. The results from different study sites will be pooled using the meta-analysis approach. **Conclusions:** We demonstrated that medical records could be successfully converted to a common data format, and this common data format was utilized to conduct a case multi-center clinical observational study. More importantly, once converted, this common data format can be used in future multi-center clinical observational studies to address other research questions. Compared with the commonly used pooling approach, the "common data model" approach is more efficient since it does not require data centralization and only one-time data harmonization is needed for various research questions.

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Poster Session A

A new modality for high-resolution deep-tissue fluorescence imaging of cancer *Baohong Yuan, The University of Texas at Arlington; T. Yao; S. Yu*

Introduction: Fluorescence imaging of tumor structural, functional and molecular information has been widely investigated and is playing an important role in preclinical cancer research and clinical cancer diagnostics. It has high sensitivity and specificity with benefits of low cost, use of non-ionizing radiation and capability of multiplex imaging. However, fluorescence imaging suffers from limitations in different applications. For example, fluorescence microscopy has high spatial resolution (sub-microns) but is limited in imaging depth (<1 mm). Fluorescence diffuse optical tomography can image tissue as deep as several centimeters but is limited with poor spatial resolution (a few millimeters). Ultrasound is another commonly used medical imaging modality and has relatively high resolution with a penetration depth of several centimeters. While ultrasound is sensitive to acoustic impedance mismatch, it is insensitive to tissue (bio)chemical or molecular features. X-ray based CT has very high spatial resolution, but is limited by its poor sensitivity to soft tissues. **Methods:** To achieve high spatial resolution of fluorescence imaging while maintaining its unique features, such as high sensitivity and multi-color imaging, a new hybrid imaging modality, ultrasound-switchable fluorescence (USF) imaging, was recently developed, which overcomes the limitations and achieves high-resolution fluorescence imaging in centimeter deep tissue. In USF imaging, an excellent USF contrast agent and a sensitive imaging system are required. Different types of USF contrast agents have been synthesized and characterized. Several USF imaging systems have been developed. **Results:** High-resolution USF imaging in centimeter-thick tissue phantoms and in-vitro tissue samples has been very successfully achieved. Simultaneously imaging multiple targets via multi-colored USF signals is also achieved and demonstrated. Furthermore, ex-vivo USF imaging of mouse organs and in-vivo USF imaging of mouse tumors have been studied and demonstrated. A commercial micro-CT is used to validate USF images in tissue-mimic phantoms, ex vivo tissue samples and in vivo mice with breast tumors. The results indicate that USF can accurately image tissue with high resolution in centimeter deep tissues and maintaining high sensitivity and multi-color imaging capability. The 3D USF and micro-CT images match well and the quantitative comparison will be presented. **Conclusions:** USF can provide high resolution imaging with fluorescence contrast, which will be very useful for cancer structural, functional and molecular imaging with high sensitivity and specificity in the future.

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Poster Session B

TeSLA: A Method for Measuring the Distribution of the Shortest Telomeres in Cells and Tissues *Tsung-Po Lai, The University of Texas Southwestern Medical Center; N. Zhang; J. Noh; I. Mender; E. Tedone; E. Huang; W. Wright; G. Danuser; J. Shay*

Introduction: Replicative senescence is triggered when the shortest telomeres in a cell lose the ability to protect chromosome ends. Short telomeres in combination with other oncogenic changes can result in genomic instability and cancer progression. **Methods:** To address this problem, we developed TeSLA (Telomere Shortest Length Assay), a technique that permits the detection of the telomeres from all chromosome ends from less than 1 kb to 18 kb using small amounts of input genomic DNA. This assay significantly improves the specificity and efficiency of TL measurements. We have also developed user friendly image-processing software to automatically detect bands from Southern blot images, to annotate band sizes, calculate average TL, as well as the percent of the shortest telomeres. **Results:** By comparing TeSLA with other TL measurement methods, TeSLA provides more detailed information about the shortest telomeres. As part of validating TeSLA we measured the length of telomeres longitudinally in peripheral blood mononuclear cells (PBMCs) during normal human aging, in tissues during colon cancer progression, in telomere-related genetic diseases such as idiopathic pulmonary fibrosis, as well as in mice and other organisms. **Conclusions:** The results indicate TeSLA is a robust method that provides a better understanding of the shortest length of telomeres.

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Poster Session A

Non-invasive and real-time assessment of brain tumor aggressiveness through hyperpolarized magnetic resonance imaging and spectroscopy *Travis Salzillo, The University of Texas M.D. Anderson Cancer Center; J. Gumin; J. Lee; N. Zacharias; R. Colen; F. Lang; P. Bhattacharya*

Introduction: Glioblastoma is the most common type of brain tumor but has the worst prognosis with minimal improvement of patient outcome in the past 30 years. The primary cause of treatment inefficacy is late diagnosis when tumors have become too advanced and invasive. There is a need for innovative techniques to predict prognosis early in a tumor's evolution for optimal treatment planning. Metabolic imaging is one such technique since metabolic changes in tumors precede anatomical and morphological changes. Additionally, metabolic aberrations, such as

high levels of glycolysis, are indicative of tumorigenesis. Through in vivo and ex vivo metabolic assays, we sought to show that tumor metabolism correlates with and can be predictive of tumor aggressiveness. **Methods:** Mice were intracranially injected with patient-derived glioma sphere-forming cells (GSC). The six GSC lines have established genomic profiles and produce distinct survival times in mice. Tumor development was followed with T1-weighted, T2-weighted, and fluid-attenuated MRI. At specific time points throughout tumor development, hyperpolarized 13C MRI experiments were performed to measure the dynamic metabolic flux of pyruvate to lactate in the tumor which is an important metabolic event at the end of glycolysis. Following in vivo hyperpolarization experiments, the mice were euthanized and their brains excised. Tumor samples were lysed to extract the water-soluble metabolites, and the global, steady-state metabolite concentrations in each GSC line were measured with nuclear magnetic resonance (NMR) spectroscopy. **Results:** An initial cohort of mice (N=5) has been imaged to completion. Tumor growth and mouse survival curves have been established and MRI pulse sequences optimized for follow-up studies. In the hyperpolarization experiments, the most aggressive GSC tumors produced the highest real-time flux of pyruvate to lactate, while the least aggressive tumors possessed the lowest flux. We have quantified the concentrations of 25 metabolites from NMR analysis of ex vivo tumor samples and are in the process of identifying the specific metabolic pathways that are affected in the different GSC lines. **Conclusions:** This initial study demonstrates the capability of hyperpolarized MRI to non-invasively measure tumor metabolism in order to stratify GSC-derived tumors based on their aggressiveness. The next step in this experiment is to correlate the in vivo hyperpolarization data with T1-weighted, T2-weighted, and fluid-attenuated MR images and corresponding ex vivo NMR metabolomics data.

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Poster Session B

High Throughput Mechanical Phenotyping of Cancer Cells *Md Shamim Ahmmed, Texas Tech University; S. Vanapalli*

Introduction: Mechanical phenotyping is a marker free way to quantify pathophysiological changes in cell state and their metastatic potential. One important finger print in mechanical phenotyping is cell deformability as it plays a vital role in tumor metastasis. In this study, we introduce a new high throughput microfluidic device that uses shear induced deformation of adherent cancer cell lines in narrow microchannels to phenotype them. **Methods:** Our newly engineered device contains a dozen constricted microchannels of hydraulic diameter slightly bigger than the mean size of breast cancer cell lines MCF7 and MDA-MB231 and non-tumorigenic breast epithelial cell line MCF10A. The flow conditions are chosen such that these cell lines experience enough fluid shear to deform them. A microfluidic manifold was designed to apply the same driving pressure to each channel enabling us to increase the throughput (>100 cells/sec). High speed video-imaging and automated image processing allows us to measure the undeformed cell size, velocity and deformation index of each cell. We use these readouts to phenotype highly metastatic (MDA-MB231), lowly metastatic (MCF7) and non-tumorigenic (MCF10A) breast cell lines. We also evaluate how these readouts vary with cytoskeletal drug interventions **Results:** We find that for a given driving pressure, cell undergoes a certain amount of deformation as it enters the constriction channel. This initial deformation happens very fast and then the cells slowly deform more to a maximum final deformation before exiting the constriction channel. Comparing the final deformation index, we find that highly metastatic breast tumor cell line MDA-MB231 deforms more than the lowly metastatic MCF7 and non-tumorigenic MCF10A. Although the lowly metastatic MCF7 deforms less than the highly metastatic MDA-MB231 but deforms more than the nontumorigenic counterpart which is in line with the findings in literature. By changing the driving pressure, we were able to evaluate the onset of deformation of above cell lines. Comparing the onset, we see that onset of deformation of MDA-MB231 happens at relatively lower driving pressure than MCF7 and MCF10A. We also use the multidimensional readouts to find the dose response curve of actin intervening drug Cytochalasin D as our device enables parallel analysis of drug concentrations in a single experiment. **Conclusions:** We developed a novel microfluidic device that enables high throughput mechanical phenotyping of tumor cells. This device provides a simple and high throughput way to phenotype cancer cells for application in cancer diagnostics and cancer biology.

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Poster Session A

Surfaceome profiling enables isolation of cancer-specific exosomal cargo in liquid biopsies from pancreatic cancer patients *Vincent Bernard, The University of Texas M.D. Anderson Cancer Center; J. Castillo; F. San Lucas; K. Allenson; M. Capello; D. Kim; M. Katz; G. Varadhachary; M. Javle; H. Alvarez; A. Maitra; S. Hanash*

Introduction: Detection of circulating tumor DNA (ctDNA) can be limited due to their relative scarcity in circulation, particularly while patients are actively undergoing therapy. Exosomes provide a vehicle through which cancer- specific material can be enriched from the compendium of circulating non- neoplastic tissue-derived nucleic acids. We performed a comprehensive profiling of the pancreatic ductal adenocarcinoma (PDAC) exosomal "surfaceome" in order to identify surface proteins that will render liquid biopsies amenable to cancer-derived exosome enrichment for downstream molecular profiling. **Methods:** Surface exosomal proteins were profiled in 13 human PDAC and 2 non- neoplastic cell lines by liquid chromatography-mass spectrometry. A total of 173 prospectively collected blood samples from 103 PDAC patients underwent exosome isolation. Droplet digital PCR (ddPCR) was used on 74 patients (136 total exosome samples) to determine baseline KRAS mutation call rates while patients were on therapy. PDAC-specific exosome capture was then performed on additional 29 patients (37 samples) using an antibody cocktail directed against selected proteins, followed by ddPCR analysis. Exosomal DNA in a PDAC patient resistant to therapy were profiled using a molecular barcoded, targeted sequencing panel to determine the utility of enriched nucleic acid material for comprehensive molecular analysis. **Results:** Proteomic analysis of the exosome "surfaceome" revealed multiple PDAC specific biomarker candidates: CLDN4, EPCAM, CD151, LGALS3BP, HIST2H2BE and HIST2H2BF. KRAS mutations in total exosomes were detected in 44.1% of patients undergoing active therapy compared to 73.0% following exosome capture using the selected biomarkers. Enrichment of exosomal cargo was amenable to molecular profiling, elucidating a putative mechanism of resistance to PARP inhibitor therapy in a patient harboring a BRCA2 mutation. **Conclusions:** Exosomes provide unique opportunities in the context of liquid biopsies for enrichment of tumor-specific material in circulation. We present a comprehensive surfaceome characterization of PDAC exosomes which allows for capture and molecular profiling of tumor-derived DNA.

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Poster Session B

A nanoprobe-based strategy for gastric cancer detection in PDX mice model *Xinyi Zhang, The University of Texas Southwestern Medical Center; G. Huang; J. Gao*

Introduction: Despite its declining incidence, gastric cancer is still among top 5 of the most prevalent cancers globally. Incidence and mortality rates remain high in Asia and Latin America. With a library of ultra-pH sensitive (UPS) polymer nanoprobes, we are able to utilize the acidic and angiogenic tumor microenvironment to achieve detection of the tumor in its early stage. Here we test this possible application in mice patient derived xenograft (PDX) model of gastric cancer. **Methods:** Engraft PDX tissue onto mice, each carrying two tumors on bilateral flanks. After tumors grow to desired size, inject intravenously poly(ethylene glycol)-b-poly(ethylpropylaminoethyl methacrylate) copolymers (PEG-b-(PEPA)), or poly(ethylene glycol)-b-poly(2-(dibutylamino)ethyl methacrylate) copolymers (PEG-b-(PDBA)) with conjugated indocyanine green (ICG) dye. After 24h, use fluorescence camera to take in vivo image, after that, sacrifice the mice to make tissue sections. Scan section fluorescence image at 785nm, then stain with haematoxylin and eosin (H&E stain) and scan. Compare images between two nanoprobes. **Results:** Both nanoprobes light up tumor quite well without much signal in normal tissues except liver and spleen where nanoparticles are cleared. Microscopic fluorescence imaging shows that main contrast arises from tumor margins. Comparing the two probes, PDBA has less liver accumulation. ICG fluorescence and H&E staining scanned image shows a good overlap between fluorescence and actual tumor area. **Conclusions:** UPS nanoprobes are useful tools to help with the detection of tumor. When used during gastric cancer operation, it can potentially show up metastatic places and aid the surgeon to clear all of the cancer sites.

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Poster Session A

Salivary S100P Protein as a Potential Biomarker for Oral Cancer Detection *Yi-Shing Cheng, Texas A&M University System Health Science Center; L. Jordan; H. Chen; T. Rees*

Introduction: Using salivary biomarkers for early detection of oral cancer is a promising approach. However, the key challenge is to find reliable indicators among salivary constituents, because of possible confounding factors such as chronic periodontitis (CP), which affects approximate 48% of the US adult population. We previously found that levels of salivary S100P mRNA were significantly higher in patients with oral squamous cell carcinoma (OSCC) compared to levels found in healthy controls, plus 1) patients who had CP (both smokers and non-smokers); and 2) patients who had oral lichen planus. Those findings suggested that S100P mRNA would be a promising salivary biomarker for OSCC detection. Recent research findings also suggest that S100P is involved in cancer invasion and metastasis, a feature that is not seen in inflammatory diseases-

-which further supports S100P being a cancer biomarker. However, whether the level of S100P protein is also elevated in OSCC patients' saliva was unknown. Therefore, the purpose of this study was to measure the salivary levels of S100P protein in OSCC patients and compare with levels found in CP patients. **Methods:** Saliva samples were collected from a total of 121 human subjects from four study groups: OSCC (n=30); CP-S (Smokers with CP, moderate to severe degree, n=31); CP-NS (Non-smokers with CP, moderate to severe degree, n=30); and Healthy Controls (n=31). Levels of S100P protein were determined by enzyme-linked immunoassay (ELISA), and normalized by total salivary protein level, which was determined by bicinchoninic acid (BCA) assay. Normalized S100P protein levels between each pair of patient vs. non-cancerous groups were analyzed by independent T tests and ANOVA with Scheffe post hoc tests, because data distribution was found to be normal and had equal variance. **Results:** S100P protein showed significantly higher levels in OSCC patients compared to both CP-NS patients (p=0.002), and the Healthy Controls (p= 0.001). S100P protein levels in OSCC patients were higher than those found in CP-S, but not at a statistically significant level (p= 0.091). There was no significant difference in S100P protein levels between CP-S and CP-NS patients (p>0.05) or Healthy Controls (p=0.858); and no significant difference between CP-NS patients and Healthy Controls (p>0.05). **Conclusions:** Salivary S100P protein appears to be a promising biomarker for OSCC detection in individuals without CP and in CP patients who are non-smokers. Smoking, in the presence of CP, appears to raise salivary S100P protein to a level approaching that in OSCC patients.

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Poster Session B

High resolution microendoscope to improve early detection of bladder cancer *Imran Vohra, Rice University; K. Cherry; T. Quang; Y. Tang; J. Carns; R. Schwarz; N. Dhanani; R. Richards-Kortum*

Introduction: Bladder cancer is the 6th most common cancer in the United States. When detected early, bladder cancer can be treated successfully. However, bladder cancer has a high rate of recurrence, and as a result, is the most costly cancer to treat. Standard cystoscopic surveillance has several shortcomings; many bladder cancers present as small, subtle, flat lesions that are difficult to distinguish from benign changes. While new endoscopic techniques such as narrow-band imaging can improve sensitivity, there is an important need to improve the ability of cystoscopy to characterize lesions as benign or malignant with high specificity. We report the development and initial evaluation of a high-resolution microendoscope (HRME) to characterize bladder lesions during cystoscopy. The HRME is a low-cost (<$3000) fiber-optic microscope that provides images with subcellular resolution in real time, revealing morphologic detail that is traditionally only available following biopsy and histology. The HRME has received an investigational device exemption from the FDA but has not been FDA-approved for clinical use. **Methods:** Patients scheduled to undergo standard of care cystoscopy were recruited for in vivo imaging at Lyndon B. Johnson Hospital in Houston, Texas. Imaging was performed in the operating room during cystoscopy. In addition, bladder specimens were obtained through a tissue bank for ex vivo imaging. A preliminary analysis was performed to explore the microscopic appearance of bladder lesions and to develop methods to distinguish precancerous and cancerous lesions from non-neoplastic tissue. **Results:** To date we have imaged 11 patients in vivo and 7 bladder specimens ex vivo using the HRME. Preliminary results indicate that cell nuclei are larger, more crowded, and more erratically shaped at lesion sites than in normal bladder tissue. These images and results are comparable with published images and results obtained by other groups using commercially available confocal microscopes that cost on the order of 50x as much as the HRME. **Conclusions:** To the best of our knowledge this ongoing study represents the first use of a low-cost imaging system to image the human bladder in vivo with subcellular resolution. The ability to image microscopic morphologic features to characterize bladder lesions in real time may have the potential to assist in the early detection of bladder cancer.

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171 **CPRIT Grantee**
Poster Session A

Expression & Purification of ALCL Lymphoma-Characteristic NPM-ALK Fusion Protein and Development of a Sensitive Detection Immunoassay *Richard Willson, University of Houston; K. Kourentzi; M. Crum; A. Prebisch; U. Patil; B. Vu; Z. Zeng; Y. Zu*

Introduction: Anaplastic large cell lymphoma (ALCL) is the most common T-cell lymphoma of children and young adults. In 90-95% of ALCL cases a chromosomal translocation results in the Anaplastic Lymphoma Kinase (ALK) gene being fused to the Nucleophosmin (NPM) gene, producing a 680-amino acid fusion protein. Since the NPM-ALK fusion protein is not normally expressed after birth and is stable enough (half-life > 48 hours) to accumulate to significant amounts in tumor cells, this protein has become a reliable biomarker for lymphoma diagnosis. Detection of this fusion protein in tumor biopsies by immunohistochemistry (IHC) is the gold standard for confirmation of the diagnosis of ALCL. Although a relatively simple technique, IHC is labor-intensive, biopsies are painful, and an adequate amount of tissue is not always available for analysis. Our goal is to enable and simplify the early detection of cellular NPM-ALK protein levels in lymphoma cells with greater sensitivity and precision than IHC staining. Currently no commercial source of the fusion protein is available that is needed for the development of an immunoassay. **Methods:** We have cloned, expressed in E. coli, and purified recombinant NPM-ALK fusion protein. **Results:** The recombinant NPM-ALK fusion protein was used as a positive control and test standard for development of a detection immunoassay. Furthermore, we optimized the immuno-detection of NPM–ALK in samples spiked with cultured human lymphoma cells positive for the NPM-ALK fusion protein after screening various antibody pairs. **Conclusions:** We have demonstrated the first quantitative measurements of NPM-ALK fusion protein expression in human lymphoma cells. There is a realistic possibility that we will be able to detect the NPM-ALK protein in peripheral blood samples instead of by painful, invasive tissue biopsies.

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172 **CPRIT Grantee**
Poster Session B

Genetics of Embryonal and Alveolar Rhabdomyosarcoma Study: The GEARS Cohort Profile *Philip Lupo, Baylor College of Medicine; J. Amatruda; S. Skapek; D. Hawkins; A. Sabo; L. Spector; S. Plon*

Introduction: Approximately 10% of children with rhabdomyosarcoma (RMS) are thought to have mutations in cancer predisposition genes. However, there have been no population-based assessments to support this estimate. Another limitation in previous studies has been the inability to evaluate the frequency of de novo germline mutations (DNMs) in cancer predisposition genes due to the absence of any well-characterized cohorts of RMS case-parent trios. The goals of this project are to: 1) determine the prevalence of pathogenic variants in cancer predisposition genes among children with RMS; and 2) characterize the contribution of DNMs in genetic susceptibility to RMS. **Methods:** First, we conducted a systematic literature review to identify genes associated with RMS susceptibility. Second, we leveraged the Children's Oncology Group (COG) Soft Tissue Sarcoma Biology and Banking Protocol to identify a set of 1,400 unselected and well-annotated RMS samples. Third, we are utilizing the Childhood Cancer Research Network (CCRN), which is the pediatric cancer research registry established by COG, as well as the newly developed registration and biobanking protocol, Project:Every Child (PEC), to prospectively enroll >700 independent case-parent trios in what will be one of the largest family-based studies of the origins of RMS. The combination of these activities makes up the Genetics of Embryonal and Alveolar Study (GEARS). **Results:** Our literature review has resulted in the identification of 25 genes previously implicated in RMS, including the well-characterized TP53, NF1, DICER1, and CDKN1C. The creation of custom capture reagents covering the selected genes is underway in the Human Genome Sequencing Center at Baylor College of Medicine. In August 2017, the COG Soft Tissue Sarcoma Committee approved our request to obtain 1,400 unselected germline DNA samples from children newly diagnosed with RMS (ARST17B2-Q). Additionally, in August 2017, the Cancer Therapy Evaluation Program (CTEP) approved our COG Groupwide Non-Therapeutic Study to enroll RMS case-parent trios through CCRN/PEC for the GEARS Cohort (AEPI15N1). We anticipate enrollment to begin in Fall 2017. **Conclusions:** The studies proposed here combine novel molecular genomic strategies and rigorous epidemiologic analyses of cancer predisposition genes in children with RMS to allow for a more systematic approach to genetic diagnosis, reproductive risk counseling, and identification of at-risk relatives. At the completion of GEARS, we will better understand the genetic mechanisms underlying one of the deadliest pediatric tumors. This, in turn, may lead to future preventive and therapeutic strategies.

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173 **CPRIT Grantee**
Poster Session A

A two-phase convolution neural network based model for automatic brain tumor segmentation *Yuanyuan Liu, The University of Texas Health Science Center at Houston; F. Zhou; T. Li; H. Li; K. Yu; Y. Wang; H. Zhu*

Introduction: We aim to utilize multi-institutional pre-operative MRI scans to automatically segment tumor subregions. We build a two-phase patch-based convolution neural network (TP-CNN) to classify all pixels in brain regions into the normal area, enhancing tumor, peritumoral edema, and necrotic core, using T1 post-contrast, T2, and T2 Fluid Attenuated Inversion Recovery (FLAIR) volumes. The major difficulty here is the multi-institutionality and the large training sample size, in contrast to limited computational power and random-access memory. We trained a simple neural network as the first stage to determine the rough tumor

location, and then extract patches around the segmented tumor to refine the previous segmentation results by a second-phase CNN model. The approach is shown to have a prominent improvement on the segmentation dice coefficient using the dataset acquired from 19 institutions collected by the Brats 2017 challenge. **Methods:** The dataset includes 210 glioblastoma and 75 lower grade glioma patients in the training set, and 46 patients in the validation set, each with T1, T2, FLAIR scans and manual annotations. In the TP-CNN first phase, we adopt the structure of the 2-dimensional CNN model described in Zhao, et.al., 2017, who extracted a larger patch 65x65 and a smaller patch 33x33, and merged them together at a certain layer after passing through several convolution and pooling layers. In our second phase, we combined 4 different models: Model1 uses the same setting as the model in phase1; Model2 uses a 13x13 simple single-size patch input and the network structure is similar; the third and fourth model jump from 2D models to 3D, and adopt the fully-connected CNN (FCNN) setting similar to Kamnitsas, et.al. 2017. In phase2, the center of all the sampled patches are within six-pixel distance from the tumor mask built by phase1. Finally, we use XGBoost to combine all generated probability maps to predict the final tumor labels. **Results:** The dice coefficient, sensitivity, and Hausdorff distance were evaluated on the validation set for the enhancing core, tumor core (enhancing core+neucrosis core) and whole tumor (tumor core+edema), respectively. Dice coefficient for phase1 segmentation: 0.472, 0.526, 0.630, and for phase2: 0.730, 0.722, 0.880; sensitivity for phase1: 0.722, 0.668, 0.921, and for phase2: 0.783, 0.789, 0.916; Hausdorff distance for phase1: 64.09, 64.88, 64.89, and for phase2: 5.62, 12.44, 7.40. **Conclusions:** The TP-CNN made great improvement comparing to its first phase in terms of dice-ratio and Hausdorff distance. The high sensitivity implies that few tumor regions were misclassified as normal.

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174 **CPRIT Grantee**
Poster Session B

Genome-wide profiling of DNA methylation in peripheral blood leukocytes and prostate cancer aggressiveness *Chia-Wen Tsai, The University of Texas M.D. Anderson Cancer Center; W. Chang; J. Gu; Y. Han*

Introduction: DNA methylation at CpG sites plays important roles in cancer development and progression. Hypermethylation of the promoter regions of tumor suppressor genes leads to gene silencing whereas global hypomethylation may affect chromosome structure and cause genomic instability. The goals of this study are to investigate the role of global DNA methylation in prostate cancer aggressiveness and identify CpG site methylations as predictors of aggressive prostate cancer. **Methods:** We measured global DNA methylation level of long interspersed nucleotide elements (LINE-1), pericentromeric repeat (NBL2), and subtelomeric repeat (D4Z4) in leukocytes and determined their associations with clinicopathological variables at diagnosis and biochemical recurrence (BCR) upon active treatments. We also used Illumina's HumanMethylation450K beadchip to profile individual genome-wide CpG site methylation in leukocytes and analyzed their associations with prostate cancer aggressiveness. **Results:** There was no significant differences in the methylation level of LINE-1, NBL2 and D4Z4 between clinically defined aggressive and non-aggressive PCa at diagnosis. LINE-1 and NBL2 methylation was not associated with BCR either. However, the methylation of subtelomeric region D4Z4 was associated with BCR. We found that patients with higher methylation of D4Z4 exhibited an increased risk of BCR in localized patients receiving definitive therapy. In tertile analysis, patients in the highest tertile of D4Z4 methylation had an increased risk of BCR (HR=2.17, 95% CI, 1.36-3.48) compared to patients in the lower tertiles after adjustment of age, BMI, smoking status, pack year, D'Amico risk groups, and treatments. Among the four CpG sites we measured in this region, the association was mostly attributable to the methylation of the 2nd CpG site of D4Z4. When analyzing individual CpG site methylation, we identified a number of CpG site that can distinguish aggressive from non-aggressive prostate cancer and found a CpG methylation signature that can identify a subgroup of patients with aggressive prostate cancer. **Conclusions:** These data suggest that methylation in the subtelomeric region D4Z4 may be able to predict worse prognosis of localized prostate cancer patients. Individual CpG site methylation may become promising biomarkers for the identification of aggressive prostate cancer.

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175 **CPRIT Grantee**
Poster Session A

Preliminary study for salivary metabolomic biomarkers for oral cancer detection *Teodoro Bottiglieri, Baylor Research Institute; L. Yi-Shing; E. Arning; C. Harmon; X. Wang*

Introduction: Worldwide, cancers of the oral cavity and pharynx are the 6th most common type. More than 90% of oral cancers are oral squamous cell carcinoma (OSCC), which typically are not diagnosed until an advanced stage. Early detection of OSCC is essential to improve clinical outcome, reduce suffering and reduce medical costs. We have therefore undertaken a targeted metabolomic analysis of saliva to identify possible reliable OSCC biomarkers for early detection, from subjects with OSCC as well as non-cancerous control groups with common oral inflammatory diseases including chronic periodontitis (Perio) and oral lichen planus (Lichen). **Methods:** Unstimulated whole saliva samples were collected from a total of 235 participants, from the following groups: OSCC (n=38), control non-smoker (n=38), control smoker (n=16), Lichen active (n=35), Lichen inactive (n=32), periodontal disease non-smoker (n=38) and periodontal disease smoker (n=38). All samples were centrifuged, and the supernatant was stored at -80°C until analysis. We measured salivary metabolites using the P180 platform (Biocrates Lifesciences, Austria) by LC-MS/MS, which determines 90 glycerophospholipids, 15 sphingolipids, 40 acyl-carnitines, 20 amino acids and 22 biogenic amines. The unprocessed raw data was downloaded from metIDQ software program (Biocrates Lifesciences, Austria) and then uploaded to MetaboAnalyst 2.0 for pre-processing. The processed data was then depicted by principal component analysis (PCA) and hierarchical clustering to illustrate possible grouping/clusters. Linear regression analysis was used to account for the age effect the statistical significance cutoff set at P-value <0.05 between any two conditions of interest with false discovery rate (FDR) assessment. **Results:** There was no significant difference in age between the OSCC and other non-cancerous control groups, with the exception of the perio-smoker group, which was significantly younger. We found numerous metabolites in salvia that are significantly increased in the OSCC group compared to other non-cancerous control groups. Overall, the levels of 59 glycerophospholipids and 8 sphingolipids were significantly increased in the OSCC group compared to the control non-smoking group. In contrast, 6 glycerophospholipids and 1 sphingolipid were significantly increased in the OSCC compared to the periodontal disease non-smoker group. **Conclusions:** Our preliminary findings reveal a panel of promising glycerophospholipids and sphingolipids in saliva that may be useful as metabolomic biomarkers for detection of oral cancer. Further validation with larger controlled studies are warranted and in planning.

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176 **CPRIT Grantee**
Poster Session B

Filopodia dynamics as a potential label-free biomarker for detection of highly metastatic cancer cells *Jose C. Contreras-Naranjo, Texas A&M University; A. Jayaraman; V. Ugaz*

Introduction: Detection of highly metastatic cancer cells is critical for patient prognosis and treatment when performing single cell analysis, for instance, in rare cells isolated from blood in a liquid biopsy. Filopodia, thin (200-400 nm) "finger-like" plasma membrane protrusions, have emerged as important contributors to cancer metastasis and could reveal the presence of these cells. Reflection interference contrast microscopy (RICM) is used here for label-free imaging of filopodia-like structures in cancer cells of different metastatic potential (e.g., PC3 and LNCaP) as they interact with a flat glass substrate. Our preliminary observations illustrate the potential for detection of highly metastatic cancer cells using filopodia dynamics as a label-free biomarker. **Methods:** Prostate cancer cells with high (PC3) and low (LNCaP) metastatic potential were maintained under RPMI medium with 10% fetal bovine serum at 37°C and 5% carbon dioxide. After cells reach 80-90% confluence, they were detached by Trypsin-EDTA, centrifuged down and re-suspended in fresh media. RICM images, recorded every ~10-15 s over ~1.5-2.5 h after loading cells into a microchamber, were obtained using a Zeiss Axiovert 200M inverted microscope with a Zeiss Antiflex EC Plan-Neofluar 63x/1.25 Oil Ph3 objective, X-Cite exact light source (546 nm monochromatic light), and maximum illumination numerical aperture. **Results:** Close cell-glass interaction (< ~40 nm) is eventually observed in most cells, with PC3s consistently forming a more well-defined adhesion patch. The adhesion behavior, readily accessible to RICM with its "view from below" perspective, is essentially hidden in bright field images where no apparent changes in cell morphology are evident. During the adhesion process, PC3 and LNCaP cells probe their environment with filopodia-like structures, which are easily visualized when producing bright intensities (possibly corresponding to filopodia-substrate separation ~100-150 nm). A color-coded composite RICM image of maximum intensities for a given adhered cell enables visualization of its filopodia dynamics "fingerprint". Despite similar size and sphere-like morphology, PC3 cells exhibit a higher degree of activity and highly uniform substrate probing using filopodia when compared to LNCaP cells. **Conclusions:** RICM-based label-free analysis of PC3 and LNCaP's adhesion and filopodia dynamics, although semi-quantitative in the current stage, allows filopodia-based discrimination between these cell lines. Further research, using blood cells and cells with high/low metastatic potential from different cancer sites, will enable the development of an integrated microfluidic-based platform for liquid biopsy analysis. In such platform, the filopodia dynamics "fingerprint" of isolated rare cells will be probed with RICM for label-free detection of highly metastatic cancer cells.

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Desorption Electrospray Ionization for Diagnosis of Non-Small Cell Lung Cancer *Alena Bensussan, The University of Texas at Austin; T. Zaidi; R. Katz; E. Cressman; L. Eberlin*

Introduction: Fine needle aspiration (FNA) biopsy is well established in the primary diagnosis of lung cancers and is often used to determine cancer subtype and tailor cancer therapies. However, histologic distinction between adenocarcinomas and squamous cell carcinomas, two major subtypes of non-small cell lung cancer (NSCLC), from FNA biopsy material can be challenging due to morphologic overlap between these subtypes. Thus, new technologies are needed to provide accurate pre-operative diagnosis of NSCLC. We propose a new avenue for rapid detection and diagnosis of lung biopsies based on diagnostic metabolic signatures detected by desorption electrospray ionization mass spectrometry (DESI-MS). **Methods:** Normal lung, adenocarcinoma and squamous cell carcinoma tissues were obtained from the Cooperative Human Tissue Network and MD Anderson Cancer Center Tissue Bank. Samples were sectioned and analyzed using an LTQ-Orbitrap Elite mass spectrometer coupled to a 2D Omni Spray DESI-MS imaging source. DESI-MS imaging was performed in negative ion mode at 200 μm resolution. Then, the tissue sections were H&E stained for pathological evaluation. The mass spectra from regions of clear histologic diagnosis identified by pathologists were extracted to build classification models by the Lasso statistical method. **Results:** DESI-MS imaging of normal lung, adenocarcinoma, and squamous cell carcinoma tissue sections allowed spatial and chemical characterization of metabolic profiles of each lung cancer subtype, including several diagnostic fatty acids and glycerophospholipids. Tissue samples presented histologic heterogeneity including regions of stroma and adjacent cancerous tissues with distinct mass spectral profiles. Mass spectra were extracted from annotated tissue regions presenting predominantly cancerous tissue or normal lung identified through histological evaluation. A statistical classifier was generated providing overall accuracy of 93.4% for lung cancer diagnosis. Further, classification of adenocarcinoma and squamous cell carcinoma was achieved with accuracies of 79.3% and 87.5%, respectively. **Conclusions:** DESI-MS was used to identify molecular markers of adenocarcinoma and squamous cell carcinoma subtypes of NSCLC.

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Molecular Discrimination of Follicular Thyroid Adenomas and Carcinomas using Desorption Electrospray Ionization Mass Spectrometry *Rachel DeHoog, The University of Texas at Austin; J. Zhang; E. Alore; J. Lin; W. Yu; R. Tibshirani; A. Engelsman; S. Sidhu; J. Suliburk; L. Eberlin*

Introduction: Fine needle aspiration (FNA) biopsy is well-established for diagnosis of suspicious thyroid lesions. However, due to similar cytological features, histologic discrimination between malignant follicular thyroid carcinoma (FTC) and benign follicular thyroid adenoma (FTA) from FNA is unachievable. Patients with indeterminant FNA diagnosis are subject to diagnostic surgery. In the majority of cases, the resected thyroid is found to be benign, and the surgery was, therefore, unnecessary. New technologies that could provide accurate pre-operative diagnosis of thyroid lesions are highly needed. Here, we employ desorption electrospray ionization mass spectrometry imaging (DESI-MSI) to rapidly diagnose FTC, FTA, and normal thyroid tissues based on molecular profiles. **Methods:** Human thyroid tissue samples including 25 FTC, 52 FTA, and 37 normal thyroid were obtained from the Cooperative Human Tissue Network, the Baylor College of Medicine (BCM) and the Kolling Institute of Medical Research Tumor Banks. Tissue sections were prepared and analyzed using a Q Exactive mass spectrometer (Thermo Fisher Scientific, CA) fitted with a 2D Omni Spray DESI-MSI source. The Lasso statistical method was used to build classification models. FNAs were prospectively collected from clinical practice at BCM. **Results:** DESI-MSI was performed in the negative and positive ion modes on FTA, FTC, and normal thyroid samples. In the negative ion mode, DESI allowed detection and characterization of glycerophospholipids, sphingolipids, fatty acids, and small metabolites. In the positive ion mode, DESI allowed the detection and characterization of glycerophosphocholines, diacylglycerols, and triacylglycerols. The Lasso statistical method was used to build classification models to predict FTA and FTC from the molecular information obtained, and select predictive molecular markers. Using negative ion mode data, discrimination between FTA and FTC was achieved with a 70.2% overall accuracy, and sensitivity and specificity of 79.9% and 65.7%, respectively. Using positive ion mode data, an overall accuracy of 88.9% was achieved with sensitivity of 82.1% and specificity of 91.8%. We are currently adding a third class, normal thyroid, to our classification models. Further, we are using a data fusion approach to incorporate positive and negative ion mode data into a unified classification system to further increase its predictive performance. Preliminary DESI-MSI analysis of 10 FNA samples was also performed, providing rich molecular information with similar molecular patterns to those detected in tissues. We are continuing to analyze FNA samples to determine the value of DESI-MSI for preoperative diagnosis of thyroid lesions. **Conclusions:** DESI-MS was used to identify molecular markers of follicular thyroid tumors for rapid clinical diagnosis of FNA biopsies.

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Molecular Targeting of MUC1 in Colorectal Cancer Using Hyperpolarized Magnetic Resonance Imaging of Silicon Particles *Dan Carson, Rice University; N. Whiting; S. Pudakalakatti; C. McCowan; J. Davis; N. Millward; D. Menter; P. Constantinou; P. Bhattacharya; J. Hu*

Introduction: Hyperpolarized silicon nano- and microparticles are potentially well-suited to act as targeted molecular imaging agents due to their overall biocompatibility and long-lasting enhanced MRI signals. In this study, dynamic nuclear polarization was performed on silicon particles functionalized with an antibody to MUC1, a mucin glycoprotein that is aberrantly expressed in colorectal cancer. Antibody conjugation to the particle surface did not affect ^{29}Si hyperpolarization characteristics. Conversely, the dynamic nuclear polarization process did not hamper the targeting ability of the antibody. In vivo magnetic resonance imaging was performed X minutes after particle administration into humanized MUC1-expressing orthotopic colorectal cancer mouse models, and indicated the particles actively targeted the tumor sites. These results were supported by chemical and biological controls, as well as correlative immunohistochemical analysis. These surface-functionalized silicon particles are under development as a platform technology that will allow non-invasive molecular targeting of colorectal cancer using hyperpolarized magnetic resonance imaging. **Methods:** Antibodies (MUC1-targetted or control) were conjugated to silicon particles of various sizes (2000 nm or 70 nm) and subjected to dynamic hyperpolarization using a specialized apparatus. These particles were tested for their ability to specifically bind to MUC1-expressing colon cancer cell lines in vitro or early stage colon tumors in mice harboring the human MUC1 gene. Detection in mouse colons was done using standard MRI methods. **Results:** Antibody conjugated silicon micro or nanoparticles retained both their ability to become hyperpolarized with a sustained (> 40 min) signal as well as to specifically target MUC1 expressing colon cancer cells in vitro or in vivo. Particles that were conjugated to control antibodies failed to target these cancer cells or tumors and MUC1-targetted particles did not bind to normal colonic epithelia. **Conclusions:** We find that silicon micro- or nanoparticles can be used as effective, sensitive targeting agents in colon cancer by directly conjugating specific antibodies to their surfaces that detect the cancer biomarker, MUC1, that appears in cancerous, but not normal colonic epithelia. Such particles can be hyperpolarized and retain specificity and robust hyperpolarization signal following the hyperpolarization procedure. This approach can potentially be used to target other cell surface antigens not only in colon cancer, but also in other cancers as a new early detection method.

180 **CPRIT Grantee Poster Session B**

A membraneless high-throughput micro-separator for high-throughput isolation and enrichment of circulating tumor cells *Victor M. Ugaz, Texas A&M University; B. Choi; A. Jayaraman*

Introduction: We have developed a microfluidic platform capable of performing precision isolation of micron-scale particles and cells. Our design uniquely merges the most favorable aspects of (1) continuous operation at high flow rates (mL/min range) with (2) the high selectivity of a physical membrane barrier. Preliminary results demonstrate size-based isolation and enrichment of cancer cells from whole blood with throughput 1 – 2 orders of magnitude faster than currently possible, while simultaneously preserving viability. **Methods:** Human prostate cancer cell line PC3 obtained from ATCC was maintained in RPMI 1640 medium supplemented with 10 % fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin at 37°C under a humidified 5% CO_2. PC3 cells were then stained with CellTracker Red CMTPX and spiked into fresh human blood (K2 EDTA anticoagulant). The ratio of blood cells and PC3 cells were adjusted by addition of phosphate buffered saline solution to achieve equal amount of WBCs and PC3 cells. Cell counts were obtained using a Multisizer 3 Coulter counter (Beckman Coulter) and confirmed with a hemocytometer. Erythrocytes were lysed with Zap-oglobin II lytic reagent (Beckman Coulter) for determination of leukocyte and cancer cell counts. The harvested PC3 cells were observed and imaged under fluorescence microscopy (Axiovert 200M, Carl Zeiss). Cells numbers are expressed with respect to the total collected sample volume. Viability was assessed using trypan blue exclusion. **Results:** Whole blood spiked with PC3 human prostate cancer cells (20 – 30 μm dia.) was injected into the inner lane of the microfluidic separation device at flow rates up to 1 mL/min. Phosphate buffered saline (PBS) was co-injected into the outer lane at the same flow rate. Injected component densities were PC3: 1.43 x

10^6 cells/mL, WBC: 1.22 x 10^6 cells/mL, RBC: 7.32 x 10^8 cells/mL. Cell counts indicate that PC3 cells were separated with > 99% efficiency with 1.6x enrichment upon recovery from the inner lane owing to the unequal depths on each side of the centerline barrier. The enriched cells were maintained in the as-injected blood environment with no discernable change in viability (before filtration: 98.7% ± 0.6 %, n = 3; after filtration: 98.9% ± 0.1 %, n = 3). **Conclusions:** Separation efficiencies up to 80% are achievable in a single stage across flow rates from 0.1 – 2.0 mL/min, making this approach well suited for high-throughput processing of large sample volumes.

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181 **CPRIT Grantee Poster Session A**

Improving the identification of genomic allelic imbalance in multisample, tumor-only studies using synthetic normals *Jerry Fowler, The University of Texas M.D. Anderson Cancer Center; F. San Lucas; S. Sivakumar; T. McDowell; E. Ehli; G. Davies; P. Scheet*

Introduction: Tumor genomic characterizations are typically performed by comparing the genomes of tumor samples to genomes of paired-normal samples. However, there are a variety of common scenarios in which matched normal samples are not available. In mutation detection, this is commonly addressed by comparing tumor samples to the reference human genome for variant detection and then applying filtering algorithms to remove likely germline events. Study designs are evolving however, and the inclusion of multiple samples through multi-region or longitudinal sampling is becoming more common. Here we devised a strategy to improve somatic aberration detection in multisample, tumor-only studies by generating "synthetic normal" samples. Given multiple tumor samples, we aggregate putatively normal components of each sample's genome into a surrogate normal genome to allow for conventional tumor-normal analyses. Our initial focus here is on improving allelic imbalance (AI) event detection in such studies, but the concept is also applicable to mutation and copy number profiling. **Methods:** We called genotypes for 163 samples from 29 non-small cell lung cancer patients using the Illumina GSA array. We characterized AI events using hapLOH, which detects regions of haplotype imbalances. Conventionally, these haplotypes are inferred using paired-normal samples, but this study lacked such samples. Thus, we inferred haplotypes and called AI events using 3 different strategies: (1) analyzing samples independently, (2) identifying the "most normal" sample for each patient and treating that sample as a surrogate paired-normal, and (3) aggregating high-quality genotypes for all samples of an individual into a "synthetic normal" for use in AI calling. **Results:** Numbers of heterozygous genotypes increased from strategies 1 to 3, resulting in improved haplotype estimation and higher numbers of AI event calls. There were two scenarios in which AI sensitivities were improved: (1) where complete cn-LOH was observed, and (2) where there was variability in genotype quality within a patient's samples. In the first case, heterozygous genotypes were recovered where previously long stretches of haplotypes appeared missing. In the second case, synthetic normals provided increased genotype densities across the genomes of lower-quality samples, improving power to detect AI. **Conclusions:** The synthetic normal concept provides a strategy for dealing with tumor-only analyses in settings where multiple samples are available from single individuals. We demonstrated its benefit in AI profiling using SNP array data; however, the synthetic normal concept could also be applied to sequencing data as well for potentially improved AI, copy number or mutation detection.

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182 **CPRIT Grantee Poster Session B**

GPU-based feature selection using multidimensional biomedical images to enable fast infrared imaging using DFIR *Rupali Mankar, University of Houston; S. Prasad; M. Walsh; D. Mayerich*

Introduction: Mid-infrared spectroscopic imaging has the potential to overcome human errors and automate histopathological analysis. Unfortunately, long imaging times and large data sizes are a barrier to clinical applicability. Recent advances in quantum cascade laser (QCL) light sources can potentially address these issues. However, extensive data mining must be performed in order to effectively use discrete-frequency imaging systems. We have propose an approach based on genetic algorithms combined with linear discriminant analysis (GA-LDA) as a feature selection algorithm for dimensionality reduction of IR spectroscopic data. GA-LDA serves two purposes - it reduces dimensionality and enables discrete frequency imaging by finding spectral markers for classification. We further improved GA-LDA computational efficiency by implementing it on inexpensive graphics processors (GPU). We demonstrate the viability of this approach by classifying cancer-relevant cell types in tumor biopsies from tissue micro-arrays for breast, bone, and kidney. **Methods:** Hyperspectral images (HSI) of multiple tissue micro-arrays were are collected using both an Agilent FTIR spectroscopic microscope and Spero QCL (quantum cascade laser) system. Adjacent histology sections were used to annotate cancer-relevant tissue sub-types in HSI images. Our proposed GA-LDA algorithm was used for dimension reduction, and classification was performed using a random forest. In addition, a GPU implementation for GA-LDA was generated to make the algorithm practical in a clinical time frame. **Results:** GA-LDA features were compared to traditional methods, including mRMR, PCA, and LDA. Sequential feature selection algorithms like mRMR work better when data is simple with binary classes only but for complex data with more number of classes, GA-LDA performance is better. Validation results of both FTIR imaged data and DFIR imaged data classified using only GA-LDA selected features are very promising: area under ROC curve for classes blood, epithelium, collagen and necrosis are around 0.95, for lymph 0.90 and for fibroblasts and myofroblasts 0.85 and 0.80 respectively. **Conclusions:** GA-LDA provides an effective method for dimension reduction of FTIR images. In addition, this algorithm provides features that are viable for DFIR imaging and provide high accuracy when tested against alternative approaches. While GA optimization is generally time-consuming, our GPU-based approach addresses this by taking advantage of data-parallel computation on an inexpensive local workstation. Classification based on spectral signature provides high accuracy for cancer-relevant tissue types, better than PCA on complex data sets. This also enables use selected spectral markers for Discrete Frequency IR (DFIR) imaging.

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Copy Number Profiles and Locoregional Metastatic non-Small Cell Lung Cancer *F. Anthony San Lucas, The University of Texas M.D. Anderson Cancer Center; T. McDowell; S. Sivakumar; N. Kallsen; J. Beck; S. Peyton; E. Ehli; G. Davies; J. Fujimoto; I. Wistuba; G. Eapen; J. Stewart; J. Fowler; P. Scheet*

Introduction: Advanced non-small cell lung cancer is difficult to treat, with a 15% five-year survival rate. Mortality is high because most cancers are diagnosed after metastasis to the lymph nodes (LNs) or distant organs, where LN metastasis is a significant prognostic indicator for early stage non-small cell lung cancer (NSCLC). It is believed that LN metastasis is a gateway to distant metastases. Therefore understanding the biology of LN metastasis should provide potential opportunities for improved staging, diagnosis, prognosis and treatment. Recent advances in non-invasive sampling of LN tissue (endobronchial ultrasound; EBUS) offer an additional motivation to discover genomic signatures that may predict tumor involvement in the LNs. **Methods:** We obtained Affymetrix SNP6 data from lung adenocarcinoma patients of The Cancer Genome Atlas (TCGA). We then applied an Illumina SNP microarray to DNA from a retrospective collection of EBUS-guided transbronchial needle aspirates, surgically-resected LNs, and primary NSCLC tumors. On these two SNP data sets we then ran hapLOH, a haplotype-aware statistical technique that sensitively detects copy number alterations (ie, deletions, duplications and copy-neutral loss of heterozygosity; collectively, CNAs) with mutant cell fractions as low as 3-5%. **Results:** TCGA analyses confirm a higher AI burden in primary tumors may be associated with both LN metastasis and a decrease in overall survival. Analyses of our own data set showed that AI events in LN are strongly associated with tumor status (positive/negative) assessed through pathology. AI events identified in LN were often but not exclusive to events identified in corresponding primary tumors. In TCGA analyses, AI of chromosome arm 4q was identified as being enriched in patients with LN metastases, which was further supported in genomic profiles of our LN samples **Conclusions:** Our current study identified AI events that are putatively associated with LN metastasis in lung cancer patients. Our current analysis suggests that AI of chromosome arm 4q may be involved in LN metastases, possibly by promoting genomic instability. Finally, our study, which is ongoing with additional samples and analyses forthcoming, helps to explore genomics as a complement to traditional pathology in this setting.

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184 **CPRIT Grantee Poster Session B**

An eight channel bow-tie slot coil for parallel transmit MRI/MRS *Dheyaa Alkandari, Texas A&M University; N. Hollingsworth; C. Huang; J. Cui; S. Wright*

Introduction: High field magnetic resonance imaging (MRI) significantly improves signal to noise ratio (SNR) and spatial resolution. Both of which increase the MRI capability towards better cancer diagnostic [1]. However, key challenges obstruct the use of high field MRI in clinical practice. A main challenge relates to B_1 inhomogeneity due to interactions between RF waves and tissue [2]. Multi-channel RF transmission shows significant improvement in B1 homogeneity for high field MRI. However, multi-channel coils requires further investigation to mitigate the effects of coupling between elements. Several approaches show promise in sufficiently decoupling coil elements. Many of these approaches, however, either enforce geometrical restrictions or require custom design

circuits [3-5]. Slot elements may serve as intrinsically isolated elements simplifying the theses coupling concerns. In addition, slot elements possess the unique characteristic of operating as a part of a ground plane, or a shield. This characteristic allows for more compact multi-channel transmit coil designs with a cleaner imaging area by placing all the electronic components associated with RF coils behind the shield. **Methods:** We present a volume coil consisting of 16 bow tie slot elements arranged in eight independent modules without the use of decoupling circuits. To provide significant coverage in the sagittal and coronal planes, each of the modules consist of two slots. The enclosed modules host all feed lines, matching/tuning circuit, and balun; resulting in a shielded clean imaging area. This shielded imaging area reduces the Electric field generated from the coil's feed cables and electrical components, and simplifies interactions with the receive coil. We evaluated the eight channel coil by performing bench tests and MRI experiments at 4.7T. **Results:** The acquired 8×8 decoupling matrix confirms the good isolation between the coil's eight modules. Without the addition of decoupling networks or preamplifier, the highest case of coupling did not exceed -14.5 dB and only occurred between neighboring modules. The imaging results demonstrated localized patterns about the single excited modules. These localized patterns likely resulted from the low intrinsic coupling between the single excited module and the remaining non-excited modules. **Conclusions:** The slot array appears ideally suited for use in a multi-channel transmit array due to the high degree of intrinsic isolation between elements. In addition, the ability to shield all of the matching elements and, potentially, power amplifiers may make slot arrays an excellent option for either combined transmit/receive coils or separate transmit and receive coils.

185 **CPRIT Grantee**
Poster Session A

Label-free classification of infrared images of tumor biopsies using convolutional neural networks *Sebastian Berisha, University of Houston; M. Walsh; D. Mayerich*

Introduction: Histopathology continues to be the main tool utilized in the diagnosis of cancer. The current methods for cancer detection rely on the examination of a biopsy tissue by a pathologist, after the tissue has been processed (including clinical staining). Even though these methods continue to remain the gold standard, they are prone to human error (staining quality) and non-quantitative. Fourier Transform Infrared (FTIR) spectroscopic imaging provides quantitative chemical and spatial information that allows the extraction of both biochemical composition and morphology information in a noninvasive manner. The absorbance spectra obtained via FTIR spectroscopy provide biochemical fingerprints for each pixel in the imaged tissue, which can be used for classification. FTIR imaging coupled with advanced machine learning tools may offer the potential for histopathological recognition without the use of dyes, probes, or human interpretation. Convolutional neural networks (CNNs) are the current state-of-the-art in image classification and speech recognition and can learn interpretable representations of the data. **Methods:** Traditional FTIR image classification methods rely only on the spectral information of an individual pixel to perform classification. In our approach, a CNN is trained using a local tensor region around the classified pixel. This allows the classifier to utilize the local spatial information embedded in the infrared image. CNN training is performed using multiple annotated tissue micro-arrays obtained from AMSbio consisting of cancer biopsies as well as adjacent normal samples. Training is performed using TensorFlow on a GPU accelerated server. Classification accuracy is then validated on separate annotated tissue microarrays. **Results:** When compared to traditional classification methods using a Random Forest on individual spectra, a CNN with utilizing spatial information exhibited performance gains from 10% to 15% on the same images with improvements in ROC curve areas across classes. This demonstrates a significant improvement over the use of individual spectra, with no additional cost for image acquisition. **Conclusions:** We show that CNNs can be efficiently used to classify biomedical FTIR spectroscopic data. Our CNN-based method outperforms standard classification algorithms used in FTIR spectroscopy, such as random forests and Bayesian-based classifiers, in terms of accuracy when applied to independent test data. We report classification results and analysis by applying a CNN architecture to data from tissue microarrays consisting of five cell types, namely blood, collagen, epithelium, necrosis, and myofibroblasts. Our goal is to explore the application and efficiency of deep learning algorithms in improving the diagnostic techniques in clinical and research activities related to cancer.

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Poster Session B

Clinical Language Annotation, Modeling and Processing Toolkit (CLAMP) for Extraction of Tumor Attributes in Cancer Pathology Reports *Ergin Soysal, The University of Texas Health Science Center at Houston; J. Wang; H. Xu*

Introduction: Natural Language Processing approaches have been successfully applied to cancer-related data requirements, since exponentially increasing data size and information exchange requirements make it crucial to use computational methods to process clinical narratives. Pathology reports are gold standards in cancer diagnosis, which holds the most important information for cancer management decisions. A set of cancer-specific components created for CLAMP to extract tumor attributes mentioned in the pathology reports. **Methods:** We developed a set of state-of-art natural language processing components to process pathology reports that were embedded into an integrated development environment to visually develop custom algorithms specific to clinical information requirements. Knowledge resources required by these accompanied components like dictionaries, section header list or medical abbreviation list were provided with the toolkit. CLAMP components were fine-tuned to use with pathology reports, including a set of tumor-specific information such as morphology, tumor grade, tumor location (topology) and procedure. **Results:** CLAMP completely automated natural language processing projects as an all-in-one solution for extraction of tumor attributes from pathology reports. It helped users with limited technical skills to develop hybrid cancer pipelines, containing both machine learning and rule based algorithms for best results in a completely integrated environment. **Conclusions:** CLAMP can successfully be utilized in pathology reports of cancer patients by contributing to extract valuable tumor information. CLAMP promises an easy to use desktop application without sacrificing functionality. It serves a complete set of components to achieve the best possible results for clinical natural language processing, with the best proven approaches using a mixture dictionary based, rule based and machine learning methodologies.

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Image improvement in digital breast tomosynthesis *Nikolai Slavine, The University of Texas Southwestern Medical Center; S. Seiler; R. Lenkinski*

Introduction: To evaluate in clinical use a novel rapidly converging, iterative deconvolution method to enhance contrast and image resolution in digital breast tomosynthesis. **Methods:** The method was tested on clinical breast imaging data. Data acquisition was performed on a commercial Hologic Selenia Dimensions breast tomosynthesis system. This method was applied to patient breast images previously processed with Hologic software to determine improvements in resolution and contrast to noise ratio. **Results:** In all of the patients' breast studies the improved images proved to have higher resolution and contrast as compared with images obtained by conventional methods. **Conclusions:** A rapidly converging, iterative deconvolution method with a resolution subsets-based approach that operates on patient DICOM images has been used for quantitative improvement in digital breast tomosynthesis. The method can be applied to clinical breast images to improve image quality to diagnostically acceptable levels and will be crucial in order to facilitate diagnosis of cancer progression at the earliest stages. The method can be considered as an extended Richardson-Lucy algorithm with multiple resolution levels.

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A Database of Cancer Associated SNPs in DNA Repair Genes (CSNP-DNAR) *Pavel Silvestrov, University of North Texas; G. Cisneros*

Introduction: Cancer is a complex disease that can involve concurrent malfunction of different cellular pathways, and can be caused by mutations in various genome locations. DNA repair enzymes play an important role in maintaining DNA integrity, and thus ensure faithful propagation of genetic information. Furthermore, cells that result from the carcinogenesis themselves depend on DNA repair enzymes for further growth. Therefore, it is of particular interest to study the mutations that occur in DNA repair genes and to analyze their possible links to various types of cancer. **Methods:** We will present the development of a new database, CSNP-DNAR. The aim of this database is to provide a comprehensive compendium of mutations on DNA repair enzymes statistically linked to various types of cancer together with data on the structural manifestations of these mutations in DNA repair proteins. **Results:** Initial results will be presented, including a number of SNPs that translate into missense mutations in ALKBH7, and POLL genes. Computational simulations based on molecular dynamics of ALKBH7 and POLL provide insights on how the respective cancer variants affect these proteins' structure and function. **Conclusions:** A better understanding of structure and function of the DNA repair genes is a good ground for development of cancer diagnostic and treatment methods.

189 **Poster Session A**

PancanQTL: systematic identification of cis-eQTLs and trans-eQTLs in 33 cancer types *Jing Gong, The University of Texas Health Science Center at Houston; L. Han*

Introduction: Extensive evidence indicated that single nucleotide polymorphisms (SNPs), the most common type of human genetic variation, could contribute to tumor initiation, progression, diagnosis and

prognosis through affecting gene expression. Expression quantitative trait locus (eQTL) analysis, which links SNPs to gene expression levels, is critically essential for understanding gene regulation as well as for interpreting disease-associated loci. Current eQTLs are identified mainly in blood samples and other normal tissues. There is limited comprehensive analysis to identify eQTLs in large number of cancer samples. Therefore, our goal is to systematic identification of cis-eQTLs (SNPs affect local gene expression) and trans-eQTLs (SNPs affect distant gene expression) in multiple cancer types. **Methods:** Using the genotype and expression data from The Cancer Genome Atlas (TCGA), we performed systematic and large-scale investigation of both cis- and trans- eQTLs in multiple cancer types. Combined with TCGA clinical data, we further analyzed eQTLs which are associated with different survival and. To help interpreting disease-associated loci, we also mapped these eQTLs to GWAS loci. **Results:** We identified 5 606 570 cis-eQTLs-gene pairs and 231 210 trans-eQTLs-gene pairs from 9 196 tumor samples in 33 cancer types. We further performed survival analysis and identified 22 212 eQTLs associated with patient overall survival. Furthermore, we linked the eQTLs to GWAS data and identified 337 131 eQTLs overlap with existing GWAS loci. We developed PancanQTL, a user-friendly database (http://bioinfo.life.hust.edu.cn/PancanQTL/), to store cis-eQTLs, trans-eQTLs, survival associated eQTLs and GWAS related eQTLs for searching, browsing, and downloading. **Conclusions:** In summary, we systematically identified cis-eQTLs, trans-eQTLs, survival associated eQTLs, and GWAS related eQTLs in 33 cancer types. We constructed a user-friendly database, PancanQTL, for users to query, browse, and download eQTLs. Millions of vector diagrams of eQTL box plots and Kaplan-Meier plots were provided for scientific usage. PancanQTL will serve as an important resource for human cancer genetics and provide opportunities to bridge the knowledge gap from variants in sequence to phenotypes. Acknowledgement: UTHealth Innovation for Cancer Prevention Research Training Program Post-Doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant # RP160015). Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.

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Predictive Ability of Sialic Acid Measured by Surface-Enhanced Raman Spectroscopy in Early Stage Breast Cancer *Ekaterina Vinogradova, The University of Texas at San Antonio; H. Navarro-Contreras; A. Hernandez-Arteaga; J. Zermeno Nava; E. Kolosovas-Machuca; J. Velazquez-Salazar; M. Jose-Yacaman*

Introduction: In the United States, breast cancer (BC) is the most common non-skin-related type of malignancy in women and is the second leading cause of cancer death in women. Early-stage detection of breast cancer (stages 0, I and II) through screening plays a crucial role in saving women's lives as well as in reducing devastating emotional, physical and economic impacts of advanced stage cancer treatment. While screening mammography is currently the best available screening method for early detection of BC, it is associated with the harmful effects of ionizing radiation and its benefits are not the same for all women. Using the nanoplasmonic effect of silver nanoparticles, we have developed a novel method to measure very low concentrations levels of sialic acid (SA) in human saliva. Elevated levels of SA have been shown to be a characteristic feature in saliva of BC patients, and therefore, they have been suggested as a non-invasive predictive marker for patients with this type of cancer. **Methods:** We examined the feasibility of Raman spectroscopy as a method for quantification of SA in saliva, using citrate-reduced silver nanoparticles as a surface-enhanced Raman spectroscopy (SERS) substrate. We apply this method on salivary specimens from 106 healthy women and 100 diagnosed BC patients to test the hypothesis that cancer-related changes in the concentration of SA in saliva may be quantitatively detectable by measuring the intensity of selected SERS peaks. Quantification of the salivary SA levels was accomplished by measuring the intensity of Raman bands of SA in saliva and comparing it with a calibration curve obtained from a series of aqueous solutions of known concentrations of SA. **Results:** The mean concentration of SA was found to be significantly higher among BC patients (18.3 mg/dL) compared to the healthy controls (3.5 mg/dL). The SERS method shower sensitivity of 94% and specificity of 98% for detection of patients with BC, assuming a cutoff threshold of 7 mg/dL. Furthermore, our preliminary results suggest a positive correlation between the saliva levels of SA and cancer stage that will require further examination. **Conclusions:** Our findings illustrate the potential of the method and support the hypothesis that monitoring of SA concentrations afforded by SERS of saliva would allow differentiate patients with cancer from those without cancer. In addition, our results indicate that our technology can potentially be used for monitoring of BC patients during and after treatment.

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Hepatocellular Carcinoma Screening is Underused in Patients with Cirrhosis *Debra Choi, Texas A&M University System Health Science Center; H. Kum; S. Park; R. Ohsfeldt; A. Singal*

Introduction: Hepatocellular Carcinoma (HCC) incidence and mortality are rapidly increasing in the United States. Implementation of routine HCC screening is crucial for early tumor detection and curative treatment receipt to mitigate HCC mortality. Our study's aim was to characterize utilization of HCC screening among at-risk patients in the United States. **Methods:** We conducted a retrospective cohort study using SEER-Medicare linked data among patients (n=11,659) diagnosed with HCC between 2006 and 2011. Patients were required to have continuous enrollment in Medicare Part A and B for ≥3 years prior to HCC diagnosis. We excluded patients enrolled in Medicare health maintenance organizations (HMOs). We defined a subset of patients with known cirrhosis (n=1,836) based on ICD-9 codes. The primary outcome of interest was receipt of HCC screening over a 3-year period, which was defined using two measures. We first used three mutually exclusive categories: 1) consistent screening 2) some screening and 3) no screening. Consistent screening was defined as having ≥1 abdominal ultrasound per calendar year; some screening was defined as having ≥1 abdominal ultrasound but less than annual. Our second measure was proportion of time up-to-date with screening (PUTD). PUTD was defined as the proportion of the 36-month study period in which patients had received screening, with each abdominal ultrasound providing 7 months of screening coverage. We assessed screening receipt using claims for abdominal ultrasound within the 3-year surveillance period prior to HCC diagnosis. In a sensitivity analysis, we applied a validated algorithm to infer when ultrasounds were done for purposes of HCC screening. **Results:** Most (60%) patients did not receive any screening, with only 35% (n=4,110) having some screening and 5% having consistent screening in the 3 years prior to HCC diagnosis. Only 36% of ultrasounds were performed with screening intent, resulting in only 2% of patients with consistent screening. Approximately 67% of HCC patients with consistent screening were detected at a localized stage compared to 59% who had some screening, and 47% of those who did not receive screening (p<.0001). The subset of patients with known cirrhosis had similarly low rates of consistent screening at only 9%; however, there were higher rates of some screening at 51%. The mean PUTD was 10.4% ± 18.5%, although this decreased to only 3.8% ± 11.8% after accounting for screening intent. **Conclusions:** HCC screening is underutilized in the United States; likely contributing to high rates of late stage diagnosis and poor survival.

192 **Poster Session B**

Nanophosphors: Highly Sensitive Reporters for Smartphone-Based Diagnostics *Richard Willson, University of Houston; A. Paterson; B. Raja; V. Mandadi; B. Townsend; M. Lee; H. Goux; A. Danthanarayana; B. Vu; K. Kourentzi; J. Brgoch*

Introduction: The lateral flow immuno-chromatographic assay (LFA), most widely known as the home pregnancy test, is ideal for point-of-care diagnostic testing because of its low cost, simplicity, and freedom from elaborate and costly instrumentation. Inorganic phosphorescent materials exhibiting persistent luminescence are commonly found in electroluminescent displays and glowing paints but are not widely used as reporters in diagnostic assays. Persistent luminescence nanoparticles offer advantages over conventional photoluminescent probes, including the potential for enhanced sensitivity by collecting time-resolved measurements or images with decreased background autofluorescence while eliminating the need for expensive optical hardware, superior resistance to photobleaching, amenability to quantitation, and facile bioconjugation schemes. **Methods:** We have introduced persistent luminescent nanophosphors produced by grinding, sizing and silica-coating "glow-in-the-dark" $SrAl_2O_4:Eu^{2+},Dy^{3+}$ powder as LFA reporters. Nanophosphors are first briefly excited with the phone's camera flash, followed by switching off the flash, and subsequent imaging of nanophosphor luminescence with the camera. **Results:** Using this approach, we demonstrated LFA detection of human chorionic gonadotropin with strontium aluminate nanoparticles as reporters, giving a detection limit of ~ 45 pg/mL (1.2 pM) in buffer, 50-fold better than the detection limit of the average commercial pregnancy test. **Conclusions:** We have demonstrated LFAs based on persistent luminescence strontium aluminate nanoparticles. The extremely bright and long-lived emission of persistent nanophosphors allows sensitive analyte detection with a smartphone app by a facile time-gated imaging strategy. Time-gated imaging on a smartphone can be readily adapted for sensitive and potentially quantitative testing using other point-of-care formats, and is workable with a variety of persistent luminescent materials. Future work with phosphorescent strontium aluminate and other persistent luminescence materials could lead to a new class of reporters for diagnostics and environmental monitoring.

193 **Poster Session A**

Multivalency design of VEGFR targeting molecular probe for tumor imaging *Zhen Yang, Houston Methodist; F. Li; Z. Li*

Introduction: Design ligands that exhibit specific binding to tumor targets is highly desirable in the molecular imaging of tumors. The strong correlation between angiogenesis and tumor growth provides vascular enthothelial growth factor receptors (VEGFR) exceptional targets for the tumor imaging and therapy. Despite a variety of anti-angiogenic drugs approved by FDA, early detection of tumors is still limited to the further improvement of their specificity to tumor targets. In this work, we present a multivalency design strategy to remarkably enhance the specificity of vandetanib compound to VEGFR. The developed vandetanib tetramer exhibits 1000-fold improvement in specificity to VEGFR compared to the FDA-approved monomer. This work not only provides a very promising anti-angiogenic agent for tumor imaging and even therapy, but also demonstrates a multivalency design strategy for tumor-targeting molecular probes. **Methods:** Adhesion force measurement of atomic force microscopy was used to decipher the binding force of vandetanib ligand to VEGFR on live human umbilical vein endothelial cells. Then the spatial distribution information of VEGFR on live cells was calculated, which guided the right design of multivalent vandetanib compounds. The imaging probes were synthesized via organic chemistry. **Results:** Using the right architecture design for the multivalency, the vandetanib tetremer exhibits 1000-fold improvement in specificity to VEGFR compared to its FDA-appoved monomer. **Conclusions:** Multivalency is a powerful strategy in the design of imaging probes for tumor targeting. The single-force measurement design could work as an universal design platform for tumor targeting compounds. The designed vandetanib tetramer provides a promising anti-angiogenic agent for tumor imaging and even therapy.

194 **Poster Session B**

Micro-thermal sensor technology for non-volatile fluids and cellular level thermal conductivity measurement *Rohini Atluri, University of North Texas; R. Shrestha; D. Simmons; T. Choi*

Introduction: Cancer is the leading cause of death worldwide and, for 2017, U.S. cancer statistics project 602,900 deaths and about 1.7M new cancer cases diagnosed. However, when cancer can be diagnosed early survival rates improve dramatically. Traditional diagnostic tools for cancer screening include clinical/physical examinations, endoscopy, X-ray, ultrasound imaging and magnetic resonance imaging (MRI). Still, these existing techniques are not very powerful methods in detecting cancer at very early stages. Researchers have extensively focused their studies in two mainstream fields: biomarkers and micro/nano-technology to develop powerful diagnostic methods for detection of cancer at early stages. The few research works that investigated the thermal properties at tissue level use transient hot wire technique and use thermal properties as a biomarker for cancer diagnosis. Yet, due to the size of commercially available sensors (>25 μm), measurement at the cellular level has not been possible. Therefore, we herein propose and test a unique technique that utilizes a micro-pipette thermal sensor (<2 μm) for measuring transient temperature changes to determine thermal conductivity. This thermal conductivity is a characteristic of a "material" such as fluids (e.g. water, cell growth medium) and cells. Thus, at the cellular level, a cell's determined thermal conductivity can be used as a thermal signature biomarker for early stage cancer diagnosis. **Methods:** The technique is based on laser point heating thermometry and transient heat transfer: a 532nm laser is focused at the sensor tip immersed in a few microliters of test fluid. A voltage signal is recorded from an oscilloscope when a pulsed laser of width 500μs irradiates the tip to obtain the temporal temperature profile. In COMSOL software, a 2D-axisymmetric model is created to determine the transient temperature profile for the experimental conditions. Through MATLAB algorithm, a multi-parameter minimization method was used to determine the optimizing parameters (conductivity, laser power) that will fit the simulation result with the experimental data. Thermal conductivities of each material evaluated are compared against known values for error calculation. **Results:** The thermal conductivities for the 3 test fluids: 50% glycol, 70% glycol and water, evaluated as 0.3448, 0.2717 and 0.5938 W/m.K, respectively, were within 2% of their literature values. **Conclusions:** We demonstrate the capability of the sensor by testing 3 different fluids with known properties and determine their thermal properties with an accuracy of <2%. This technique can be used to measure thermal properties of group/individual normal and cancer cells to develop an early diagnostic method for cancer.

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Ecological Model-generated hypothesis for high prostate cancer incidence in African-Americans: TRPV6a gene variant and calcium-ion hypersensitivity *Constance Hilliard, University of North Texas*

Introduction: Latest medical research identifies over-consumption of calcium as a trigger for metastatic Prostate Cancer. However, the fact that African-American males suffer twice the rate of fatal cancer as Caucasians continues to confound researchers. This is because 75% of Blacks are lactose-intolerant and have been identified as calcium-deficient, by Federal nutritional standards. African-American males consuming low-lactose dairy products have a calcium intake considered insufficient by American standards yet constitute four times the intake of their African ancestors. Thus, the evolutionary advantage in 200 milligrams calcium/day African food environment has proven maladaptive in the United States. This study proposes an Ecological Model System (EMS) to address this Prostate Cancer health disparity by applying an evidence-based hypothesis to adaptive population genetics The EMS contends increased incidence of Prostate Cancer in African-American males is correlated with unusually high calcium absorptive capacity of their ancestral TRPV6a genetic variant of the TRPV6 calcium ion channel. **Methods:** This EMS mines and synthesizes retrospective data from multi-disciplinary scientific methods to produce a data profile that captures (1) geographical mapping TRPV6a, TRPV6b genetic populations (2) metastatic Prostate Cancer: triggers, genetics, epigenetics; (ii) Black/White differences: TRPV6 function, calcium retention, homeostasis (iii) TRPV6 gene, TRPV6a/TRPV6b polymorphisms and related genes, free calcium-ion retention rates (3) historical/ecological investigations of Prostate Cancer susceptibility rates, (4) regulatory guidelines: male calcium intake. Cox proportional hazards regression models were used to estimate the relative risks and 95% confidence intervals for Blacks/Whites developing metastatic prostate cancer as a function of calcium consumption. **Results:** Use of this EMS reveals 17% of Black males diagnosed with metastatic Prostate Cancer consume 400 mg calcium/day or less, while zero % Whites exhibit this low calcium intake level. At 900 mg calcium intake/day 64% Black Americans, 41% White Americans, have developed the disease. 100% of the Black incidence of advanced Prostate Cancer will occur at/or below 1150 mg calcium intake/day in sharp contrast to 41% White Americans. **Conclusions:** This Ecological Model System identifies the TRPV6 gene as a therapeutic target for metastatic Prostate Cancer, thus posing clinical and basic research questions, e.g., 'Can the use of TRPV6 calcium channel blockers and restrictions of dietary calcium reduce the African-American male risk profile? Is there a divergent mechanism of action of TRPV6 variants and regulation of calcium homeostasis that can identify additional targets?' Furthermore, results demonstrate the feasibility of EMS as a scientific approach to generate evidence-based hypotheses, stimulate new research questions and collaborations in population driven studies.

196 **Poster Session B**

Multimodal optical imaging for early detection of oral cancer *Kristen Maitland, Texas A&M Engineering Experiment Station; J. Jo; Y. Cheng; J. Wright*

Introduction: Several optical technologies are available as clinical adjuncts to improve detection and identification of oral cancers and premalignant lesions. However, current systems based on widefield reflectance and autofluorescence intensity have low and varying specificity limiting clinical utility. We hypothesize that biochemical, metabolic, and morphological biomarkers for oral cancer and dysplasia can be quantified by endogenous fluorescence lifetime imaging (FLIM) and reflectance confocal microscopy (RCM), thus enabling levels of sensitivity and specificity adequate for early detection of oral cancer and dysplasia. **Methods:** We have developed handheld endoscopes for macroscopic FLIM and high resolution RCM designed to access the oral cavity. Multispectral FLIM detects biochemical and metabolic changes using endogenous fluorescence of structural proteins and metabolic cofactors. 1 cm field of view FLIM images are acquired in 0.5 sec. RCM provides information on subcellular morphology. RCM videos with 800-micron field of view are acquired at 6 frames per second scanning ~200 microns into the oral mucosa. The nonsignificant risk investigational devices are not approved for use by the FDA. A pilot study for prototype feasibility was approved by the Texas A&M College of Dentistry Institutional Review Board. Following informed consent, subjects presenting with clinically suspicious oral lesions were imaged with the FLIM and RCM endoscopes prior to excisional tissue biopsy, which is processed for histopathology for diagnostic purposes. **Results:** Endogenous multispectral FLIM images were acquired from clinically suspicious oral lesions of 70 subjects undergoing tissue biopsy. The results indicate that mild dysplasia and early stage oral cancer could be detected and distinguished from benign lesions using a computer aided diagnosis system. The diagnostic performance of FLIM was estimated using a cross-validation approach, showing levels of sensitivity >90%, specificity >80%, and area under the receiver operating curve >0.9. RCM videos were acquired from oral lesions in 16 subjects. Although only 2 imaging sites were diagnosed as dysplasia in this limited dataset, RCM videos and images demonstrate resolution of subcellular features of the oral mucosa in vivo. **Conclusions:** Precancerous lesions can be heterogeneous, and and share clinical features with many other nonprecancerous oral conditions, complicating accurate diagnosis

of pre-malignancy. Therefore, development of sensitive and specific clinical tools to aid detection and identification of pre-malignancy and cancer will improve the overall screening process. If this technology proves successful, it may enable real-time detection of premalignant and malignant oral mucosal lesions, surgical margin detection, and treatment monitoring.

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197 **Poster Session A**

Characterization of Monoclonal Antibodies reactive to HPV-positive Head and Neck Cancer *Hsuan-Chen Liu, Baylor College of Medicine; A. Sikora; F. Parikh; T. Kraus; T. Moran*

Introduction: Head and neck cancer (HNSCC) is the 6th common cancer in the world. While HNSCC caused by its traditional risk factors, tobacco and alcohol, has declined in Western countries, HNSCC caused by the human papillomavirus (HPV) are among the fastest growing cancers. Currently, there are no effective clinically-approved therapeutic reagents. Due to the unique biology of HPV infection, there is no targeted therapy approach for HPV-driven cancer. Our ongoing efforts focus on the identification of antigens on the cell surface of the host proteins that are altered by HPV infection. We present an "antigen-agnostic" approach for generating monoclonal antibodies as a potential tool for HPV- induced cancer diagnosis and treatment which does not require advance knowledge of the identities of target antigens. **Methods:** Immunogenic membrane vesicles made of HPV- positive head and neck squamous cancer cells (HNSCC) were used to immunize mice for generation of hybridomas by conventional methods. The supernatant produced by the hybridomas and/or purified antibodies were collected and screened for binding specificity with multiple HPV-positive cancer cell lines (2 HNSCC and 2 Cervical Cancer) and HPV-negative cancer cell lines (4 HNSCC and 1 CC) by Flow Cytometry. As an alternative approach to enriching for antibodies binding exclusively to HPV-driven membrane proteins, we generated an inducible HPV E6/E7 expression construct as a tool for hybridoma screening and understanding HPV-regulated biology. **Results:** Five thousand hybridoma colonies were picked up as potential candidates, after the initial screening of the supernatant for SCC-47 cells; results revealed 44 monoclonal antibodies that were specific to SCC-47 were identified. We have identified seven which preferentially bind to HPV-positive cancer cells; furthermore we have identified the binding targets of two clones, 6D8 and 6B3, via immunoprecipitation and mass spectrometry. These targets are integrin alpha6 (ITGA6) and tissue factor (F3) respectively. We validated the inducible HPV E6/E7 expression construct by qPCR and western-blot; unfortunately, we haven't identified the clone that specifically binds to HPV E6/E7 overexpressed cells. **Conclusions:** Our screenings of mAbs have revealed promising candidates that bind selectively to HPV-driven HNSCC. Future work will validate the biological function of these mAbs in in vitro and in vivo models, and continue identifying additional mAb binding targets. We propose mAbs specifically targeting membrane-expressed antigens on HPV-related cancer cells as a potential tool for clinical use and preclinical research. It is anticipated that these HPV- specific mAbs could supplement imaging methods for early diagnosis of HNSCC and other HPV+ cancers.

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Poster Session B

Pragmatic RCT design to test navigation for lung cancer screening in an urban safety-net system *Molly McGuire, The University of Texas Southwestern Medical Center; S. Lee; H. Hamann; N. Santini; S. Abbara; H. Chiu; L. Quirk; H. Zhu; D. Gerber*

Introduction: The National Lung Screening Trial (NLST) demonstrated improved lung cancer mortality with annual low-dose computed tomography (CT) screening, leading to lung cancer screening endorsement by the United States Preventive Services Task Force and coverage by the Centers for Medicare and Medicaid. Adherence to annual screening exceeded 90% in the NLST; however, the trial population was disproportionately white, educated, and received care in the tightly controlled environment of a clinical trial. Rates of adherence in real-world settings are likely to be far lower. CT-based lung cancer screening represents a complex clinical undertaking, and for some patients could require multiple referrals, appointments, and time-intensive procedures. **Methods:** We proposed a pragmatic, two-arm randomized clinical trial of patient navigation for lung cancer screening in an urban safety-net system. Pursuant to PRECIS explanatory-pragmatic continuum, our design reflects key pragmatic dimensions: (1) study eligibility based on usual care with recruitment from guideline-based referrals by primary care physicians, not researchers; (2) although algorithm-driven, telephone-based patient navigation intervention similar to usual care for other clinical service lines in our setting, here tested de novo for lung cancer screening; (3) both patient and provider adherence to screening follow-up assessed unobtrusively by EMR data abstraction, without research intervening on program delivery; and (4) intent-to-treat analysis for primary outcomes. With these features, our trial design balanced issues of internal and external validity. **Results:** Using EMR data analysis, we proposed to compare rates of completion between study arms for clinically recommended steps in the lung cancer screening process. We will also compare changes in patient-reported outcomes, using validated measures (waves at 6- and 18-month). We proposed to assess moderating effects by theory-based patient attitudes and beliefs. We proposed semi-structured interviews with a subsample of participants to complete interviews (12 per time-point, per arm, n=48). Interviews were designed to assess experiences of screening and its effects on attitudes toward screening, diagnosis, treatment, care quality, quality of life, competing demands/structural barriers to access, and health behaviors. **Conclusions:** In an era of significant cost constraints, this randomized control trial of telephone-based patient navigation will provide critical evidence to support provision of these services to strengthen lung cancer screening adherence and patient-reported outcomes. Indeed, sustainability of widespread dissemination of CT-screening for early detection of lung cancer may well hinge on patient capacity to complete all steps of this complex process.

199 **CPRIT Grantee**
Poster Session A

Early detection of pancreatic cancer by targeted molecular MRI Imaging of hyperpolarized silicon nanoparticles *Shivanand Pudakalakatti, The University of Texas M.D. Anderson Cancer Center; N. Whiting; J. Hu; C. McCowan; D. Carson; C. Farach-Carson; P. Bhattacharya*

Introduction: Pancreatic cancer, one of the leading causes of cancer-related deaths in Texas in 2016, is an aggressive and initially insidious lethal disease that develops relatively symptom-free. The absence of early symptoms and lack of a reliable screening test has created a critical need for developing a new noninvasive imaging strategy for pancreatic cancer early detection. The goal of my research project is to develop a non-invasive Magnetic Resonance Imaging (MRI)-based in vivo molecular imaging modality to detect pancreatic cancer at an early stage with high sensitivity and specificity. The high sensitivity is be achieved by hyperpolarized (HP) Silicon nanoparticles (SiNPs) by Dynamic Nuclear Polarization (DNP) that leads to over 10,000 fold sensitivity enhancement. In contrast to the hyperpolarization of carbon -13 nucleus, wherein MR signals are lost within a few minutes, hyperpolarization of 29Si produces MR signals with a characteristic decay time of >1 hour. The high specificity is achieved by functionalizing SiNPs with an antibody. For the detection of pancreatic cancer at early stage we are employing mucin-1 (MUC-1) as receptor molecule which is a membrane protein overexpressed in pancreatic cancer tumors. In this study described, we are functionalizing SiNPs with anti-MUC1 antibody, 214D4 for real-time MR based molecular imaging application in pancreatic cancer. **Methods:** SiNPs of size 5 - 70 nm are coated with (3 amino propyl) triethoxy silane and then cross linked with poly ethylene glycol (PEG). Maleimide chemistry will be used to covalently link PEG-functionalized SiNPs with the MUC-1 antibody, 214D4. Home built silicon DNP polarizer operating at ~2.5 K and 3 Tesla will be used to hyperpolarize the functionalized SiNPs. The in vitro phantom and in vivo mice study will be performed on 7T Bruker MR Scanner situated next to the DNP polarizer. **Results:** The 214D4 functionalized SiNPs optimize for maximum hyperpolarization signal and longer decay of hyperpolarized signal. The optimized SiNPs are injected into a MUC1 transgenic mice (MUC1.Tg) that expresses human MUC1 in a similar pattern and level as observed in humans that is crossed with LStopL-KrasG12D pancreatic cancer developing mouse model. The presence of MUC1 in these transgenic mice enhances pancreatic intraepithelial neoplasia (PanIN) progression and development of pancreatic adenocarcinoma. Functionalized hyperpolarized SiNPs are employed to non-invasively image the human MUC-1 expressing cancer cells in these animals to track the tumor progression from precursor lesion, PanIN to pancreatic cancer. **Conclusions:** Targeted molecular imaging of pancreatic cancer progression with hyperpolarized SiNPs is feasible in vivo.

200 **CPRIT Grantee**
Poster Session B

Using intervention mapping to develop and adapt two educational interventions to increase HPV vaccination among Hispanic adolescents *Serena Rodriguez, The University of Texas Health Science Center at Houston; A. Roncancio; L. Savas; D. Lopez; S. Vernon; M. Fernandez*

Introduction: HPV vaccination among Hispanic adolescents falls below the national goal. Tailored interventions to increase vaccination among Hispanic populations are needed to reach national goals and to reduce HPV-related cancer disparities. This study used Intervention Mapping (IM) to develop and adapt two educational interventions for parents of Hispanic adolescents to increase HPV vaccine uptake and completion of the vaccine series. **Methods:** To develop the interventions, we followed IM Steps 1-6 to 1) develop a logic model of the problem; 2) develop behavioral outcomes, identify determinants, and develop a matrix of change objectives; 3) develop a program theme and program components, identify theoretical methods, and operationalize methods as practical applications; 4) develop an intervention design plan; 5) develop an implementation intervention; and 6) evaluate the interventions. To adapt the two interventions, we followed IM Steps 1-6 for the new target population, Hispanic parents of adolescent males. Throughout the adaptation process, we assessed the outputs from the original intervention development process to identify needed adaptations. **Results:** Through formative research, we identified determinants associated with parental decision-making about vaccinating their daughters. We identified a behavioral outcome ("Parent will obtain the HPV vaccine for daughter") and performance objectives, and we created a matrix of change objectives. We identified tailoring, modeling, skill building, and education and counseling as theoretical methods. We developed and produced a print fotonovela and a tailored interactive multimedia intervention (TIMI) to be delivered by lay health workers in clinic settings. In adaptation formative research, we identified new knowledge gaps as parents were less informed about the HPV vaccine for males. No new determinants were identified. We made surface adaptations including filming new scenes and produced a new fotonovela and TIMI targeting Hispanic parents of adolescent males. **Conclusions:** IM systematically guided program development and adaptation to produce two educational interventions to increase HPV vaccination among Hispanic adolescents. We adapted the TIMI and fotonovela while identifying and maintaining core elements. A strength of this study was the opportunity to leverage the same formative work and systematic approach to create two parallel educational interventions based on the same theoretical constructs and methods and strategies.

201 **CPRIT Grantee**
Poster Session A

Toward safer use of health information technology (HIT): A strategy to mine HIT–related events from FDA reports *Hong Kang, The University of Texas Health Science Center at Houston; Y. Gong*

Introduction: Each year in the United States, 650,000 cancer outpatients who receive chemotherapy are at high-risk of infection. These infections may lead to hospitalization, treatment disruptions, or even death. Health information technology (HIT) devices may compound risks because they can disrupt established work patterns, create new risks in practice, and encourage workarounds. For example, a baby died from an overdose of chemotherapy due to a transcription error that occurred when a handwritten order was entered into the electronic chemotherapy order system, which could have been prevented if automated alerts had been designed and activated to the system. Analyzing and learning from HIT-related events (HREs) could reduce their risks and improve safety, though HRE information resources are scarce. In this study, we propose a strategy to initialize and grow an HRE database from FDA resources. **Methods:** The U.S. FDA Manufacturer and User Facility Device Experience (MAUDE) database is a potential resource to identify HREs since it contains over 6 million reports about medical device malfunctions and problems leading to serious injury or death. Using structured data of MAUDE, we developed an inclusion and exclusion keyword list to pre-

screen HRE in the 2015 MAUDE. For unstructured data, we compared six popular classification algorithms on the filtered reports by using term frequency-inverse document frequency (TF-IDF). Then, we applied a word co-occurrence-based topic model that learns information from word combinations to further improve the best classifier of the six. **Results:** Inclusion (132) and exclusion (21) keywords were selected to filter potential HREs. By applying the filter, 4,871 reports were identified from the 860,915 reports in the 2015 MAUDE database. Three domain experts randomly reviewed 10% of the identified reports and estimated that 50-60% of the reports were HIT-related, an improvement over the original 0.1%. The classifier combing TF-IDF and topic modeling features further improved identification based on the filter and thereby proposed a dataset with 95% HRE reports, which initializes the first HRE database in the patient safety community. **Conclusions:** We proposed a strategy to initialize and grow a database for HREs from FDA reports by retrieving the information from both structured and unstructured fields. This strategy and our HRE database can help fill the void of HIT-related resources and hold promise in aiding the understanding, characterization, discovery, and reporting of HREs toward improved patient safety.

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202 **CPRIT Grantee**
Poster Session B

A Model for Emotion-based Visualizations for Conversational Agents in HPV Vaccine Counseling *Rebecca Lin, John Hopkins University; M. Amith; C. Tao*

Introduction: Patient-centric conversational agents, software systems that dialog with human participants, hold potential in HPV vaccine counseling. Emotions influence perceptions and decisions and are especially strong in healthcare situations. When enabled to express emotions, conversational agents could impact a patient's willingness to be vaccinated and may improve patient satisfaction. The objective of our study is to create an ontological model that allows emotions to be visualized as colors, shapes, and lines. We can integrate the ontology with patient-facing software tools, like embodied conversational agents, in clinical settings to improve patient-provider interaction. **Methods:** Using published emotion taxonomies, we matched 25 emotions to a set of visualizations that used colors, shapes, and lines. The visualizations were from a review of published research. We used Stanford's Protégé ontology authoring tool to create our model, termed the Visualized Emotions Ontology, that aggregated the published taxonomies and the emotion-associated visualizations. Using a scoring metric, we compared our ontology with a set of cognitive-related ontologies to assess domain coverage, readability, and linguistic quality. **Results:** The final model was published as an ontology with 126 concepts and 11 unique links among the various concepts. For example, machine-level syntax encoded that a black downward triangle with purple strong lines is emotionally linked to the OCC emotion of fear. In addition, we have aligned the visualizations with each of the 25 emotions. Compared with other cognitive ontologies, ours exhibited better machine readability (0.76, z=1.12), linguistic quality (0.97, z=0.61), and domain coverage (0.82, z=0.39). **Conclusions:** We plan to validate and assess the visualizations of emotions by surveying CPRIT fellows in addition to crowd-sourcing through Amazon Mechanical Turk**. Also, we plan on developing software that will harness the model to create reusable voice user interfaces that could enhance the power of health communication. Acknowledgement: UTHealth Innovation for Cancer Prevention Research Training Program Pre-Doctoral (Cancer Prevention and Research Institute of Texas grant # RP160015). Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.

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203 **CPRIT Grantee**
Poster Session A

Targeting the G-Triplex Intermediate in G-Quadruplex Folding for Potential Chemoprevention Applications *Sean Kerwin, Texas State University; H. Bracey; D. Lee; I. Demundo; N. Navipan; K. Tippayasak; B. Tuesuwan; K. Vasquez*

Introduction: The mechanisms underlying genetic instabilities that lead to events such cancer-associated chromosomal deletions, translocations, and rearrangements have yet to be fully clarified, but it has recently been shown that DNA sequences with the capacity to adopt alternatively structured DNA (i.e. non-B DNA) often co-localize with hotspots of genetic instability. We hypothesize that the genetic instability associated with non-B DNA-forming sequences is a function of the stability of the non-B DNA structures that these sequences form, and that ligands that destabilize these structures will decrease the DNA damage and cancer-associated genomic instability associated with these sequences. **Methods:** Our approach to identify non-B DNA destabilizing ligands exploits recent findings that specific non-B DNA structures (G4-DNA and H-DNA) fold via long-lived (i.e. seconds) intermediates. We propose that ligands that target these intermediates will effectively destabilize these non-B DNA structures by inhibiting their folding. We used CD spectroscopy, UV thermal-difference spectroscopy, and Tm measurements to characterize the topology and thermal stability of the folding intermediates (G-triplexes) for a variety of truncated G4-DNA sequences. We also carried out a virtual screen in order to identify ligands that bind to a structurally well-characterized G-triplex, the truncated thrombin-binding aptamer (TBA) G4 DNA. **Results:** G-triplex formation is a general phenomenon for a wide range of truncated G4 DNA sequences. We examined 16 different variants of the G>1T1-4G>1T1-4G>1 sequence as well as truncated versions of the TBA and human telomeric G4 DNA in both forward and reverse permutations. All of these sequences can adopt G-triplex structures. However, we note that the number of nucleotides in the loop and sequence direction affect G-triplex topology. Sequences with longer G-tracks tends to form parallel G-triplex, as do sequences with fewer loop residues. Permutation of the direction of the truncated G4 DNA sequence also affect G-triplex folding topology. Environmental effects on topology were also noted, with divalent metal ions (Mg2+ and Ca2+) favoring parallel topologies. Virtual screening against the antiparallel truncated TBA G-triplex reveals a number of viable ligand binding sites that are predicted to interfere with folding to G4 DNA. **Conclusions:** G-triplex folding intermediates of G4 DNA structures are promising targets for small molecule G4 DNA destabilizing ligands. The effect of the destabilization of G4 DNA on the genetic instability associated with these sequences in human cells will provide crucial evidence for the role of structural stability in genetic instability and potential lead chemopreventive agents

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204 **CPRIT Grantee**
Poster Session B

Preliminary Big Data Textual Analysis of HPV-related Discourse on Reddit *Muhammad "Tuan" Amith, The University of Texas Health Science Center at Houston; P. Cuccaro; L. Savas*

Introduction: Vaccination against HPV, a known cause of cancer, is lower than projected, and the rate is lower for boys than for girls. Online health information has an impact on individual health efficacy, and through social media, plays an important role in consumer health literacy. To further understand this demographic and their discourse of HPV information, we investigated the use of the social media platform Reddit, skewed toward young, white males, for HPV- and vaccine-related content. To the best of our knowledge, this is the first study to utilize Reddit for HPV-related research and one of a couple for health research. **Methods:** We utilized big data and natural language processing tools, like MongoDB, Stanford's Deep Learning for Sentiment Analysis, and custom Java code, to retrieve, analyze, and store data from the Reddit corpus of submissions (n=282,925,243). We queried and analyzed Reddit submissions between 2007 and 2016 based on keywords pertaining to HPV and its vaccine (n=10,205). Using regression analysis, we measured submissions for valence (positive, negative, neutral connotations), character length, and ratings (up and down votes) for their impact on engagement (number of comments to the submission). **Results:** Most HPV-related submissions to Reddit appeared to have negative or neutral disposition. While valence and character length had no influence on engagement of the HPV-related topic, the increased number of the up votes and the decreased number of the down votes did affect user engagement ($p<0.05$). **Conclusions:** We assumed that numerical ratings associated with a Reddit submission may have an effect on health consumer engagement with an HPV-related topic. This study may help health experts engage a population on social media and stimulate further research to analyze health content from Reddit. Future directions could include applying informatics methods from our previous research, qualitative analysis of the content, and associated comments from the submissions to extrapolate new knowledge from health discourse on Reddit. Acknowledgement: UTHealth Innovation for Cancer Prevention Research Training Program Pre-Doctoral (Cancer Prevention and Research Institute of Texas grant #RP160015). Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.

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205 **CPRIT Grantee**
Poster Session A

Tracking negative information about HPV vaccination on social media using machine learning *Jingcheng Du, The University of Texas Health Science Center at Houston; C. Tao*

Introduction: There is a significant and increasing number of parents who choose to refuse or delay vaccinations. In particularly, the refusal/delay of human papillomavirus (HPV) vaccine leaves the public vulnerable for various cancers such as anal and cervical cancer. The information and opinions shared on social media demonstrate significant influence on health behaviors. Anti-vaccine rhetoric directly targeting HPV vaccine on social media is generating new obstacles to vaccine promotion. **Methods:** We developed a machine learning system that automatically extracts public opinions on HPV vaccine from the massive

Twitter data. Unlike previous efforts primarily focusing on high-level sentiment extraction (i.e., "Positive", "Negative" and "Neutral"), our system can further identify the exact reasons that caused the negative opinions (i.e., "Safety", "Efficacy"). Combinations of related keywords were used to collect English language tweets. A gold standard consisting of 6,000 tweets was manually curated. Different machine learning algorithms were compared and the system performance was improved by using hierarchical classification and parameters tuning. 10-fold cross-validation was used to evaluate system performance. We then applied the system on a large-scale Twitter corpus (184,214 tweets, collected from 11/02/2015 to 03/28/) and analyze the changes and patterns of different opinions on HPV vaccines. **Results:** The inter-rater agreement value of the gold standard was high (Kappa=0.851). The hierarchical classification model with optimized parameters increased the micro-averaging F score (harmonic mean of precision and recall) from 0.6732 to 0.7442. 110,778 (60.13%) of the collected tweets were targeting HPV vaccine. Among these tweets, 35,482 (32.0%) tweets were categorized as "Negative". For the "Negative" tweets, safety concerns take up to 79.2%. We identified a coincidence between real world events and Twitter contents. The trends of different opinions were extracted. The rate of negative information was found much higher on weekends than the middle days of the week. **Conclusions:** Our system provides us an automatic and efficient way to extract public opinion and understand negative information on HPV vaccine spread on Twitter and provides real-time feedback to the clinical and public health professionals so that they can identify rumors or mis-facts on HPV vaccines. Acknowledgement: UTHealth Innovation for Cancer Prevention Research Training Program Pre-Doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant #RP160015). Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.

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206 **CPRIT Grantee**
Poster Session B

Esophageal and gastric adenocarcinoma arise from identical stem cell precursors *Yanting Zhang, University of Houston; M. Duleba; S. Wang; R. Mahalingam; J. Xie; W. Rao; W. Kern; K. Manyam; Y. Yamamoto; J. Ajani; M. Teh; K. Ho; W. Xian; F. McKeon*

Introduction: Gastric adenocarcinoma (GAC) is only surpassed by lung cancer in worldwide deaths. Common in Asia, GAC is linked to chronic H. pylori infections that trigger a sequence of gastric intestinal metaplasia (GIM), dysplasia, and finally invasive GAD. In the West, GAD is relatively rare but esophageal adenocarcinoma (EAC), linked to acid reflux disease, is frequent and this disease shares many parallels with GAC including an intestinal metaplasia (Barrett's esophagus or "Barrett's"), dysplasia, and finally EAC. We have cloned the stem cells of GIM and Barrett's from multiple cases of GAC and EAC, respectively, and found them to be identical despite their distinct triggers and sites of initiation. Moreover, both GIM and Barrett's are present in the respective populations at rates that overwhelm any attempt at monitoring, and far in excess of cases that progress to GAC and EAC. Therefore the critical need in both diseases is to identify means of distinguishing "high-risk" Barrett's and GIM from the majority that remain dormant and never progress to dysplasia. Therefore we are reconstructing the evolution of GAC and EAC from stem cells of intestinal metaplasia, dysplasia, and adenocarcinoma of advanced cases and comparing them with GIM and Barrett's derived from the majority of patients whose intestinal metaplasia will never progress to cancer. **Methods:** Sets of patient-matched stem cells of intestinal metaplasia, dysplasia, and adenocarcinoma were cloned at the single cell level from 1mM endoscopic biopsies of GAC patients and propagated in individual cell lines (Wang et al., 2015; Yamamoto et al., 2016) and analyzed by molecular genetics. **Results:** The stem cells of Barrett's and GIM are clearly distinct from those of normal surrounding epithelia and identical with regards to gene expression, behavior in 3-D differentiation, and overall mutational profiles. In patients with either EAC or GAC, we have been able to generate multiple stem cells representing intestinal metaplasia, dysplasia, and adenocarcinoma. As the intestinal metaplasia of these patients will likely include both high and low risk lesions, our clonal analysis has the potential to identify both high-risk lesions and markers that enable their unique detection. **Conclusions:** We have successfully cloned stem cells from all stages of EAC and GAC and are using them to reconstruct the evolution of these adenocarcinomas that occurred over a period of 5-20 years. This work has the potential to identify the molecular features of the intestinal metaplasia that confer a high-risk of progression to incurable adenocarcinoma.

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207 **CPRIT Grantee**
Poster Session A

Epigenetic variant stem cells in COPD patients: origin of COPD-linked lung cancer? *Wei Rao, The University of Texas Health Science Center at Houston; K. Goller; S. Niroula; R. Mahalingam; M. Metersky; F. McKeon; W. Xian*

Introduction: Patients with chronic obstructive pulmonary disease (COPD) have a greatly enhanced incidence of lung cancer over smokers without COPD (>16/1,000 vs 1.5/1,000 person-years). The elevated risk of COPD patients for lung cancer has been attributed to the mutagenic effects of chronic inflammation marked by high levels of chemokines, cytokines, and activated leukocytes in the COPD lung, though the mechanisms underlying this inflammation remain obscure. Using methods we developed to clone and characterize stem cells from the upper and lower airways, we have now examined the spectrum of stem cells in patients with advanced COPD. Surprisingly, COPD patients harbor two novel variants of lung stem cells that are marked, respectively, by hyperinflammatory gene expression profiles and goblet cell hypertrophy. The predominance of these stem cell types likely explains the two salient features of COPD to wit chronic inflammation and small airway obstruction as well as represent likely drivers of and even cell types that contribute to the high rates of lung cancer in these patients. **Methods:** Airway stem cells were cloned on lawns of irradiated 3T3 cells from tissue of resected lobes of patients with advanced COPD using methods we described earlier (Kumar et al., Cell 2011; Zuo et al. Nature 2015). Differentiation was performed in vitro and via injection into immunodeficient mice. **Results:** In addition to normal tracheobronchiolar stem cells (TBSC) of the conducting airways and distal airway stem cells (DASC) of the lung (Kumar et al., 2011), COPD patients show a predominance of two variant stem cell types (COPD#1 and COPD#2). Unlike normal TBSCs that differentiate to ciliated and goblet cells, or DASCs that differentiate to type I and type II neumocytes, COPD#1 has a differentiation fate restricted to a squamous metaplasia. Moreover, COPD#1 cells express enormously high levels of pro-inflammatory chemokines and cytokines. Similarly, COPD#2 cells differentiate to epithelia dominated by hypertrophic goblet cells and express gastric markers. These divergent stem cells are common to all COPD patients and are epigenetically stable despite months of in vitro proliferation. **Conclusions:** The variant stem cells we have identified potentially play a key role in the pathogenicity underlying the development of COPD in that they separately contribute to hyperinflammation and small airway constriction. We are presently exploring the possibility that these same variant stem cells are early precursors of lung cancer itself. We anticipate that these studies may be of general significance for the origin of lung cancers in patients.

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208 **CPRIT Grantee**
Poster Session B

Development of Novel Pateamine A Derivatives as First-In-Class Translation Initiation Inhibitors Targeting the Vulnerabilities of Cancer *Mingzhao Zhu, Baylor University; R. Chen; Y. Kim; M. Safari; Y. Chen; W. Skillern; Q. Qin; W. Wierda; K. Hull; C. Deng; S. Bates; W. Plunkett; D. Romo*

Introduction: Many oncoproteins turn over rapidly and have relatively short half-lives. The translation of these oncogenes represents a cancer-specific vulnerability, which may be exploited by novel targeted therapies. The formation of the eukaryotic translation initiation factor 4F (eIF4F) complex is an essential step for initiation, and thus an attractive target for developing therapeutics that are directed at protein translation. The natural product pateamine A (PatA) has been shown to be a potent inhibitor of translation initiation through binding to eIF4A, one of the components of the eIF4F complex. Subsequent medicinal chemistry identified des-methyl, des-amino pateamine A (DMDAPatA), a simplified and more stable analog of the natural product PatA. However, preliminary data suggests that DMDAPatA is highly protein bound in human plasma and may lack sufficient in vivo potency. To address this, we designed several new PatA analogs with the goal of improving the physical properties and potency against cancer cells. This led to the identification of three novel derivatives that met these criteria. The new PatA analogs reduce the levels of intrinsically short-lived anti-apoptotic protein Mcl-1 in chronic lymphocytic leukemia (CLL). One of the new PatA analogues, namely MZ-735, was comprehensively investigated in diffuse large B-cell lymphoma (DLBCL), double hit lymphoma (DHL), and pancreatic ductal adenocarcinoma (PDAC) that are all associated with highly dysregulated c-Myc. DLBCL is the most common aggressive lymphoma, DHL is the most chemo-resistant lymphoma, and PDAC remains the most lethal malignancy to date. **Methods:** Cytotoxicity of PatA analogs was evaluated using CellTiter-Glo in lymphoma cell lines. Cytotoxicity to normal cells was also evaluated in peripheral blood mononuclear cells (PBMC) of healthy donors. Immunoblot was used to study the molecular effects of MZ-735 on translation of oncogenes. **Results:** DMDA-PatA and MZ-735 were studied in 13 lymphoma cell lines and MZ-735 showed higher potency than DMDAPatA. MZ-735 induced apoptosis in DLBCL, DHL, and PDAC, with an IC_{50} below 5 nanomolar (nM) in most cell lines without showing significant cytotoxic effect in PBMC. MZ-735 potently suppressed the expression of the c-Myc oncoprotein in these cancer cell lines and effectively suppressed the protein level of cyclin D1 in MCL cells. **Conclusions:** PatA analogue MZ-735 has potent pharmacological activity in lymphoma cell lines by suppressing the production of critical

oncogenes, including C-MYC, CCND1, and MDM2. MZ-735 failed to induce any significant cytotoxicity in normal blood cells suggesting this PatA analogue may be safe to human hematopoietic system.

209 **CPRIT Grantee**
Poster Session A

Physician-reported human papillomavirus vaccination (HPV) recommendation and initiation among adolescent patients (11-12 years): Does wording matter? *Lara Savas, The University of Texas Health Science Center at Houston; A. Farias; J. Eska; E. Frost; C. Healey; R. Shegog; M. Fernandez; S. Coan; S. Spinner; S. Vernon*

Introduction: Low rates of Texan adolescent HPV vaccination initiation in 2015 (60.1% and 41.4% of girls and boys), compared with Tdap (85.1%) and meningococcal vaccination (89.6%) highlight a significant problem of missed opportunities to prevent HPV-related cancers. A bundled healthcare provider HPV vaccine presumptive recommendation may be a strong determinant of patient initiation. We examined the association of message delivery of provider recommendation and HPV vaccination initiation rates. **Methods:** In 2015, we conducted a cross-sectional survey in a large urban Texas pediatric clinic network (51 clinics) to ascertain the method of delivery of HPV vaccination recommendations for patients (11-12 years). Survey data were merged with electronic medical records to ascertain the HPV vaccination initiation status of over 18,000 patients. We used multivariable multilevel generalized linear models clustered by physician to calculate the adjusted odds ratios controlled for patient and physician demographics. **Results:** A total of 134 pediatricians responded to the survey (60%). After controlling for patient and physician demographics, a bundled, presumptive HCP recommendation was significantly associated with HPV initiation. A recommendation of "Your child is due for three vaccines: Tdap, HPV, and meningococcal vaccine" was significantly associated with an increased odds of HPV vaccination initiation compared with a more ambivalent message of "Your child is due for two vaccines, Tdap and meningococcal. There is also the HPV vaccine, which is optional" (OR: 1.99, 95% CI 1.52-2.60). **Conclusions:** While the CDC identifies providers' strong recommendations as critical to HPV vaccination initiation, including promoting the bundled approach, to our knowledge, this study is the first to provide strong evidence that bundling the HPV vaccination recommendation increases vaccine uptake. These findings will inform development of interventions to increase bundled presumptive HPV vaccination recommendations.

210 **CPRIT Grantee**
Poster Session B

Correlates and patterns of participation in a comprehensive cancer survivorship program among safety-net patients *Sandi Pruitt, The University of Texas Southwestern Medical Center; Z. Ge; E. Berry; E. Borton; K. Argenbright; D. Heitjan*

Introduction: Currently, there is no single, evidence-based standard of care for the provision of diverse comprehensive cancer survivorship services such as nutrition counseling, support groups, and nurse education. Thus, survivors can self-select the number and type of services they receive. To increase the evidence base on patterns of participation and factors influencing participation, we studied cancer survivors receiving care at an urban safety-net healthcare system serving low-income, under- and un-insured cancer patients in Tarrant County. **Methods:** We merged data from three sources: tumor registry data from the health system, electronic medical records from the health system, and the Moncrief survivorship program database. We identified patients diagnosed with any cancer type, 2008–2015, using registry data. We compared participants to non-participants by tumor characteristics, diagnosis year, sociodemographic and behavioral factors, and insurance type using logistic regression. We examined characteristics associated with intensity of program participation by negative binomial regression. We identified patterns of utilization by cluster analysis. **Results:** Among 8,325 cancer patients, 467 (5%) enrolled in the survivorship program and completed at least one session. Program participants were largely women (72%) and minorities: Black (32%), Hispanic (38%), and white (28%). Most participants completed at least one nurse visit (76%), whereas fewer completed group nutrition sessions (13%) or individual exercise sessions (5%). Fewer than 4% completed social work visits, support groups, psychology sessions, or individual nutrition counseling. Odds of participation in any program differed ($p<.05$) across multiple patient and tumor factors. Briefly, program participants were more likely to be female, younger, and black or Hispanic. Participation also varied by cancer type and diagnosis year. Variables significantly and independently influencing intensity of participation included cancer type, stage, and grade; diagnosis year; insurance type; and alcohol and tobacco use. For example, intensity was greater for patients with in situ and localized tumors and less for patients with regional and distant tumors. The cluster analysis identified four distinct patterns of program participation. **Conclusions:** Our results provide novel evidence about patterns of participation in a comprehensive cancer survivorship program among patients of an urban safety-net health system. Findings describe the services survivors seek and receive and the factors that drive their participation. Our analysis suggests that bundling different services may better meet survivors' needs and interests. Additional research is needed to understand the impact of survivorship care on healthcare utilization and patient outcomes.

211 **CPRIT Grantee**
Poster Session A

HPV vaccination in the digital age: Development of HPVcancerFree, a parent-focused smartphone app to increase HPV vaccination rates *Elisabeth Becker, The University of Texas Health Science Center at Houston; R. Shegog; L. Savas; C. Healy; E. Gabay; E. Frost; S. Spinner; M. Fernandez; S. Vernon*

Introduction: In Texas, parents are more likely to refuse or delay the Human Papillomavirus (HPV) vaccine, leading to lower HPV vaccination rates compared with other adolescent vaccines. In the largest U.S.-based pediatric clinic networks, located in Houston, TX, 53% of 13-15 year olds had completed HPV vaccination in 2016, below the Healthy People 2020 goal of 80% completion. Mobile health technology (mHealth) presents enormous potential to reach parent audiences and deliver health promotion interventions. The purpose of this study is to iteratively design and develop HPVcancerFree, a smartphone app designed for parents of primarily privately insured patients ages 10-17 who have not initiated HPV vaccination. Objectives of HPVcancerFree are to: 1) raise awareness of HPV and its prevention 2) reduce barriers to HPV vaccination, and 3) enable parents to initiate HPV vaccination scheduling through their smartphone. **Methods:** We used Intervention Mapping, an evidence-based systematic framework for developing health education interventions and user-centered design principles. Procedures included: 1) literature review and online focus groups with parents (n=22) from the pediatric clinic network to assess HPV attitudes, barriers, beliefs, and needs related to an mHealth solution; 2) matrices describing target behaviors, psychosocial determinants of behavior, and change objectives; 3) delineation of theoretical methods and practical applications; 4) prototype build; 5) in-house alpha testing; and 6) formative micro-usability testing to assess parameters of ease of use, acceptability, understandability, utility, credibility, and appeal. **Results:** Needs assessment, including literature review and focus groups, revealed pediatrician recommendation as a strong influence on vaccine decision-making. Further, parents requested: 1) detailed, reliable information about risks and benefits of HPV vaccination;2) opportunity to discuss the HPV vaccine with providers before the recommended vaccination age; and (3) reminders about follow-up doses. The resultant HPVcancerFree is iOS and Android compatible and contains four self-tailored features: 1) HPV A-Z (a compendium of content domains (n=9) providing facts regarding HPV and HPV vaccine), 2) Bust-A-Myth (educational modules (n=7) including peer and provider testimonials addressing the most salient HPV vaccination barriers); 3) Notes4Doc (a medium to facilitate communication with providers on HPV vaccine), and 4) Get the Vax (enabling parents to schedule HPV vaccination appointment(s) and to receive tailored reminders). **Conclusions:** HPVcancerFree was informed by the literature and created with parent and provider input. The app provides a novel mHealth approach to motivating parents in a large pediatric clinic network to initiate HPV vaccination.

212 **Poster Session B**

A soft, wireless implantable device for the treatment and prevention of local recurrence by photodynamic therapy in a murin model *Sonny Gunadi, Leeds Institute of Biomedical & Clinical Sciences, University of Leeds; D. Jayne; S. Park*

Introduction: A more recent option for such patients is photodynamic therapy (PDT) which uses a combination of light, oxygen, and a drug known as a photosensitizer. However, the effectiveness has been limited by three important factors, (i) the major side effects of the treatment, which includes skin reactions due to uptake of the photosensitiser drug by skin cells and requires patients to stay out of sunlight for at least a week after treatment, (ii) an incomplete understanding of the differing response of cancer and normal tissues to photodynamic therapy, and (iii) lack of methods to monitor tumour response and adjust drug dosage accordingly. These factors represent technical challenges that this paper addressed and a proposed system showed the potential for use in research or settings. **Methods:** Repetitive ultra-low-fluence PDT (uPDT) is a novel form of PDT that uses repetitive low light irradiance with repeated photosensitiser (PS) doses that are applied over longer periods to ensure treatment completion. Previously, intraoperative PDT has been administered using a single PS dose with intense light irradiance due to the limited surgical window. Consequently, oxygen, which is essential in ROS generation, is not adequately replenished for sustained PDT effect, limiting its efficacy. Our strategy to overcome this limitation is to apply uPDT through a novel implantable device. **Results:**

Current light delivery technologies are largely impractical for preclinical and clinical application. The efficacy of uPDT has been established in studies using glioma spheroids with only 1.5 J/cm2 at an irradiance of 17 uW/cm2 over 24 hours in 3-day cycles with additional PS doses5– in comparison, the typical light dose for conventional PDT is about 50 J/cm2 at an irradiance of 5-50mW/cm2, and clinical PDT uses fluences of 10-100 times magnitude. Our preliminary work using HT-29 CRC cell-line has demonstrated effective cancer killing effect using uPDT at only 12uW/cm2 to a total of 1J/cm2 over 24h treatment in 2 days. **Conclusions:** The key challenge in applying uPDT to the intraoperative environment is to develop a suitable implantable system that can deliver uniform illumination for extended periods of time for sustained PDT effect to ensure treatment completion. We have successfully achieved critical first steps towards meeting the above technical challenges, and the work demonstrated here would enable the extension of these successes to provide the platform for revolutionary discoveries and therapeutics for the prevention and treatment of local recurrence.

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Attitudes, Barriers and Knowledge of HPV Vaccination in Health Professional Students *Monaliza Evangelista, The University of Texas Health Science Center at Houston; H. Smith; J. Patel; M. Sanders; L. Love; A. Geltemeyer; R. Patel*

Introduction: Significant research has evaluated the attitudes, knowledge and barriers of obtaining HPV vaccination in college students, and a few studies have investigated similar parameters in health professional students; however, most were limited to a single profession and performed outside the United States. It is important to evaluate these factors in health professional students as it may impact their future practice with advice and delivery of HPV vaccination. The objective of this study is to assess the attitudes, barriers and knowledge of HPV vaccination in health professional students. **Methods:** This is a cross-sectional study. A survey was offered to every student accessing clinic services. Participation was voluntary and respondents could choose to omit any questions they did not wish to answer. The clinic takes care of students enrolled in medical, dental, nursing, public health, graduate school, and the school of biomedical informatics in a health university. **Results:** A total of 266 surveys were collected during the initial collection phase of 4 months. The majority of students who completed the survey were medical students, female, aged 18-26 years, and Caucasian. The majority (96%) of the respondents know about the HPV vaccine. Interestingly, 58% of respondents had not received or completed a 3-dose series; of those who hadn't initiated vaccination, 64% did not wish to, while 68% of incompletely-vaccinated respondents were not interested in completing the series. 'I've only been with 1 partner and have low risk of acquiring the infection was the most common reason cited. When looking at knowledge of cancers caused by HPV, students in medical school knew the most. A similar finding was seen when asked for which population the vaccine is approved. Both results were statistically significant. **Conclusions:** Our study suggests that a majority of health professional students have heard of the vaccine and about half have been appropriately vaccinated. However, more than half did not receive or complete the series, and a majority of these individuals are not interested in starting or completing vaccination. Majority of respondents were medical students and had a higher mean knowledge score compared to other groups of healthcare students. These results are unforeseen and could be an impetus for intervention to increase compliance with vaccination in this population. Moreover, these students will be involved in patient care or research in the future, and their current approach to HPV vaccination may have potential effects upon their advice and delivery of vaccination.

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Stakeholder engagement to initiate lung cancer screening in an urban safety-net health system *Simon Lee, The University of Texas Southwestern Medical Center; H. Hamann; N. Santini; S. Abbara; D. Balis; T. Browning; H. Chiu; B. Moran; M. McGuire; D. Gerber*

Introduction: Although several reports have demonstrated successful lung cancer screening programs, even those in community settings have focused largely on insured populations. There is little guidance describing how best to implement computed tomography (CT) -based screening in settings that care for minority, underinsured, and other medically-underserved populations that face highest risk of and worst outcomes from lung cancer. While these patients stand to benefit most from guideline-based screening, they may also be those least likely to complete the complex, multi-step process of screening. Drawing on relevant literature, we developed a stakeholder engagement plan to identify and address logistical challenges to implementing CT-based screening as clinical standard of care in an urban, integrated safety-net health system. **Methods:** Parkland Health & Hospital system provides care for uninsured patients through a combination of federal, state, and county-supported programs for more than one million under- and uninsured residents (39.5% Hispanic, 34.4% Non-Hispanic White, and 20.8% African American) of Dallas County, Texas. Over a 14-month period (February 2016-April 2017), our program team worked closely with a range of institutional stakeholders. We presented to patient and caregivers drawn from the community to solicit patient-level guidance regarding barriers and facilitators to completing the screening process, including knowledge and perceptions. We engaged multiple institutional stakeholders (including primary care providers, radiologists, pulmonary medicine physicians, and smoking cessation personnel) to develop a health system process for guideline-based referral, initial CT screening, results reporting and clinical follow-up. **Results:** Through an iterative process based on patient and stakeholder feedback, we developed an EMR-based order designed to (1) capture demographic data relevant to screening eligibility, (2) provide CMS-mandated documentation of patient counseling, and (3) deploy Lung-RADS standardized reporting to minimize additional workload on referring clinicians. Employing available population data from earlier screening programs and research studies– including smoking rates, screening adherence, and demographic characteristics– we organized an in-service campaign to inform primary care sites of order availability. As the campaign proceeded, we reviewed patient volumes, process performance, clinician and patient feedback to inform screening program development and adaptation to our system setting. **Conclusions:** Medically underserved populations face the highest risk of and worst outcomes from lung cancer. Health systems seeking to implement lung cancer screening programs should employ robust patient and stakeholder engagement plans to optimize patient and provider uptake of evidence-based screening.

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Soft tissue microstructure evaluation using high frequency ultrasound *Jeremy Stromer, University of Connecticut*

Introduction: Due to the emotional and esthetic benefits of breast-conserving therapy (BCT) when compared with the traditional mastectomy, BCT is largely the preferred method for treatment of breast cancer. Composed of a lumpectomy and radiation treatments, the success of BCT depends heavily on the outcome of the lumpectomy. The success of the procedure, in which the tumor along with a small margin of healthy tissue is removed, is determined by the presence or absence of malignant cells present in the margin and is conducted by a trained pathologist. Failed lumpectomies result in increased cost and stress from the need for additional surgeries. Methods that could rapidly quantify and determine the presence of cancerous tissue would be invaluable in BCT. Here we investigate quantitative high-frequency ultrasound methods for studying soft material microstructure for its potential use in margin detection. **Methods:** Our study focused on the ultrasound measurement peak density. This parameter studies the material's frequency to the applied ultrasonic pulse. We investigated peak density through experimental, computational, and analytical means in order to understand how the material attributes affect the measurement. Tissue-like phantoms featuring varying sizes and concentrations of glass microspheres were measured for peak density using 31.5 MHz ultrasound transducers. Finite element analysis using COMSOL modeled the acoustical response of a system of glass scatterers. These simulated results were then compared with experiment. Theoretical scattering cross-sections were determined and are discussed. **Results:** The phantom experiments showed peak density to vary with both the size and concentration of the scatterers present. Simulations showed similar trends to the phantom experiments. Analytical scattering cross-sections, which consider the total amount of scattering present in the system, were calculated. These cross-sections were found to behave analogously to the peak density results suggesting a relation to the materials' scattering properties. Expanded simulations using different materials showed peak density to change with the scatterers' material properties as well. These values were also compared with the scattering cross-sections and showed similar behavior further implying the relation between peak density and scattering. **Conclusions:** From our experiments and simulations it was observed that the ultrasonic parameter of peak density was responsive to changes in the microstructural environment. This work has also provided insight into how the material characteristics affect the measurement. Based on the sensitivity to microstructure and our knowledge of the underlying physics, peak density shows potential for distinguishing healthy and malignant tissue.

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216 **Poster Session B**

Sun protection and skin examination practices in patients with chronic lymphocytic leukemia *Mary Tripp, The University of Texas M.D. Anderson Cancer Center; A. Ferrajoli; J. Wang; S. Garrison; C. Simon; P. Pandit Talati; K. Tsai; S. Peterson*

Introduction: Patients with chronic lymphocytic leukemia (CLL) are at increased risk for other cancers, most commonly skin cancer. Skin cancer risk is increased in patients with CLL compared to the general population and these patients experience poorer outcomes. Individuals

at higher skin cancer risk are advised to practice sun protection, undergo full-body physician skin examination (PSE) and conduct skin self-examination (SSE). Very little is known about these risk-reduction practices in patients with CLL. We evaluated sunburn, sun protection, skin examination practices and relevant correlates in patients with CLL. **Methods:** Eligible patients were diagnosed with CLL, aged ≥18 years and fluent in English. Patients (n=100) attending the outpatient leukemia clinic of a comprehensive cancer center completed a survey about their sun protection and skin examination practices. **Results:** Most patients were male (62.2%), non-Hispanic white (88.5%), married (80.4%), and had completed college/graduate school (62.3%). Average age was 64.7 (SD=10.7, range=37-87) years. Skin cancer personal history was reported by 36.8%. Almost one-third (29.6%) reported one or more sunburns during the past year. Most reported routinely wearing sunglasses (68.0%) and sleeved shirts (81.0%); fewer routinely used sunscreen (42.0%), reapplied sunscreen (19.6%), used SPF lip balm (25.0%), wore a wide-brimmed hat (31.0%) or stayed in the shade (35.4%). Overall, patients "sometimes" practiced sun protection (M=3.34, SD=.66; 1-5 "never" to "always" scale). Most (70.0%) reported having had a PSE; 51.0% in the past year. Some (22.2%) reported SSE in the past 3 months. In multivariable analyses, significant sunburn correlates included younger age (p<.01), male sex (p<.05) and having had skin cancer (p<.01). Patients were more likely to conduct SSE if they had been shown how to perform SSE (p<.01) and reported greater confidence in performing SSE (p<.05). The odds of having had a PSE also increased with patients' SSE confidence (p<.01). Willingness to prepare for sun protection was positively associated with practicing sun protection (p<.001). **Conclusions:** Some patients reported significant sunburn history. SSE and use of sunscreen, wide-brimmed hats and shade was relatively infrequent. Most reported having had a PSE; some had not had one recently. To our knowledge, this is the first study of sun protection and skin examination correlates in patients with CLL, a population with a long life expectancy and increased skin cancer risk. Findings provide direction for developing risk-reduction interventions. In particular, it is important to show patients how to perform SSE, improve patients' SSE confidence, and increase their willingness to prepare for sun protection.

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Low serum carotenoids are associated with inflammatory markers and subjective cognitive impairments in breast cancer survivors *Krystle Zuniga, Texas State University; N. Moran*

Introduction: Cancer related cognitive impairment (CRCI) can have significant and persistent impacts on quality of life in cancer survivors. Recent evidence has reported cognitive impairments are associated with inflammation due to cancer and its treatment. Modifiable factors, such as diet, may reduce the risk or severity of CRCI. Carotenoids, primarily found in fruits and vegetables (F&Vs), have shown promise in reducing the risk of age-related cognitive decline, potentially via anti-inflammatory activities. The objective of the study was to explore if serum carotenoids predicted cognitive function in breast cancer survivors (BCS) and to examine inflammation as a potential mechanism by which carotenoids modulate cognitive function. **Methods:** In this cross-sectional study, 29 female BCS and 38 controls were recruited from the Central Texas area. BCS had to have completed chemotherapy, radiotherapy or both within the past 5 years, and healthy controls must have had no previous cancer diagnosis. Dietary intake was assessed with a food frequency questionnaire. Cognitive function was assessed with the NIH Toolbox Cognition Battery. The Functional Assessment of Cancer Therapy-Cognitive Function Questionnaire assessed perceived cognitive impairment. Serum levels of carotenoids were measured by HPLC-PDA, and serum soluble TNF receptor type II (sTNF-RII), interleukin-6 (IL-6), and interleukin-1 receptor agonsit (IL-1ra) were measured by immunoassay. BCS were split into two groups: (1) BCS with serum carotenoid levels lower than, and including, the median; and (2) BCS with serum carotenoid levels above the median. A median split analysis was also conducted for the non-cancer controls. Univariate ANCOVAs, including age and/or BMI as covariates, were conducted to compare cognitive function and inflammatory markers as a function of group (low carotenoid BCS, high carotenoid BCS, low carotenoid controls, high carotenoid controls). **Results:** Serum carotenoids and F&V intake were not significantly different between BCS and controls. Reported F&V intake was positively correlated with serum carotenoid levels (r=.415, p<0.01). BCS performed similarly to controls on objective cognitive measures. Both high and low carotenoid BCS had significantly more cognitive complaints than high and low carotenoid controls (p<0.05); however, high carotenoid BCS had significantly fewer cognitive complaints than low carotenoid BCS (p=0.36). Low carotenoid BCS, but not high carotenoid BCS, had significantly greater sTNF-RII and IL-6 levels than both high and low carotenoid controls (p<0.05). **Conclusions:** Higher serum carotenoid levels may have cognitive and anti-inflammatory benefits in BCS. Future research should continue to identify dietary patterns that can reduce memory complaints and support cognitive health in cancer survivors.

218 **Poster Session B**

A novel statistical approach to improve social network measure for HIV prevalence estimates among young MSM *Ming Cao, The University of Texas Health Science Center at Houston; K. Fujimoto; J. Schneider*

Introduction: People infected with HIV have a substantially higher risk of some types of cancer, e.g. anal, liver, lung cancer, and Hodgkin lymphoma, due to reduction in the body's ability to fight infections. Men who have sex with men (MSM) made up a large portion of people living with HIV as well as the total estimated new diagnoses. Knowing the HIV prevalence among this type of "hidden" populations has a fundamental impact on cancer prevention policy making, especially when the long-term cancer causing effects are considered. The Young Men's Affiliation Project (YMAP), focuses on a high risk population in a cohort study of risk and health venue affiliation networks and HIV risk and prevention among young MSM. Subjects were recruited into YMAP, using Respondent-driven sampling (RDS) to reach this "hard-to-reach" problem. The validity of estimating disease prevalence using RDS relies heavily on the accuracy in measuring the number of contacts or peers a respondent has (network degree) . However, in practice, this measure is often problematic because it is self-reported. **Methods:** We propose a new statistical approach to adjust self-reported network degree by using information of YMSM's venue attendance to better approximate the network degree. Then, this new venue-based degree measure can be used for RDS estimators. Our new method yields a higher efficiency (smaller variance) and less bias. The rationale supporting this approach is that peer referral is likely to occur when young MSM meet sex partners at social and public cruising venues, i.e., MSM with more frequent venue attendance tend to meet and have more social contacts, and thus have a higher probability of peer recruitment. **Results:** Our method tended to have narrower CIs compared to the self-reported degrees for HIV estimates. Our simulation study to assess validity also showed that proposed method yields less biased estimates than the standard one. **Conclusions:** YMSM represent a population most at risk of new infections, developing novel approaches that can inform cost and intervention strategies are critical as we move toward HIV elimination and cancer prevention in U.S. This work was supported by the National Institutes of Health (1R01MH100021, 1R01DA039934, and 1R21GM113694). Ming is supported by UTHealth Innovation for Cancer Prevention Research Training Program Pre-doctoral Fellowship (Cancer Prevention and Research Institute of Texas grant # RP160015). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Cancer Prevention and Research Institute of Texas.

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Unveiling Multicultural Communication Barriers to Improve Marrow Donor Recruitment *Lauren Lee, Texas State University; R. Lozano; J. Hudson*

Introduction: Blood cancers are commonly treated by transplant of bone marrow and stem cells harvested directly from donor marrow or peripherally through the donor's bloodstream. National marrow registries like Be the Match Registry reflect low numbers of donors from underrepresented minority populations. Consequently, African American, Hispanic, and Asian American populations are experiencing health disparities when in need of marrow transplants. In partnership with the Cancer Advocacy Movement for Colleges & Outreach (CAMCO) we conducted surveys, focus groups and simulated donor recruitment lab sessions to explore barriers recruiters experience when enrolling multicultural community members in marrow registries. Barriers were identified among both recruiters and potential donors. Donor barriers were based on two recurring themes, mistrust and misinformation. Recruiter barriers included ineffective verbal and nonverbal messages. **Methods:** Following a recruiter appreciation dinner, 27 volunteer recruiters completed a cross-cultural competency self-evaluation designed to measure their cultural competence. Subsequently, they participated in videotaped focus groups to unveil community barriers. Lastly, recruiters engaged in videotaped simulated recruitment sessions with student actors hired to play culturally diverse participant roles to explore recruiter barriers. **Results:** Recruiters believe they are motivated and able to communicate effectively with culturally diverse populations. However, they indicated the need for future training to improve their cultural competence. Donor barriers listed during focus group discussions were associated with one of two overarching themes, mistrust or misinformation. Barriers linked to mistrust were concerns about marrow donation: "What if I catch something because you use dirty needles when getting my marrow", or "How do I know you will really use my marrow for someone who needs it?" Barriers associated with misinformation were based on the registry and donation process. Donor barriers included comments describing why they would not be allowed to sign up for the registry, "I have tattoos", or "I am gay". Donation barriers associated with misinformation included remarks like "It takes too long" or "I can't afford to take off work." Simulated recruitment

sessions showed the need for recruiters to improve their rate of speech, eye contact, and body posturing. Verbal communication barriers included language incompatibilities between recruiter and potential donor including, recruiters' use of jargon, and their inability to adapt information to differing cultural norms. **Conclusions:** Recruiters require training focused on improving mistrust and misinformation using effective verbal and nonverbal messages. The training should include nonverbal communication modules focused on vocalics and kinesics and verbal communication modules focused on adapting and perception checking.

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A Prospective Investigation of the Effects of Pre-cessation Reduction of Anxiety Sensitivity and Dysphoria on Withdrawal in a Tobacco Cessation-Anxiety Reduction Clinical Trial *Alicia Lopez, University of Houston; J. Bakhshaie; A. Ruiz; K. Manning; L. Garey; N. Mayorga; P. Kulesz; M. Zvolensky*

Introduction: Prevailing theory and research suggests the psychological and physiological discomfort associated with tobacco withdrawal may play a formative role in the risk of cessation failure. Yet, research elucidating affective vulnerability characteristics that contribute to increased tobacco withdrawal severity during periods of planned abstinence is highly limited. In the current study, we explored whether smokers with greater reductions of Anxiety Sensitivity (AS) and dysphoria during a smoking cessation intervention would experience less severe post-quit tobacco withdrawal. **Methods:** The interactive effect of change (from pre-intervention baseline to quit-day) in AS and dysphoria in relation to post-quit withdrawal severity (quit-day through 12-weeks post-quit) was examined among treatment seeking adult smokers enrolled in a smoking cessation trial (N = 198; 55.3% female; 86.8% Caucasian; Mage = 38.8, SD =14.0). **Results:** Results indicated that the interactive effect of change in AS and dysphoria was related to linear change in post-quit withdrawal symptoms. Specifically, larger reductions in AS were associated with a faster decline in the severity of withdrawal symptoms across the 12-week post-quit period only for individuals with lower (but not higher) reductions in dysphoria. **Conclusions:** The findings indicated that reducing levels of AS and dysphoria pre-quit is broadly related to the degree of change in post-quit withdrawal symptoms. Collectively, these data suggest there is apt to be clinical merit to employing strategies to address AS and/or dysphoria to more effectively manage emergent withdrawal symptoms following smoking cessation treatment. Keywords: Anxiety sensitivity, dysphoria, smoking cessation, tobacco withdrawal

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A Bayesian Framework for Evaluating Leukemia Risk From Electronic Health Records *Ahmad Al Kawam, Texas A&M University; A. Sen; A. Datta*

Introduction: Cancer risk assessment (CRA) models are considered an efficient tool for identifying high-risk individuals. CRA models have an important role in cancer prevention and early detection by promoting a cost-effective distribution of finite resources, such as cancer screening tests. However, these models have two major limitations: 1) they are usually presented in the form of questionnaires, which limits their automated application to large-scale medical data and 2) they are generally static and cannot easily be adapted to account for the differences between local populations across counties, states, and countries. **Methods:** To overcome these challenges, we utilize Electronic Health Records (EHR) available in most areas in the US. EHRs are composed of patient and clinical information routinely collected at each healthcare visit. We use diagnosis codes stored in the EHR data to identify a list of risk factors associated with leukemia. Furthermore, we develop a Bayesian framework for adaptive risk assessment. The Bayesian framework utilizes prior information and available data to perform accurate risk assessment. The developed model adapts to the existing data and can be updated as more data becomes available. We apply our method to EHR data collected at the Beth Israel Deaconess Medical Center between 2001 and 2012. Our model includes three steps: (i) prior information is incorporated into the Bayesian model in the form of a probability distribution for the different risk factors of leukemia; (ii) the prior is combined with a likelihood function to produce a posterior distribution of coefficient values; and lastly, (iii) simulates are drawn from the posterior distribution to create an empirical distribution for the population using a generalized linear model. **Results:** Our method was able to detect a clear separation between the leukemia subjects and the controls. We tested the significance of this separation and achieved a p-value less than 1.00e-12. According to this risk score distribution, 82% of the leukemia subjects were assigned a higher than average cancer risk score. Furthermore, most of the identified diagnosis codes found were tightly linked to leukemia. **Conclusions:** Through utilizing EHR data and a Bayesian framework, we have developed an effective leukemia CRA model that overcomes the challenges of traditional CRA methods.

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Ecological comparisons of inter-regional and temporal variations in sex-ratios of age-standardized cancer incidence rates *Syed-Ahsan Raza, Baylor College of Medicine; R. Tahir*

Introduction: Comparisons of cancer incidence rates from international cancer registries are valid if ascertainment of cases approaches 100%. Sex ratio (SR) analysis of cancer incidence (age-standardized incidence rates in males relative to females) mitigates some of methodological challenges caused by imperfect case ascertainment. The study presents SR as a useful and robust measure of cancer occurrence, to infer on causes through worldwide comparisons. **Methods:** Cancer Incidence in Five Continents (CI-5) from International Agency for Research on Cancer was used to access incidence data on 30 different cancers in 3 time-periods (i.e., 1974-77; 1988-92 and 2003-07) from 77, 142 and 281 cancer registries. Descriptive methods were used with recourse to mixed-effect regression. **Results:** Cancer types with consistently high variation of SR (SRv) over time were lung, bladder, esophagus, larynx, and oral-cavity. Cancers with consistently low SRv time were colon, Hodgkin's and non-Hodgkin's lymphoma, leukemia, thyroid, gallbladder and skin melanoma. In 1973-77, highest SR were observed for following cancers: larynx (112.0 in Doubs, France) followed by lip (59.0 in Zargoza, Spain), pharynx (31.0 in Doubs, France), tongue (30.0 in Slovenia), esophagus (21.3 in Bas Rhin, France), mouth (15.5 in Slovenia), lung (15.1 in Bas Rhin, France), and kidney (11.6 in Doubs, France). The lowest SR was noted in Warsaw, Poland for thyroid cancer (0.1). Compared to 1973-77, SR of Hodgkin's lymphoma was high in both 1988-92 and 2003-07 (9.0 in Lima-Peru and Karunagappally-India versus 3.5 in South Australia). In mixed-effect analysis with 76 registries from 1983 to 2007, cancer of larynx had highest SR on average in baseline year (i.e., 20.20) and lowest for cancer of thyroid (0.54). The highest inter-regional variation in SR was observed for larynx and lung and the lowest for thyroid cancer. **Conclusions:** A change in the SR over time for some cancers indicates a role of environmental factors. However, some of the unexplained sex differences are unlikely to be explained by environmental factors and it is plausible that there is a significant role of intrinsic sex-specific factors that modify the effect of environmental causes. The patterns of incidence rates based on SR supports that environmental, genetic and lifestyle factors, and even random error in cell replication can influence individual risk. From a prevention perspective, understanding the contribution of known or unknown causes along with the potential gender-disparities (in terms of socio-cultural context) in cancer registration is critical to public health practitioners.

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Does Anxiety Sensitivity Explain the Path from Visceral Sensitivity to Smoking Cognitions among Treatment-Seeking Smokers? *Sahar Anjum, University of Houston; A. Ruiz; J. Bakhshaie; K. Manning; L. Garey; N. Mayorga; J. Smits; M. Zvolensky*

Introduction: It is widely recognized that smoking is related to abdominal pain and discomfort, as well as gastrointestinal disorders. Research has shown that visceral sensitivity, experiencing anxiety around gastrointestinal sensations, is associated with poorer gastrointestinal health and related health outcomes. Visceral sensitivity also increases anxiety symptoms and mediates the relation with other risk factors, including gastrointestinal distress. No work to date, however, has evaluated visceral sensitivity in the context of smoking despite the strong association between smoking and poor physical and mental health. The current study sought to examine visceral sensitivity as a unique predictor of cigarette dependence, threat-related smoking abstinence expectancies (somatic symptoms and harmful consequences), and perceived barriers for cessation via anxiety symptoms. **Methods:** Eighty-four treatment seeking adult daily smokers (Mage= 45.1 years [SD = 10.4]; 71.6% male) participated in this study. **Results:** There was a statistically significant indirect effect of visceral sensitivity via general anxiety symptoms on cigarette dependence (b = .02, SE = .01, Bootstrapped 95% CI [.006, .05]), smoking abstinence somatic expectancies (b = .10, SE = .03, Bootstrapped 95% CI [.03, .19]), smoking abstinence harmful experiences (b = .13, SE = .05, Bootstrapped 95% CI [.03, .25]), and barriers to cessation (b = 0.05, SE = .06, Bootstrapped 95% CI [.01, .13]). **Conclusions:** Overall, the present study serves as an initial investigation into the nature of the associations between visceral sensitivity, anxiety symptoms, and clinically significant smoking processes among treatment-seeking smokers. Future work is needed to explore the extent to which anxiety accounts for relations between visceral sensitivity and other smoking processes (e.g., withdrawal, cessation outcome). Key words: Visceral sensitivity; anxiety; smoking; gastrointestinal distress

224 **Poster Session B**

Can a cognitive-behavioral intervention improve cognitive functioning in breast cancer survivors? *Heather Becker, The University of Texas at Austin*

Introduction: Cognitive problems following cancer diagnosis and treatment are among the most difficult side effects to deal with. Moreover, many breast cancer survivors find that providers do not validate their concerns or suggest ways to address the problems. **Methods:** Twenty women from a community oncology practice and cancer resource center were recruited to participate in a 6-week group intervention to build cognitive abilities. Consistent with Social Cognitive Theory, the intervention focused on self-efficacy for using compensatory strategies as well as discussions about other factors identified from previous literature to affect cognitive abilities, such as fatigue, insomnia, physical inactivity, and emotional distress. In addition, women were assigned specific cognitive exercises from a commercially available brain training program and asked to practice 45 minutes for 3-4 times a week. Women served as their own controls. Outcome measures consisted of performance on well-established neurocognitive tests and self-reported measures of cognitive concerns, emotional distress, fatigue, sleep disturbance, memory and cognitive strategies, and health-related quality of life. Participants were tested twice prior to the intervention to control for testing effects and to investigate naturally occurring changes over time in outcome measures before exposure to the intervention. **Results:** Women had an average age of 53 years; most were employed and well educated. Half had been diagnosed within the past two years, and nine were taking endocrine therapy. Eighteen of the 20 participants completed the study, and two-thirds of the women attended at least 5 of the six classes. Scores on neuropsychological tests did not increase from immediately prior to the intervention to post-test, but scores on PROMIS measures of cognitive concerns, emotional distress, sleep disturbance, and fatigue decreased significantly following participation in the intervention. Reported use of cognitive strategies also increased significantly. **Conclusions:** This exploratory study demonstrated the feasibility of combining a health promotion intervention designed to build cognitive abilities coupled with brain training homework. At the post-intervention debriefing session, participants emphasized that the interaction with the facilitator was an important motivator for behavioral change in this area. While results should be interpreted cautiously because of the small sample size and lack of a control group, these findings add to the growing body of evidence supporting the efficacy of cognitive interventions to help survivors address their cognitive concerns. Funded by the Shivers Foundation.

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225 **Poster Session A**

Clinical factors affect long-term survival of advanced hepatocellular carcinoma patients *Melissa Kok, The University of Texas M.D. Anderson Cancer Center; J. Davis; K. Al-Assi; D. Li; R. Hatia; R. Abdel-Wahab; M. Akce; M. Uemura; A. Kaseb; S. Chang; M. Hassan*

Introduction: Most hepatocellular carcinoma (HCC) patients are diagnosed at late stages, and the 5-year relative survival rate for patients with advanced HCC is only 3%. Many factors – demographic, clinical, and other - affect survival of patients with advanced HCC. A recent study using the Surveillance, Epidemiology, and End Results (SEER) data found that a small proportion (10%) of patients diagnosed with advanced HCC survived longer than 12 months. Notably, longer survival was correlated with age, female sex, year of diagnosis, tumor grade, and surgery status. The aim of this study was to explore additional clinical factors associated with longer survival in advanced HCC, such as smoking history and presence of liver disease. **Methods:** To analyze additional characteristics not examined in the SEER data, we identified 249 individuals with Stage IVA and IVB HCC from patients who participated in a University of Texas MD Anderson Cancer Center clinical-epidemiological study from 2000-2014. We used the median overall survival of patients who received systemic therapy (5.8 months) to stratify patients into two groups: long-term survivors (survival > 5.8 months) and short-term survivors (survival ≤ 5.8 months). Using data from personal interviews and medical records, we compared the two groups by clinical, demographic, and other factors. Variables that differed significantly between the two groups were included in a multivariate Cox proportional hazards model used to identify independent predictors of prolonged survival among patients diagnosed with late-stage HCC. **Results:** Clinical features of long-term survivors differed significantly from those of short-term survivors while demographic and other factors, such as age and hepatitis virus status, did not differ between the two groups. Cox model analysis indicated that clinical factors, such as absence of cirrhosis and better Child-Pugh scores, were independent predictors of prolonged survival. **Conclusions:** Clinical characteristics of HCC patients diagnosed with advanced disease predicts prolonged survival. Therefore, better management of liver disease may help improve survival from HCC, and understanding the mechanism of this benefit is worthy of further inquiry.

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226 **Poster Session B**

Implementation costs of a multi-component intervention to increase human papillomavirus (HPV) vaccination in a network of pediatric clinics *Jarrod Eska, The University of Texas Health Science Center at Houston; D. Lairson; L. Savas; R. Shegog; C. Healey; S. Spinner; M. Fernandez; S. Vernon*

Introduction: HPV vaccination is both a clinically and cost effective way to prevent HPV-related cancers of the cervix, oropharynx, and others. Increased focus on preventing HPV infection and HPV-related cancers has motivated development of intervention strategies to increase vaccination rates of young adolescents to realize Healthy People 2020 national goals. As providers and healthcare organizations consider vaccination initiatives, it is important for decision makers to understand the costs associated with implementing these programs. We estimated the implementation costs of an evidence-based multi-component intervention in a large network of pediatric clinics. **Methods:** Healthcare provider assessment and feedback, reminders, and education; and parent education/reminder strategies were implemented in a network of 51 pediatric clinics to improve HPV vaccination rates. We used a micro-costing method to prospectively estimate program costs. Project and clinic staff logs, system-generated reports, and vendor contracts were used to measure personnel time and material costs. A sensitivity analysis assessed the effects of uncertain and variable cost factors. **Results:** Implementation costs of the four intervention strategies totaled $134,999. The $97,228 in fixed costs include contracted services from third-party vendors to implement automated electronic health record vaccination reminders for providers and parents and to introduce a network-tailored mobile application to educate parents on HPV and HPV vaccination. Variable costs, totaling $69,335, include staff time, supplies, and training necessary to implement each intervention strategy. Assessment and feedback was implemented at an average cost of $672 per clinic. The provider education and provider reminders increased the average cost to $939 and $1,762 per clinic, respectively. The parent education/reminder component increased total average cost of implementation per clinic to $2,845. Including an additional ten clinics reduced the total average cost per clinic to $2,532 with an average reduction of $31 for each additional clinic. **Conclusions:** Fixed costs represented the largest share of the four-pronged intervention strategy, including additional clinics reduced the total average cost per clinic, however, only by a fraction of the total program implementation cost. This analysis serves to inform decision makers on the costs of implementing a multi-component intervention to increase HPV vaccine uptake. Additional research is required to assess the effectiveness and the cost-effectiveness of each strategy in achieving the goal of higher immunization rates.

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227 **Poster Session A**

Imaging glucose-stimulated zinc secretion from the prostate by MRI for the detection of prostate cancer lesions *Veronica Clavijo Jordan, The University of Texas Southwestern Medical Center; D. Sherry*

Introduction: Zinc (II) is essential in the correct function of secretory organs like the pancreas, and prostate. It is known that total zinc(II) concentrations in the prostate are the highest in the body (1-10 mM), and also that those levels are decreased in prostate cancer, while remaining unchanged in the prostate with benign conditions. Here we report the use of a Gd-based zinc(II) sensor for the distinction of prostate cancer from healthy tissue in a transgenic adenocarcinoma of the mouse prostate model (TRAMP) in vivo with MRI and the validation of glucose-stimulated zinc secretion from prostate glands with Synchrotron Radiation- X-Ray Fluorescence (SR-XRF). **Methods:** 9 C57Bl6 healthy and 10 TRAMP fasted mice received 0.07 mmol/Kg Gd-based zinc(II) sensor (IV) and 2.2 mmol/kg D-glucose or saline (IP). Subsequently, mice were imaged in a 4.7 T MRI and serial 3D T1-weighted MRI scans were collected for 10 minutes, the prostates were immediately resected and frozen. 50 um-thick sections were scanned using SRXRF and Zn, Gd, Fe, Cu, and P maps were generated. The concentration values obtained were evaluated for statistical significance by one-way ANOVA. **Results:** Given that the mechanism of glucose-stimulated zinc secretion (GSZS) MRI relies on the effective release of Zn(II) into the Gd-laden extracellular space and also on the availability of Zn(II), we evaluated the distribution of zinc, and gadolinium within the gland after a GSZS experiment in order to elucidate the nature of MRI-identified malignant lesions. We found that there is no statistically significant difference in Gd distribution in the gland as a result of either disease or treatment with D-Glucose. Additionally, Zn(II) loss was only found in the lateral lobe of the prostate of TRAMP mice and with high-resolution SR-XRF we found that effective movement of zinc pools from the luminal acinar gland into the basal cells and extra-glandular space of the prostate secreting glands. A combination of zinc content and metal movement sensitivity to glucose were evaluated and found to be decreased with statistical significance during the progression of prostate cancer in TRAMP mice. **Conclusions:** These results indicate that GSZS MRI as a technique to detect prostate cancer malignant lesions is multi-factorial comprising of the loss of zinc content, Gd-based zinc sensor distribution, and also on the secretory capacity of prostatic secreting cells. Elucidating the interplay between these factors in the transport and zinc homeostasis could prove valuable in understanding the underpinnings of prostate cancer onset and progression.

228 **Poster Session B**

Colorectal cancer screening among urban safety-net patients: Using longitudinal electronic health records to measure multilevel social disadvantage *Amy Hughes, The University of Texas Southwestern Medical Center; J. Tiro; B. Balasubramanian; C. Sugg Skinner; S. Pruitt*

Introduction: Social disadvantage significantly predicts CRC screening, incidence, stage at diagnosis, and survival across populations and places. Social disadvantage is part of meaningful use electronic health records (EHR) requirements. EHRs can be linked to other sources to create measures of social disadvantage at multiple levels. In our study, we aim to: (1) demonstrate novel measures of social disadvantage through linking patient residential address in EMRs with secondary geospatial datasets; and (2) investigate associations between measures of social disadvantage and CRC screening while controlling for healthcare utilization. **Methods:** We geocoded longitudinal EHR data and linked them with cadastral and Census data to generate measures of social disadvantage at multiple levels. We assessed heterogeneity of social disadvantage measures. We employed unadjusted and adjusted multilevel logistic regression models to assess associations. **Results:** We identified 32,965 CRC screening-eligible patients from an existing cohort study within an urban safety-net healthcare system. We used the EHR to assess one-time receipt of CRC screening, via colonoscopy or FIT, in the 18 months following patient enrollment in the existing cohort study. For our safety-net population, neighborhood-level variance and variance in social disadvantage measures was extremely low. In fully-adjusted logistic regression models, measures of patient-level disadvantage and healthcare utilization were associated with CRC screening receipt, but measures of patient-level housing disadvantage and neighborhood-level physical and social disadvantage were not. **Conclusions:** EHRs offer a plethora of data, and linking these data with secondary datasets can enable creation of longitudinal, multi-sector measurements of social disadvantage. More research is needed to apply these methods and measures to EHR data from more heterogeneous patient populations.

229 **Poster Session A**

Nonsteroidal anti-inflammatory drug use, obesity and survival from colorectal cancer *Janelle Chavez, The University of Texas M.D. Anderson Cancer Center; J. Davis; Y. San Miguel; M. Overman; Z. Jiang; S. Manuel; S. Kopetz; S. Chang*

Introduction: Regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with decreased risk of developing colorectal cancer (CRC), and emerging evidence suggests improved overall survival for a subset of patients who regularly use NSAIDs following diagnosis. Conversely, obesity is a known CRC risk factor, however due to mixed findings in the literature, its impact on survival is unclear. The effect of regular NSAID use on CRC survival in the context of obesity is largely unknown. Due to potentially adverse side effects of regular NSAID use, such as gastrointestinal bleeding, it is critical to determine which patients, if any, may benefit from regular use of these drugs after diagnosis. The purpose of this project is to analyze the influence of pre-diagnostic obesity with and without post-diagnostic NSAID use on overall survival in CRC patients. **Methods:** Patients participating in the Assessment of Targeted Therapies Against Colorectal Cancer (ATTACC) protocol at MD Anderson were invited to complete an environmental survey that includes data on NSAID use and self-reported weight history. These data were combined with information from the medical record to describe recent and ongoing NSAID use. Patients are followed-up for disease and survival outcomes through contact with study personnel and periodic letters from the institution. Survival was compared by obese vs non-obese and NSAID users vs nonusers. Results were adjusted for gender, race/ethnicity, and stage at diagnosis using Cox Proportional Hazards models and adjusted survival curves were generated using the 'DIRECTADJ' option in SAS (v9.4). **Results:** Obesity (BMI ≥ 30 kg/m^2) was associated with worse overall survival compared to normal weight, HR = 1.45 (95% CI 1.10 – 1.90 P = 0.02). NSAID use was significantly linked to improved overall survival, HR = 0.81 (95% CI 0.67 – 0.98; P = 0.03). However, when stratified by BMI category, the protective effects of NSAIDs were only evident in the patients with a BMI of ≤ 25 kg/m^2, HR = 0.75 (95% CI 0.60 – 0.94; P = 0.04). **Conclusions:** Among colorectal cancer patients, obesity bodes a worse prognosis while NSAID use significantly improves overall survival, but only in patients of BMI ≤ 25 kg/m^2. These results may help further understand how modifiable CRC risk factors could also impact survivorship. Furthermore, identifying subsets of patients who are most likely to benefit from post-diagnostic NSAID use is an important step toward minimizing toxicities through individualized recommendations, potentially improving treatment and survivorship for colorectal cancer patients.

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Poster Session A

Design, synthesis and SAR of novel EYA2 Inhibitors for Triple Negative Breast Cancer *Stanton McHardy, The University of Texas at San Antonio; H. Wang; B. Campos; G. Li; B. Yuan; S. McCowen; D. Wilson; D. Wristers; S. Smith; M. Hart; R. Li*

Introduction: Triple negative breast cancer (TNBC) is a subtype of breast cancer that lacks the expression of estrogen receptor, progesterone receptor, and HER2. ER-beta is expressed in more than half of breast cancer cases across all major subtypes, thus providing the opportunity of stimulating its antitumor activity as a potential therapeutic approach. Previous work in Dr. Rong Li's lab (UTHSCSA) uncovered eye absent 2 (EYA2) as the tyrosine phosphatase that directly dephosphorylates pY36-ER-beta in vitro and in vivo. EYA2 is a known oncoprotein in ovarian and breast cancers. The goal of this program focused on testing the central hypothesis that pharmacological targeting of the oncoprotein EYA2 with small molecule inhibitors can effectively inhibit breast cancer cell proliferation and tumor-initiating function. **Methods:** Screening assays have been developed to assess and characterize small molecule inhibitors of EYA2, including a standard MTT assays, tumorsphere assay, as well as a recombinant EYA2 phosphatase binding assay. The EYA2 high throughput screening (HTS) assays developed used fluorescence and absorbance-based assays based on OMFP hydrolysis and molybdate green absorbance as readouts. Small molecule leads were optimized using SAR and existing X-ray structural and modeling data on known EYA2 inhibitors to design and synthesize novel EYA2 targeting compounds. Compound design cycles incorporated "drug-like" physical chemical property parameters such as MW, LogP, tPSA and pKa. Cytotoxicity of drug leads was determined using 3-(4,5 dimethylthiazol-2-yl)-2,5-phenyltetrazolium bromide (MTT) assays as well as in tumorsphere assays **Results:** This poster will highlight our collaborative program results, wherein more than 430 analogs from different chemical series were designed, synthesized and screened. Efficient synthesis strategies were developed across different structural classes to support subsequent in vitro studies. Using the fluorescence-based OMFP EYA2 phosphatase and MTT assays, new lead EYA2 inhibitors of varying potencies (IC50 2-50uM) were identified. Structure-activity relationship studies across three chemical series suggested specific structural requirements for inhibition of EYA2 activity. Target specificity of lead compounds was tested using EYA2 CRISPR knockout in cultured cells. **Conclusions:** To date, >430 analogs from different chemical series for the EYA2 program have been designed, synthesized and screened, which has resulted in the identification of multiple lead compounds possessing potent EYA2 inhibition and activity in the MTT cell proliferation and tumorsphere assays. Lead compounds identified also possess favorable physical chemical properties which should deliver good solubility and ADME properties for future in vivo studies. In vitro ADME studies are currently underway.

231 **CPRIT Grantee**
Poster Session B

Predicting binding modes of peptide-HLA complexes with molecular docking *Didier Devaurs, Rice University; G. Lizée; L. Kavraki*

Introduction: Immunotherapy is an innovative cancer treatment that has shown promising results, inducing dramatic tumor regression in numerous patients, for various cancer types. It leverages the immune system to eliminate tumor cells, through cancer vaccines or cell therapies. Since every cell presents at its surface numerous peptides, a patient's immune system can be "trained" to identify tumor cells by recognizing specific tumor-derived peptides. Peptides are presented by human leukocyte antigen (HLA) proteins that bind them; these peptide-HLA complexes can then be recognized by white blood cells that eliminate diseased cells. What hinders the exploitation of this defense mechanism for immunotherapy is that every patient presents a unique set of tumor-derived peptides and requires a personalized treatment. The problem resides in determining which peptides are promising targets for immunotherapy, among the thousands of tumor-derived peptides presented by a patient and identified by experimental techniques. Because of such prohibitive numbers, selecting target peptides cannot be done experimentally and has traditionally relied on computational methods that can predict how strongly peptides bind to HLA proteins. Most methods for HLA-binding prediction involve looking for similarities between sequences of candidate peptides and available datasets containing reported sequences of experimentally-identified HLA-binders. However, due to dataset biases, these methods can fail to identify actual HLA-binding peptides. To address this issue, we aim to develop structure-based computational methods to complement sequence-based methods and improve HLA-binding prediction, by analyzing the three-dimensional structure of peptide-HLA complexes using molecular docking techniques. **Methods:** Protein-ligand docking consists of computationally predicting possible binding modes between ligands and protein receptors. Since most docking tools can handle only small drug-like molecules and not large ligands, such as peptides, we are currently developing a novel docking tool, called DINC, using an innovative incremental protocol. DINC will be used to model peptide-HLA complexes of interest and identify strong HLA-binders. The core of this project will consists of enhancing DINC to account for receptor flexibility. **Results:** We will evaluate this enhanced version of DINC by trying to replicate structures of peptide-HLA complexes reported in the protein data bank and to achieve consistency with HLA-binding experimental data. **Conclusions:** The expected outcome of this project is a computational tool complementing traditional sequence-based methods to predict target peptides for cancer immunotherapy.

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Poster Session A

Collateral lethality as a therapeutic strategy in cancer *Prasenjit Dey, The University of Texas M.D. Anderson Cancer Center; R. DePinho; J. Baddour; F. Muller; C. Wu; H. Wang; W. Liao; Z. Lan; A. Chen; T. Gutschner; Y. Kang; J. Fleming; N. Satani; D. Zhao; A. Achreja; L. Yang; J. Lee; Q. Chang; G. Genevese; A. Viale; H. Ying; G. Draetta; A. Maitra; Y. Wang; D. Nagrath*

Introduction: Cancer genomes possess many deletion events targeting tumor suppressor genes (TSG) and neighboring genes in these loci. These deletion patterns prompted us to consider a systematic approach, termed "collateral lethality", designed to identify cancer-specific vulnerabilities resulting from the deletion of neighboring genes. These bystander genes do not appear to be involved in cancer pathogenesis, yet encode cell-essential functions and are members of multi-gene families that are functionally redundant and co-expressed. Homozygous deletion of SMAD4 is a frequent event in pancreas cancer and other cancer types, totaling >30,000 US cases annually. SMAD4 deletion often results in co-deletion of the neighboring mitochondrial malic enzyme 2 (ME2) gene. In mammalian cells, two genes (ME2 and ME3) encode redundant cell-essential mitochondrial ME activity. Together, ME2 and ME3 function to generate pyruvate to fuel the TCA cycle, and NADPH to maintain ROS homeostasis. These observations prompted our hypothesis that genetic or pharmacological extinction of ME3 activity in a ME2 null cell would specifically compromise cancer cells yet be tolerated in normal host cells possessing ME2 activity. **Methods:** Inducible shRNA strategies were employed to genetically deplete ME3 in ME2-null versus ME2-intact cells followed by apoptosis measurements, integrated metabolomics, and molecular investigations. **Results:** Genetic depletion of ME3 in ME2-null, but not ME2-intact, cells resulted in apoptosis and blocked tumorigenic potential. Mechanistically, integrated metabolomic and molecular investigation of mitochondrial ME-deficient cells revealed diminished NADPH production and consequent high ROS that activates AMP activated protein kinase (AMPK) and in turn directly suppresses sterol regulatory element-binding protein 1 (SREBP1)-directed transcription of its direct targets including the BCAT2 (Branched chain amino acid transaminase 2) gene. We also determined that mitochondrial MEs regulate the utilization of branched chain amino acid (BCAA) via BCAT2, a transaminase required for BCAA catabolism. BCAA is critical for PDAC tumor progression, and inhibition of BCAT2 leads to a decrease in the availability of nitrogen pool required for de novo nucleotide biosynthesis. Notably, enforced expression of BCAT2 can restore tumorigenic potential of ME2/3 deficiency, and free nucleotides can restore proliferation in cell culture. **Conclusions:** Thus, a key mechanism driving cancer cell lethality involves BCAAs as crucial metabolites under the critical regulation of the mitochondrial MEs. These studies reveal a collateral lethal vulnerability in pancreas and other cancers that can be targeted pharmacologically in genotype-defined patient populations. We propose that highly specific ME3 inhibitors could provide an effective therapy across a substantial number of cancer patients.

233 **CPRIT Grantee**
Poster Session B

Engineered apoptotic bodies/vesicles carrying the suicide gene encoding cytosine deaminase suppress growth/metastasis of human breast cancer in mice *Thomas Bartosh, Texas A&M University System Health Science Center; M. Ullah; J. Beaver; H. Nerber; B. Clough*

Introduction: Gene-directed enzyme/prodrug therapy (GDEPT), also known as suicide gene therapy, shows considerable potential as a targeted cancer treatment platform. However, routine application in patients remains overshadowed by challenges associated with fabrication of highly efficient transgene/enzyme vectors. Extracellular vesicles (EVs), natural membrane-bound conveyers of bio-molecular information (nucleic acids, proteins, bioactive lipids), have emerged as promising enzyme/drug delivery vehicles. However, no study has exploited the unique ability of apoptotic cell-derived vesicles, known as apoptotic bodies (ABs), to dump their molecular cargo willingly into genetically unstable cells, a hallmark feature of cancer. Thus, in this study we assessed the applicability of ABs in suicide gene therapy. **Methods:** Genetically engineered ABs were generated from tumor-tropic iPS cell-derived mesenchymal stem cells

transduced with the suicide gene hybrid yeast cytosine deaminase::uracil phosphoribosyltransferase (CD::UPRT). CD is a well-known enzyme that converts the prodrug 5-fluorocytosine (5-FC) into the chemotherapeutic agent 5-fluorouracil (5-FU). The transduced 'donor stem cells' were characterized, expanded extensively, and then cryopreserved to create a master cell bank. ABs were produced by depriving CD::UPRT-expressing donor cells of nutrients in three-dimensional (3D) cultures, which naturally encouraged apoptotic cell death. The engineered ABs were enriched by differential centrifugation and filtration. Expression of CD::UPRT, as well as markers of apoptotic cells and EVs, was determined by RT-PCR and/or Western blots. Efficacy of the CD::UPRT-expressing ABs was evaluated in culture and then in vivo using a human breast cancer xenograft model. All animal procedures were approved by the IACUC of Texas A&M University and Baylor Scott&White Health. **Results:** The genetically modified ABs expressed high levels of CD::UPRT mRNA/protein, pro-apoptotic genes Bax and Bad, as well as common markers of EVs, including CD63 and CD81. Importantly, the ABs were readily internalized by breast cancer cells (BCCs) and transferred their therapeutic cargo. In the presence of 5-FC, CD::UPRT-expressing ABs showed remarkable ability to kill all cancer cell lines tested in vitro. Level of killing was dependent on time, concentration of 5-FC, and the number of ABs used in the assay. Moreover, the ABs suppressed BCC expression of genes involved in drug metabolism and metastasis. In immune-deficient mice harboring human breast tumors, intravenous injections of engineered ABs limited cancer growth and metastasis, an effect that was significantly augmented by systemic application of 5-FC. Importantly, the ABs did not cause substantial non-specific tissue inflammation or damage. **Conclusions:** Taken together, the results here provide evidence that ABs have immense potential as carriers of therapeutic transgenes.

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234 **CPRIT Grantee Poster Session A**

Cisplatin triggers shifts in central carbon metabolism through changes in the tumor cell redox state *Vlad Sandulache, Baylor College of Medicine; W. Yu; Y. Chen; J. Dubrulle; F. Stossi; V. Putluri; A. Sreekumar; N. Putluri; D. Baluya; S. Lai*

Introduction: Cisplatin is utilized in the treatment of multiple solid tumor histologies. Its anti-tumor effectiveness is primarily driven by DNA binding causing DNA damage. Prior to DNA binding, cisplatin interacts with cellular reducing equivalents. Our objective was to determine whether transient fluctuations in the cellular redox state are associated with measurable changes in central carbon metabolic flux. To answer this question we utilized a preclinical model of head and neck squamous cell carcinoma (HNSCC) to measure cisplatin uptake, DNA binding, generation of DNA damage and cisplatin effects on the cellular redox state and carbon metabolism. **Methods:** We utilized a preclinical model of head and neck squamous cell carcinoma (HNSCC). Previously characterized, STR validated, HNSCC cell lines were used for measurements of cell death, cell cycle, senescence, platinum uptake and metabolomic changes. Platinum measurements were conducted using inductively coupled plasma mass spectrometry. Tumor metabolites were evaluated using a high-performance liquid chromatography / liquid chromatography mass spectrometry platform following administration of pan-labeled 13C glucose. Cisplatin effects on lactate production and tumor growth delay were measured using a previously described flank xenograft murine model of HNSCC. **Results:** Cisplatin binds DNA, generates DNA damage and decreases clonogenic survival in HNSCC. DNA-bound cisplatin represents a small fraction of total cellular cisplatin. Cisplatin interacts with the cellular redox state on a time scale consistent with that of DNA binding and DNA damage, triggering measurable drops in intra-cellular NADH/NAD+ and NADPH/NADP+ ratios. Regeneration of cellular reducing potential using N-acetyl cysteine decreases cisplatin DNA binding, generation of DNA damage and cisplatin associated senescence. Glucose uptake by HNSCC cells is rapid and the majority of 13C labeled glucose flux generates pyruvate and lactate. Following cisplatin exposure, lactate levels are decreased, resulting in secondary shunting of labeled carbon into the citric acid cycle and pentose phosphate pathways. **Conclusions:** Cisplatin induced metabolic changes provide a unique opportunity for biomarker development and development of novel cisplatin sensitization strategies in HNSCC and other solid tumors.

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235 **CPRIT Grantee Poster Session B**

Alpha-ketoglutaric acid analogs functionally mimicking the oncometabolite D-2HG for epigenetic therapy of higher grade gliomas *Kalkunte Srivenugopal, Texas Tech University Health Science Center at Amarillo; H. Madala; S. Punganuru*

Introduction: Mutations at the active site of IDH1 gene (R132H) occur in >70% in lower grade malignant gliomas, and result in a dramatic accumulation of the oncometabolite D-2 hydroxyglutarate (D-2HG) in place of the normal metabolite alpha-ketoglutaric acid (AKG). AKG is a substrate for TET1, TET2 DNA -demethylases [5m-cytosine to 5-OH cytosine] and histone demethylases [H3-K-meX to H3-K-meX-1] that control the epigenetic landscape. D-2HG effectively competes with AKG and potently inhibits these enzymes leading to transcriptional silencing of targets such as the MGMT DNA repair, which removes the mutagenic alkylation damage in gliomas. This may also explain superior therapeutic responses to alkylating agents in IDH1-mutated patients. As an innovative strategy, we hypothesized AKG derivatives that can replace AKG in epigenomic dioxygenase reactions will serve as potent anti-glioma drugs either by themselves or in combination with alkylating agents. **Methods:** We synthesized a D-2HG diethyl ester to enhance cellular uptake and tested its effects on human brain tumor cell lines (DAOY, T98G, SF188 and UW18). Also synthesized a 2,4-dimethyleneglutaric acid (DMG), a AKG mimic with methylene groups inserted at the C2 and C4 positions. Effect of DMG in cell survival assays, oxidative stress assays, metabolic flux analyses, western blotting, and flow cytometry were used. Mitochondrial damage was assessed. Preclinical studies in normal mice and nude mice bearing intra cranial glioblastoma (luciferase expressing) xenografts were performed. **Results:** D2-HG ester at 5-10 mM and 24 h treatment caused moderate oxidative stress and inhibited MGMT, increased temozolomide cytotoxicity by 1.5 to 3-fold, and induced histone H3-methylations in glioma cells. The hydrophobic DMG-ester was more potent, by itself was cytotoxic with IC50 up to 500 μM, however, when combined at 100 μM with TMZ resulted in a great synergistic cell killing (9 fold, but 28-fold with UW-18 GBM cells). 0.25 mM DMG inhibited the cellular MGMT activity by >80%, induced the degradation of TET1 protein and greatly increased the histone methylation (H1K25me1, me2 and H2BK25me2). Other experiments showed a mild to strong, both acute and chronic induction of oxidative stress including elevated reactive oxygen species, decreased ATP, NADPH levels, and increased 5-hydroxy methyl cytosine and 8-OH-guanine levels and mitochondrial membrane damage. The orthotopic glioblastoma xenografts showed significant tumor regression. **Conclusions:** The AKG analogs can alter the cellular epigenetic makeup and raise the tumor oxidative stress in a manner ascribed to D-2HG, and open up the much-needed exciting avenues of oncometabolite-based therapy for brain tumors.

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236 **CPRIT Grantee Poster Session A**

Structural modeling and hierarchical clustering of peptide-HLA complexes for cross-reactivity assessment *Dinler Antunes, Rice University; K. Jackson; G. Vieira; G. Lizée; L. Kavraki*

Introduction: Immunotherapies that utilize cytotoxic T-cells have proven very effective at eradicating large tumor burdens in both animal models and human cancer patients. These therapies leverage special attributes of T-cells, such as the specific recognition of non-self peptides. Each T-cell expresses a unique T-cell receptor (TCR) that is capable of recognizing non-self peptides displayed by class I Human Leukocyte Antigen (HLA) molecules on the surface of tumor cells. This recognition can activate the T-cell and lead to the elimination of the tumor. Unfortunately, the progress of T-cell-based immunotherapies was tempered with reports of serious (even fatal) side effects. In fact, a given TCR can recognize different peptide-HLA (pHLA) complexes, triggering an often unwanted response that is referred to as T-cell cross-reactivity. As a consequence, there is a growing interest in elucidating the structural features driving T-cell activation and specificity. In addition, there is a need for the development of computational tools to help assess the risk for cross-reactivity in T-cell-based immunotherapies. **Methods:** Structural data of pHLA complexes involved in described cases of cross-reactivity was obtained from the Protein Data Bank (PDB). Docking-based methods (e.g., DockTope and DINC) were used to model additional pHLA complexes of interest. Hierarchical clustering was used to predict structure-based similarities among unrelated pHLA complexes. Computational predictions were confronted with available experimental data. **Results:** Our docking-based methods for pHLA structural modeling were capable of accurately reproducing known crystal structures, including key structural features for T-cell activation. Moreover, our hierarchical clustering analysis was able to reproduce observed patterns of cross-reactivity among unrelated peptide-targets. Finally, the combined use of computational analysis and T-cell cytotoxicity assays provided structure-based explanations for observed inconsistencies in cross-reactivity experiments. **Conclusions:** Our results corroborate the recently proposed link between pHLA structural similarity and T-cell cross-reactivity. Our analyses suggest that apparent inconsistencies in reported cross-reactivities, such as a preferential directionality, might also be driven by particular structural features of the pHLA complex. In addition, we provide evidence that structural analyses of pHLA complexes can be used to assess the intrinsic risk for cross-reactivity among unrelated pHLA-targets. Further work in this field will certainly contribute to safer T-cell-based immunotherapies.

237 **CPRIT Grantee**
Poster Session B

Development of a novel non-diuretic brain-penetrating ethacrynic acid analog and demonstration of its potent efficacy in orthotopic glioblastoma *Kalkunte Srivenugopal, Texas Tech University Health Science Center at Amarillo; S. Punganuru; H. Madala*

Introduction: The incidence of pediatric and adult brain tumors has continued to rise and there is an urgent need for new chemotherapy drugs. The BBB, intratumoral heterogeneity, overexpression of MGMT and bone marrow toxicity due to alkylating regimens, all impede a successful glioma therapy. We are interested in exploiting the elevated oxidative stress present in gliomas and have synthesized a hydrophobic, non-diuretic analog of ethacrynic acid (EA) called KSS72 [1-(2,3-dichloro-4-methoxyphenyl)-2-methylenebutan-1-one] by removing the carboxylate side chain. EA, by itself is not hydrophobic, is an inhibitor of GSTP1, and has weak anticancer effects. **Methods:** KSS72 was synthesized by standard chemistry and characterized. It retained alpha-beta carbonyl group of EA and underwent Michael addition. Pharmacokinetics of KSS72 after IP or oral administrations was performed in CD1 mice. Diuresis after administering a single-dose of EA or KSS72 to normal mice was compared. GSTP1 catalytic activity, ROS induction, cytotoxicity against a panel of glioma cell lines, autophagy /apoptosis assays, and the efficacy of KSS72 in orthotopic glioblastoma xenografts were quantitated. **Results:** In contrast to EA (edecrin used for hypertension), KSS72 was devoid of diuresis. It was 10-times more potent inhibitor of GSTP1 and exacerbated the redox imbalance in glioma cells. It was selectively cytotoxic to cancer cells including gliomas. Compared to EA which does not cross the BBB, pharmacokinetics following intravenous or oral administrations in mice showed its excellent penetrance through the BBB, with KSS72 accumulating at levels equivalent to TMZ (25% of plasma levels) in the brain. In vitro assays measuring protein carbonyl content, GSH content, ROS generation, GST-pi enzyme activity and others showed that KSS72 triggers a redox imbalance by inhibiting GST-pi and by lowering the GSH and reducing equivalent (NADPH) levels, leading to a significant elevation of ROS. The upregulation of ER stress-responsive proteins, activation of MAPK, autophagy and apoptotic pathways by KSS72 were also noted in tumor cell lines. KSS72 also induced autophagy as a post event of redox perturbation. Nude mice bearing intracranial SF188 GBM mice (expressing luciferase) were given 25 mg/kg/day of KSS72 intraperitoneally for 2 weeks. There was a complete elimination of intracranial tumors by bioluminescence and H&E staining of brain sections in all KSS72 administered animals. **Conclusions:** KSS72 acts through multiple pathways of oxidative stress and is a highly promising non-toxic anti-glioma drug with potential to enter clinical trials.

238 **CPRIT Grantee**
Poster Session A

Metabolomic Profiling Improves Prediction of Early Disease Response and Relapse in Pediatric Acute Lymphoblastic Leukemia *Jeremy Schraw, Baylor College of Medicine; M. Scheurer; K. Rabin; P. Lupo*

Introduction: Although outcomes for pediatric acute lymphoblastic leukemia (ALL) have improved dramatically, five-year survival following relapse remains dismal. Initial response to therapy, measured by minimal residual disease (MRD) at end-induction, is the most important predictor of outcome. However, approximately half of relapses occur in MRD-negative patients. We hypothesized that global metabolomic profiling of diagnostic bone marrow plasma could improve prediction of MRD positivity and relapse when combined with clinical features, and provide insights into the biology of chemoresistance. **Methods:** The study population (n=100) included children age 0-18 years with ALL treated at Texas Children's Cancer Center. 39 cases had MRD ≥ 0.01% at end-induction and 23 relapsed. Diagnostic bone marrow plasma specimens were obtained with informed consent and subjected to metabolomic profiling via UPLC-MS/MS by Metabolon. Analysis was limited to named compounds that were detected in at least two samples. We used Welch's two-sample t-test to compute p-values comparing mean concentrations in MRD positive vs. negative and relapsed vs. non-relapsed plasma and X^2 test to assess differences in the frequency of detection. Compounds demonstrating significance at the $p < 0.001$ level were then evaluated in logistic regression models for MRD and relapse, and the best predictors were obtained by backward elimination. Finally, we assessed the performance of models for MRD and relapse using (1) clinical features alone; (2) metabolomic data alone; and (3) clinical features + metabolomic data. DeLong's test for correlated receiver operating characteristics curves was used to compare model performance. **Results:** A higher concentration of pyruvate was associated with MRD positivity ($p = 0.005$). Conversely, a reduced OR for MRD was identified for arachidonylglycerol ($p = 0.01$). Reduced ORs for relapse were identified for increasing concentrations of picolinic acid and N-carboxyethylphenylalanine ($p = 0.04$ and 0.02, respectively), as well as for gamma-CEHC ($p = 0.03$). Several glycerophospholipids demonstrated inverse associations with MRD positivity and relapse. Metabolomic profiling improved prediction of both MRD and relapse as compared to clinical features alone ($p = 0.001$ and $p = 0.03$ respectively). Incorporating metabolomic data gave an absolute improvement in sensitivity of 8% for MRD and 19% for relapse. **Conclusions:** We demonstrate that global metabolomic profiling improves prediction of MRD positivity and relapse in ALL. Differences in pyruvate and lipid concentrations suggest metabolic changes associated with chemoresistance or disease recurrence which may be therapeutically targetable. If validated, these metabolomic biomarkers may improve clinical risk prediction and further our understanding of disease biology.

239 **CPRIT Grantee**
Poster Session B

Identification of Potential K-Ras Inhibitors by Hierarchical Virtual Screening and Experiments *Amit Gupta, The University of Texas Health Science Center at Houston; S. Sarkar-Banerjee; P. Prakash; C. Pagba; X. Wang; J. Putkey; J. Hancock; A. Gorfe*

Introduction: K-Ras is a small GTPase that plays a critical role in the regulation of cell growth and proliferation. Somatic mutations on K-Ras are associated with many different cancers, accounting for about 85% of all Ras-associated cancers or 25-30% of all human cancers. K-Ras is a very dynamic allosteric enzyme, and our previous studies revealed that K-Ras harbors four allosteric ligand-binding pockets and suggested that targeting K-Ras directly is a viable strategy to abrogate its abnormal functions. **Methods:** In the current study, we used structural analysis and knowledge-based filters on conformers obtained from all-atom MD simulations of oncogenic mutant K-Ras to select representative structures for docking. The physicochemical and geometric features of these representative structures were used to tailor complementary pocket-specific chemical libraries from the large purchasable chemical space of the ZINC database. We performed ensemble docking of these tailored ligand libraries to each pocket with the standard precision (SP) module of the Glide docking software. The docking outputs were prioritized using hierarchical post-docking analysis based on common residue interaction patterns and chemical scaffold diversity. These hits were further tested using N15 heteronuclear single quantum coherence (HSQC) NMR, microscale thermophoresis (MST) and cellular assays. **Results:** Our K-Ras focused virtual screening yielded a list of 761 potential hits and about 100 of these were tested for their ability to bind to K-Ras using HSQC NMR. Of the 100 tested, 10 compounds showed significant amide chemical shift perturbation at several residues, suggesting potential binding. The binding affinity of these compounds were calculated by MST, and their ability to interfere with RAS-RAF-MEK-ERK and RAS-PI3K-AKT signaling was monitored by measuring changes in the phosphorylation of ERK and AKT in BHK-21 cells expressing G12D K-Ras. **Conclusions:** Our combined hierarchical virtual screening and experiments yielded potential lead compounds targeting K-Ras. We will discuss these results and their implications for future efforts in K-Ras drug discovery.

240 **CPRIT Grantee**
Poster Session A

Exploring flow effects on BOLD MRI with oxygen challenge in orthotopic lung tumor model *Ralph Mason, The University of Texas Southwestern Medical Center; H. Zhou; Z. Zhang; J. Wagner; J. Campbell; Z. Zhang; D. Saha; M. Takahashi; S. Zhang*

Introduction: Blood oxygen level dependent (BOLD) can provide information on tumor oxygenation. However, the measurements are affected by blood flow, which is known to affect the signal of BOLD (so-called FLOOD: Flow and Oxygen Level Dependent). This is a particular concern for lung cancer imaging, where there are often large blood vessels around the region of interest. This study explored the extent of flow sensitivity by comparing the BOLD signal intensity and T_2* values with and without flow suppression using an orthotopic lung tumor model. **Methods:** H460-luc human lung cancer cells were surgically implanted in the right lung of sixteen nude rats. MRI was performed at 4.7 T. BOLD (multi-echo gradient echo; TR = 150ms, ten echo time from 2 to 29 ms, flip angle = 20°) MRI was acquired with the intervention of an oxygen challenge (from air to 100% O2). Five sets of maps were acquired during air breathing and eight sets during oxygen breathing. Images were acquired in sagittal plane. BOLD was acquired with ECG triggering to reduce motion artifacts. Spatial saturation bands were placed on each side of the imaging plane for flow suppression. We examined the effect of flow on temporal, spatial and regional basis. **Results:** T2* values increased in tumor and liver in response to oxygen. No temporal differences were observed in the tumor regions. T2* maps during air and oxygen breathing, as well as the ΔT2* (oxygen-air) showed negligible differences comparing the paired scans with and without flow suppression for tumor regions. However, the semi-quantitative %ΔSI maps showed different enhancement patterns. Statistical analysis was performed on the mean values from ROIs of tumor, liver and muscle of 16 rats. Most of the values were not significantly

different between the sequences. Greater differences were observed for the liver regions with two of the parameters (T2*air and ΔT2*) reaching statistical significance. Strong correlations between the measurements were found in all four parameters. **Conclusions:** Quantitative measurements of BOLD appeared to be insensitive to flow for the tumor regions as observed in this preliminary study, while semi-quantitative ΔSI was strongly affected by flow. For well vascularized normal tissue (such as liver), flow suppression will be necessary for accurate measurements.

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241 **CPRIT Grantee**
Poster Session B

Contemporary surgical outcomes of venous tumor thrombectomy managed with intraoperative Doppler ultrasound for kidney cancer *Deepak Pruthi, The University of Texas Health Science Center at San Antonio; H. Wang; K. Iffrig; M. Cajipe; A. Satsangi; G. Haidar; T. Hicks; E. Sako; M. Liss; W. Chowdhury; R. Rodriguez; D. Kaushik*

Introduction: Radical nephrectomy (RN) with venous tumor thrombectomy (VTT) carries a significant morbidity and mortality risk. Examination of a contemporary single-institution series provides the capability to develop a management algorithm and examine its results. Our multidisciplinary integrated surgical pathway includes the use of intraoperative color Doppler ultrasound. We report our surgical outcomes after implementation of this technique. **Methods:** We retrospectively reviewed the records of all patients who underwent RN with VTT for kidney cancer between January 1, 2013 and October 1, 2016. Our protocol includes intraoperative color Doppler ultrasound to precisely delineate the extent of VTT and guide cavotomy. Surgical complications, major postoperative complications (Clavien-Dindo classification >= 3), 90-day readmission rates, and outcomes are reported. Multivariate linear regression, logistic regression, and Cox proportional hazard modeling were used to identify associations. **Results:** Fifty-eight patients underwent RN with VTT. Many were Hispanic (62%), current smokers (45%), and symptomatic (98%). The median age, body mass index, Charlson comorbidity score, American Society of Anesthesiologists score, hemoglobin, and tumor size were 58 years, 29 kg/m2, 3, 3, 106 g/L, and 9.4 cm, respectively. Twenty-six (45%) patients had Mayo Clinic level III or IV thrombus; of these, 19 required venovenous or cardiopulmonary bypass; three required patch grafting. There were fewer major bleeding complications with cautious administration of anticoagulation in the perioperative period. The median length of hospital stay was 8 days and there were 20 major complications. The 30-day readmission rate was 21% and the 90-day mortality rate was 8.9%. In multivariate analysis, low serum albumin and age-adjusted Charlson comorbidity score predicted length of stay. Increased intraoperative blood loss was significantly associated with increasing body mass index, serum creatinine, tumor thrombus level, and a history of significant weight loss >9.1kg. Low serum hematocrit predicted 90-day mortality. **Conclusions:** Intraoperative color Doppler ultrasound is a useful tool and can facilitate caval preservation. Caval grafting can be avoided in most cases. Venovenous bypass can be avoided in many level III cases. Early therapeutic anticoagulation should be instituted with caution.

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242 **CPRIT Grantee**
Poster Session A

Clinical and genomic landscape of gastric cancer with a mesenchymal phenotype *Yun Seong Jeong, The University of Texas M.D. Anderson Cancer Center; B. Sohn; J. Shin; J. Lee*

Introduction: Heterogeneity of gastric adenocarcinoma is reflected in the unpredictable outcomes when patients with similar stage of cancer are treated with empiric approaches. Molecular subtypes and their associated biomarkers need to be established to optimize therapy of gastric adenocarcinoma. **Methods:** We analyzed gene expression profiling data from 93 patients with gastric adenocarcinoma to uncover subtypes and identify a gene expression signature associated with prognosis and response to adjuvant chemotherapy. The association of the signature with prognosis was validated in four independent cohorts of 646 patients. **Results:** We identified 2 distinct molecular subtypes of gastric cancer: mesenchymal phenotype (MP) and epithelial phenotype (EP). Molecularly, MP subtype tumors showed high genomic integrity characterized by low mutation rates and microsatellite stability, whereas EP subtype tumors showed low genomic integrity. Clinically, the MP subtype was associated with markedly poor survival and resistance to standard chemotherapy, whereas the EP subtype was associated with better survival rates and sensitivity to chemotherapy. Integrative analysis showed that signaling pathways driving epithelial-to-mesenchymal transition and insulin-like growth factor 1 (IGF1)/ IGF1 receptor (IGF1R) pathway were highly activated in MP subtype tumors. Importantly, MP subtype cancer cells were more sensitive to inhibition of IGF1/IGF1R pathway than EP subtype. Detailed characterization of these 2 subtypes could identify novel therapeutic targets and useful biomarkers for prognosis and therapy response. **Conclusions:** This novel molecular subtype of gastric cancer was highly associated with benefit from adjuvant chemotherapy and prognosticated outcome of gastric cancer patients who underwent gastrectomy.

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243 **CPRIT Grantee**
Poster Session B

Does DNA double strand break repair deficiency play a role in the sensitivity of cells to therapeutic proton beams? *Gabriel Sawakuchi, The University of Texas M.D. Anderson Cancer Center; K. Thallapureddy; S. Bright; D. Flint; D. Yoon; C. McFadden*

Introduction: Nearly 150,000 patients have been treated with proton therapy worldwide. Proton therapy has physical advantages compared to conventional x-rays. However, on the biological standpoint, when and how to best apply proton therapy is still debated. Relative biological effectiveness (RBE) is fixed at 1.1 for clinical applications, however there is evidence to support that using a variable RBE may allow a more complete exploitation of proton therapy. Particularly, the ionization density or linear energy transfer (LET) of proton beams increases as a function of depth in tissue, which causes different biological damage that in turn produces different RBEs. In addition the RBE is a function of radiation dose, cell type and the endpoint analyzed. It is hypothesized that a major factor that dictates RBE is the induction of complex DNA damage which persists and the DNA repair mechanisms tasked with repairing these lesions. This work investigates the role of LET on RBE and on how DNA double strand break (DSB) repair deficiency affects the RBE. **Methods:** An un-modulated proton beam with range in water of 4.3 cm (nominal energy of 100 MeV) was used for irradiations in three different depths (1.1, 3.8 and 4.3 cm) along the proton beam Bragg curve. These depths corresponded to dose averaged LET in water values of 1.3, 2.5 and 8.9 keV/mm, respectively. Clonogenic cell survival assays were performed at each of these conditions in several well characterized cancer cell lines and in a modified cell line where we can selectively inhibit DNA DSB repair pathways. RBE was calculated relative to 6 MV X-rays at a 10 cm depth. **Results:** Our results indicate that RBE strongly depends on LET, cell line, and deficiency of a particular DNA DSB repair pathway. **Conclusions:** We believe the interplay between DNA repair deficiency and LET is an essential component to exploit the full potential of proton therapy. Furthermore, a better understanding of proton therapy RBE could result in optimizing treatment plans and associated models ultimately increasing the efficacy of proton therapy. We next plan to identify the essential biological components at the protein level involved in RBE, with a particular focus on DNA DSB repair and attempt to use this information to predict tumors that will respond favorably to proton therapy and those that will not benefit.

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244 **CPRIT Grantee**
Poster Session A

Development of an Effective Cancer Vaccine Platform Using Attenuated Salmonella to Deliver Recombinant Tumor-Associated Antigens *Xin Xu, Baylor College of Medicine; L. Metelitsa*

Introduction: Inadequate antigen delivery is one of the major limitations of modern cancer vaccine vectors. To overcome this challenge, we exploited Salmonella Pathogenicity Island 2 (SPI2) and its type III secretion system (T3SS) to deliver a tumor-associated antigen (TAA) of choice into the cytosol of antigen-presenting cells (APC) in situ. The goal of this study was to explore and exploit the potential of SPI2-encoded T3SS of clinically validated S. typhi strain CVD908 for construction of an effective cancer vaccine. **Methods:** We engineered the clinically validated S. typhi strain CVD908 to express SPI2-regulated dominant-negative oncoprotein survivin and MYCN. To adapt CVD908 to stably express recombinant antigens without antibiotic-dependent selection, we used a recently reported plasmid stabilization system that encodes the single-stranded binding protein (SSB), an essential protein in DNA metabolism, which was deleted from the bacterial chromosome. The SPI2-regulated expression cassette was then cloned into the SSB plasmid, so that the resultant construct maintained bacterial vector stability while expressing and translocating antigens in mouse model and human dendritic cells. **Results:** We found that CVD908-htrAssb vector effectively infects human dendritic cells in vitro and translocates recombinant human survivin and MYCN oncoproteins into their cytosol. DCs infected with salmonella induce potent antigen-specific CTL responses able to recognize and kill tumor cells. Furthermore, CVD908-htrAssb remains stable and immunogenic in mice, not only increased the frequency of antigenic-specific CTLs but resulted in a dense tumor infiltration with CD8 T cells and enhanced antitumor activity in the neuroblastoma cancer model. **Conclusions:** Oral antigen delivery via SPI2-encoded T3SS of Salmonella typhi may be the foundation of an effective cancer vaccine platform and for clinical trials in human.

245 **CPRIT Grantee**
Poster Session B

Targeted hypoxia reduction restores T cell infiltration and sensitivity to immunotherapy in prostate cancer *Priyamvada Jayaprakash, The University of Texas M.D. Anderson Cancer Center; M. Ai; P. Budhani; T. Bartkowiak; J. Sheng; C. Ager; C. Nicholas; A. Jaiswal; Y. Sun; K. Shah; S. Balasubramanyam; N. Li; G. Wang; J. Ning; A. Zal; T. Zal; M. Curran*

Introduction: Tumors evade host immune responses through creation of an immune suppressive and hostile hypoxic microenvironment. T cell checkpoint blockade with anti-CTLA-4 and anti-PD-1 is effective in "hot" tumors like melanoma with pre-existing immune infiltrates. However, "cold" tumors like prostate and pancreatic cancers respond poorly. Hypoxia fosters metabolic alterations resulting in extracellular acidification of the microenvironment, depletion of essential amino acids like Arginine and Tryptophan, extracellular adenosine accumulation, dense expression of inhibitory ligands like PD-L1 and recruitment and polarization of immature myeloid cells into immune suppressive MDSCs and TAMs, all of which dampen T cell responses. For prostate cancer, increased hypoxia has been shown to strongly correlate with more aggressive disease. **Methods:** We treated both transgenic (TRAMP) and transplantable (TRAMP-C2 cell line) models of murine prostate cancer with TH-302, a hypoxia-activated prodrug alone or in combination with anti-CTLA-4+anti-PD-1 antibodies and studied the effects on tumor growth, survival and the tumor immune microenvironment. **Results:** The combination of TH-302 with checkpoint blockade exhibited superior therapeutic efficacy compared to either monotherapy evidenced by decreased tumor growth and increased survival. In the TRAMP transgenic model, tumor control was maintained even after 3 months of discontinuation of therapy. Efficacy correlated with a reduction in tumor hypoxia, increased effector CD4 and CD8 proliferation, higher CD8 to Treg and CD8 to MDSC ratios. Combination-treated mice showed a decreased capacity to polarize adoptively transferred immature myeloid cells into granulocytic MDSCs and a reduced ability to fully upregulate Arginase and downregulate MHC II showing incomplete suppressive polarization. **Conclusions:** Disruption of tumor hypoxia synergizes with checkpoint blockade to promote tumor regression in transplantable and transgenic models of prostate cancer. Breaking down hypoxic regions compromises the integrity of the suppressive stromal myeloid network and facilitates T cell entry into previously hypoxic regions, which are further activated by checkpoint blockade. This study provides a rationale for combining hypoxia ablation with agonistic and antagonistic antibodies to boost anti-tumor immunity. We are currently testing other drugs that interfere with cancer cell metabolism while sparing T cell metabolism and investigating their effects on enhancing immune responses by breaking down immune suppressive barriers.

246 **CPRIT Grantee**
Poster Session A

A C. elegans platform for the identification of small molecule inhibitors of the mitochondrial UPR *Mark Pellegrino, The University of Texas at Arlington; A. Qureshi*

Introduction: The relationship between mitochondrial function and cancer has been considered for many decades. Otto Warburg was first to observe that cancer cells rely on glycolysis in the presence of oxygen that he believed was evidence of defective mitochondrial function and the source of its pathogenesis. This view has since changed and today, increasing evidence suggests that cancer cells actually rely on important mitochondrial activities such as the generation of energy through oxidative phosphorylation, and often times display enhanced organelle function. Nonetheless, it is clear that cancer cells are in need of mitochondrial recovery programs to survive including the stress response pathway known as the mitochondrial unfolded protein response (UPRmt). Here, mitochondrial stress activation of the bZIP transcription factor ATFS-1 (ATF5 in mammals) results in the induction of a diverse set of mitochondrial protective genes that help support repair of the organelle. Consistent with an activation of the UPRmt, multiple cancer types display increased expression of known UPRmt target genes, including mitochondrial chaperones that help promote organelle protein homeostasis. Importantly, inhibition of the UPRmt pathway results in reduced survival of cancer cell populations but has negligible effects on healthy cells. This supports the targeting of the UPRmt as a possible therapeutic strategy in selectively reducing cancer cell populations without affecting neighboring healthy cells. **Methods:** With this in mind, we present here a platform to identify small molecule inhibitors of the UPRmt using the model organism Caenorhabditis elegans. We tested a collection of small molecules, including the Prestwick Chemical Library of FDA approved drugs, that could silence the UPRmt using a transgenic C. elegans UPRmt model as a read-out. **Results:** Our primary screen of approximately 1300 small molecules yielded 298 UPRmt inhibitors, of which 43 repeated in the secondary screen. **Conclusions:** Current work is focused on validating these hits using similar compounds and/or genetic means (grant ID: RR160053).

247 **CPRIT Grantee**
Poster Session B

Preliminary Treatment Planning Guidance for Superior Radiation Treatments for Cancer Patients *Christopher Kabat, The University of Texas Health Science Center at San Antonio; D. Defoor; N. Papanikolaou; S. Stathakis*

Introduction: Radiotherapy treatments are limited by the dose delivered to normal tissues. Conceptual and technological advances have led to new radiotherapy technologies (e.g. intensity modulated radiation therapy, rotational or helical delivery) which can deliver high dose to the tumor volume while sparing healthy tissues. During treatment planning the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) recommendations are employed to strategically guide us towards optimized treatment plans. Currently, RT plans are finalized and ready for delivery when QUANTEC criteria are met. Thus, current treatment plans often only meeting QUANTEC criteria and fail to further venture if doses to healthy tissues can be reduced. An application is purposed to address this issue by providing information to physicians and dosimetrists about the feasibility of reducing the dose to healthy tissue while maintaining tumor dose coverage. **Methods:** An application was developed using MATLAB software to generate theoretical dose distributions(TDD). For this study, a 10 MV VMAT delivery field was employed to generate optimized dose distributions for twenty previously treated patients. Each patient's TDD was calculated using their segmented tumor and organs at risk and their individual CT images. Tumor volumes were set to receive 100% of the patient's prescribed dose. The TDD for the volumes outside the tumor were simulated based on our homegrown theoretical model using the information from a 10MV photon beam model. **Results:** For all twenty patient plans, our method demonstrates the possibility for improved tumor coverage and/or reduction of healthy tissue dose. Maximum dose to regions near tumor sites had minor differences, however distal regions contained greater sparing possibilities as predicted. Prostate cancer plans showed possible dose reduction for the rectum, without losing prostate coverage. Differences in the bladder dose between our TDD and delivered plans were more drastic, most likely due to varying bladder size of each patient and the organ's proximity to the tumor. **Conclusions:** The TDD is a representation of the ideal treatment plan. The information that the TDD provides is used by the radiation dosimetrists and physicians as guidance during inverse optimization of the treatment plan. Our results have provided guidance in improving current treatment plans by indicating the volumes of healthy tissue where dose distributions can be improved. Data collected from this study has provided insight into the challenges produced by altering dose distributions and developed an understanding of which dose distribution could possibly have the greatest improvements to patient plans.

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Poster Session A

Bone Targeted Nanoparticles for Metastatic Prostate Cancer *Andrew Gdowski, University of North Texas Health Science Center at Fort Worth; A. Ranjan; M. Sarker; J. Vishwanatha*

Introduction: Overall survival and serious toxicities in patients with bone metastatic prostate cancer remain problematic despite an expansion of therapeutic options approved in recent years. We have developed a bone targeted nanoparticle (NP) system to deliver cabazitaxel to bone lesions. The objective of this strategy is to increase therapeutic concentration at the bone metastasis site to achieve an improved therapeutic index. **Methods:** Poly (lactic-co-glycolic acid) NPs were fabricated with cabazitaxel encapsulation and subsequent conjugation of alendronate to the outer surface of the NP. Physico-chemical characterization of NPs was performed. In vitro studies with C4-2B and PC3 prostate cancer cell lines and spheroids were performed. Ex vivo NP bone affinity studies were completed. In vivo efficacy studies were carried out in male athymic nude mice implanted with intraosseous tumors. After bone tumor development, mice were treated via tail vein injection with either saline, free cabazitaxel, non-targeted NPs, or targeted NPs for one month (starting n=6 per group. In addition, animal behavior experiments were performed on all treatment groups to assess functional status through gait analysis and pain through von frey filament assay. **Results:** NPs were successfully synthesized to size of 236 nm with a PDI of .120. High encapsulation efficiency and drug loading was achieved. Ex vivo bone binding experiment showed targeted NP had an 8-fold increase in bone binding at 72 hours compared to non-targeted NP. Tumor efficacy experiment showed targeted NP and non-targeted NP had a statistically significant overall reduction in tumor measured by bioluminescence (P value < 0.005). Interestingly, mice treated with targeted NP had no bone lesions on x-ray, whereas, 100% of mice in saline group, 100% of mice in cabazitaxel group, and 33% of mice in non-targeted NP group developed

bone lesions. Von frey assay showed a significant reduction in relative response in the targeted NP group (P value < 0.005). **Conclusions:** We have successfully synthesized a bone targeted NP system. In this project, we have shown that targeted NPs help maintain bone structure in tumor burdened limbs as well as decrease tumor size. We have also shown that these targeted NPs reduce the relative response to von frey filament pain stimulation in the tumor limb. This bone targeted NP system is a promising potential therapeutic in developing improved treatments for bone metastatic prostate cancer patients.

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249 **CPRIT Grantee**
Poster Session B

Transcriptional Axis of EZH2-ERα-GREB1 Regulates Tamoxifen Resistance in Breast Cancer *Yanming Wu, The University of Texas Health Science Center at San Antonio; Z. Zhang; M. Cenciarini; C. Proietti; M. Yang; Y. Liao; P. Elizalde; K. Xu*

Introduction: The efficacy of endocrine therapy in estrogen receptor (ER)-positive breast cancer is often limited by either intrinsic or acquired resistance. Emerging evidence suggests that epigenetic alterations contribute to the development of endocrine resistance. Enhancer of zeste homolog 2 (EZH2), a histone methyltransferase, is frequently overexpressed in breast cancer and strongly associated with aggressive phenotypes of cancer cells. However, the involvement of EZH2 in endocrine resistance remains poorly explored. Here we discovered a critical transcriptional axis consisting of EZH2, ERα and its cofactor GREB1 in driving tamoxifen resistance (TamR). **Methods:** Association between EZH2 and tamoxifen resistance was investigated bioinformatically, qRT-PCR, Western blot, cell proliferation assays and immunohistochemistry (IHC) staining. RNA-seq and ChIP-qPCR were applied to confirm epigenetic reprogramming of specific transcriptomes to favor the endocrine resistant phenotypes. Xenograft models were established to further validate the efficacy of EZH2 inhibitors in vivo. **Results:** Our studies demonstrated that higher EZH2 levels are associated with poorer response to tamoxifen in breast cancer patients. EZH2 represses the expression of the ERα cofactor GREB1 by maintaining DNA hypermethylation of a particular CpG-enriched region at the GREB1 promoter, which is negatively correlated with GREB1 levels in clinical specimens and highly associated with cell sensitivity to endocrine treatment. We also revealed a novel function of GREB1 in ensuring proper cellular responses to different ligands by recruiting distinct sets of ERα cofactors to cis-regulatory elements. This explains the opposing biological effects of GREB1 on breast cancer cell growth in response to estrogen or anti-estrogen. EZH2-dependent repression of GREB1 in hormone refractory cells results in chromatin reallocation of ERα coregulators, converting the anti-estrogen into an agonist. Levels of EZH2 and GREB1 are negatively correlated in clinical samples from patients receiving adjuvant tamoxifen treatment, and together predict response to endocrine therapy. **Conclusions:** Our work provides insights into an epigenetic mechanism of endocrine therapy resistance and a potential novel therapeutic strategy to overcome tamoxifen resistance in aggressive breast cancer.

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250 **CPRIT Grantee**
Poster Session A

Personalized transcriptomic profiling and high-throughput drug screen of metastatic pancreatic ductal adenocarcinoma using ex vivo tumoroid models *Vincent Bernard, The University of Texas M.D. Anderson Cancer Center; F. Mulu; J. Ling; D. Kim; B. Stephens; M. Katz; G. Varadhachary; M. Javle; C. Stephan; R. Powell; P. Davies; S. Muthuswamy; H. Alvarez; A. Maitra*

Introduction: By 2030, pancreatic ductal adenocarcinoma (PDAC) will likely become the second leading cause of cancer-related death in North America. A lack of actionable mutations continues to be a significant challenge in addressing the disease in a precision medicine setting. As a result, current treatment options are often limited to genotype-independent cytotoxic agents. We developed a methodology for establishing three-dimensional patient derived tumor organoids (PDOs) that mirror multiple phenotypic traits to that of the parental tumor. Using PDOs to model the in vivo molecular phenotype and treatment response of patient tumors, we characterized gene expression profiles and screened for sensitivity to a FDA approved drug library for therapeutic stratification. **Methods:** Established PDOs were profiled through single cell RNA-Seq analysis while tumor heterogeneity was characterized using differentiation status phenomics via the Amnis ImageStream system. The PDOs were then subjected to a high-throughput drug screen of 1593 agency approved candidates. Top candidates, including combinatorial drug selections, were orthogonally validated through single cell gene expression analysis and evaluated for efficacy and synergistic interactions. **Results:** High throughput protein expression analysis of PDOs revealed vast intra-tumoral heterogeneity with subpopulations exhibiting epithelial, stem-like, and mesenchymal traits. Single-cell transcriptomic profiling of PDOs revealed multiple subpopulations with effective therapies projected based on pharmacogenomic predictions targeting opposite gene expression patterns. Predicted in silico therapeutic candidates were validated in high throughput drug screens. Common sensitivity nodes involving epigenetic modifiers were detected among all tumor derived subpopulations in a PDO. A synergy matrix seeded with PDOs and evaluated using Bliss independence revealed that combinatorial treated with HDAC-inhibitors and PARP1-inhibitors produced the most profound synergistic result. Mechanistically, HDAC inhibitors limit the activity of DNA repair proteins, which in conjunction with PARP-inhibition leads to synergistic outcomes. **Conclusions:** We have demonstrated the utility of our PDO system in modeling in vivo patient tumor response and successfully executed our high-throughput drug screening approach to predict vulnerability nodes. Transcriptomic profiling revealed sophisticated heterogeneity and allowed us to identify viable treatment options using a pharmacogenomic strategy. Furthermore, our combinatorial drug testing revealed an exciting synergistic interplay between HDAC and PARP1 inhibitors, an interaction that has never before been shown in a PDAC case. Looking forward, our model not only may be a vehicle used to discover new drug candidates and elucidate novel mechanisms, but may also be the first step towards the establishment of a true precision medicine paradigm for PDAC.

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251 **CPRIT Grantee**
Poster Session B

Proteolytic hinge cleavage of the HER2 targeting antibody pertuzumab impairs its ADCC function and antitumor activity *Xuejun Fan, The University of Texas Health Science Center at Houston; H. Hsiao; R. Jordan; N. Zhang; Z. An*

Introduction: Proteolytic impairment of monoclonal antibodies (mAbs) in the tumor microenvironment compromises antitumor efficacy of therapeutic antibodies such as the HER2 targeting antibody trastuzumab and serves as one of the cancer immune evasion mechanisms. Specifically, proteolytic cleavage at a susceptible peptide bond in one of the two strands of the hinge region of human immunoglobulin G1 (IgG1), termed single hinge cleavage, renders an IgG1 antibody dysfunctional as regard to its Fc effector functions such as ADCC, ADCP, and CDC. Pertuzumab is a humanized IgG1 monoclonal antibody targeting the epidermal growth factor receptor (HER2/ErbB2) and has been widely used in the clinic in combination with trastuzumab for treatment of HER2 overexpressing breast cancer and other cancer types. The effect of single proteolytic hinge cleavage of pertutumab on its Fc effector function and anti-tumor efficacy has not been studied. **Methods:** In this study, we determined the single hinge cleavage of pertuzumab (IgG-P) in high HER2 expressing cell cultures. Single hinge cleaved pertuzumab (scIgG-P) was evaluated for its ability to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) activity using a xCELLigence instrument, and anti-tumor efficacy was assessed in a mouse xenograft tumor model as compared to intact pertuzumab. In addition, we constructed a protease-resistant version of anti-hinge cleavage site monoclonal antibody (AH-mAb), and assessed the restored ADCC activity and antitumor function of IgG-P in a protease-rich environment. Further, we tested the effect of a combination treatment applying pertuzumab and trastuzumab on the single hinge cleavage and ADCC activity in vitro. **Results:** Single hinge-cleavage of pertuzumab caused substantial loss of ADCC activity and reduced antitumor efficacy in a mouse xenograft model. The reduced ADCC function of single hinge-cleaved pertuzumab was restored by a specific AH-mAb. Interestingly, we observed an increase of hinge cleavage of pertuzumab in a combination treatment with trastuzumab. The AH-mAb restored antibody mediated effector function to a mixture of dysfunctional single hinge-cleaved trastuzumab and pertuzumab. **Conclusions:** Our results suggest a therapeutic strategy to restore the immune effector function of the proteolytic inactivated anticancer antibodies in the tumor microenvironment by a protease-resistant version of anti-hinge cleavage site monoclonal antibody (AH-mAb).

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252 **CPRIT Grantee**
Poster Session A

Relative Biological Effect of Proton Therapy in Hypothyroidism *Pablo Yepes, Rice University; D. Mirkovic; R. Mohan; U. Titt; A. Adair*

Introduction: Compared with traditional photon therapy, protons have unique and highly attractive physical properties in that they have a finite range in tissue, high dose at the end of their range and low entrance dose, allowing normal tissues surrounding the tumor target to be spared to a greater degree. However, there is a defensible argument that such potential has not been convincingly demonstrated. This may be attributable to, among other reasons, the assumption that the relative biological effectiveness (RBE) of protons compared to photons, is a constant of 1.1. Many in-vitro and in-vivo studies indicate that RBE is a complex function of dose, linear energy transfer (LET), tissue type, and the endpoint. However, there is very little clinical evidence for variable RBE. In order to bring PT to its full potential a better understanding of its RBE needs to be achieved using clinical data. **Methods:** We have

performed a retrospective study of patients treated with proton therapy, whose thyroid received a significant radiation dose (>20 Gy), and were followed for symptoms of hypothyroidism. The Normal Tissue Complication Probability (NTCP) was calculated as a function of volume and mean dose. The mean Dose was calculated with a Monte Carlo program using a fixed RBE=1.1 and with two models of variable RBE. The obtained NTCP for the three cases were compared with the NTCP obtained for a similar cohort of patients treated with photons. **Results:** The NTCP results obtained for protons with the variable RBE models were closer to the NTCP curve for photons. This suggests that the assumption of a fixed RBE for protons may lead to an underestimate of the dose actually delivered. **Conclusions:** To our knowledge this is one of the first studies where clinical results are utilized to improve our knowledge of the true RBE for proton therapy. It demonstrates that retrospective analysis of clinical outcomes combined with accurate dose calculation could lead to a significant improvement in our understanding of biological characteristics and, eventually, outcomes of proton therapy.

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253 **CPRIT Grantee**
Poster Session B

Direct measurement of a change in biological damage between low and high energy x-ray beams using a novel DNA dosimeter *Kristen McConnell, The University of Texas Health Science Center at San Antonio; X. Li; M. Obeidat; N. Kirby; E. Shim*

Introduction: Published data indicates that low energy x-rays, as compared with higher energy x-rays, have higher relative biological effectiveness (RBE). Conventional detectors for radiotherapy dosimetry are incapable of directly measuring this increase in biological damage. **Methods:** By using a novel DNA dosimeter that uses DNA double-strand breaks (DSB) as the mechanism for dose detection, RBE was directly measured between a low and high energy x-ray beam. Additionally, a mouse neural stem cell line (mNS-5) was used as a biological RBE reference. A DNA dosimeter consisting of magnetic streptavidin beads attached to 4 kilobase pair DNA strands labeled with biotin and fluorescein amidite on opposing ends was created. mNS-5 cells were passaged and cultured in RHB-A media. Both were irradiated over a range of doses in low (160 kVp) and high (6 MV) energy x-ray beams. A RaySafe XI R/F detector was used to verify the dose in the low energy (Faxitron Model 43855F), and OSLD measurements were used to verify dose in the high energy (Varian 600 C/D). Probability of DSB (PDSB) was measured by DNA dosimeters, and survival fraction was computed for the mNS-5 cells. Doses corresponding to the same level of damage (PDSB or SF) between the low and high energy beams were identified and used to calculate RBE. **Results:** For the DNA dosimeter, 6 Gy in the low energy beam produced the same PDSB as 7.2 Gy in the high energy beam, yielding an RBE of 1.20±0.16. For the mNS-5 cells, 6 Gy in the low energy beam produced the same SF as 7.62 Gy in the high energy beam, yielding an RBE of 1.27±0.12. **Conclusions:** Given the RBE agreement, the DNA dosimeter potentially has the capability to directly measure the biological effect of radiation. More refinement and measurements will be performed to confirm these results.

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254 **CPRIT Grantee**
Poster Session A

Novel scoring algorithm for patient specific radiotherapy plan evaluation *Ara Alexandrian, The University of Texas Health Science Center at San Antonio; S. Stathakis*

Introduction: A unique feature of radiation oncology is the ability to visualize how radiation interacts in a patient's anatomy before any dose is administered by integrating intricate beam modeling with CT scans. This feature enables the creation of sophisticated treatment plans, but never answers the question of whether the current treatment plan can be improved to the best possible plan. By providing physicians a metric to evaluate treatment plan performance, it would allow them to empirically ensure radiation oncology patients receive optimal care. A novel scoring algorithm has been developed to quantify how effective a treatment plan has met clinically established standards. **Methods:** Treatment plans are evaluated by analyzing the dose volume histograms of critical structures to see if they meet literature established criteria points. Our scoring algorithm geometrically evaluates the area between the dose volume histograms and a line drawn from max volume to the criteria points to see how well structures are spared. A larger sum of areas between a curve and its criteria points results in a better score than a plan with less area between a curve and its criteria point. The scoring algorithm uses a polygon-based area integration to assess how well the dose distributions meet literature-based dose constrains. After computing an area for all criteria points in all structures, the areas are summed to give a composite score for the treatment plan. **Results:** With our scoring algorithm, we are capable of scoring radiotherapy treatment plans such that a quantized metric provides a more complex indicator of plan quality than previously existed. **Conclusions:** Development of a robust scoring algorithm for treatment plans reduces the uncertainty about whether cancer patients are receiving optimal treatments prior to radiation delivery. In addition to improving treatment plans in the short term, a robust scoring algorithm can improve the standard of care in the long term by training a machine learning algorithm to avoid features from poorly scored past plans in the automation of future plans.

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255 **CPRIT Grantee**
Poster Session B

Digital histopathology and automated learning to interpret chemotherapy response in high-grade osteosarcoma *Patrick Leavey, The University of Texas Southwestern Medical Center; H. Arunachalam; R. Mishra; D. Leonard; A. Sengupta; D. Rakheja; O. Daescu*

Introduction: Response to pre-operative chemotherapy, estimated by histological evidence of necrosis, has been the most important prognostic indicator for patients with non-metastatic osteosarcoma for 3 decades. However, efforts to adjust therapy based on this have to date been unsuccessful. We propose to refine the interpretation of chemotherapy response, utilizing advances in digital imaging and automated learning. **Methods:** Fifty patients diagnosed with high-grade osteosarcoma at Children's Medical Center Dallas between 1995-2015 were identified. Resected specimens after chemotherapy were processed with standard procedures to provide the largest surface area for histology evaluation of tumor response. Using a pre-determined grid, each area within the grid was harvested to produce a single histology glass slide, which was then digitized as whole slide image (WSI). Each WSI allows for viewing across multiple resolutions of up to 40X magnification, while each magnified field is represented by a digital tile. Nine-hundred and forty-two histology slides (mean 19 slides/patient; 4-51 slides) were digitized. From a selected set of 40 WSIs, representing features of viable tumor (VT), necrotic tumor (NEC) and areas of non-tumor (NT), 1,144 feature tiles at 10x magnification were randomly identified for annotation, segmentation and development of automated learning algorithms. Annotation was performed by two pathologists, classifying tiles and areas within tiles into VT, NEC and NT areas, using a purpose-built tool. As an initial validation step, both machine learning and deep learning neural networks were trained with these 1,144 tiles. **Results:** Unsupervised deep learning neural network modeling identified VT regions with 92% accuracy, necrotic regions with 90% accuracy and NT with an accuracy of 95%. Supervised classical machine learning methods using support vector machines resulted in an average accuracy of 89.9% with per class accuracy of 91% for VT, 87% for NEC and 91% for NT. **Conclusions:** We have completed the 1st step in validating an automated learning tool to refine the interpretation of chemotherapy response in osteosarcoma. In the next phase, we will continue to optimize automated learning and interrogate tumor features from all 942 WSIs. We will compare this output to the chemotherapy response estimate by two pathologists blinded to each other's estimation of necrosis and to the clinical value generated at the time of surgery.

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256 **CPRIT Grantee**
Poster Session A

Targeting Barrett's stem cells to preempt esophageal adenocarcinoma *Marcin Duleba, University of Houston; J. Xie; Y. Zhang; R. Mahalingam; S. Wang; R. Nupane; K. Goller; W. Rao; C. Stephan; K. Ho; J. Ajani; P. Davies; W. Xian; F. McKeon; W. Kern*

Introduction: Three million Americans have a condition known as Barrett's esophagus ("Barrett's"), a precancerous metaplastic lesion that can progress, through low- and high-grade dysplasia, to highly lethal esophageal adenocarcinoma. Current standard-of-care for Barrett's patients includes arduous and expensive endoscopic monitoring for the detection of dysplasia, as well as non-specific physical ablation of these lesions using radiofrequency ablation (RFA) or endoscopic mucosal resection (EMR), both of which are arduous, expensive, and plagued by variable rates of recurrent disease. We have employed advanced stem cell cloning technologies to capture patient-matched sets of stem cells of Barrett's and adjacent esophageal epithelia, and have now adapted these stem cells to 384-well formats for high-throughput screening of small molecule libraries in an effort to identify ones that selectively eliminate Barrett's lesions for preemptive therapeutics. **Methods:** Patient-matched stem cells of Barrett's, esophageal, and gastric epithelia were cloned at the single cell level from 1mm endoscopic biopsies and propagated is individual cell lines (Wang et al., 2015; Yamamoto et al., 2016). After characterization by whole genome expression analysis, 3-D differentiation, and epigenetics profiling, these stem cells were grown as colonies in 384-well formats for identifying known and drug-like small molecules that selectively eliminate Barrett's stem cells. **Results:** The screening platform comparing patient-matched stem cells of Barrett's and esophageal epithelia is robust and yields highly reproducible results (Z-factor 0.89). We have identified a number of known and experimental drugs that eliminate Barrett's stem cells at concentrations far below those

affecting normal esophageal stem cells, and many of these cluster into several discrete bins of chemical and functional similarity. In our co-culture models of Barrett's and esophageal stem cells, these drugs selectively eliminate Barrett's while enabling repair by the unaffected esophageal stem cells. These data have now been extended to five additional Barrett's cases that behave is a similar manner in response to these drugs and drug candidates. **Conclusions:** We have successfully adapted ground state stem cells of Barrett's and normal surrounding tissue to high-throughput drug screening and have identified multiple lead compounds that selectively eliminate Barrett's stem cells in this format and in co-culture models of Barrett's and esophageal epithelia. We are presently analyzing compounds from different functional classes for synthetic lethal effects to optimize a potential therapeutic regimen that could specifically eliminate Barrett's and dysplastic Barrett's to enable repair by adjacent normal epithelia.

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257 **CPRIT Grantee**
Poster Session B

Novel strategies for preempting colorectal cancer in inflammatory bowel disease *Yutao Qi, University of Houston; W. Xian; Y. Yamamoto; R. Mahalingam; R. Neupane; S. Wang; M. Duleba; A. Liew; H. Chen; Y. Zhang; W. Rao; M. Estecio; M. Vincent; J. Hou; K. Ho; F. Sylveste; J. Hyams; F. McKeon*

Introduction: Of the 1.5 million Americans with inflammatory bowel disease (IBD), approximately 200,000 will die of an unusual form of colorectal cancer (CRC) that is both multifocal and enormously difficult to detect. As IBD is the key risk factor for this type of CRC, efforts to mitigated IBD itself, though metadata with IBD therapies such as purine analogs and TNF-alpha inhibitors do not support a "chemoprevention" property of these drugs. Using advanced stem cell cloning technologies, we have discovered that patients with IBD possess two types of colonic stem cells including normal ones seen in patients without IBD and one marked by potentially pathogenic features. This novel, IBD-associated colonic stem cell expresses a hyperinflammatory gene signature, shows defective barrier function upon differentiation, and is 100-fold more sensitive to the toxins of C. difficile, a bacterium linked to nosocomial cases of diarrhea. We have adapted IBD patient-matched normal and pathogenic stem cells to a 384-well screening format to identify drugs that might selectively eliminate the pathogenic stem cells and the risk they present for CRC in patients with IBD. **Methods:** Stem cell clone libraries are generated from endoscopic biopsies of terminal ileum, colon, and rectum of patients with Crohn's and ulcerative colitis as well as control patients without IBD. Stem cells are grown on irradiated 3T3 cells in media that maintains their ground state in procedures we previously described (Wang et al., 2015; Yamamoto et al., 2016). **Results:** The patient-matched normal and IBD-linked stem cells yield highly reproducible data from differential drug screens of various bioactive, experimental, and drug-like small molecule libraries. We are presently leveraging combinations of C. difficile toxins and small molecules at very low concentrations in efforts to identify optimal synthetically lethal therapeutics directed at the aberrant stem cell that likely drives both the IBD and the CRC that arises in patients with these conditions. Initial screens of these candidates on these patient-matched stem cells sensitized with very low concentrations of C. difficile toxins show synthetic lethality toward the IBD-linked stem cells at very low concentrations of candidate small molecules. **Conclusions:** High rates of CRC in IBD patients remain an unsolved medical need. We have discovered epigenetically altered mucosal stem cells in IBD patients that likely underlie this disease, as well as small molecule and biological drugs that eliminate them selectively while sparing stem cells with normal phenotypes from the same patient.

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258 **CPRIT Grantee**
Poster Session A

FDA-approved Drugs Inhibit Oncogenic RUNX1-ETO in Acute Myeloid Leukemia with Chromosome Translocation t(8;21) *Yongcheng Song, Baylor College of Medicine; L. Lu; Y. Wen; Y. Yao; F. Chen; G. Wang; F. Wu; J. Wu; P. Narayanan; M. Redell; Q. Mo*

Introduction: Acute myeloid leukemia (AML) is a major blood cancer with poor prognosis. New therapies are needed to target oncogene driven leukemia stem cells, which account for relapse and resistance. Chromosome translocation t(8;21), which produces RUNX1-ETO (R-E) fusion oncoprotein, is found in ~13% AML. R-E dominant-negatively inhibits global gene expression regulated by RUNX1, a master transcription factor for hematopoiesis, causing increased self-renewal and blocked cell differentiation of hematopoietic progenitor cells, and eventually leukemia initiation. **Methods:** Bioinformatics methods followed by biological activity testing were used to find compounds that can inhibit R-E mediated gene expression. Molecular biology studies were conducted to find a possible molecular mechanism. **Results:** Connectivity-Map was used to find candidate compounds that can alter gene expression pattern as R-E knockdown does in t(8;21) AML. It yielded 78 compounds showing selective activity against Kasumi-1 cells. The most active compounds are several FDA-approved drugs showing low nM activity against R-E leukemia including primary cells from t(8;21) AML patients as well as >1000-fold selectivity. These compounds are non-cytotoxic. Rather, they inhibited the R-E mediated gene expression and reactivated that of RUNX1, which caused significant differentiation and apoptosis. Particularly noted are potent activities (as low as 2 nM) against self-renewal of R-E containing leukemia initiating cells and strong synergy when combined with cytarabine and doxorubicin. One compound showed potent antitumor activity in a mouse model of R-E leukemia. We also found the protein target of these drugs associates with RUNX1, but not R-E. Such interaction increased RUNX1's binding affinity and capacity to DNA and switched to a RUNX1 dominance in R-E containing leukemia cells. This is therefore a targeted therapy. **Conclusions:** Favorable human PK, highly potent and selective activities of these drugs as well as synergism in combination therapies strongly support that these drugs could be used in the clinic to treat AML with t(8;21) chromosome translocation.

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259 **CPRIT Grantee**
Poster Session B

Dihydroceramide increase precedes golgi dispersal, pro-survival autophagy, ER stress, and UPR in fenretinide + safingol treated neuroblastoma cells *Nikhil Vad, Texas Tech University Health Sciences Center; D. Wang; H. Cho; D. Verlekar; C. Linch; C. Reynolds; M. Kang; B. Maurer*

Introduction: We have reported that fenretinide (4-HPR) is active against high-risk neuroblastoma (NB) in vitro and in vivo; our Phase I trials of novel 4-HPR formulations evidenced clinical activity. Mechanisms of activity include increase of cytotoxic dihydroceramides. Fenretinide activity in vitro is enhanced by safingol (S), the L-threo diastereomer of sphinganine. Here, we identify stress pathways activated in response to 4-HPR±S and identify ixazomib, a proteasomal inhibitor, and antimalarial, mefloquine, a disruptor of autophagy, as new potential synergizing agents for 4-HPR±S. **Methods:** Sphingolipids were assessed by LC/MS/MS; cytotoxicity by fluorescence-based plate assay in 2% and 5% oxygen; apoptosis by TUNEL assay. Organelles, ER stress markers, unfolded protein response (UPR), and autophagy, were assessed using immunoblotting, immunoprecipitation, and electron/confocal microscopy. Target validation was by gene silencing. **Results:** 4-HPR rapidly increased D-erythro-dihydroceramides; safingol was catabolized to L-threo-dihydroceramides. Safingol (2-3 μM) caused multi-log cytotoxic synergy of 4-HPR in eight of ten GBM and five NB cell lines (CI<0.7). Treatments resulted in golgi fragmentation (+6-12h) without decrease of stack proteins, GM-130, α-Mannosidase-II, and TGN-38, and preceded increase of ER stress transducer, GRP78, critical for manifestation of unfolded protein response (UPR) and pro-apoptotic CHOP protein; UPR was evidenced by increase of poly-ubiquitinated proteins and increased autophagic flux (+12-48h). Cell death was apoptotic (cleaved caspase-3/PARP; TUNEL-positive) and non-apoptotic (caspase-independent)(+12-48h). Disruption of autophagy by mefloquine, or siRNA-silencing of BECN1 or ATG7, temporally-accelerated cytotoxicity and increased total apoptosis ($p<0.05$) in GBM cells. Consistent with cytotoxicity being dependent on misfolded protein stress, Ixazomib further increased ER stress markers and accelerated/increased cytotoxicity ($p<0.05$). Treatment produced early inhibition (+4h) of tyrosine phosphorylation of p97/VCP, an AAA^+-ATPase critical for the fusion of transitional ER membrane vesicles into golgi stacks. Knockdown of p97/VCP recapitulated features of 4-HPR±S treatment, including golgi fragmentation and increase of ubiquitinated proteins and autophagic vacuoles. Treatment with D-erythro-sphinganine plus dihydroceramide desaturase inhibitor, GT-11, plus safingol increased both D-erythro and L-threo-dihydroceramides and recapitulated morphological, biochemical, and cytotoxic effects. **Conclusions:** Delineation of response pathways allowed the identification of mefloquine and ixazomib as new potential co-drugs to synergize 4-HPR±S. Confirmatory studies in NB xenografts are in progress. Intravenous fenretinide is in a CPRIT-supported, registration-enabling, Phase 2 trial in PTCL. An adult Phase I trial of fenretinide + safingol is in progress in the South Plains Oncology Consortium.

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260 **CPRIT Grantee**
Poster Session A

Cancer vaccine formulation dictates synergy with CTLA-4 and PD-L1 checkpoint blockade therapy *Yared Hailemichael, The University of Texas M.D. Anderson Cancer Center; W. Overwijk*

Introduction: Therapeutic blockade of the checkpoint receptors, cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), on T cells can cure patients with metastatic cancer. However, many patients do not experience clinical benefit and significant hurdles remain in increasing checkpoint blockade therapeutic benefit. Anti-cancer vaccination is a promising approach to increase the efficacy of checkpoint blockade therapies. However, the landmark FDA registration trial for anti-CTLA-4 therapy revealed a complete lack of benefit of

adding vaccination with gp100 peptide formulated in Incomplete Freund's Adjuvant (IFA)[1]. Thus, it is currently unclear how to combine anti-CTLA-4 or by extension anti-PD-1/ anti-PD-L1 with vaccination. We recently reported[2] that vaccination with gp100 peptide in IFA creates a persisting antigen depot that primes antigen-specific CD8+ T cells, followed by their undesirable sequestration at the vaccination site, and eventually their exhaustion and apoptosis, resulting in negligible anti-tumor activity. **Methods:** To understand the mechanism by which vaccination failed to synergize with checkpoint blockade therapy, we studied the widely used standard treatment model of anti-CTLA-4 therapy of established subcutaneous B16 melanoma[3] and added concurrent vaccination with gp100/IFA together with adoptively transferred transgenic TcR pmel-1 T cells that specifically recognize the gp100 melanoma. For a more comprehensive assessment of anti-CTLA-4 and vaccine activated CD8+ T cells (Teffs), we included CD44, CD11a and CD8 to better quantify their number and survey their localization at the tumor and vaccination site. **Results:** Here, we show that gp100 vaccination induces gp100-specific Teff which dominantly force trafficking of anti-CTLA-4-induced, non-gp100-specific Teff cells away from the tumor, reducing tumor control. The inflamed vaccination site subsequently also sequesters and destroys the systemic pool of anti-CTLA-4 induced Teff with specificities for tumor antigens other than gp100, reducing the anti-tumor efficacy of anti-CTLA-4 therapy. Mechanistically, Teff at the vaccination site recruited inflammatory monocytes, which in turn attracted additional Teff in a vicious cycle mediated by IFN-g, CXCR3, ICAM-1 and CCL2. This process was dictated by the specific vaccine formulation, and altering the vaccine formulation prevented the inflammatory cascade and resulted in potent synergy with both anti-CTLA-4 and anti-PD-L1 checkpoint blockade. **Conclusions:** In conclusion, gp100/IFA vaccination induces an inflamed vaccination site that recruits, functionally impairs and eventually destroys tumor-specific Teff induced by anti-CTLA-4 checkpoint blockade therapy whereas a non-persistent vaccine formulation can reverse the undesirable effect of the persistent vaccine formulation and synergizes with anti-CTLA-4 and/or anti-PD-L1 therapies, resulting in significantly improved anti-tumor activity.

261 **CPRIT Grantee**
Poster Session B

GSK3-beta regulates epithelial-mesenchymal-transition and cancer stem cell properties in triple-negative breast cancer *Rama Soundararajan, The University of Texas M.D. Anderson Cancer Center; G. Vijay; M. Toneff; J. Chang; J. Rosen; S. Mani*

Introduction: Triple-negative breast cancers (TNBCs), which lack receptors for estrogen, progesterone, and amplification of epidermal growth factor receptor 2, are highly aggressive. Consequently, patients diagnosed with TNBCs have reduced overall- and disease-free survival rates compared to patients with other subtypes of breast cancer. TNBCs are characterized by the presence of cancer cells with mesenchymal properties, indicating that the epithelial-to-mesenchymal-transition (EMT) plays a major role in the progression of this disease. The EMT program has also been implicated in chemoresistance, tumor recurrence, and induction of cancer stem cell (CSC) properties. Currently, there are no targeted therapies available for TNBC. This study was hence focused on identifying novel EMT targets to treat TNBC. **Methods:** We analyzed published patient gene expression databases to identify EMT-associated genes predictive of poor clinical outcome in TNBC. We also simultaneously conducted a high throughput drug screen to select compounds that could serve as modifiers of novel therapeutic targets for TNBC, and shortlisted GSK3-beta inhibitors for further studies. Using drug sensitivity assays, we tested both epithelial and mesenchymal breast cancer cells for preferential loss of viability towards GSK3-beta inhibitors. We next profiled these cell populations for surface CSC markers ($CD44^{hi}/CD24^{lo}$, FACS) and functional mammosphere-forming ability, to test if GSK3-beta inhibitors selectively affect CSCs. We also tested the ability of GSK3-beta inhibitors to alter the EMT-related migratory properties of mesenchymal breast cancer cells (using wound-healing assays), as well the expression of mesenchymal markers (by immunoblotting). **Results:** We observed that enhanced expression of GSK3-beta, a ubiquitous serine-threonine kinase known for regulating the Wnt signaling pathway, correlated with poor overall patient survival. We concurrently identified the GSK3-beta inhibitor in our drug screen as one of the most potent inhibitors of EMT, supporting our clinical observation. We found that GSK3-beta inhibitors selectively kill breast cancer cells with mesenchymal attributes, while sparing cells with epithelial properties. Furthermore, GSK3-beta inhibitors decreased both the CSC properties of mesenchymal cells, as well as the expression of mesenchymal markers. Inhibition of GSK3-beta also reduced EMT-related migratory properties of mesenchymal breast cancer cells. **Conclusions:** Our data demonstrate that GSK3-beta is a novel target for CSC-enriched TNBCs, and that GSK3-beta inhibitors may serve as selective inhibitors of EMT and CSC properties for the treatment of aggressive TNBC.

262 **CPRIT Grantee**
Poster Session A

Spinal Nerve Tolerance to Single-Session Stereotactic Ablative Radiotherapy *Paul Medin, The University of Texas Southwestern Medical Center; B. Hrycushko; L. Phillips; J. Sayre; R. Foster; A. Van der Kogel*

Introduction: Stereotactic ablative radiotherapy (SAbR) is a rapidly expanding treatment modality utilized for an increasing number of cancers. The radiosensitivity of healthy normal tissues, including neural structures, is poorly understood in the setting of SAbR. In recent years, numerous cases of peripheral neuropathy following SAbR have been published. A better understanding of tolerated dose limits is critical to avoid overestimation, thus prescribing radiation doses that will lead to catastrophic normal-tissue injury, or underestimation resulting in lower prescription doses that are less likely to ablate tumors. A study is underway to define the dose-related incidence of neuropathy resulting from single-session SAbR to the spinal nerve using a porcine model. **Methods:** To date, 25 Yucatan minipigs have been entered into this study. Each animal has received CT and MRI scans for treatment planning followed by single-session SAbR using an image-guided, 6MV linear accelerator. A 1.5cm length of the left-sided C6, C7 and C8 spinal nerves was targeted. Animals were distributed into 5 dose groups receiving 16(n=7), 18(n=5), 20(n=5), 22(n=5) or 24(n=3)Gy. The neurologic status of all animals is being followed by electrodiagnostic exam (-1, 2, 10, 20, 30, and 50 weeks) and daily observation of gait. Currently, all animals have been followed until gait change or a minimum 46 weeks after irradiation. Animals will continue to be evaluated with electrodiagnostic exams and gait observation until gait change occurs or the 52-week maximum followup period is reached. Histopathologic examination has been performed on the irradiated spinal nerves and the corresponding unirradiated contra-lateral nerves of 16 pigs. **Results:** To date, a change in gait has been observed in animals that were in the 18(n=2/5),20(n=5/5), 22(n=5/5), and 24(n=3/3) Gy dose groups presenting a clear dose-response curve. Affected animals presented with a limp in their left front limb and electromyography demonstrated evidence of denervation in C6 and C7 innervated muscles. Deficits were first observed 9-15 weeks following irradiation. All symptomatic pigs had demyelination and fibrosis in their irradiated nerves while contralateral nerves and spinal cord were normal. **Conclusions:** The neurologic deficits observed following spinal nerve irradiation have occurred at the same dose levels and latency periods as observed in our previous study of spinal cord tolerance; however, spinal nerves were irradiated along with the spinal cord in our previous study. We conclude that the tolerance of the spinal nerve must be less than or equal to the tolerance of the spinal cord.

263 **CPRIT Grantee**
Poster Session B

SHP2: sailing against tumor-mediated inhibition of chimeric antigen receptor T-cell therapy *Khaled Sanber, Baylor College of Medicine; D. Landi; C. Lee; L. Brunetti; M. Mukherjee; N. Ahmed; M. Hegde*

Introduction: A phase I study of autologous HER2-specific chimeric antigen receptor (CAR) T-cells for progressive glioblastoma (GBM) demonstrated an excellent safety profile and tumor regression/stabilization in 8/16 evaluable patients resulting in improved median survival. However, GBM is highly immunosuppressive and can dampen the effector function of CAR T-cells by exploiting multiple co-inhibitory pathways. While concurrent immune-checkpoint blockade using monoclonal antibodies may improve the anti-GBM activity of CAR T-cells, the unreliable pharmacokinetics of antibodies in the CNS remains a challenge. Therefore, our lab attempted to convert the native PD-1/PD-L1 inhibitory signal into a stimulatory one by expressing PD-1 fusion molecules (native PD1 extracellular domain linked to a stimulatory intracellular domain: 41BB or CD28) in HER2 CAR T-cells (Landi et al., SITC 2016). These HER2-CAR/PD-1-fusion T-cells exhibited improved effector functions and anti-tumor activity. Subsequent evaluation of the immune synapses using confocal microscopy revealed decreased recruitment of SHP2 and decreased negative microcluster formation. This is in line with the known role of SHP2 in multiple co-inhibitory signaling pathways (PD-1, CTLA-4, BTLA, LAG3). Thus, SHP2 antagonism may ameliorate the tumor-induced functional exhaustion of CAR T-cells. **Methods:** The CRISPRscan online tool was used to identify potential CRISPR/Cas9 target sequences within the PTPN11 (SHP2-encoding gene) exon sequence and design corresponding oligonucleotides. Target sequences with the least possible number of predicted off-target events were selected based on two published algorithms. The microhomology-based CRISPR RGEN online tool was used to determine the target sequences with high likelihood of creating out-of-frame insertions/deletions at the CRISPR/Cas9 cleavage site via the error-prone non-homologous end joining. The oligonucleotides encoding the 20 nucleotide target sequences were then incorporated into the gRNA scaffold derived from the PX458 plasmid (Addgene #48138) using a PCR-based method. The resulting DNA template was purified

and in-vitro transcribed to synthesize the individual gRNAs. The resulting gRNAs were purified in preparation for their electroporation into T-cells expressing a clinically-utilized, second-generation HER2-CAR (CD28ζ-endodomain) with or without the PD1 fusion molecules. **Results:** We synthesized five gRNAs targeting distinct PTPN11 exons that are involved in SHP2 localization and enzymatic activity. The purified gRNAs will be electroporated singly or in pairs into HER2-CAR only and HER2-CAR/PD-1 fusion T-cells for comparative functional and mechanistic studies. **Conclusions:** SHP-2 knockout may facilitate targeting multiple inhibitory pathways to counteract tumor-induced exhaustion of CAR T-cells and improve their anti-tumor activity. Our methodology will also allow us to investigate the fundamental mechanisms of CAR-mediated signaling and their effect on T-cell function.

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264 **CPRIT Grantee Poster Session A**

Size-Dependent Heating of Magnetic Iron Oxide Nanoparticles *Sheng Tong, Rice University; G. Bao*

Introduction: Magnetic iron oxide nanoparticles (MIONs) have great potential as an effective clinical thermal modality in cancer hyperthermia, thermoablative therapy, and controlled drug delivery. Upon exposure to an alternating magnetic field (AMF), MION can convert magnetic energy into thermal energy. The efficiency of energy conversion, i.e., heating efficiency, is determined by the magnetic relaxation of MION with respect to the applied AMF. A major challenge in the applications of MION-based heat induction is the low heating efficiency of commercially available MIONs. To this end, we investigated the heating of superparamagnetic and ferromagnetic MIONs in a set of clinically relevant AMF. Experimental measurements of the magnetic properties and the heating efficiency of MIONs were compared with theoretical analysis based on a dynamic hysteresis model to gain insight into the mechanisms leading to efficient heat induction. **Methods:** Magnetite nanocrystals were synthesized by thermodecomposition of Iron acetylacetonate. The DC and AC susceptibilities of the nanocrystals were measured using a superconducting quantum interference device (SQUID). Water-dispersible MIONs were obtained by coating the nanocrystals with DSPE-PEG copolymers using a dual solvent exchange method. For heat induction measurements, MIONs were exposed to an AMF generated with an inductive coil for 90 seconds under close-to-adiabatic conditions. The specific absorption rate of MIONs was calculated from the temperature slope. Numerical analysis of the heat induction was performed with a Matlab program developed in the lab. **Results:** 8 batches of uniform magnetite nanocrystals were synthesized with the average size increasing from 6 to 40 nm. The nanocrystals from 6 to 15 nm and from 19 to 40 nm exhibited typical superparamagnetic and ferromagnetic properties respectively in the room temperature micro hysteresis. MIONs with large sizes (> 19 nm) have significantly higher specific absorption rate (SAR) than that predicted by the widely used linear theory of magnetic fluid heating. The heating efficiency of MIONs in both the superparamagnetic and ferromagnetic regimes increased with size, which can be accurately characterized with a modified dynamic hysteresis model. The 40 nm ferromagnetic nanoparticles have an SAR value approaching the theoretical limit under a clinically relevant AMF. An in vivo study further demonstrated that the 40 nm MIONs could effectively heat tumor tissues at a minimal dose. **Conclusions:** This study elucidates the size-dependence of superparamagnetic and ferromagnetic iron oxide nanoparticles in clinically relevant AMF and provides the guidance for implementing clinical thermal therapies with minimal AMF exposure and optimal dosage of MIONs

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265 **CPRIT Grantee Poster Session B**

Designing realistic microfluidics devices for modeling micro-vascular flow *Jiaming Guo, University of Houston; P. Ruchhoeft; J. Slater; D. Mayerich*

Introduction: Realistic models of microvascular networks are important for understanding tissue structure and function. This is particularly true in tissue samples, such as tumors, that are highly vascularized and unstructured. Since a strong microvascular component is seen in many diseases, there is an unmet need for microvascular models that accurately portray what occurs in vivo during normal tissue development and disease progression. Advances in microfabrication techniques that allow imaging microvessels and modeling them in hydrogels have opened the door to analyzing microvascular flow and behavior in developing or diseased tissue. **Methods:** We first collect a three-dimensional image of a mouse brain microvascular system at sub-micrometer resolution using KESM. We then select a region of interest (ROI) that will be used to build a microfluidics model. This ROI is segmented in order to extract the microvascular structure and connectivity. We then allow the user to specify the desired network flow, based on prior information, such as in vivo measurements taken at subregions in the network. A simplified flow model is used to extrapolate flow properties throughout the network. We then augment the reconstructed network with additional connections that force all terminating fibers to converge to a single input and output. **Results:** We compare our simulation results with CFD simulation results using SimScale and COMSOL Multiphysics v5.3 software. We start from 2D models for a better visualization and then 3D models for more practical demonstrations. The CFD simulation results match our simulation results in predicting flow directions. It also demonstrates that we can control flow characteristics in the ROI network. In addition, quantitative comparison demonstrates that the proposed simulation method succeeds in computing the velocity and pressure field across the whole network. **Conclusions:** In this project, we develop software for simulating and visualizing flow in microvascular networks. We've demonstrated that our microvascular model has a high level of flow predictive capability based on comprehensive CFD models. This opens the door to creating realist microfluidics models of microvascular flow representative of any sample network imaged with sufficient resolution. This can be used to study nutrient diffusion within developing tumors, as well as the behavior of cancer metastases within localized regions or normal tissue.

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266 **CPRIT Grantee Poster Session A**

Computer-implemented predictive model of hepatocellular carcinoma response to sorafenib *Rony Avritscher, The University of Texas M.D. Anderson Cancer Center; D. Fuentes; N. Muñoz; R. Bouchard; K. Michel; A. Cortes; H. Taghavi; J. Bankson*

Introduction: Sorafenib is the only approved systemic therapy for advanced hepatocellular carcinoma (HCC). Disease control rate is achieved in less than 50% of advanced HCC patients, while nearly 10% experience grade 3-4. Therefore, imaging biomarkers are needed to identify patients most likely to respond to sorafenib therapy. The purpose of this study is to correlate multiparametric MR imaging with histopathological features of tumor response using a computer-implemented predictive model. This work quantifies MR imaging parameters and pathology correlations in a HCC rat model treated with sorafenib. Correlations of characteristic tissue hypoxia and nuclear crowding pathology features with MRI enable a non-invasive 'virtual biopsy' for understanding HCC response to sorafenib. **Methods:** Rat hepatoma McA-RH7777 cells were orthotopically implanted in the liver of 22 male Buffalo rats, and, after 2 weeks, the animals were assigned to receive 7.5mg/kg of sorafenib daily for 2 weeks (n=12) or to remain untreated (n=10). MR Imaging at 4.7T was performed weekly, including anatomic, dynamic contrast-enhanced (DCE) and blood oxygenation level-dependent (BOLD) sequences. Pathology was co-registered with imaging using anatomical landmarks. Pimonidazole, a biomarker of tissue hypoxia, and Hematoxylin and Eosin (H&E) staining were segmented using Gaussian mixture model to identify hypoxia, viable, and necrotic tissue, respectively. Tumor heterogeneity on pathology was quantified using the entropy of the hypoxic, viable, and necrotic tissue. The Maurer distance of each tissue type was computed to characterize the necrotic core and hypoxic regions relative to the HCC tumor boundary. **Results:** The untreated group showed significantly lower entropy of the necrotic tissue compared to the treatment group ($p<0.05$). Additionally, the distance of the hypoxic tissue in the treatment group was closer to the tumor boundary than in the control group ($p=0.1$). Entropy in the pathology staining was also strongly correlated with T2star imaging but weakly correlated with BOLD effect ($r=29$). **Conclusions:** Our initial findings demonstrate the feasibility of establishing quantitative correlations of imaging and histopathology in this HCC rat model. Significant differences in entropy between groups can be used to evaluate treatment effect. Our analytical modeling platform has the potential to help predict response to sorafenib.

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267 **Poster Session B**

Engineered Fc variant for the enhanced pharmacokinetics *Chang-Han Lee, The University of Texas at Austin; T. Kang; M. Watanabe; G. Georgiou*

Introduction: Therapeutic monoclonal antibodies (mAbs) have been successfully demonstrated in clinics and are now widely used for the treatment of a variety of diseases such as cancer, autoimmune diseases and infectious diseases. There have been several attempts to improve the therapeutic effect of antibodies. One of the representative methods is to obtain an improved therapeutic effect by manipulating the Fc domain of the antibody against the Fc neonatal receptor (FcRn) to improve the pharmacokinetics (PK) of the antibody in the body. **Methods:** IgG-Fc domain library was displayed on the inner membrane of E.coli using APEXs technique. And the Fc library was screened with single chain FcRn and the isolated Fc variants were characterized their binding properties for FcRn by ELISA and SPR. Next, the pharmacokinetics of Fc variants were evaluated in human FcRn transgenic mice. **Results:** We examined the pH-dependent FcRn binding properties of DHS using SPR and ELISA. As results, DHS preserved the pH-dependent FcRn-binding properties of EDHS, similar KD values (111 ± 20 nM) at endosomal pH 5.8 with EDHS

and neglectable binding response for dFcRn at pH 7.4. In order to detect the weak binding activities of antibody variants to FcRn at physiological pH 7.4, SPR experiments with three different densities of scFcRn, 500 RU (low density), 2,000 RU (medium density), 4,000 RU (high density), were performed. DHS showed a non-detectable response to high density scFcRn as well as WT. DHS also showed equivalent antibody-dependent cellular cytotoxicity (ADCC) by PBMC and antibody-dependent cellular phagocytosis (ADCP) by M1-macrophage activities in Her2-positive SK-BR3 cancer cells comparing with WT. Serum clearance of antibody variants harboring the engineered Fcs were tested in hemizygous human FcRn transgenic mice (Tg276) to investigate whether the differences observed in the in vitro pH-dependent binding with scFcRn correlated with improved pharmacokinetics. DHS exhibited β phase T1/2 (dissociation half-life) of 336 hours, approximately 6.8-fold longer than wild type IgG. **Conclusions:** Here, we report DHS, an engineered Fc variant with higher affinity to FcRn at endosomal pH and lacking affinity for the high density FcRn at neutral pH and a longer serum half-life than WT and LS in human FcRn transgenic mice.

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Pre-Clinical Evaluation of Cinobufotalin as a Potential Anti-Ovarian Cancer Agent *Syeda Afroze, Texas A&M University System Health Science Center; A. McDowell; D. Dean; S. Henderson; V. Speights; T. McCormick; T. Kuehl; M. Uddin*

Introduction: Cinobufotalin (CINO), a cardiotonic steroid (CTS) or bufadienolide, is extracted from the skin secretions of the traditional Chinese medicine giant toads (Chan su). Recently it has been demonstrated that CINO inhibits lung and ovarian cancer cell function. In this study, we evaluated the molecular mechanism of CINO by which it inhibits ovarian cancer cell function by utilizing three ovarian cancer cells; SK-OV-3, CRL-1978 and CRL-11731. We also performed CRL1978 tumor xenograft model in nude mice and evaluated whether CINO inhibits the tumor growth. **Methods:** Each Cell lines were treated with different concentrations of CINO (0.1, 1, 5 and 10 μM). For each cell line cell proliferation, migration and invasion were measured by using a CellTiter Assay (Promega), Cytoselect Assay (Cell Biolabs) and by using a FluoroBlock Assay (BD) respectively. Proliferating Cell Nuclear Antigen (PCNA) was also evaluated in cell lysates of CINO treated these 3 ovarian cancer cells by western blot analysis. Cell Cycle arrest and Cell viability were determined by fluorescence-activated cell sorting (FACS) analysis. We also performed Annexin V staining on CINO treated these 3 ovarian cancer cell lines by immunofluorescence to evaluate the pro-apoptotic protein expression and mitochondrial membrane potential (MMP) has also been measured using MMP kit utilizing FACS analysis. Male nu/nu mice were injected with CRL-1978 cells. When tumor volumes are measured at approximately 200–300 mm3, treatment with CINO was initiated. Upon completion of treatment mice were monitored for up to a week before euthanasia, xenografts were excised, then measured, weighed, and preserved. The sections were observed by microscopic examination. **Results:** Concentration of CINO at 0.5μM inhibit SK-OV-3, CRL-1978, and CRL-11731 cells proliferation, migration and invasion without cell death and loss of cell viability. Each cell lines differ in response to CINO doses for PCNA expression as well as Annexin V pro-apoptotic protein expression. CINO decreases mitochondrial membrane potential for SK-OV-3 but not for CRL-1978 and CRL-11731. A statistically significant decrease ($p<0.05$) in tumor size was observed after treatment with both 1 and 5 mg/kg concentrations of CINO when compared to vehicle. **Conclusions:** CINO is cell specific, as each cancer cell line responds differently. These data demonstrate that the mode of action of CINO is different on these 3 types of ovarian cancer cells. Treatment with Cinobufotalin inhibits the growth of Clear cell ovarian cancer cell line CRL-1978. This model is a valid testing platform for additional tumor cell cultures.

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269 **Poster Session B**

The correlation of biological effects and physical parameters in proton therapy *Fada Guan, The University of Texas M.D. Anderson Cancer Center; L. Bronk; M. Kerr; D. Ma; X. Wang; N. Sahoo; R. Mohan; D. Grosshans*

Introduction: The relative biological effectiveness (RBE) of protons to reference photons currently used in clinic is assumed to be 1.1, regardless of physical characteristics of proton beams and target cell types. However, recent biological experiments have indicated the spatial variety of RBE. Therefore, it is imperative to find the correlation of biological effects with physical parameters in proton therapy. The knowledge gained from this line of study will facilitate the introduction of biologically-optimized proton therapy into the clinic to increase the therapeutic index. **Methods:** We have designed a versatile irradiation system to investigate the biological effects of protons with different physical parameters along a pristine Bragg curve. We used an 81.4 MeV scanning proton beam to irradiate H460 lung cancer cells cultured in 96-well plates. Two sets of cell irradiation experiments have been performed: the clonogenic survival versus physical dose and LET, and the DNA double-strand break (DSB) induction (quantifying the established DSB marker 53BP1) versus the spatial ionization density. We used Monte Carlo toolkit Geant4 to calculate the dose and LET in cell layers. We used the track-structure Monte Carlo package Geant4-DNA to model the detailed interactions (ionization and excitations, etc.) of particles with cell layers. **Results:** The clonogenic survival data showed the variation of RBE as a function of LET. From the entrance to Bragg peak the proton RBE increases slowly from 1.0 to 1.3 at the surviving fraction of 0.1, corresponding to the LET from 0.9 to 10.6 keV/μm. In the distal edge, the RBE increases sharply from 1.5 to 2.8 with the LET from 12.1 to 18.0 keV/μm. The foci data of 53BP1 were normalized to obtain the average number of foci per nucleus per ionization at different time points post-irradiation. For column #1 in the entrance area of a Bragg curve, the spatial ionization density is 42.0 per incident proton per micron, and the average number of foci per nucleus per ionization is 1.58E-12 ± 1.23E-13 at 24 hours post irradiation. For column #7 at Bragg peak, the corresponding values are 335.7 and 4.58E-12 ± 1.23E-13. For column #12 in the distal edge of a Bragg curve, the values are 543.4 and 1.31E-11 ± 3.55E-13. **Conclusions:** The clonogenic survival data show a non-linear relationship between proton RBE and LET. The foci data of 53BP1 show that DNA damage has a strong dependence on the spatial ionization density and increases in a non-linear trend as well.

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Laser-induced Metallic Poly(Methyl Methacrylate) Nanoparticle: In Vitro Biofluid Model Informs Nanoparticle Design and In vivo Biomolecule Interaction *Yelixza Avila, University of North Texas; D. Korir; D. Simmons; M. Omary*

Introduction: Design, engineering, synthesis and characterization studies provide a suite of approaches to probe the use of nanoparticles (NP) in therapeutic applications, such as for targeting specific cancer cells. Near Infrared Metallic Nanoparticles (NIRM-NP) offer an intriguing window of opportunity to revolutionize cancer therapeutics, including thermal therapy. However, recent studies indicate that NP size matters and suggest that interacting biomolecules can change the designed size of these NPs by formation of a Protein Corona during NP transit to the target cell. This study uses a Biofluid Assay Model of the T Cell Leukemia cell line, Jurkat clone E.6-1, and its growth media components to characterize design and evaluate behavior of in-house synthesized NIRM NPs. **Methods:** Free radical polymerization, using sodium-dodecyl-sulfate (SDS) size driven synthesis yielded 28-30nm poly methyl methacrylate nanoparticles (PMMA-NP) which were Ag loaded to generate AgPMMA-NP. To mimic in vivo transit, an in vitro biomolecule fluid assay (BFA) model was developed, which used dispersion media of RPMI-1640 and/or fetal bovine serum. To capture Protein Corona physical effects on the design step synthesis product and final metallic-loaded product, the Malvern Zetasizer was used to determine Dynamic Light Scattering (DLS) size distribution and zeta potential. To evaluate the Protein Corona effect on NP tumor cell killing, NP-cell interactions were screened for ATP production in the Promega-Cell-Titer-Glo cytotoxicity assay. **Results:** Time-course dispersion media results showed PPMA-NP product size increased in magnitude orders 10-100 fold, a fluctuating net charge (-) with zeta potential magnitude changes of 1-2 fold; Jurkat treated PMMA-NP alone or laser-PMMA treated tumor cells ATP levels are approximately equal to that of untreated tumor cells. AgPMMA-NP: Time exposure with different dispersion media revealed increased size, fluctuating net charge (-) and zeta potential changes 1-1.5 fold, treated NP alone or laser alone Jurkat tumor cells ATP levels approximate that of untreated tumor cells; however, combined laser-treatment reduced tumor live cells' ATP 25%. **Conclusions:** These preliminary studies suggest that laser-induced activation of AgPMMA-NPs that results in cell-killing of a Leukemia Jurkat clone. However, the biomolecular microenvironment forms a Protein Corona that affects size, stability, and net charge of designed nanoparticles. Characterization and evaluation studies using the BFA model could be used to refine NP design and synthesis protocols and improve tumor cell killing. Nevertheless, additional physical-chemistry BFA studies (e.g. shear affects, binding) related to nanoparticle-cell interaction are required to understand possible effects of the Protein Corona on tumor cell killing and thus the nanoparticle design.

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271 **Poster Session B**

Interleukin-21 maintains CD62L expression during natural killer T cell ex vivo expansion and enhances antitumor activity of natural killer T cell therapy in vivo *Ho Ngai, Baylor College of Medicine; G. Tian; A. Courtney; E. Marinova; W. Huang; L. Guo; L. Metelitsa*

Introduction: Valpha24-invariant natural killer T cells (NKTs) have potent antitumor properties and are being developed for cellular immunotherapy of cancer. Such therapy requires extensive ex vivo expansion of

NKTs while preserving their longevity and function. In a recent report from our group, CD62L+ subset of NKTs has been shown to have longer persistence in vivo and stronger antitumor activity than CD62L- counterpart. However, the requirements for the preservation of CD62L+ NKTs during ex vivo expansion remain largely unknown. The comparative gene expression analysis of CD62L+ and CD62L- NKT subsets revealed a significantly higher expression of IL-21R in the former, which was confirmed at protein levels by flow cytometry. Hence, we hypothesized that IL-21 preferentially supports CD62L+ NKTs. **Methods:** We expanded primary human peripheral blood NKTs using in vitro stimulation with their cognate antigen, alpha-galactosylceramide. The culture was supplemented with IL-2, IL-21, or both cytokines. To determine differential effects of IL-21 on CD62L+ and CD62L- NKT-cell subsets, we performed cell count, flow cytometry, NanoString gene expression analysis, and functional tests, including cell-mediated cytotoxicity and cytokine release. For in vivo studies, we performed adoptive transfer of IL-2 or IL-2/IL-21-expanded NKTs or CD19-specific CAR-modified NKTs to lymphoma-bearing NOD-SCID IL-2Rgamma null (NSG) mice followed by analysis of NKT-cell persistence and therapeutic efficacy. **Results:** We found that in contrast to IL-2, IL-21 alone failed to support NKT-cell expansion. However, a combined treatment with IL-2 and IL-21 produced more NKTs or CAR NKTs compared with IL-2 alone. Moreover, the former condition significantly increased frequency of CD62L+ NKTs that was associated with the selective downregulation of a pro-apoptotic gene BCL2L11 in the CD62L+ NKT-cell subset. We also found that IL-2/IL-21-expanded NKTs were more cytotoxic against lymphoma cells that correlated with enhanced expression of granzyme B. Importantly, after transfer to NSG mice, IL-2/IL-21-expanded NKTs or CAR NKTs persisted significantly longer and had higher therapeutic efficacy in a xenogenic lymphoma model compared with IL-2-expanded CAR NKTs. **Conclusions:** Our results instruct inclusion of IL-21 in the NKT-cell expansion protocols for cancer immunotherapy applications.

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Palbociclib resistant breast cancer cells are sensitized to inhibition of DNA repair and cancer stem cell pathways *Nicole Kettner, The University of Texas M.D. Anderson Cancer Center; S. Vijayaraghavan; T. Bui; B. Liu; K. Hunt; D. Tripathy; K. Keyomarsi*

Introduction: The CDK4/6 inhibitor palbociclib is currently being used in combination with endocrine therapy to treat advanced ER positive breast cancer patients. While this treatment has shown great promise in the clinic, about 25-35% of the patients do not respond initially, and almost all patients eventually acquire resistance. The precise biological mechanism(s) of the resistance to CDK4/6 inhibitors are still unknown and there are no independent biomarkers to predict response and/or resistance. Hence, understanding the mechanism(s) of acquired resistance to CDK4/6 inhibition is crucial to devise alternate treatment strategies. **Methods:** We developed MCF7 and T47D resistant cells by treating them with increasing doses of palbociclib over a 6-month period. These cells not only are resistant to palbociclb, but cross resistant to the other CDK4/6 inhibitors; ribociclib and abemaciclib, suggesting common mechanisms of resistance for this class of inhibitors. To elucidate mechanisms of resistance, we performed genome-wide expression analysis via RNA-seq, in comparison with the parental (sensitive) cells. **Results:** RNA- seq analysis revealed 2888 differentially expressed genes in the resistant cells. Gene set enrichment analysis (GSEA) revealed enrichment of immune pathways and pathways known to regulate EMT and cancer stem cells in the resistant cells. Additionally, GSEA analysis revealed downregulation of G2/M checkpoint, estrogen response, and DNA repair pathways. Palbociclib resistant cells exhibited mammosphere formation and CD44high/CD24low population indicating the presence of increased cancer stem cells (CSCs). Given the recently elucidated role of IL-6/STAT-3 mediated CSCs in drug resistance, we examined IL-6 mRNA levels, which increased by >12-fold in the resistant cells. Further, treatment with a STAT-3 inhibitor, napabucasin significantly decreased the CSC population and mammosphere formation, indicating a crucial role for the IL-6/STAT-3 pathway in driving CSCs and palbociclib resistance. Since DNA repair pathways were collectively downregulated in the palbociclib resistant cells, we examined their sensitivity to DNA damaging agents. Results showed that resistant cells were more sensitive to olaparib (PARP inhibitor), with no effect on CSCs. Next, we examined if combined treatment with agents targeting IL-6/STAT-3 and DNA repair pathways would be synergistic in palbociclib resistant cells. Results show that combined treatment with olaparib and napabucasin significantly decreased CSC population, colony formation and increased cell death via apoptosis, when compared to no-treatment or single treatment controls of the palbociclib resistant cells. **Conclusions:** Our data suggests that combined targeting of two or more pathways that are altered in the palbociclib resistant cells can provide a novel therapeutic strategy to combat CDK4/6 inhibitor resistance.

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Novel agents targeting a specific oxidative stress generating biochemical pathway block castrate-resistant prostate cancer cell growth *Hirak Basu, The University of Texas M.D. Anderson Cancer Center; G. Wu; I. Fokt; W. Priebe; G. Wilding; N. Wilganowski*

Introduction: Castrate-resistant prostate cancer (CRPC) is the second leading cause of cancer deaths among US men. Currently, a large number of small and low grade prostate cancers (PCa) are being diagnosed. Only a few of them will metastasize and become lethal. A clinical method to distinguish aggressive from the indolent tumors is warranted. An enhanced glucose metabolism (Warbürg effect) and invasion of cells from their organs of origin and metastasis to distant organs are two characteristics that are ubiquitous in most metastatic solid tumors including PCa. In the last few years, the non-glycolytic activities ("moonlighting functions") of glycolytic enzymes have been investigated in relation to cancer cell invasion. We propose that oxidatively stressed PCa cells, as a countermeasure, redirect some of the glycolytic enzymes to their moonlighting functions. We have discovered a bio-chemical pathway of spermidine/spermine N1 acetyl transferase (SSAT) overexpression leading to polyamine oxidation as one major oxidative stress generating pathway in the PCa cells. We have developed targeted agents to block this pathway and thus prevent PCa progression to CRPC and metastatic CRPC (mCRPC). **Methods:** We used a novel microfluidic device that separates the invading from the non-invading PCa cells based in a 3D collagen I matrix mimicking bone microenvironment. We performed ICC analysis of the separated cells for SSAT, glycolytic enzymes, GAPDH and F-actin levels. We also carried out proteomic analysis of GAPDH levels and its oxidation state and metabolomic analysis for enzymatic activities of the enzyme. **Results:** Under identical conditions, LNCaP cells show minimum invasion, whereas between 30-40% of C4-2 cells invade into the matrix. ICC assay shows that most migratory C4-2 cells as well as PCa cells isolated from some patients prostate tissues overexpress SSAT, while stationary cells do not. Proteomic analysis shows that androgen increases GAPDH oxidation in C4-2 cells. Our targeted agent markedly inhibits growth of the C4-2 cells both in culture as well as in vivo. **Conclusions:** SSAT expression and a consequent increase in oxidative stress are related to invasion of CRPC. Oxidation of certain glycolytic enzymes such as GAPDH in CRPC cells diverts them to their moon-lighting functions related to cellular invasion and metastasis. These effects may be monitored in patient biopsies and/or prostatectomy tissues for PCa prognosis. Targeted agents can be developed for precision therapy of mCRPC patients dependent on this mechanism of metastasis.

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Screening for novel therapeutic agents for the treatment of aggressive childhood hepatoblastoma *Kristi George, The University of Texas Health Science Center at San Antonio; J. Peralba; M. Hart; H. Bansal; G. Tomlinson*

Introduction: Hepatoblastoma is the most common malignant liver tumor in pediatric patients, and its' incidence has been rising annually over the past several decades. Despite improved survival outcomes, a subset of patients has more aggressive tumors which are refractory to conventional cisplatin therapy and surgery. We are focused on identifying novel compounds for the treatment of aggressive hepatoblastomas. Initial research involved screening four chemical libraries; including LOPAC, the Prestwick Chemical Library, Chembridge DiverSet, and the Maybridge HitFinder Library for compounds with selective cytotoxic activity against two aggressive hepatoblastoma cell lines; HEP293TT and HUH-6. Twenty-nine potential hits were identified from the LOPAC and Prestwick chemical libraries and eighteen additional hits from the Chembridge Diverset and Maybridge Hitfinder libraries. Based on their biological significance two of these compounds were selected for further investigation. Secondary screens completed using sulforhodamine B assay to determine the cytotoxic activities of each compound on each cell line. In addition, testing for synergy by treating cells with each compound in combination with Cisplatin. **Methods:** Two aggressive hepatoblastoma cell lines, Hep293TT and HUH6 were utilized for these experiments. During initial screen, cells were cultured in 96-well plates at 1,000 cells/well in 50μL media on day 1. After 24hr compounds were added, at 6.2μM for compounds from Diverset /HitFinder libraries and 2.5 μM for LOPAC/Prestwick libraries. Cells were treated in presence of 15 μM Cisplatin. After 72hr of incubation ATP level assay performed to identify compounds with cytotoxic activity. For secondary screens, cells were cultured in 96-well plates at 3,000 cells/well in 100μL media. After 24 hours cells were treated with increasing concentrations of each compound and each compound plus Cisplatin 15 μM. Cells were treated for 24, 48, and 72 hours. SRB assay then completed to determine each compound's cytotoxic effect. **Results:** HitFinder, Diverset Library, LOPAC, and Prestwick library screening completed with 40% cell viability cutoff utilized. Twenty-nine potential hits were identified from the LOPAC and Prestwick chemical

libraries and eighteen additional hits from the Chembridge Diverset and Maybridge Hitfinder libraries, which demonstrated cytotoxic activity against both cell lines. **Conclusions:** Despite improved outcomes in hepatoblastoma patients, there is still a significant number of patients who will succumb to their disease. As a result, it is critical that new treatments be identified to treat these aggressive tumors. High throughput screening offers an efficient and effective way to rapidly screen large libraries of compounds for potential cytotoxic activity against these tumors.

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275 **Poster Session B**

Modelling Spread of Oncolytic Viruses in Heterogeneous Cell Populations *Hana Dobrovolny, Texas Christian University*

Introduction: One of the most promising areas in current cancer research and treatment is the use of viruses to attack cancer cells. A number of oncolytic viruses have been identified to date that possess the ability to destroy or neutralize cancer cells while inflicting minimal damage upon healthy cells. Mathematical models that correctly describe the evolution of infected tumor systems are critical to the successful application of oncolytic virus therapy. Existing mathematical models are focused on the effects of virus infection on tumor cells, but do not consider possible spread of the virus to normal healthy cells. **Methods:** We have developed a mathematical model of oncolytic virus infections of tumors that includes both tumor cells and neighboring normal cells. We use mathematical analysis and computer simulation to examine the conditions which lead to eradication of the tumor without serious damage to normal cells. **Results:** We find that differences in infection rate between the two cell types are necessary for eradication of tumors while leaving normal cells unharmed. Differences in production rate or infected cell lifespan are not sufficient to protect healthy cells from infection. **Conclusions:** Mathematical models can assist in the safe development of oncolytic viral therapy by identifying conditions that limit spread of the virus to non-cancerous cells.

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Metabolic adaptations establish immunotherapy resistance in melanoma *Ashvin Jaiswal, The University of Texas M.D. Anderson Cancer Center; S. Pudakalakatti; P. Dutta; A. Liu; T. Bartkowiak; C. Ager; M. Davies; J. Allison; R. Davis; J. Wargo; P. Bhattacharya; D. Hong; M. Curran*

Introduction: Despite the success of T cell checkpoint blockade antibodies in treating an array of cancers, the majority of patients still fail to respond to these therapies, or respond transiently and then relapse. The molecular mechanisms which drive lack of response to checkpoint blockade, whether pre-existing or evolved on therapy, remain unclear. **Methods:** To address this critical gap in clinical knowledge, we established a mouse model of melanoma designed to elucidate the molecular mechanisms underlying immunotherapy resistance. Through multiple in vivo passages, we selected a B16 melanoma tumor line that evolved complete resistance to combination blockade of CTLA-4, PD-1, and PD-L1, which cures ~80% of mice of the parental tumor. Using gene expression analysis, proteomics, and immunogenomics, we determined the adaptations engaged by this melanoma to become completely immunotherapy resistant. NMR spectroscopy, Seahorse XF Analysis, flow cytometry, confocal microscopy and western blot analysis provided further insight into the mechanisms driving checkpoint blockade resistance. **Results:** Acquisition of immunotherapy resistance by these melanomas was driven by coordinate upregulation of the glycolytic and aldose reductase pathways to create a metabolically hostile microenvironment in which T cell function is profoundly suppressed. When re-introduced into the parental tumor, the genes most closely associated with these metabolic adaptations confer enhanced immunotherapy resistance. We have validated upregulation of these pathways in a unique cohort of melanoma patients who failed dual checkpoint blockade. Additionally, we employed MRI imaging to visualize metabolic changes acquired by resistant tumors in live mice. Clinical application of this technique could provide a much-needed non-invasive tool to predict immunotherapeutic sensitivity of patients. **Conclusions:** Upregulation of glycolytic metabolism and the aldose reductase pathway by melanoma tumor cells cripples T cells in the microenvironment and confers resistance to checkpoint blockade.

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Exfoliated single-cell genomics for assessing prostate cancer progression and treatment options *Chun-Lin Lin, The University of Texas Health Science Center at San Antonio; X. Tan; C. Lin; P. Osmulski; M. Liss; M. Chen; A. Chen; C. Wang; J. Liu; A. Horning; G. Huang; K. Mitsuya; Y. Wang; J. Taverna; K. Xu; V. Jin; Z. Lai; N. Kirma; M. Gaczynska; C. Chen; T. Huang*

Introduction: Exfoliated prostate cancer cells undergoing epithelial-mesenchymal transition (EMT) may enter the bloodstream and invade organs for distant colonization. Different from primary tumor cells, these circulating tumor cells (CTCs) may exhibit unique biophysical properties, enabling their active intravasation and extravasation in the circulation. To date, there is limited information on genomic selection of tumor cells transitioning from active in situ proliferation to effective distant colonization. Here we constructed whole-genome copy number profiles on prostate single cells isolated from urine and blood for comparative genomic analysis of primary and disseminated tumor cells in a patient. **Methods:** With specific markers, we isolated 407 single prostate cells exfoliated in urine and blood of 19 patients or from two cancer cell lines. These single cells were subjected to multiple displacement amplification known to unbiasedly amplify a cell genome and confirmed by PCR analysis of a reference gene panel. Barcoded libraries prepared from amplicons were pooled for whole genome sequencing. On average 4 x 10^7 paired-end reads per cell were processed for genome mapping. From ~1.2X genome coverage, we calculated copy-number alterations (CNAs) at the 250 Kb resolutions. **Results:** Clonal abnormalities of well-known oncogenes and tumor suppressors, including amplified MYC and deleted RB1, were common in prostate cells exfoliated in urine of advanced patients, but less frequent in indolent cancer patients. We further identified amplified regions harboring novel loci, their upregulation of which is linked to recurrent prostate cancers. Among these loci, amplified MEN1 and HSF1 known to promote castration resistance and EMT were frequently present in CTCs. Different from exfoliated tumor cells in urine, these CTCs exhibited biophysical phenotypes with high adhesive capability likely for vascular permeation and distant invasion. In vitro testing of CTCs revealed potential therapeutic targeting of these two amplified loci **Conclusions:** This parallel genome analysis of exfoliated cells in both urine and blood opens the possibility of minimally invasive evaluation of disease progression and treatment options for a man with advanced prostate cancer.

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Aspergillus candidus is a newly recognized source of sphaeropsidin A: Isolation, semi-synthetic derivatization and anticancer evaluation *Annie Hooper, Texas State University; Y. Li; R. Scott; G. Bartholomeusz; A. Kornienko; G. Bills*

Introduction: This report details a search for alternative strains that produce the diterpenoid sphaeropsidin A (SphA) among A. candidus strains from the USDA Northern Regional Research Laboratories Culture Collection. We identified two strains that produced SpA using a limited set of test media. **Methods:** An initial scaled-up fermentation of NRRL 313 and isolation effort led to the procurement of sufficient quantities of SphA to prepare five semi-synthetic analogues (1-5) and evaluate their anticancer effects against glioblastoma cells grown in 2D and 3D cultures. **Results:** Although, the effectiveness of the synthetic analogues varied depending on the cell line and the type of cell culture, compound 5, bearing an aromatic ring at C16, displayed a stronger toxicity towards these glioma cells in 2D cultures than either SphA or compounds 1-4. **Conclusions:** Optimization and engineering of SphA biosynthesis and production in A. candidus can be facilitated because genetic transformation and manipulation methods are readily available for Aspergillus species. 0ur first scale-up attempt resulted in sufficient quantities of SphA to make five new derivatives. The synthetic derivatization of SphA at the positions C6 and C16 led to compounds that exceeded the potency of the natural product itself. However, the effectiveness of the synthetic analogues varied depending on the cell line and the type of cell culture, underscoring the differences in cell response between the 2D and 3D cultures.

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279 **Poster Session B**

Association of anti-tumor activity in neuroblastoma patient-derived xenografts with levels of GD2 expression *Michelle Keyel, Texas Tech University Health Sciences Center; H. Davidson; T. Nguyen; C. Reynolds*

Introduction: Maintenance therapy with a chimeric anti-GD2 antibody, ch14.18 (dinutuximab) combined with cytokines and isotretinoin improves outcome for high-risk neuroblastoma (NB). A phase II clinical trial combining dinutuximab with temozolomide + irinotecan (temo + irino) showed promising activity in recurrent NB (Lancet Oncol, 18(7): 946-957, 2017), but a report that ~ 12% of NB patients have low or negative GD2 expression (Pediatr Blood Cancer 64(1): 46-56, 2017) indicates the need to assess GD2 expression on NB and to define expression levels necessary for activity. **Methods:** Using dinutuximab and flow cytometry we quantified GD2 surface expression from patient derived NB cell lines and xenografts (PDXs) established at diagnosis (DX, n = 12) or at progressive disease (PD, n = 19). Activity of dinutuximab in combination with temo + irino was assessed in PDXs in nu/nu mice established from late-stage PDs with high and low GD2 surface expression. **Results:** GD2 expression was low or negative on 16% of 31 NB cells lines. Low GD2 (≤ 50% of median fluorescence intensity) was seen in 26% of PD NB cell lines but in 0% of DX NB cell lines. In COG-N-452x (a GD2- high NB PDX) dinutuximab enhanced ($P < 0.001$) mouse event-free survival (EFS) when combined with temo + irino (> 60% EFS at 150 days vs 0% with temo + irino alone). In COG-N-471x (a GD2-low NB PDX) dinutuximab

did not significantly increase EFS over temo + irino alone. We developed a two color flow cytometry assay employing directly-labeled dinutuximab + directly-labeled HSAN 1.2 (neuroblastoma specific, marrow negative) that enables quantifying GD2 expression in bone marrow aspirates. **Conclusions:** Our data with patient-derived NB cell lines and PDXs are consistent with a prior report and indicate that low GD2 expression can occur in NB and may be more frequent in PD patients. NB PDXs in nu/nu mice provide a preclinical model to assess dinutuximab activity when combined with chemotherapy. Dinutuximab enhanced activity of temozolomide + irinotecan in a NB PDX with high-GD2 expression but not in a NB PDX with low GD2. Quantifying GD2 expression in NB is a potential biomarker of activity that warrants evaluation in patients treated with dinutuximab combined with temozolomide + irinotecan.

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Robust Anti-Tumor Immunity is Transient and Limited by Immune Escape in a Novel Model of HPV-Associated Head and Neck Cancer *Neeraja Dharmaraj, The University of Texas Health Science Center at Houston; S. Piotrowski; L. Golfman; S. Koshy; W. Li; D. Mooney; A. Sikora; S. Young*

Introduction: More than 65,000 men and women will develop head and neck squamous cell cancer (HNSCC) this year in the US alone and it accounts for 4% of all cancers in the United States. Given the well-known co-morbidities and recurrence rates associated with conventional treatments, there is a real need for innovative new approaches to treating both human papilloma virus (HPV)-related and non-HPV related HNSCC. Immune checkpoint inhibitors have been the most successful cancer immunotherapy approach thus far, although they are only effective in about 15-20% of patients. The challenges and limitations of immunotherapy can be overcome by biomaterial-based combinatorial therapies to treat HNSCC. Herein, we describe a novel preclinical mouse model for immunologic targeting of HPV-related HNSCC to investigate the efficacy of an injectable therapeutic cancer vaccine. **Methods:** MOC2-E6E7, a murine oral cancer cell line expressing the oncogenic HPV viral proteins E6 and E7, was generated by retroviral transduction of HPV16 E6E7 in parental MOC2 cells obtained from the Uppaluri Lab, Harvard University. Orthotopic tumors in mice were established by intra- oral injection of MOC2-E6E7 cells for our studies. We used mesoporous silica rod (MSR)-based vaccines to examine efficacy of an injectable therapeutic cancer vaccine system. MSR-vaccines loaded with bioactive reagents (recombinant murine GM-CSF, CpG-ODN, and E7 long peptide or tumor lysate), were injected subcutaneously in the bilateral flanks of mice that were previously inoculated with MOC2-E6E7. Several independent approaches were used to determine efficacy, expression of E6E7, and immune profile expression. **Results:** In vivo tumor growth kinetics reveal that MOC2-E6E7 tumors had delayed growth in immunocompetent mice when compared to parental MOC2 tumors. In contrast, MOC2-E6E7 tumor growth rate was similar to MOC2 in immunocompromised mice. By flow cytometry and multiplex imaging, we determined MOC-2-E6E7 tumors have a T-cell inflamed phenotype. Efficacy studies with a MSR-based vaccine showed slowed MOC2-E6E7 tumor growth and increased survival. **Conclusions:** We developed a syngeneic murine model of HPV-related HNSCC, MOC2-E6E7 that expresses well-defined tumor specific antigens that can be targeted by the immune system. The eventual loss of E6 and E7 expression led to escape of resistant tumor cells from immune control, causing a delayed tumor growth phenotype in this model. Additionally, MSR-based vaccines show promise in delaying tumor growth and increase median survival time in HPV- related HNSCC. Future studies will explore the efficacy of MSR-based vaccines in combination with other immunotherapy modalities.

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Development of a robust high throughput luminescent assay for lysyl hydroxylse 2 *Ashwini Devkota, The University of Texas at Austin; J. Veloria; H. Guo; J. Kurie; E. Cho; K. Dalby*

Introduction: Lysyl hydroxylase-2 (LH2), an Fe(II) and alpha-ketoglutarate (α-KG) dependent oxygenase, catalyzes the hydroxylation of telopeptidyl lysine residues on collagen, leading to the formation of stable collagen cross-links. By promoting accumulation and stabilization of hydroxylysine aldehyde-derived collagen cross-links (HLCCs) in fibrotic and various other tissues, LH2 is believed to cause fibrotic diseases, and enhance progression and metastasis of various cancer types such as lung cancer, breast cancer and sarcoma. Therefore, LH2 is a potential therapeutic target for fibrotic diseases and cancer. Identification of small molecule inhibitors for the treatment of these diseases requires a suitable assay system that is amenable to high throughput screening. Currently no such assays are available for LH2. Therefore the purpose of our research was to develop a robust bioluminescence-based high throughput assay that can facilitate the identification of potent, specific small molecule inhibitors of LH2. **Methods:** Chinese hamster ovary cell-derived LH2 and collagen helical peptide substrate (IKGIKGIKG) were used for the assay. Enzyme concentration, substrate concentrations and reaction times were optimized to maximize signal to background ratio while being within the linear initial velocity of the assay. A commercially available bioluminescent succinate detection assay was used to convert succinate product to luminescent signal. Assays were miniaturized to a 10 μL volume in a 384 well plate format. The robustness of the assay was further tested and validated in a screen of 65,000 compounds. **Results:** The assay cost was significantly reduced by miniaturizing the assay to 10 μL volume in a 384 well plate format. The optimized assay demonstrated a 15-20 fold higher signal compared to the background. The average z' for the screen was above 0.8, suggesting high confidence in the identified hits. A 3.8% hit rate was obtained from the primary screen of 65,000 compounds (compound showing greater than 50% inhibition was considered a 'hit'). Top 1000 hits from primary screen were further confirmed in a secondary screen using the same assay and ultimately in a dose response assay to determine the potency. The screen identified several specific hits with potency in the low micromolar to nanomolar range. **Conclusions:** Overall, the assay was very robust and cost-effective for high throughput screening of small molecule libraries. The assay will facilitate screening of larger libraries for identifying potent, specific small molecule inhibitors for LH2.

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A novel LC-MS/MS assay using pH gradient for quantitation of underivatized polyamines in cancer cells *Hwangeui Cho, Texas Tech University Health Sciences Center; D. Verlekar; M. Kang*

Introduction: Altered levels of polyamines in biological specimens have been suggested as potential biomarkers for cancer. Difluoromethylornithine (DFMO, an irreversible inhibitor of ornithine decarboxylase), a modulator of polyamines has shown in vitro cytotoxic activity in neuroblastoma, and a clinical trial is being conducted to evaluate DFMO in neuroblastoma. In order to determine the role of DFMO in the cytotoxic activity against neuroblastoma cells it is necessary to accurately measure the changes in polyamines in the cells. Existing analytical methods include a use of derivatives or ion-pairing reagents to improve the sensitivity or retention. However, these methods may cause incomplete reactions, contamination, and signal suppression as well as they are time consuming. In this study, we present a novel pH gradient method for the quantitation of polyamines (putrescine, spermidine and spermine) in cancer cells. **Methods:** To separate polar and basic amines under the conventional reversed-phase conditions, a multi-mode column composed of C18 and weak ionic ligands was adopted. The pH gradient was generated from pH 5.3 to pH 2.5 with 2 mM ammonium acetate and 0.4% acetic acid in 10% acetonitrile as mobile phase. The detection of polyamines was performed using multiple reaction monitoring on electrospray ionization mass spectrometry operated in the positive ion mode. The developed method was validated according to the FDA guidance on bioanalytical method validation. Polyamines levels were measured using the developed method for NB cells treated and non-treated with DFMO. **Results:** A pH gradient method increased resolution and decreased peak width of conventional analytical assays. Mobile phases without ion-pairing reagents were more LC-MS compatible and eliminated the possibility of signal suppression and MS contamination. The validation parameters including selectivity, limits of detection (LOD), lowest limits of quantification (LLOQ), linearity, precision, accuracy, recovery, and the matrix effect were satisfactory. The developed method was successfully applied to the analysis of polyamines in cancer cells. Of the three polyamines measured, only putrescine levels were significantly altered in both SK-N-BE(2) and CHLA-119 neuroblastoma cells treated with DFMO relative to vehicle control: putrescine (30.2 vs 18.6 ng/mg protein, $p<0.05$), spermidine (686.2 vs 521.9 ng/mg protein, $p>0.05$), spermine (2314.1 vs 2209.0 ng/mg protein, $p>0.05$). **Conclusions:** The method developed to quantitate polyamines is sensitive and reliable. The assay will provide useful information in determining the polyamines that are responsible for the cytotoxic activity of DFMO in cancer cells.

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Microfluidic cell isolation technology for drug testing of single tumor cells and their clusters *Swastika Bithi, Texas Tech University; S. Vanapalli*

Introduction: There is a growing interest in conducting drug screens with primary cells derived from human tissues and biofluids to predict patient outcomes. These primary cells contain inherent heterogeneity of cancer that demands single-cell analysis. In contrast to immortalized cell lines, primary cells are a scarce resource and yet preclinical studies demand diverse assays probing specific targets, off-targets and cytotoxicity. Drug assays with patient-derived cells such as circulating tumor cells requires manipulating small sample volumes without loss of rare disease-causing cells. **Methods:** Here, we report an effective technology for isolating and analyzing individual tumor cells and their clusters from minute sample volumes using an optimized microfluidic device integrated with pipettes. The method involves using hand pipetting to create an array of cell-laden nanoliter-sized droplets immobilized in a microfluidic device without

loss of tumor cells during the pipetting process. **Results:** Using this technology, we demonstrate single-cell analysis of tumor cell response to the chemotherapy drug doxorubicin. We find that even though individual tumor cells display diverse uptake profiles of the drug, the onset of apoptosis is determined by accumulation of a critical intracellular concentration of doxorubicin. Experiments with clusters of tumor cells compartmentalized in microfluidic drops reveal that cells within a cluster have higher viability than their single-cell counterparts when exposed to doxorubicin. This result suggests that circulating tumor cell clusters might be able to better survive chemotherapy drug treatment. **Conclusions:** Our technology is a promising tool for understanding tumor cell-drug interactions in patient-derived samples including rare cells.

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Synergistic Activity of Fenretinide (4-HPR) and the BCL-2 Inhibitor ABT-199 in Human Neuroblastoma Preclinical Models *Thinh Nguyen, Texas Tech University Health Sciences Center; B. Koneru; S. Wei; M. Makena; W. Chen; E. Urias; M. Kang; C. Reynolds*

Introduction: Despite current intensive treatment with chemotherapy and radiation, ~35% of neuroblastoma patients still die of the disease. Fenretinide (4-HPR), a synthetic retinoid formulated as an oral powder in Lym-X-Sorb (4-HPR LXS), has shown multiple complete responses and encouraging event-free survival in a phase 1 neuroblastoma clinical trial. Anti-apoptotic BCL-2 family of proteins play critical roles in neuroblastoma cell survival, with a subset of neuroblastoma dependent on BCL-2. Synergistic activity of fenretinide and the pan-BCL-2 family inhibitor ABT-737 (clinical version, ABT-263) has been demonstrated in neuroblastoma preclinical models, but ABT-263-associated thrombocytopenia led to development of ABT-199 (venetoclax), a platelet-sparing selective BCL-2 inhibitor that has achieved an FDA approved indication for chronic lymphocytic leukemia. The purpose of the current study is to investigate the preclinical activity of ABT-199 in combination with 4-HPR activity in BCL-2-dependent neuroblastomas. **Methods:** Cytotoxicity was assessed by combining ABT-199 (0-10 mM) with 4-HPR (0-10 mM) using DIMSCAN, synergy by combination index, and apoptosis by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. Protein expression was determined by western blot. Gene expression manipulations were conducted with lenti-viral induction. **Results:** Cytotoxic synergy was observed between 4-HPR and ABT-199 in 18 out of 20 tested NB cell lines in vitro. 4-HPR + ABT-199 induced greater apoptosis than single agents. BCL-2 protein expression was significantly higher in cell lines with the highest sensitivity to ABT-199 ($p<0.05$). The synergy of the combination was greater in NB cell lines that are highly sensitive to ABT-199 as a single agent compared with ones that are relatively resistant to ABT-199. 4-HPR + ABT-199 + Keto (as a CYP3A4 inhibitor used to increase 4-HPR plasma concentration) significantly ($p<0.0001$) improved the event-free survival (EFS) of mice relative to single agents in a patient-derived xenograft (PDX) model with high-BCL-2 established from progressive disease/ post mortem (PD/PM); median EFS of 4-HPR + ABT-199 + Keto group = 93 days versus 43 days for 4-HPR + Keto and 46 days for ABT-199 + Keto. 4-HPR + ABT-199 + Keto did not improve EFS of mice versus single agents in a low BCL-2 PDX model. 4-HPR showed significant induction of NOXA protein expression, NOXA knock-down abrogated the synergistic cytotoxicity of 4-HPR + ABT-199, and overexpressing NOXA sensitized NB cell lines to single agent ABT-199. **Conclusions:** Induction of NOXA- by 4-HPR mediates synergistic cytotoxicity of 4-HPR + ABT-199 for neuroblastoma.

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Selective delivery of potent anticancer agents facilitated by hypoxia mediated cleavage of corresponding prodrug conjugates *Zhe Shi, Baylor University; B. Winn; T. Strecker; L. Devkota; Y. Wang; J. Gerberich; A. Winters; E. Lin; C. Maguire; M. MacDonough; D. Mondal; G. Carlson; J. Ford; D. Chaplin; R. Mason; M. Trawick; K. Pinney*

Introduction: Small molecules such as paclitaxel, vinblastine, and monomethyl auristatin E that interfere with the tubulin-microtubule protein system are clinically relevant anticancer agents. The natural products colchicine, combretastatin A-4 (CA4), and combretastatin A-1 (CA1) are potent inhibitors of tubulin polymerization that have inspired the discovery of several small-molecule inhibitors of tubulin polymerization (KGP03 and KGP18 are representative) that bind to the colchicine site on tubulin and demonstrate profound cytotoxicity (low nM to pM) against human cancer cell lines. Tumor associated hypoxia provides a unique opportunity for targeted therapy through selective reductase enzyme-mediated release of highly potent anticancer agents from bioreductively activatable prodrug conjugates (BAPCs). **Methods:** A series of substituted nitrothiophene, nitrofuran, and/or nitroimidazole-triggered BAPCs that incorporate CA1, phenstatin, KGP03, KGP18, and CA4 (for reference comparison) were synthesized, and evaluated in the following assays: (1) cleavage under anoxic conditions by the reductase enzyme, NADPH cytochrome c P450 oxidoreductase (POR), that is implicated in the bioreductive cleavage of compounds with nitrothiophene and nitroimidazole triggers; and (2) differential cytotoxicity under hypoxic versus normoxic conditions in cancer cell lines with the established bioreductive compound tirapazamine (TPZ) as the control. **Results:** The CA4-gem-dimethylnitrothiophene BAPC (KGP372) proved exemplary in comparison to its nor-methyl and mono-methyl congeners. It was stable in phosphate buffer (pH 7.4, 24 h), was cleaved by POR, was inactive (desirable BAPC attribute) as an inhibitor of tubulin polymerization (IC_{50} > 20 μM), and demonstrated hypoxia-selective activation in the A549 cell line [hypoxia cytotoxicity ratio (HCR) = 40]. The monomethyl nitroimidazole BAPCs of KGP03 and KGP18 produced positive HCRs in these initial assays, and the gem-dimethyl nitrothiophene and nitrofuran phenstatin BAPCs underwent efficient POR-mediated cleavage. In a preliminary in vivo dynamic bioluminescence imaging (BLI) study, KGP372 (dosed at 180 mg/kg) induced a decrease in light emission in two of three tumors within 4 h in an orthotopic 4T1 syngeneic mouse breast cancer model. This is potentially indicative of in vivo cleavage by POR and subsequent vascular disruption by the released CA4. The related CA1-gem-dimethylnitrothiophene BAPC (KGP461) was also promising (HCR = 12) and demonstrated cleavage upon treatment with POR. However, KGP461 was not stable to long exposures (24 h) in phosphate buffer (pH 7.4), suggesting that pharmacokinetic (PK) considerations may prove crucial for the successful future development of these (and related) BAPCs as therapeutic agents. **Conclusions:** The gem-dimethyl BAPCs were the most promising from this series and warrant further evaluation and development.

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Graphene Oxide Vehicles for Molecular Imaging and Cancer Detection *Anton Naumov, Texas Christian University; E. Sizemore; M. Hasan; C. Pho*

Introduction: In order to address adaptability and variability of multiple cancer types, novel transformative approaches to cancer treatment imaging and detection are required. A new interdisciplinary field of nanomedicine provides effective routes for cancer prevention, detection and treatment through remarkable properties of novel nanomaterials. One of those graphene has only started finding its applications in biotechnology. In this work we explore the properties of its functional derivative, graphene oxide (GO) that can perform multiple functions of drug delivery, imaging and cancer detection. Unlike many carbon nanomaterials, GO is water soluble and exhibits fluorescence over the functionalization-induced band gap. A large graphene platform with oxygen containing groups that can be easily functionalized with active agents or analyte binding sites makes GO attractive for biosensing and drug delivery applications. In addition, an intrinsic GO fluorescence in red/near-infrared region with reduced biological autofluorescence background provides a possibility of fluorescence imaging without the need in additional fluorophores. **Methods:** We explore these properties to develop a multifunctional delivery/imaging/sensing GO platform for cancer therapeutics. GO utilized in our work shows little to no apparent cytotoxicity in concentrations of up to 15 mg/mL. We optimize the size of the commercially available GO flakes via ultrasonic processing for the most efficient cellular internalization and use spectrally-resolved fluorescence imaging for in vitro detection in the spectral range specific to GO emission. Furthermore, ozone processing adding extra oxygen-containing functional groups to GO surface is used to spectrally adjust GO emission and enhance its intensity. Concomitantly, such processing provides the basis for versatile covalent functionalization of anticancer agents to the new addends on GO platform via synthetic route akin to peptide synthesis. **Results:** Optimized GO moieties show efficient intracellular accumulation at 1h after transfection in both cancer (MCF-7, HeLa) and healthy (HEK-293) cells and clearance through 24h post transfection. A pH dependence of GO emission discovered in our previous work provides a sensing mechanism for the acidic environment of cancer cells. In this regard, spectrally-resolved fluorescence microscopy imaging confirms enhancement of red GO emission features and of GO fluorescence in green in cancer versus healthy cell environments. **Conclusions:** As a result we propose GO as efficient multifunctional candidates for delivery of active agents, fluorescence imaging and sensing of cancerous environments in vitro, ex vivo and intravitally.

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Systemic depletion of serum methionine by engineered methioninase for cancer therapeutics *Achinto Saha, The University of Texas at Austin; K. Garrison; J. DiGiovanni; E. Stone; G. Georgiou; W. Lu*

Introduction: In cancer biology research, it has been found that cancer cells exhibit altered metabolism compared to normal cells and it has been shown that some types of cancer cells are far more sensitive than normal cells to methionine starvation. Past studies have shown that methionine-dependent tumor cells are not able to survive if the

serum methionine is decreased to ≤ 5uM. We engineered human cystathionine gamma-lyase to accept methionine as a substrate and have isolated several human Methioninase (hMETase) variants with high activity to systemically deplete of serum methionine. The engineered Methioninase was then tested in vitro and in vivo for effects on inhibition of cell survival, cell cycle arrest, generation of reactive oxygen species (ROS), Western blotting and tumor growth inhibition. **Methods:** We engineered and characterized several variants of human Methioninase (hMETase) for catalytic activity, thermostability, pharmacokinetics and, pharmacodynamics. The enzyme was also tested in cultures of prostate cancer (PCa) cells for effects on cell survival by crystal violet assay, cell cycle analysis by PI staining, measurement of glutathione and ROS and Western blotting for cell signaling changes. Allograft and xenograft tumor studies were performed to assess the inhibition of PCa tumor growth in vivo using pharmacologically optimized hMETase. **Results:** The best variant, hMETase V8.4 isolated from phylogenetic library showed a 10-fold better k_{cat}/K_M values (0.59 to 5.3 $s^{-1}mM^{-1}$) in degrading methionine and also greater stability in thermal melting analyses compared to our previous version of variant, hMETase V3.1. In pharmacokinetics analyses, its half-life is ~39 hours and furthermore, it efficiently lowered serum methionine concentration from 113 μM to 17 μM in 48 hours without the requirement of a methionine restricted diet (one dose: 50 mg/ kg). Treatment with this enzyme selectively induced cell cycle arrest and death in PCa cells, depletion of intracellular GSH and elevation of ROS. Methioninase suppressed the growth of PCa allografts (mouse PCa cells) and xenografts (human PCa cells) with no apparent signs of toxicity. Mechanistically, Methioninase treatment caused activation of AMPK signaling, reduced mTORC1 activity and induced formation of LC3 II indicating induction of autophagy. **Conclusions:** The hMETase V8.4 efficiently lowered serum methionine concentration in pharmacodynamic analyses, suppressed the growth of PCa cells both in vitro and in vivo, and was very well tolerated. These results suggest that Methioninase represents a potentially safe and effective therapeutic modality for the treatment of prostate and possibly other cancers.

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Identification of Tumor-Reactive B Cells and Systemic IgG in Sentinel Lymph Nodes of Breast Cancer Patients *Jonathan McDaniel, The University of Texas at Austin; S. Pero; W. Voss; G. Shukla; Y. Sun; S. Schaetzle; C. Lee; A. Horton; S. Harlow; J. Gollihar; J. Ellefson; C. Krag; Y. Tanno; N. Sidiropoulos; G. Georgiou; G. Ippolito; D. Krag*

Introduction: Understanding the complex interactions between tumors and the adaptive immune system is key to advancing the field of cancer immunotherapy. Breast cancer offers unique insight into the generation of anti-tumor antibodies because the sentinel lymph node (SN), typically resected during treatment, is the site of affinity maturation and clonal expansion of B and T cells responding to antigens draining from the tumor. Herein, we sought to identify and characterize the antigen-specific B cells and circulating IgG from a TNBC patient sero-positive for the tumor antigen NY-ESO-1. **Methods:** We utilized two high-throughput technologies to determine the cellular and serological antibody repertoires elicited by the tumor antigen. In a process termed BCR-Seq, we isolated B cells from the SN to build a patient-specific next-generation sequencing database that preserves the natural VH:VL pairing of heavy (VH) and light (VL) chain variable regions from a single B cell. Putative antigen-specific antibodies derived from highly expanded and branched B cell lineages were selected for expression and characterization. The serological repertoire was determined by Ig-Seq, a process by which antigen-specific IgG was isolated from blood by affinity chromatography, proteolytically digested, analyzed by LC-MS/MS, and identified by mapping the MS spectra to the VH:VL sequencing database. **Results:** In this work, we demonstrated that the SN is a rich source for tumor-reactive B cells that give rise to circulating autoantibodies. From a single patient, we determined that two of the top three expanded B cell lineages targeted the tumor antigen NY-ESO-1, a highly immunogenic protein typically restricted to germ cells but expressed in several cancers including breast cancer. In characterizing these two B cell lineages, we observed that they each displayed hallmarks of affinity maturation against NY-ESO-1: clonal expansion, somatic hypermutation, and affinity-driven selection. Finally, we demonstrated an unequivocal link between affinity-matured expanded B-cell clones in the SN and antitumor Ig in the blood. These findings highlight the unique and specialized niche the SN can fill in the discovery of anticancer therapeutics. **Conclusions:** Using high-throughput VH:VL B cell sequencing and antibody proteomics to study coordinated antitumor immunity in breast cancer patients, we simultaneously demonstrated that the SN is a localized source of expanded antitumor B cells undergoing affinity maturation and that their secreted antibodies are abundant as systemic IgG circulating in blood. Furthermore, we developed a bioinformatics method for the prospective identification of tumor-reactive B cells based on clonal frequency in the sentinel lymph node.

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The O6-methylguanine-DNA methyltransferase inhibitor O6-benzylguanine enhanced the activity of temozolomide + irinotecan against in vitro and in vivo models of progressive disease high-risk neuroblastoma *Ashly Hindle, Texas Tech University Health Sciences Center; B. Koneru; M. Makena; T. Nguyen; W. Chen; C. Reynolds*

Introduction: Patients with high-risk neuroblastoma (NB) treated with DNA-damaging chemotherapy often relapse with treatment-refractory disease. Temozolomide (TMZ; DNA-methylating agent) and irinotecan (IRN; topoisomerase I inhibitor) are well-tolerated and have clinical activity in relapse/refractory NB. We hypothesized that DNA repair genes with increased expression in alkylator-resistant NB models would provide potential therapeutic targets for enhancing chemotherapy. **Methods:** TaqMan Low Density Arrays (TLDA) were used to analyze mRNA expression of 62 DNA repair genes in 9 alkylator-resistant and 4 alkylator-sensitive NB cell lines. Genes with differential expression were validated in an expanded NB cell line panel (n=26) by qRT-PCR. Gene overexpression was by lentiviral transduction of pLenti plasmid constructs. In vitro cytotoxicity was assayed using a digital imaging microscopy system (DIMSCAN). Double strand DNA breaks, apoptosis, and DNA fragmentation were assessed using phospo-histone H2AX, cleaved caspase-3, and terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL), respectively. In vitro testing used the SN38 active metabolite of IRN. Subcutaneous patient-derived xenografts (PDXs) in nu/nu mice were treated with TMZ, IRN, +/- O6-benzylguanine (O6BG). **Results:** Relative to drug-sensitive NB cell lines, alkylator-resistant NB cell lines showed increased mRNA expression of O6-methylguanine-DNA methyltransferase (MGMT), glutamate-cysteine ligase modifier subunit (GCLM), proliferating cell nuclear antigen (PCNA), and single-strand-selective monofunctional uracil-DNA glycosylase 1 (SMUG1) ($p<0.05$). MGMT, GCLM, and SMUG1 were expressed significantly higher by qRT-PCR in alkylator-resistant compared to alkylator-sensitive models ($n=26$, $p<0.05$). MGMT was selected for further focus due to existence of a clinical-stage inhibitor and relevance to TMZ+IRN. MGMT expression positively correlated with in vitro TMZ+SN38 IC50 ($n=14$, $p<0.05$). Overexpression of MGMT in non-expressing progressive disease NB cell lines significantly decreased TMZ+SN38 cytotoxicity ($p<0.05$). In MGMT-expressing cell lines O6BG enhanced TMZ+SN38 cytotoxicity, H2AX phosphorylation, caspase-3 cleavage, and apoptosis by TUNEL. TMZ+IRN+O6BG increased median event-free survival ($p<0.05$) relative to TMZ+IRN in 2 of 5 MGMT-expressing progressive disease PDX models. **Conclusions:** High MGMT expression is associated with in vitro drug resistance. The MGMT inhibitor O6BG synergistically enhanced the activity of TMZ+IRN in a subset of MGMT-expressing NB models both in vitro and in vivo at clinically achievable drug concentrations. Further studies evaluating MGMT as a therapeutic target in recurrent high-risk neuroblastoma are warranted.

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A drug-repurposing approach to enhance immune effects of chemoradiotherapy *Aurelie Hanoteau, Baylor College of Medicine; J. Newton; C. Huang; R. Krupar; P. Jayaraman; A. Sikora*

Introduction: There is an urgent need for therapeutic strategies capable of reversing the immunosuppressive effects of solid tumors thereby rendering them more susceptible to chemoradiotherapy (CRT). Toward this goal, we have developed a therapeutic regimen using two existing drugs, a selective iNOS inhibitor, L-NIL, and cyclophosphamide (CTX). We have previously shown in syngeneic mouse melanoma models that the combination of L-NIL and CTX can inhibit the intratumoral infiltration of myeloid suppressor cells (MDSC) and regulatory T cells (Tregs), two potent immunosuppressive cell populations induced by CRT. Furthermore, our preliminary data show that while singlet CTX/L-NIL or CRT induce modest tumor regression, their combination improves median survival 1.7-fold compared to singlet treatments and promotes 25% complete tumor rejection. Thus, we hypothesized that CTX/L-NIL could reverse CRT-induced immunosuppressive effects by promoting the development and/or infiltration of a diverse pool of antigen-specific CD8 cytotoxic T cells. **Methods:** To test this hypothesis, we utilized the MTEC syngeneic tumor model transformed with HPV16 oncogenes (E6 and E7) and H-ras. Using this model, we compared immune-related gene expression changes induced by CRT (cisplatin plus 30Gy tumor-directed radiotherapy delivered in 3Gy fractions) and those induced by combinatory treatment (CTX/L-NIL plus CRT) using NanoString Technologies' immune profiling panel. We further confirmed these observations by profiling tumor-infiltrating and systemic immunocyte populations by flow cytometry. **Results:** Compared to CRT, combinatory treatment induced an 8-fold increase in the percentage of CD8 T cells, increased CD8 T cell perforin expression, and promoted a 4.8-fold increase in E7 tetramer-specific CD8 T cells. This suggests that CTX/L-NIL therapy could induce a change in favor of tumor antigen-specific and effector CD8 T cells.

Moreover, the combinatory treatment increased significantly percentages of dendritic cells (DC) (1.8-fold) and macrophages (2.7-fold) in tumor-draining lymph nodes compared to CRT. Our NanoString analysis further corroborated these effects as it showed upregulation of gene sets related to function of both cell populations in tumor after combinatory treatment, suggesting that treatment improves T cell activation by favoring antigen presentation. **Conclusions:** Overall, the enhancements in CD8 T cell specificity and activation as well as the improved treatment response suggests that CTX/L-NIL can enhance susceptibility of immune-refractory tumors to CRT by increasing the DC and macrophage function.

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Initial ex-vivo clinical validation of a dendritic cell-targeting therapeutic HPV vaccine for patients with HPV-related cancers *Falguni Parikh, Baylor College of Medicine; J. Quintana; S. Kang; Q. Yong; L. Wang; J. Patel; B. Kane; S. Oh; J. Woo; E. Chiao; A. Sikora*

Introduction: HIV-related immunosuppression puts patients at increased risk of HPV-related cancers (HPVCA) of the cervix, oropharynx, and anus. Therapeutic vaccination is one approach to treatment of HPV-related cancers; while little is known about the ability of HIV-positive patients to respond to therapeutic cancer vaccines, it is possible that highly immunologically active agents will be required to reverse persistent T cell defects. One such immunotherapeutic approach is the combination of CD40Hvac, a novel therapeutic HPV vaccine comprised of the full-length HPV E6 and E7 proteins fused with a monoclonal antibody to CD40, with a toll like receptor (TLR) agonist to boost innate immunity. Preclinical data suggests that CD40Hvac is highly immunogenic and capable of eliciting E6/7-specific CD8+ T cell responses. The immunogenicity of CD40Hvac is further enhanced by delivering a potent adjuvant such as TLR agonists to the same dendritic cells targeted with CD40Hvac. The goal of this study is to accelerate the application of therapeutic HPV vaccines in HIV/HPV co-infected patients, by determining the preliminary immunogenicity of CD40Hvac and TLR-7 agonist-conjugated CD40Hvac in peripheral blood mononuclear cells (PBMC) collected from HIV-positive HPVCA patients. Our ultimate goal, once immunogenicity of the conjugates is determined for HIV-negative donors, is to test the vaccine in HIV+ patient samples. **Methods:** CD40Hvac fusion protein was produced with a CHO cell line and conjugated to novel candidate TLR7 agonists to create CD40HvacR7. CD40HVac-TLR7 ligand conjugates were tested for their binding to human antigen presenting cells, including DCs, and for their ability to activate cells via TLR7 using TLR7 reporter cell assay. Immunogenicity of the vaccine was tested by determining IFN-γ production from proliferation of CD4+ and CD8+ T cells in PBMC isolated from HIV-negative HPV+ oropharyngeal cancer patients using an IFN-g ELISPOT assay. **Results:** All CD40HVac-TLR7 ligands were able to bind to human antigen presenting cells. In addition, CD40Hvac-TLR7 conjugates were also confirmed to activate cells via TLR7. All the conjugates were capable of inducing HPV-specific responses in ELISPOT assay. **Conclusions:** CD40HVac-TLR7 ligand can efficiently bind to human antigen presenting cells. It can also activate cells via TLR7. Although the immunogenicity of CD40HVac-TLR7 ligand still needs to be confirmed in HIV-positive patients, CD40HVac-TLR7 ligand showed immunogenicity in HIV-negative patients. Thus, CD40HVac-TLR7 ligand could be an effective vaccine prototype for HPV16-associated cancer immunotherapy in the future.

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TGF-b1- reprogrammed myeloid-derived suppressor cells promote long-term control and lose immunosuppressive function *Padmini Jayaraman, Baylor College of Medicine; F. Parikh; J. Newton; R. Krupar; R. Parihar; A. Sikora*

Introduction: Myeloid-derived suppressor cells (MDSC) are induced from myeloid-precursor cells by cancer-mediated signals, and play an important role in tumor immune evasion. TGF-β1 is a highly pleiotropic cytokine abundantly expressed in the tumor microenvironment; while immunosuppressive effects of TGF-β1 on tumor, lymphocytes, and macrophages are well-described, little is known about the direct effects of TGF-β1 on MDSC development. Therefore the goal of this study was to evaluate the effect of TGF-β1 in the generation and function of MDSC, including its effects on T cell proliferation and tumor growth. **Methods:** MDSC were generated from bone marrow of naïve mouse using tumor conditioned medium in the presence (TGFb-MDSC) or absence of TGF-b1 (Control-MDSC). They were further enriched for CD11b+ cells and used in MDSC suppression assay and tumor co-culture assay to assess T cell proliferation and tumor death. Flow cytometry was used to characterize cellular and functional markers. For invivo studies, control or TGFb-MDSC were intratumorally administered in combination with radiotherapy and tumor growth was assessed. **Results:** Control- MDSC upregulated inducible nitric oxide synthase (iNOS), reactive oxygen species (ROS), and arginase, and efficiently suppressed T cell proliferation. In contrast, TGFβ-MDSC failed to upregulate iNOS and lost the ability to suppress T cell proliferation. Conversely, they gained expression of maturation and costimulatory molecules, and acquired enhanced antigen presentation capability. TGFβ-MDSC upregulated FAS-ligand expression, leading to FAS-dependent killing of cancer cells. While intratumoral injection of control-MDSC into established MTEC tumors reversed the beneficial anti-tumor effects of external beam radiotherapy, the combination of TGFβ-MDSC and radiotherapy led to regression and long-term tumor control. TGFβ-MDSC derived from human PBMC with tumor supernatants in the presence of TGF-β1 also developed tumor killing activity and lost immunosuppressive function, associated with downregulation of PD-L1. **Conclusions:** Induction in the presence of TGF-β1 causes myeloid precursor cells otherwise destined to become immunosuppressive MDSC to take on a novel phenotype, with loss of ability to suppress T cell proliferation and acquisition of FAS-dependent killing activity capable of durable tumor control in combination with radiotherapy.

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Curcuminoid Analogs, a Novel Class of Drugs for the Treatment of Glioblastoma Multiforme *Amruthesh Shivachar, Texas Southern University; J. Nnamdiebere; O. Mathews; K. Ranganna; C. Selvam*

Introduction: Glioblastoma multiforme is one of the glial-derived malignant primary brain tumors in adults with a poor prognosis. The average survival period still remains between 14-16 months despite various treatment modalities involving combination of surgery, radiotherapy and chemotherapy with temozolomide, an imidazotetrazine derivative. The robust tumor progression is mainly attributed to its pro-angiogenic and anti-hypoxic targets that many current chemotherapeutics miss. Curcumin (#1) is a plant derived dietary constituent, and has been shown to play a role in preventing many cancers. Here we investigated for the first time the potencies and the molecular mechanisms of action of #1 and its three pyrazole analogs (#7, #20, and #32) on Glioblastoma multiforme cells in culture. **Methods:** The curcuminoid analogs were prepared through an acid catalyzed condensation with various hydrazine derivatives. Heterocyclic pyrazole modification introduces conformational constraint that may be beneficial for improving potency and in vivo chemical stability for these analogs. Cultures of grade IV glioblastoma multiforme (GBM) MG118 cells (5,000/cm2) were treated with various concentrations (0.01-30μmole) of #1, #7, #20 or #32 for 24 hr. along with temozolomide (0.1-300μmole) as positive control. Cell viability/toxicity was assessed by Cell Titer Glo 2.0 Assay kit, and by the fluorescent dyes Hoechst 33342, which stains DNA of both living and dead cells and propidium iodide, which stains the DNA of cells with disrupted membranes. Additionally apoptosis was assessed by TACS Annexin V-FITC Apoptosis detection kit. In the sister cultures, the effect of these analogs on the expression of pro-angiogenic and anti-hypoxic proteins, VEGF, HIF1alpha, and chemokine receptor 4 (CXCR4) was measured by western blotting using GAPDH as loading control. The dose response curves from 3-4 independent experiments with triplicates were plotted, EC50 and statistical significance were calculated using Prism Graph Pad 6.0 version. **Results:** Our results show that the tested analogs dose-dependently decreased cell viability and inhibited cell proliferation in the order #32> #20>> #7> #1>temozolomide, suggesting that #32 and #20 are more cytotoxic (EC_{50} in the ranges of 3-10 μmole) to Glioblastoma multiforme than their parent compound #1 and the currently used standard drug temozolomide. Additionally, we noted that #32 and #20 analogs down-regulated the expression of pro-angiogenic VEGF, and anti-hypoxic HIF1alpha, and the chemokine receptor CXCR4. **Conclusions:** Our preclinical results demonstrate that #32 and #20 may be a novel class of putative drugs for the treatment of glioblastoma multiforme by down-regulation of key targets that are critical for GBMs survival and metastasis.

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Combinatory tumor immunomodulation, radiation, and immune checkpoint inhibition promotes rejection of established HPV-associated tumors *Jared Newton, Baylor College of Medicine; A. Hanoteau; H. Liu; P. Jayaraman; F. Parikh; A. Sikora*

Introduction: Immunotherapy offers significant potential as a treatment for cancer, however, to date immunotherapies have provided minimal benefit in established solid tumors. Many contribute this lack of efficacy to a variety of factors including the immunosuppressive tumor immune microenvironment (TIME), a lack of tumor-specific T-cell generation, and T-cell exhaustion. As a result, the field of cancer immunotherapy is realizing that strategic combinatorial treatments will be necessary to overcome the challenge posed by established solid tumor cancers. **Methods:** In this study, using a syngeneic model of HPV-associated head and neck cancer, we developed a combinatorial treatment strategy optimizing localized tumor irradiation, programed-death receptor-1 (PD-1) immune checkpoint inhibition, and TIME immunomodulation using a previously optimized regimen of cyclophosphamide (CTX) and a selective iNOS inhibitor (LNIL). **Results:** Preliminary data suggests that this combinatorial strategy promotes synergistic treatment effects, with the full

regimen allowing complete rejection of 50% of large established tumors and singlet treatments promoting only minor delays in tumor growth. Furthermore, treated mice that cleared tumor had significant delays in tumor growth upon rechallenge indicating the successful generation of tumor-specific immunologic memory. Immune microenvironment analysis using flow cytometry was further used to provide therapeutic mechanistic insight. Within the tumor-draining lymph node radiation alone promoted enhanced T-cell selectivity as it induced a 19-fold increase in the tumor-specific CD8+ T-cell fraction among total CD8+ T-cells compared to control mice. However, radiation alone also appeared to induce major lymphopenia effects as it promoted a 10-fold depletion in total lymph-node dwelling T-cells with no changes in tumoral T-cell infiltration. Alternatively, CTX/LNIL immunomodulation alone promoted a 1.9-fold increase in tumoral T-cell infiltration as expected with the removal of the immunosuppressive TIME; however, minimal tumor-specific T-cell generation was observed. Finally, when CTX/LNIL and radiation were combined with PD-1 inhibition it reversed radiation T-cell depletion effects, enhanced T-cell tumor-specificity, and promoted better tumoral T-cell infiltration. **Conclusions:** Overall, these data demonstrate that our triple combinatory treatment using localized radiation, PD-1 inhibition, and TIME immunomodulation provides a synergistic treatment effect which can promote immunologic rejection of highly established tumors.

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Exosomal microRNAs as a novel mechanism of resistance to BRAF-V600E inhibitor in melanoma cells *Shaimaa Gad, Texas A&M University System Health Science Center; H. Ali; H. Ali; Z. Abd Elmageed*

Introduction: Metastatic melanoma associated with $BRAF^{V600E}$ (mBRAF) mutation is the main cause of death in 60–80% of skin cancers. Vemurafenib is an effective gene-targeted therapy for the treatment of mBRAF-associated melanomas. A progression-free survival correlates with mBRAF inhibition, however, a growing challenge emerges as a result of resistance to this drug. Thus, identifying the underlying molecular mechanisms by which resistance to Vemurafenib develops in melanoma patients is urgently needed. Hence, we aim to elucidate the anticipated role of exosomal microRNAs (miRs) and their vesicular cargoes in promoting drug resistance in mBRAF-positive melanoma cells. **Methods:** In this study, microarray analysis was utilized to profile the exosomes-derived miRs in Vemurafenib-sensitive and resistant melanoma cell lines. Quantitative real-time PCR, Western blot and other molecular techniques were utilized to validate the content of exosomes-associated miRs and their target genes. **Results:** Our results demonstrated that Vemurafenib-resistant cells exhibit differential expression of miRs and transcripts regarding the Vemurafenib-sensitive cells. Resistant cells had high expression levels of miR-302d and miR-630 compared to parental cells. Various miR-target genes have been identified such as RGS12 and CDC37. These genes were validated on transcript and protein levels. Our ongoing study designed to determine their contribution to drug resistance on the level of cells and melanoma tissue specimens. **Conclusions:** Our findings anticipate the potential role of exosomal miRs and mRNAs in developing Vemurafenib resistance in mBRAF-positive melanoma cells. Further studies are warranted to investigate the role of exosomes-cargoes in promoting such resistance in melanoma cells.

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Targeted cancer therapy: Novel Pyrazolobenzimidazole Conjugates as Checkpoint Kinase 2 (Chk2) Inhibitors *Hamed Ali, Texas A&M University System Health Science Center; S. Galal; B. Standard; S. Khairat; M. Ali; R. El-Shenawy; S. Shouman; Y. Attia; R. Ramdan; H. El Diwani*

Introduction: Recently a dramatic development of the cancer drug discovery has been shown in the field of targeted cancer therapy. Checkpoint kinase (ChK2) inhibitors offer a promising approach to enhance the effectiveness of cancer chemotherapy. **Methods:** In this study, many pyrazole-benzimidazole conjugates were designed and twenty one feasible derivatives were selected to be synthesized and subjected to study their antiproliferative effects against ChK2 activity using CycLex Checkpoint Kinase Assay kit-1. The antitumor activity of these compounds was investigated against MCF-7, Hela, and HepG2 cell lines using SRB assay. The potentiation effect of the synthesized ChK2 inhibitors was investigated using genotoxic drugs as cisplatin and doxorubicin on MCF-7 cells. Furthermore, in vivo ChK2 and antitumor activities of 5-nitropyrazole-benzimidazole carbamoylhydrazone (8d) as single-agents and in combination with doxorubicin were evaluated in breast cancer-bearing animals induced by MNU. In silico study was conducted by docking of the designed and the synthesized compounds into the Chk2 kinase (PDB: 2XBJ) in comparison to the co-crystallized XBJ ligand. **Results:** The revealed potency (IC_{50}) of the studied pyrazole-benzimidazole conjugates ranges from 9.95 to 65.07nM. Interestingly the activity of cisplatin and doxorubicin were potentiated by the effect of acid derivatives and nitropyrazole-benzimidazole conjugates. Whereas, carbamoylthiohydrazones and amide pyrazole-benzimidazole conjugates antagonized the cytotoxicity of both genotoxic agents. The in vivo study exhibited that this combination therapy inhibited the checkpoint kinase activity more than the single treatment. There was a positive correlation between ChK2 inhibition and the improvement in histopathological features. Moreover, the effect of compound 8d alone and in combination with doxorubicin was also studied on cell-cycle phases of MCF-7 cells by flow cytometry analysis. Single dose treatment with doxorubicin or compound 8d produced S phase cell cycle arrest and cell debris. Gold molecular modeling study exhibited high correlation with the biological results. Compound 8d bound into the binding site of ChK2 receptor by four hydrogen and interacted hydrophobically via its aryl and heteroaryl rings. **Conclusions:** Eleven out of twenty one synthesized 2-phenylbenzimidazoles were found to be more potent as a ChK2 inhibitor than the lead compound 1 (IC_{50}=32.40), and the most potent compound 10b (IC_{50} = 9.95). Combinations of the synthesized ChK2 inhibitors with genotoxic drugs as cisplatin and doxorubicin have potentiation effect of on MCF-7 cells. Flow cytometry analysis indicated that compound 8d as doxorubicin encouraged S phase arrest, whereas, the combination of 8d with doxorubicin induced cell cycle arrest at G2/M from 8% in case of doxorubicin to 51 % for the combination.

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Poster Session A

Comparison of a DNA Dosimeter to Conventional Dosimeters for Shallow Depth Radiation Measurements *Brian Quang Bui, The University of Texas Health Science Center at San Antonio; K. McConnell; M. Obeidat; N. Papanikolaou; E. Shem; N. Kirby*

Introduction: Radiation dosimetry plays a large role in cancer therapy by using dosimeters to determine the imparted energy, or dose, to cancer sites. This is important because the energy remaining at a target site is less than when it first originated. Before this decrease occurs, due to the natural attenuation by tissue, a condition called charged-particle equilibrium (CPE) occurs at a specific depth called D-max. Past this point, more accurate measurements can be made. The dose at the shallow depths between the surface of the skin and D-max is difficult to measure with high certainty, and this can be seen by using conventional dosimeters such as films and Optically Stimulated Luminescence Dosimeters (OSLDs) and plotting dose vs. depth to obtain a percentage depth dose (PDD) curve. Typically, this curve is used as a tool to help refine and personalize treatments, so it is very necessary to develop a way to describe dose at shallow depths. During radiotherapy, the fragmentation of double stranded DNA at cancer sites is a direct result from high doses of radiation. With this biological effect, a direct association can be made between the DNA breakages and radiation measurements, as opposed to conventional dosimeters that require correction factors. **Methods:** In hopes of using this for characterizing shallow depth doses, DNA dosimeters were synthesized via polymerase chain reaction and protein immobilization and then compared with OSLDs and GAFCHROMIC EBT3 dosimetry film at varying distances from a 6 MV radiation source. To replicate tissue attenuation, phantoms separately containing the DNA dosimeter, OSLD, and film were subjected to constant machine outputs of 3356 Monitor Units (MUs) for the former and 134 MUs for the latter at four different depths of 0.5 cm, 1.0 cm, 1.5 cm and 10 cm. The variable of interest is the percentage dose. A two-way ANOVA was used to determine any difference or interaction between the three dosimeter and the four depths. **Results:** This result of $p < 0.05$ when comparing at depths suggests there is a difference in percentage dose deposited between depths. With $p > 0.05$ when comparing dosimeter types and for interactions between the factors, the ANOVA results suggest there is no significant effect between the dosimeter types and their interaction at different depths. **Conclusions:** The next step is to increase the sample size and to refine procedures to in order to observe and specify factors of interaction.

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Poster Session B

EphA2 gene targeting using neutral liposomal small interfering RNA (EPHARNA) delivery: A phase I clinical trial *Jing Gong, The University of Texas M.D. Anderson Cancer Center; R. Coleman; A. Naing; G. Lopez-Berestein; S. Fu; A. Tsimberidou; S. Pant; A. Sood*

Introduction: EphA2 is a member of the largest subfamily of receptor tyrosine kinases, with over 14 receptors and 8 ligands. EphA2 overexpression is common in many human cancers, including lung, breast, prostate, colorectal, pancreatic, melanoma, esophageal and endometrial cancers. EphA2 can function as an oncoprotein when introduced into cells with low expression. In addition, downregulation of constitutive expression reduces tumorigenicity in breast, endometrial, ovarian and pancreatic cancers in vitro and in vivo models. EphA2 is a desirable target because of its selective expression in cancer (vs. adult normal

tissue), and its important role in promoting tumor growth and metastasis. It has kinase-dependent and independent functions, making it an ideal target for RNAi-based targeting. We have previously reported that EphA2 siRNA incorporated in DOPC nanoliposomes (EPHARNA) was highly effective in reducing EphA2 protein levels after a single dose. In addition, three weeks of treatment with EPHARNA (150 microg/kg twice weekly) in an orthotopic mouse model of ovarian cancer (HeyA8 or SKOV3ip1) significantly reduced tumor growth compared with non-silencing siRNA, and demonstrated synergistic anti-tumor activity when combined with conventional chemotherapy. EPHARNA underwent GLP development in 2 animal models (murine and primate) at M.D. Anderson to support the IND (#72924). The first-in-human trial (NCT01591356) is ongoing and recruiting study subjects. **Methods: Methods:** Adult Patients > 18 years of age with histologic proof of advanced recurrent solid tumors, who are not candidates for known regimens or protocol treatments of higher efficacy or priority. All patients (dose escalation and dose expansion phases) must be willing to undergo pre- and post-treatment biopsies. For dose expansion phase, patients must have EphA2 overexpression by IHC evaluation. Enrollment is ongoing for the dose escalation with the plan for dose expansion. **Results:** A total 24 patients have been dosed. Infusion related reactions (fever, chills, hypertension) attributed as DLT's in the first dosing cohort required amendments to the trial including, an extension in infusion time, post-treatment hydration and steroids. Currently dose level 3 (1012.5 mcg/kg) is enrolled and nearing its safety window assessment. SAE's were hypertension (n=2), Fever/Chills (N=3), Nausea/Vomiting (N=1). The median number of treatment cycles was 2, range 1 to 6. No objective responses have been observed in the first 2 dosing cohorts, however, 3 patients had confirmed stable disease at 12 weeks. **Conclusions:** Enrollment continues to the dose escalation portion. Dynamic imaging will initiate once the dose level exceeds 1800 mcg/kg.

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Spin-valve based magnetoresistive nanoparticle detector for applications in biosensing *Dmitri Litvinov, University of Houston; W. Qiu; L. Chang; Y. Liang; J. Litvinov; J. Guo; Y. Chen; B. Vu; K. Kourentzi; S. Xu; T. Lee; Y. Zu; R. Willson*

Introduction: Magnetoresistive (MR) biosensors have been studied as a possible alternative to fluorescent and enzymatic biomarker assays. Analog MR sensors are compact, inexpensive to manufacture, highly sensitive, and have shown the ability to detect ~14 16nm Fe3O4 magnetic nanoparticles (MNPs) using high precision electronics. In comparison, the quasi-digital MR sensors developed by our team can detect a single 500nm MNP using simple off-the-shelf electronics. **Methods:** The sensor is comprised of an optimized spin-valve stack (Ta/Ru/Co/Ru/Co/Cu/Co/Ru/Co/Ta) patterned into 700nm X 600nm rectangles. The sensor has two resistance states which depends on the mutual alignment of the magnetization of the two (Co/Ru/Co) trilayers: one trilayer is pinned and the other trilayer switches abruptly at a specific magnetic field. When an MNP is on the sensor, it generates a stray magnetic field that changes the switching field of the sensor. The switching field is monitored to determine the presence of bound MNP(s). **Results:** A digital voltmeter was used to record the sensor's resistance while sweeping an external magnetic field between ±400 Oe. The switching field positions of the sensor were -128 Oe and 126 Oe. For proof of concept, 5 μL of a suspension of 500 nm Fe3O4 nanoparticles in DI water at a concentration of 0.1 mg/ml was pipetted on an alumina-coated sensor. With 10 MNPs on the sensor, the switching field positions shifted to -181 Oe and 179 Oe. The switching field returned to its original state after wiping the MNPs off. To demonstrate single MNP detection, an ultra-sharp tungsten tip was used to artificially position a single MNP on the sensor surface. The switching field position is 110 Oe when there was no MNP above the sensor, and changed to 260 Oe when there is a single MNP on the sensor. **Conclusions:** The fabricated MR sensor demonstrated the detection of ten 500 nm MNPs as well as a single 500 nm MNP. This strategy may be effective in the detection of ultra-low concentrations of biomarkers that are expressed only when the disease is present. The ultimate goal of this project is the ultrasensitive detection of NPM-ALK fusion protein that is expressed in anaplastic large cell lymphoma, the most common T-cell lymphoma in children and young adults. The sensors are inexpensive to manufacture and the reader can be packaged into a low cost portable or mobile system.

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The development of a flow-proteometric platform to quantify on-target binding constant and predict treatment drug response *Chao-Kai Chou, The University of Texas M.D. Anderson Cancer Center; P. Huang; H. Lee; Y. Wang; C. Shi; J. Kameoka; M. Hung; P. Tsou*

Introduction: The use of Flow-proteometric-based single molecule digital platform to quantify biological complexes (proteins and nucleic acids) provides a unique advantage to investigate biological complexes by direct counting. We developed a new method to measure antibody on-target binding constant and complex-biomarker analysis using this technology. Therapeutic antibodies have demonstrated promising success in cancer treatment. However, an antibody with a higher on-target binding efficiency can better suppress the target with less off-target side effects. Thus, we developed a cell-based methodology to directly detect individual antigen-antibody complex after antibody treatment and quantify the on-target dissociation constant (Kd) and off-target ratio. In addition to therapeutic antibody efficacy analysis, complex biomarker measurement can be used to predict cancer drug treatment response. Because signal transduction is delivered primarily via complex formation, the detection of signaling complexes to reveal the signal status is expected to be a better functional biomarker. Since targeted therapy blocks specific cancer signaling pathways, the quantitation and identification of complexes can be used to predict the drug treatment response prior to administering the drug(s) to patients. In summary, the new technology we have developed will enable direct quantification of protein complexes with many potential applications in both drug and biomarker development. **Methods:** To measure the antibody Kd, we counted the target proteins bound to therapeutic antibody in cancer cells. Cetuximab, an anti-EGFR therapeutic monoclonal antibody, was used as a model. EGFR-GFP was expressed in EGFR-null CHO cells, which were then treated with fluorescence-labeled cetuximab at different concentrations. Cells were lysed and subjected to flow-proteometric analysis to count the amount of antibody, EGFR proteins, and antibody-EGFR complexes. The antibody on-target binding affinity and off-target binding ratio was determined based on the amount of interaction. For complex biomarker analysis, lung cancer cells were treated with and without tyrosine kinase inhibitor (TKI) gefitinib for two hours and the EGFR complex biomarker quantified to determine its sensitivity to gefitinib. **Results:** 1) The on-target-Kd of cetuximab in CHO cells with EGFR-GFP expression was 2.3 nM with an off-target ratio of about 30%. 2) Several EGFR complexes, including EGFR-JAK1 and EGFR-Met, were demonstrated for their potential to be used as complex biomarker to predict TKI response. **Conclusions:** We have developed a unique single-molecule detection platform that can evaluate the therapeutic antibody binding efficiency in cells and also measure the quantity of complex biomarker to predict targeted therapy response that can be applied to both drug development and personalized cancer therapy.

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Single molecule protein sequencing *Jagannath Swaminathan, The University of Texas at Austin; A. Bardo; E. Marcotte*

Introduction: The paucity of protein biomarkers in cancer diagnosis can be ascribed to the current technical limitations in discovering the changes occurring in the sequences, abundances and modifications in the ~20,000 proteins that occur in human cells. While a variety of technologies have been applied to this problem, including mass spectrometry and antibody arrays, they generally lack the sensitivity and digital quantitation necessary for the complete characterization of the proteome. **Methods:** Adapting principles of next generation DNA sequencing technologies, we developed fluorosequencing: a single molecule method for sequencing and identifying proteins in a highly parallel fashion. First, we selectively label peptides at one or more amino acid residues (e.g. lysines) with fluorophores. Millions of individual fluorescently labeled peptides are covalently immobilized on a glass surface. The fluorescence intensity of individual peptides are monitored, in parallel, as their N-terminal amino acids are sequentially removed though Edman degradation, providing positional information for the labeled amino acid residues within each peptide (e.g. x-K-x-x-K). The resulting fluorosequence can then be mapped to a reference proteome to identify the originating protein. **Results:** We present the theoretical foundation and experimental implementation of fluorosequencing, confirming its utility and sensitivity. With the help of Monte Carlo computer simulations, we quantitatively characterize the most significant experimental errors. **Conclusions:** We discuss fluorosequencing's potential for identifying and discriminating proteins along with their diverse modification states arising in cancerous cells.

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A Frequency Agile Mixing Front End for Multi-Channel, Multi-Nuclear Spectroscopy *Stephen Ogier, Texas A&M University; M. Wilcox; S. Cheshkov; I. Dimitrov; C. Malloy; M. McDougall; S. Wright*

Introduction: In order to better understand the behavior and treatment of cancer, it is imperative to understand the growth and metabolism of tumors. There are a number of analytical techniques available to this end, but few of them are well suited to the collection of in vivo data. In vivo NMR/MRI is a promising way to study the metabolism of cancer in vivo, but most of the work done so far has been limited to ^{1}H. This stems from the fact that most MRI systems have 16-64 ^{1}H receive channels, but only have a 1-4 receive channels for other nuclei. **Methods:** In order to increase the sensitivity to nuclei other than ^{1}H, it is advantageous to have a large number of receiver channels that are capable of receiving a broad range of nuclei. Using multiple receive channels increases the sensitivity of the NMR experiment. This is almost essential for in vivo study of nuclei such as ^{13}C, which have very poor natural sensitivity. This work shows that radiofrequency mixers can be used to adapt a system's proton array receiver for use with other nuclei, such as ^{13}C or ^{31}P. RF mixers are used to convert the frequency of the received signal from the frequency of the other nucleus to the ^{1}H frequency. By using non-magnetic active mixers, the hardware required to perform this conversion can be located in the scan room or even in the bore of the MRI magnet. **Results:** A frequency translation system has been developed to convert 16 received channels of other nuclei to ^{1}H. This system allows an MRI system's existing ^{1}H receivers to be adapted for use with other nuclei without any decrease in SNR. The system is flexible with regards to MRI field strength and nucleus. Data have been collected at 4.7 and 7T from ^{13}C, and ^{2}H. Additionally, the system is tolerant of ^{1}H decoupling, which can be used to further increase the sensitivity of ^{13}C spectroscopy. **Conclusions:** A frequency translation system has been developed to improve the sensitivity of in vivo NMR of non-^{1}H nuclei. This system allows existing multichannel MRI receivers to be adapted to receive other nuclei, greatly improving the sensitivity of these nuclei. In vivo measurement of ^{13}C NMR spectra will increase our understanding of tumor metabolism and help us to monitor the effectiveness of tumor treatment regimes.

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Poster Session B

A Blood-Based Marker Panel for Detection of Colorectal Neoplasia *Robert Bresalier, The University of Texas M.D. Anderson Cancer Center; J. Byrd; H. Nielsen; D. Brenner; Z. Feng; S. Liu; S. Hanash; A. Taguchi; G. Davis*

Introduction: Numerous screening options exist for colorectal cancer, but 40% of eligible patients in the U.S. are not screened as recommended. Available blood-based markers lack sufficient performance to be used for screening. We sought to determine the performance of blood-based markers for inclusion in a multiplex diagnostic panel. **Methods:** We evaluated serum markers including galectin-3 ligand, MAPRE1, galectin-3, CEA, CYFRA21, ferritin, CRP16 using 2 independent well annotated blinded sample sets. The EDRN set included samples from 94 normals, 50 early- and 50 late-stage cancers, and 101 adenomas. Endosocopy II trial included a similar set of 450 samples. Pairwise correlation and modeling were used to choose final markers for a multiplex assay. **Results:** Galectin-3 ligand demonstrated high performance in differentiating normals from those with cancer (all stages) and advanced adenomas, with blinded verification across sample sets (AUCs vs normal for the EDRN sample set include 0.80 all cancer, 0.84 stages III +IV cancer, 0.77 stages I + II cancer, and 0.78 advanced adenomas), and in another independent blinded EDRN test set designed to mimic cancer prevalence in the US population (AUC=0.89 for cancer vs normal). We tested the hypothesis that a combined score derived from individual markers would be higher than a minimally accepted value set at an AUC of 0.89 for CRC to meet that obtained with FIT (NEJM 2014; 370:1287). We pre-specified a goal of 45% sensitivity at a threshold of 90% specificity for detecting advanced adenomas based on the 23.8% sensitivity (AUC 0.67) for FIT and 42.4% (AUC 0.73) for Cologuard ® for detecting “advanced precancerous lesions”. Four candidate models were chosen based on smallest Akaike (AIC= 2k + Deviance, where k-number of parameters), largest AUC, and smallest number of markers. Models with 2, 3, or 4 marker combinations yielded similar performance in differentiating cancer from normal meeting our pre-specified criterion (AUCs ranged from 0.87 to 0.90). Sensitivities (at 90% specificity) were up to 70% for early stage cancer and 88% for late stage cancer. All models also met our pre-specified criteria for detecting advanced adenoma and screen relevant neoplasia (cancer + advanced adenoma). The 4 marker panel for example yielded (at 90% specificity) sensitivities of 56% for advanced adenoma (64% at 85% specificity) and 68% for SRN compared with 23.8% for FIT and 42.4% for Cologuard®. **Conclusions:** A blood-based marker panel including galectin-3 ligand may provide an alternative to FIT and other stool-based tests for early detection of colorectal neoplasia.

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3D tumor volume measurements for use in monitoring of tumor response to anticancer therapy of patients enrolled in phase I clinical trials *David Vining, The University of Texas M.D. Anderson Cancer Center; A. Pitici; A. Prisacariu; C. Popovici; N. Wagner-Bartak; A. Tsimberidou*

Introduction: Accurate, reproducible, and efficient tumor measurements are essential for serial tumor response assessment. To achieve this aim, we have combined a multimedia radiology structured reporting system with a 3D tumor volume measurement system to automate clinical trial management and analysis. **Methods:** We evaluated a 3D tumor volume measurement software system (Siemens syngo Oncology, Erlangen, Germany) combined with a multimedia structured reporting system developed at our institution, called ViSion, for use in clinical trial management for patients enrolled in Phase I clinical trials. The 3D tumor volume software automates the calculation of short-axis and long-axis diameters of target lesions and generates 3D tumor volume measurements. The ViSion software records the image processing output of the 3D analysis and a radiologist’s verbal descriptions of the image findings and results, tags the images with medical terminology using natural language processing referenced to the SNOMED-CT ontology, and presents a multimedia report with RECIST graphs of target lesions. Data from cohorts can be aggregated to automate the management and analysis of clinical trials, including the generation of Waterfall plots, Progression Free Survival (PFS), Overall Survival (OS), and Kaplan-Meier survival curves. **Results:** The combined Siemens syngo Oncology and ViSion systems has been employed in three IRB-approved clinical trials at the MD Anderson Cancer Center involving 75 subjects, and its use has improved the efficiency of radiological data collection for tumor assessments and clinical trial analyses. **Conclusions:** Multimedia structured reporting combined with automated tumor measurements provides a means to improve the efficiency of clinical trial management and analysis.

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Calculation of medical outcomes using multimedia structured reporting of radiological and pathological data combined with treatment information *David Vining, The University of Texas M.D. Anderson Cancer Center; A. Pitici; A. Prisacariu; C. Popovici; M. Kontak; A. Tsimberidou*

Introduction: The calculation of outcomes is fundamental to the creation of medical knowledge and emerging pay-for-performance reimbursement schema. Radiological and pathological data are core components of medical outcomes, but these data often reside in narrative reports that are plagued by unstructured content, variable descriptions, and discontinuity of data between serial exams which hinders the extraction of information from electronic medical records. We have developed a versatile multimedia structured reporting system that can be used to prospectively create and organize radiological and pathological data along with treatment information (surgery, radiation therapy, and/or chemotherapy) in graphical displays. The timeline organization linking related information enables the automated calculation of medical outcomes for any disease or therapy. **Methods:** We developed a multimedia structured reporting system, called ViSion, which captures key images and a physician’s voice descriptions of image findings from radiological and pathological examinations, tags the images with metadata using natural language processing referenced to standardized ontologies (i.e., controlled vocabularies with defined relationship between terms, such as SNOMED-CT and ICD-10-CM) to describe anatomical locations and diagnostic detail, and assembles a multimedia structured report with related information displayed in graphical timelines. In addition, the system integrates treatment information coded by the CPT, ICD-10-PCS, and RxNorm ontologies. Information at the beginning of a timeline often represents presenting signs/symptoms of disease, whereas the information at the end of a timeline indicates an outcome based on pathological or clinical findings. The graphical representation of information, including tumor metrics, enables the calculation of disease response criteria (e.g., RECIST, irRECIST) for cohorts of subjects enrolled in clinical trials. Data mining tools incorporating the ontological structures have been developed to enable the calculation of population statistics and answer queries such as, what percentage of patients with disease X treated with regimen Y have responded to therapy? **Results:** A solution for creating medical knowledge and calculating outcomes has been developed using a multimedia structured reporting approach that incorporates standardized ontologies and prospective linking of related medical information in graphical timelines from which queries can be performed with accurate and efficient results. The system is currently in beta testing at our institution and has been used to report on the outcomes of 300 subjects enrolled in clinical trials. **Conclusions:** Multimedia structured reporting provides a means to connect interrelated disease and treatment information in graphical timelines from which healthcare outcomes and medical knowledge can be generated. This novel reporting system could form the basis for the next generation of electronic medical records.

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PAtrace: A molecularly targeted nanoparticle platform for preclinical cancer research *Justin Harris, NanoHybrids Inc; B. Henson; J. Cook; K. Homan; C. Kim; S. Emelianov; K. Sokolov; R. Deschner*

Introduction: Photoacoustic (PA) imaging has emerged as a powerful tool in preclinical imaging where optical contrast can be detected at significant depth (up to ~5 cm). Although numerous commercial systems have recently hit the market, their applicability in cancer research is limited. PA imaging has the potential to revolutionize cancer research because it is non-ionizing, portable, and relatively inexpensive. Likewise, with the proper contrast agent, it can provide whole-body molecular specific imaging with high sensitivity and spatial resolution in small animal studies. Thus, we developed a contrast agent – PAtrace – specifically designed to enable PA imaging as a molecular imaging tool for pre-clinical cancer research, accelerating the drug discovery process. **Methods:** PAtrace is a liposomal nanoparticle loaded with J-aggregates of indocyanine green (ICG) dye. This novel construct has: (i) a strong absorbance at ~890 nm where low blood absorbance and tissue scattering results in penetration depth sufficient for whole mouse imaging; (ii) strong PA signal enhancement; and (iii) the capability of enabling simple image processing algorithms for quantitative PA imaging. Targeting and viability for at-depth imaging was confirmed through a murine model of ovarian cancer. **Results:** PAtrace shows greater than 500% PA signal enhancement over gold nanorods and 30% over silica-coated gold nanorods, and has been shown to be non-toxic, both in vitro and in vivo. Efficacy of molecular targeting has been tested in murine models of ovarian cancer using a folate target, showing high specificity and accumulation after systemic injection. Furthermore, in vitro testing shows an uptake pathway-dependent sensing mechanism of J-aggregate breakdown, resulting

in a 100 nm wavelength blue-shift and an emergence of strong near-infrared fluorescence. **Conclusions:** PAtrace shows high photostability, signal enhancement, and targeting capabilities, both in vitro and in vivo. Likewise, the sensing capabilities enabled by the spectral shift and increased fluorescence upon receptor-mediated cellular uptake provides enables a non-invasive photoacoustic (PA) imaging system capable of simultaneous anatomical, functional, cellular and molecular visualization of cancer in small animals. By developing PAtrace, we hope to enable PA imaging to significantly improve preclinical cancer research, expediting the development of new drugs, treatments, and diagnosis platforms.

305 **Poster Session B**

High-flow rate system for rapid isolation CTCs from blood *Andrew Ellington, The University of Texas at Austin*

Introduction: A key to frequent monitoring of cancer patients' response to therapy as well as characterization of oncogenesis is the ability to isolate circulating tumor cells. Unfortunately, these cells are present in vanishingly rare amounts in blood and therefore cannot be found by pin prick blood tests. Traditional cell sorting methods like flow cytometry require relatively large numbers of cells to be present. Other microfluidic methods either operate very slowly, or lack sensitivity and specificity, thereby delaying the possibilities for diagnosis or prognosis. We present a rapid, robust, and highly sensitive and selective method for the isolation of individual tumor cells from standard blood samples, and show how this method is enabling for cancer diagnostics and therapeutics. **Methods:** The basis of the method is a simple but novel patented device that utilizes a unique combination of magnetic capture and flow to directly isolate CTCs from blood. Magnetic beads bearing antibodies against one or more tumor antigens bind to particular cells, which are then in turn captured from a flow stream onto a porous surface. While the magnetic beads themselves can flit through the pores, cells bearing the magnetic beads are too large and are captured in individual pores, and residual cells that are non-specifically captured on the surface can be washed away. Upon removing the magnet, the cells can then be conveniently collected. **Results:** The system achieves capturing of extremely rare cells with 90% or better sensitivity, while discarding more than 99.99% of unwanted blood cells with remarkable speed (2 mL/min of flow rate) and simplicity. The system has so far been tested on 100s of patients of the Indiana University Simon Cancer Center as has been shown to successfully capture CTCs of non-small and small cell lung cancer, pancreatic cancer, breast cancer, bladder cancer and prostate cancer. The system is currently being used to assess how triple negative breast cancer patients with post-surgery residual disease respond to genomically directed therapy. **Conclusions:** The versatility of the system to practically capture any cell that manifests a surface antigen renders it extremely useful for numerous applications. A study in collaboration with the UT Dell Medical School for capture and genetic analysis of fetal cells in maternal is underway. The 8 issued as well as pending patents related to the technology has been licensed for commercialization.

306 **Poster Session B**

Development of the Paratus PreparedNow® System for Detection of Oral Cancer Biomarkers and High-risk Human Papilloma Viruses in Saliva *Shannon Weigum, Paratus Diagnostics; J. Carrano; M. Salmi*

Introduction: Survival rates for oral squamous cell carcinoma (OSCC) and oropharyngeal carcinoma (OPC) are among the lowest for all cancer types and have changed little over the past 30 years. This is often attributed to the advanced stage at which most oral cancers are diagnosed, suggesting that early detection and intervention offers the greatest opportunity to improve patient outcomes. Paratus Diagnostics is developing a low-cost immunoassay platform, called the PreparedNow® Point-of-Care Diagnostic System, to detect oral cancer biomarkers and high-risk human papilloma viruses (HPV-16 and HPV-18) in saliva as a tool for opportunistic screening of patients in dental clinics or other clinical settings. **Methods:** The PreparedNow® System contains three synergistic components: (i) a consumable cartridge for preparation of salivary swab-acquired samples and all immunoassay processing steps to achieve multiplexed chemiluminescent detection in a lateral flow format, (ii) a re-usable mating adapter that aligns a smartphone's CMOS sensor with the cartridge assay detection zone, and (iii) a smartphone with the PreparedNow® App to serve as the quantitative detection instrument. At the heart of the system is the patented ParatusSDS® Cartridge which enables the total automation of complex assay panels at the push of a button, without changing current clinical practice and without the need for special tools or costly equipment. All reagents and fluidic steps are contained within the single-use, disposable cartridge. **Results:** We have developed and tested a prototype device targeting two inflammatory cytokines in saliva (IL-6 and IL-1β) that are closely associated with OSCC development. Each analyte was detectable within physiological ranges (10 pg/mL – 600 pg/mL) using clinically-relevant saliva specimens. Furthermore, we have established 4-plex assay panels targeting non-OSCC/OPC infectious pathogens in saliva that can easily be adapted for detection of high-risk HPVs, which are now recognized as the causative agent in up to 85% of all oropharyngeal carcinomas. **Conclusions:** With additional development and further assay multiplexing, we aim to establish the Paratus PreparedNow® System as a low-cost screening tool to identify patients with elevated levels of OSCC biomarkers and high-risk HPVs. By including this analysis in the early detection of OSCC, care providers will be able to quickly evaluate patient risk, possibly decreasing the need for oral biopsy and increasing the rate of early intervention and treatment for OSCC or OPC.

307 **Poster Session B**

Rapid Specificity Determination and FACS Selection of Plasma Cells for Single Cell Antibody Cloning *Kevin McBride, The University of Texas M.D. Anderson Cancer Center; M. Zelazowska; J. Plummer; Y. Mu; A. Guilmette*

Introduction: Plasma cells (PC) are terminally differentiated antibody secreting cells that are the major source of serum immunoglobulins (Ig). Identifying antigen specific PCs is an important goal for both immunologic studies and monoclonal antibody production. However, the lack of Ig surface expression has impeded direct identification of PCs expressing antigen specific antibodies. **Methods:** We devised a novel method we termed antigen specificity of plasma cell determination (ASPCeD), to isolate live PCs producing antigen specific antibodies from total spleen or bone marrow populations using one-step flow cytometry. Using ASPCeD and existing single cell immunoglobulin amplification and cloning techniques we rapidly produced recombinant antibodies to desired targets. This allows rapid production of sequence defined antibodies on a cost basis lower than existing methods. **Results:** To demonstrate the utility of this technique we immunized mice against several protein, peptides and peptides with post-translational modifications as immunogens, and combined ASPCeD with established single cell immunoglobulin cloning. We rapidly produced sequence diverse, recombinant monoclonal antibodies, highly specific for the targets. Furthermore, we have produced post-translational modification specific antibodies using this technique which include sering phospho-specific and arginine methylation specific antibodies. Other targets include viral proteins and cellular proteins. **Conclusions:** We rapidly produced sequence defined antibodies. The cost basis was lower than existing methods. As a demonstration were able to produce multiple antibodies specific to a desired target in 35 days. Thus, ASPCeD is a novel method to identify antigen specific PCs and an improved means for recombinant antibody production.

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CT-179 selectively targets Olig2-positive glioma stem cells and demonstrates potent anti-tumor activity in glioblastoma *Gordon Alton, Curtana Pharmaceuticals, Inc.; G. Beaton; S. Knowles; S. Kesari; G. Stein*

Introduction: Olig2 is a lineage-specific bHLH transcription factor in normal brain development and has been shown to be a critical oncogene controlling the tumorigenesis, growth, invasion, differentiation and radiation resistance of gliomas, including glioblastoma (GBM). Importantly, Olig2-positive glioma stem-like cells (GSCs) are responsible for the recurrence of disease that occurs in most of the GBM patients. CT-179 is a small molecule (397 kD) that was designed to bind to the dimerization interface of Olig2. **Methods:** Internal research **Results:** Based on comparison to shOlig2 effects in GSCs, the mechanism of action of CT-179 is through modulation of the transcription of Olig2-targeted genes. CT-179 inhibits cellular growth and induces apoptosis of Olig2-expressing GSCs at low nanomolar concentrations (average GI50=154 nM; n=18). CT-179 also causes mitotic catastrophe and a corresponding G2/M arrest of GSCs. The compound is completely water soluble, is nearly 100% orally bioavailable, demonstrates a long duration of pharmacologic action suitable for once daily dosing, and readily crosses the blood-brain barrier. As such, it achieves therapeutically effective concentrations in the brain. Immunohistochemistry demonstrates a reduction of Olig2-positive cells in tumor bearing animals. CT-179 significantly extends survival of mice implanted orthotopically with patient-derived GSCs. Importantly, CT-179 combined with standard of care temozolomide and radiation dramatically inhibits tumor growth compared to either treatment alone. **Conclusions:** CT-179 represents a novel agent which selectively targets GSCs with great potential as an adjunctive therapy in the treatment of GBM and other gliomas.

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Stabilization of b-catenin: a potential therapeutic target for desmoid tumors? *Danielle Braggio, Beta Cat Pharmaceuticals, LLC; D. Koller; F. Jin; A. Zewdu; K. Batte; G. Lopez; R. Soldi; S. Horrigan; L. Casadei; M. Welliver; A. Strohecker; R. Pollock; D. Lev*

Introduction: Desmoid tumors (DTs) are rare mesenchymal lesions that can recur repeatedly. When feasible, DTs are surgically resected; however, this often results in high recurrence rates. While many therapeutic options are available, the standard treatment for desmoids remains uncertain and the overall response to most treatment options remains modest, suggesting a clear ongoing need for better and more individualized approaches. Most DTs commonly feature deregulation of the Wnt pathway. For that reason, the inhibition of Wnt/b-catenin signaling emerges as a potential therapeutic target for these tumors. **Methods:** A panel of DT cell strains was exposed to increasing concentrations of BC2059 in vitro and evaluated for cell proliferation and colony formation capacity. Antitumor effects were assessed in vitro by cell cycle, apoptosis, and migration and invasion analysis. Cells treated with BC2059 were analyzed the association of b-catenin with TBL1 by immunoprecipitation (IP) analysis. To further understand the effects of BC2059 treatment on DTs we analyzed the expression of b-catenin pathway components in DT cell strains treated with BC2059 using real time PCR and western blotting. **Results:** BC2059 markedly inhibited proliferation, capacity of colony formation, migration and invasion of mutated DT cells. In wild-type cells (cell strains lacking detectable b-catenin mutation), BC2059 had no effect on colony formation, migration and invasion and required a much longer time to inhibit cell proliferation. Comparison of b-catenin mutation between the original tumor and the associated cell strain was the primary method used to differentiate desmoid tumor cells from fibroblasts. Therefore, cell strains lacking detectable b-catenin mutation (a rare condition with limited clinical presentation) could be comprised of primarily fibroblast cells and not tumor cells. This is one possible explanation for the lack of effect of BC2059 on DT wild-type cell strains. The decrease in cell viability on mutated DT cells caused by BC2059 was due to apoptosis. Treatment with BC2059 led to a reduction of b-catenin associated TBL1 in all mutated DT cells, resulting in a reduction of nuclear b-catenin. Consequently, levels of genes that are targets of b-catenin (e.g MDK, AXIN2) were found to be downregulated after BC2059 treatment. **Conclusions:** Our findings suggest that BC2059 has significant antitumor activity against b-catenin mutated DTs through stabilization of b-catenin that leads to downregulation of its target genes. Thus, BC2059 may comprise an alternative strategy for the treatment of desmoid tumor patients.

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Investigational new drug (IND)-enabling studies for Sepin-1, a novel Separase inhibitor for triple negative breast cancer (TNBC) therapy *Nenggang Zhang, Baylor College of Medicine; A. Sarkar; D. Pati*

Introduction: Separase is a chromosomal cohesion-resolving enzyme. It is overexpressed in multiple human tumors including TNBC. Separase is an oncogene and its overexpression causes mammary tumorigenesis in mouse models. To modulate the activity of Separase, we identified a small molecular inhibitor called Separase inhibitor 1 (Sepin-1) that inhibits separase activity in a non-competitive way. Sepin-1 inhibits the growth of breast tumor cells in vitro and in vivo. To develop Sepin-1 for preclinical and clinical trial, we have performed a series of IND-enabling toxicokinetics (TK) studies to assess its toxicity in animals. **Methods:** Sepin-1 was administered intravenously (IV) to Sprague-Dawley rats and Beagle dogs to determine the maximum tolerated dose (MTD) of Sepin-1 with a single IV injection and potential toxicity and TK profile, once daily for 7 consecutive days. On Days 1 and 7, blood samples at various time points were collected from animals for TK evaluation. **Results:** A single IV injection of Sepin-1 to rats was toxic at 75 mg/kg. When the dose level was reduced to 40 and 60 mg/kg for males and females, respectively, except for minimal transient clinical signs of urine discoloration and/or hypoactivity, no abnormalities were observed. In 7-day toxicity study, except one female rat death at 50 mg/kg toxicity group during dosing on Day 3, there was no remarkable signs of toxicity observed in animals dosed with vehicle control and/or Sepin-1 at 5 and 20 mg/kg doses. When Sepin-1 was dosed with a single IV injection in Beagle dogs, there was no treatment-related severe toxicological events at 10, 15 and 20 mg/kg, but there were multiple clinical signs of toxicity at 25 mg/kg. When 5 mg/kg or 15 mg/kg of Sepin-1 was administered IV once daily over a period of 7 days, there was no remarkable and/or non-severe treatment-related findings in toxicological parameters. TK analysis indicated that Sepin-1 has a long half-life of 6.6 -10.7h, a high volume of distribution and high clearance in dogs. **Conclusions:** Based on the observation that there are no remarkable clinical findings, body weight changes and macroscopic findings in animals, the MTD of Sepin-1 administered intravenously once in Sprague Dawley rats and Beagle dogs are 50 mg/kg and 20 mg/kg, respectively, and the MTD of Sepin-1 administered once daily for seven consecutive days in rats and dogs are 20 mg/kg and 15 mg/kg, respectively. In both dogs and rats, Sepin-1 has a long half-life and high volume of distribution and clearance.

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Efficacy of AVB-S6 in models of human metastatic cancer and safety profile in GLP studies *Gail McIntyre, Aravive Biologics; R. Miao; D. Prohaska; R. Sheridan; A. Giaccia*

Introduction: AXL receptor tyrosine kinase (AXL) overexpression in highly metastatic cancers is associated with poor prognosis, aggressive tumor behavior, and resistance to therapy. Aravive has engineered long-half-life AXL 'decoy receptors' that bind AXL's sole activating ligand Growth Arrest Specific 6 (GAS6) with higher affinity than endogenous AXL, effectively sequestering GAS6 and abrogating AXL signaling. These decoy receptors reduce invasion/migration of highly metastatic cells in vitro, and inhibit metastatic disease in aggressive preclinical models of human pancreatic, renal, breast, and ovarian cancers. The lead candidate AVB-S6 is effective in treating models of human metastatic cancer and exhibits a benign safety profile. **Methods:** Inhibition of invasion/migration was evaluated in models for triple-negative breast (MDA-MB-231) and ovarian (OVCAR8) cancers using the Corning® Matrigel® or collagen invasion assays, respectively. In vivo efficacy of AVB-S6 alone or combined with doxorubicin was evaluated in the ovarian metastatic cancer xenograft model SKOV3.IP in nude mice. Toxicity was investigated in GLP cynomolgus monkey and mouse studies. In all studies, serum free GAS6 was determined by a proprietary ELISA to guide dose selection into the clinic. **Results:** AVB-S6 significantly inhibited MDA-MB-231 cell invasion/migration exhibiting 100-fold more potency than bosutinib, an approved tyrosine kinase inhibitor. AVB-S6 significantly inhibited OVCAR8 cell invasion/migration induced by GAS6. AVB-S6 monotherapy in the SKOV3.IP mouse xenograft model significantly decreased mean number and weight of macroscopic metastatic lesions at 10 and 20 mg/kg Q2D (equivalent to 2.5-5 mg/kg/week in humans) and abrogated serum free GAS6 levels. In this same model, AVB-S6 and doxorubicin combined significantly decreased mean weights of diseased tissue and cured 2 animals. In cynomolgus monkeys, 5 mg/kg AVB-S6 resulted in abrogation of serum GAS6 for at least 168 hours and a NOAEL of at least 150 mg/kg/day was established in weekly repeat dosing studies. AVB-S6 was well-tolerated in GLP mice studies. Pharmacokinetic/pharmacodynamic modeling as well as extrapolation of mouse efficacious doses predicts 1.5-5 mg/kg AVB-S6 may be efficacious in humans. **Conclusions:** AVB-S6 was shown to be effective in reducing metastatic cancer burden in human breast and ovarian cancer xenograft models and safe in cynomolgus monkeys and mice at much higher doses. These results are similar to those for predecessor decoy receptors with demonstrated efficacy and safety across many oncology models and support the safe use of AVB-S6 in healthy volunteers.

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Poster Session B

Depleting blood arginine with AEB1102 (Pegzilarginase) exerts additive anti-tumor and synergistic survival benefits when combined with anti-PD-L1 *Giulia Agnello, Aeglea BioTherapeutics; M. Badeaux; S. Alters; D. Lowe; S. Rowlinson*

Introduction: Tumor dependence on specific amino acids for survival and proliferation is well recognized and has been exploited effectively in the clinic through the use of asparaginases for the treatment of acute lymphoblastic leukemia. Sensitivity of tumors to L-Arginine (L-Arg) deprivation results from an impaired ability to synthesize L-Arg, most commonly due to decreased functional expression of argininosuccinate synthase. Native human arginase 1 is not a viable drug candidate due to low activity and low stability in serum. We have developed a novel cobalt substituted, PEGylated human arginase 1 (AEB1102, Pegzilarginase) with enhanced pharmacological properties. We and others have successfully utilized arginase 1 to impart an anti-tumor effect through L-Arg starvation in multiple tumor types in vitro and in vivo (e.g. AEB1102 single agent efficacy in melanoma, SCLC, sarcoma, large cell NSCLC, Merkel cell carcinoma). Given that arginase 1 has been reported to be immune suppressive, immune neutral (PMID: 23717444), or immune promoting (PMID: 27043409) in different experimental settings and by different groups, we have investigated the impact of systemic depletion of L-Arg on the anti-tumor efficacy of immune checkpoint inhibitors. **Methods:** Murine syngeneic models (e.g. CT26, MC38) were dosed with AEB1102 alone and in combination with immunomodulatory anti-PD-L1 monoclonal antibody (mAb). **Results:** Combination therapy of AEB1102 with anti-PD-L1 resulted in an additive anti-tumor effect with improved survival benefit (increased life span (ILS) 55-129%) compared to AEB1102 (ILS 29-33%) and anti-PD-L1 (ILS 7-33%) monotherapies. In addition, in the CT26 model, complete tumor regression (non-palpable tumors) was observed in 37% of the mice; importantly, complete responses were observed only in the combination therapy group. When the complete responders were re-challenged with fresh CT26 cells, tumors failed to establish, suggesting the development of an immune memory response as a result of the previously administered combination therapy of AEB1102 and anti-PD-L1. Administration of AEB1102 as a monotherapy or in combination with anti-PD-L1 in the CT26 model was associated with an increase in tumor-infiltrated CD45+ cells, indicating that AEB1102 promotes T-cells accumulation in the tumor microenvironment. **Conclusions:** Collectively, these results demonstrate that in addition to tumor growth inhibition, L-Arg depletion in the tumor microenvironment enhances the effectiveness of immunotherapy. AEB1102 is currently in Phase 1 (monotherapy) clinical trials. These data open the possibility of clinical combination of AEB1102 with immunomodulators of the PD-1 pathway to further improve outcomes in cancer patients.

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Poster Session B

NKT cells expressing a GD2-specific chimeric antigen receptor with CD28 endodomain and IL-15 undergo dramatic in vivo expansion and mediate long-term *Leonid Metelitsa, Baylor College of Medicine; W. Huang; D. Liu; M. Wood; L. Guo; G. Dotti*

Introduction: Vα24-invariant Natural Killer T cells (NKTs) preferentially localize to the tumor site in neuroblastoma and other types of cancer and have natural antitumor properties that make them attractive as a carrier of tumor-specific chimeric antigen receptors (CARs). We previously demonstrated that adoptively transferred NKTs expressing GD2-specific CARs (CAR.GD2) can effectively localize to the tumor site and mediate antitumor activity in a xenogenic model of neuroblastoma in NSG mice. In this study, we explored whether expression of IL-15, the main homeostatic cytokine for NKTs, within CAR.GD2 would further enhance NKT-cell in vivo persistence and therapeutic efficacy. **Methods:** We expanded primary human peripheral blood NKTs using in vitro stimulation with their cognate antigen, -galactosylceramide followed by retroviral transduction with CAR.GD2 constructs, encoding either CD28 or 41BB costimulatory endodomain with or without IL-15. The expanded CAR NKTs were phenotypically characterized by flow cytometry and tested for specific cell-mediated cytotoxicity against GD2+ and GD2- neuroblastoma cells. For in vivo studies, we performed adoptive transfer of NKTs or CAR-modified NKTs to NOD-SCID IL-2R null (NSG) mice engrafted with human neuroblastoma xenografts followed by analysis of NKT-cell persistence and therapeutic efficacy. **Results:** NKTs that were transduced with CD28/IL-15 and 41BB/IL-15 CARs secreted similar levels of IL-15 and significantly improved NKT-cell in vitro expansion compared with IL-15-less CARs in response to repeated stimulation with neuroblastoma cells. After transfer to NSG mice with human neuroblastoma xenografts, NKTs expressing IL-15-containing CARs persisted significantly longer compared with those expressing IL-15-less CARs. NKTs expressing CD28/IL-15 CAR underwent a progressive in vivo expansion at the sites of neuroblastoma metastases. Indeed, the frequency of CD28/IL-15 CAR NKTs reached 30% of bone marrow cells two months after a single injection. Nonetheless, human NKTs did not accumulate in normal murine tissues such as skin or intestine and did not induce xeno-GvHD. Treatment with CD28/IL-15 CAR NKTs on day 7 after tumor injection resulted in the median survival of 70 days compared to the range of 42 - 53 days in untreated control and groups treated with unmodified NKTs or NKTs expressing other CAR.GD2 constructs ($P < 0.001$). **Conclusions:** The use of CD28 costimulatory endodomain and IL-15 in the CAR design enables potent in vivo expansion and anti-tumor activity of CAR.GD2 NKTs cells that should be considered for immunotherapy of neuroblastoma and other solid tumors.

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Poster Session B

Phase 1b randomized, multi-center study of oncolytic adenovirus DNX-2401 for recurrent glioblastoma shows improved survival compared to historical controls *Brett Ewald, DNAtrix, Inc.*

Introduction: DNX-2401 is a conditionally replicative oncolytic adenovirus with enhanced, tumor-specific infectivity that elicits tumor cell killing and antitumor immunity, leading to a long-lasting therapeutic effect. DNX-2401 has been granted Fast Track designation by the FDA and PRIME designation by the EMA for high grade glioma. A product development grant from the Cancer Prevention and Research Institute of Texas (CPRIT) supports the manufacturing and clinical testing of DNX-2401. **Methods:** A multi-center, Phase 1b study of DNX-2401 with or without interferon gamma was conducted to evaluate safety and efficacy in patients with recurrent glioblastoma. Thirty-six patients with biopsy-confirmed glioblastoma at first or second recurrence received a single intratumoral injection of DNX-2401 and were randomized to receive subcutaneous interferon gamma (Actimmune, 50 mcg/m2) three times per week starting 14 days after DNX-2401 (17/36) or to be followed without further treatment (9/36) for safety and survival. Ten additional patients (10/36) received an intratumoral DNX-2401 injection via a specialized cannula (Alcyone MEMS cannula) to test delivery efficiency. **Results:** In the ten patients in which DNX-2401 was administered via the Alcyone cannula, semi-quantitative analyses indicated successful DNX-2401 infusions in all cases, without evidence of backflow. The most frequent DNX-2401-related adverse events were grade 1/2 headache, fatigue, muscular weakness, nausea, and somnolence. Prolonged survival was achieved for patients treated with DNX-2401 (n=36) in comparison to approved therapies for recurrent glioblastoma. **Conclusions:** DNX-2401 was well tolerated and showed clinical activity after a single injection when administered with or without interferon gamma. DNX-2401 administration using a specialized cannula provides a standardized method of intratumoral administration. The clinical benefit provided by DNX-2401 supports continued development of DNX-2401 for recurrent glioblastoma.

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Poster Session B

A humanized antibody blocks LILRB4 receptor-ligand interaction with potent therapeutic efficacy for acute myeloid leukemia *Xun Gui, The University of Texas Health Science Center at Houston; M. Deng; N. Zhang; A. Zhang; Z. An*

Introduction: Leukocyte Immunoglobulin-Like Receptor B4 (LILRB4) is highly expressed on acute myeloid leukemia (AML) cells, suppresses T cell activation and supports AML cells infiltration through its downstream signaling. In contrast to other molecules used as therapeutic targets, which are expressed on a wide range of normal immune cells, LILRB4 expression is restricted to monocytic AML cells. Thus, LILRB4 is a strong candidate target for novel monoclonal antibody (mAb) based therapeutics which are urgently needed for AML treatment. Previously developed immune checkpoint therapeutic antibodies only boost immune activation, but have no effect on tumor cells. Ideally, therapeutics could be developed with multiple mechanisms of action against AML. Better understanding of the interactions of receptors on AML cells and antibodies targeting these receptors will inform the development of mAb therapeutics. **Methods:** Monoclonal antibodies against LILRB4 were generated from single memory B cells from a rabbit immunized with the LILRB4 extracellular domain (ECD) antigen and screened against a battery of in vitro binding and functional assays. One of the functional assays used a stable chimeric receptor reporter cell system which tests the antibody's ability in blocking ligand-receptor interaction. By screening more than 200 LILRB4-specific antibodies, we selected one potent LILRB4 neutralizing antibody for further characterization and optimization as a therapeutic lead which include humanization, epitope mapping, binding affinity, clonal analysis, effect in AML cell migration, T cell activation, and AML cell growth in vitro and in vivo. **Results:** Three concordant anti-leukemia activities were demonstrated in vitro and in vivo for the lead antibody: 1) stimulation of T cell activation, 2) inhibition of monocytic AML cells infiltration, and 3) antibody-dependent phagocytosis (ADCP). **Conclusions:** A panel of LILRB4 targeting antibody was generated and characterized. The antibodies potently inhibit AML cell growth and migration by specifically

and competitively blocking LILRB4 activation by its ligand. These antibodies not only served as tools in validating LILRB4 as a potential drug target for the treatment of AML, but they also can be optimized as drug leads for preclinical and clinical development for AML.

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Poster Session B

Pre-IND Development of Gadolinium Texaphyrin Platinum Conjugates *Jonathan Sessler, The University of Texas at Austin; A. Watts; R. Finch; Z. Siddik; J. Arambula; G. Thiabaud*

Introduction: The FDA approved platinum agents, cisplatin, carboplatin, and oxaliplatin, are among the most important antitumor agents in the clinic. Cisplatin has demonstrated significant activity in several cancer types, but is plagued by intrinsic and acquired resistance that translates into low 5-year survival. Typically, resistance is found to be 2-3 fold higher in wild-type p53 cancers relative to mutant p53 cancers. This constitutes an unsolved problem. As formulated, current platinum drugs do not permit concurrent imaging. The ability to "see" these agents could improve mechanistic understanding and may improve treatment protocols. **Methods:** Texaphyrins are "expanded porphyrin" class of macrocycles that have been explored as experimental therapeutic agents. The gadolinium complex shows strong tumor localizing properties as evidenced by MRI analyses of patients enrolled in clinical studies. In this presentation, we will summarize efforts to develop texaphyrin-platinum conjugates designed to overcome the Pt drug resistance and permit concurrent MRI imaging. **Results:** We have found that by conjugating specific platinum agents to a texaphyrin core, we are able to overcome platinum resistance in a wild-type p53 cell line typically used as an ovarian cancer model. Of particular interest is a conjugate involving Pt(IV) and containing the diaminocyclohexyl ligand. It shows substantially reduced toxicity compared to the FDA-approved agent, oxaliplatin and is just as efficacious or better both in vitro and in vivo in several cancer cell lines and murine models. We have also shown that the texaphyrin core helps facilitate reduction of Pt(IV) to Pt(II), which is the active form. **Conclusions:** This work points the way towards what may be the pre-IND development of a new lead with promise for overcoming platinum resistance in ovarian cancer, lung, colorerctal, and possibly other malignancies. To develop this potential, a new company, Cible, Inc. has recently been launched. Jonathan L. Sessler, Jonathan F. Arambula, and Karen Strand are the cofounders. The company is based in Austin, TX and is actively seeking capital.

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Poster Session B

Estrogen receptor coregulator binding modulators (ERXs) effectively target therapy resisatnt estrogen receptor positive human breast cancers *Ratna Vadlamudi, The University of Texas Health Science Center at San Antonio; G. Raj; G. Sareddy; S. Ma; T. Lee; S. Viswanadhapalli; R. Li; X. Liu; B. Manandhar; S. Murakami; C. Chen; W. Lee; M. Mann; S. Krishnan; V. Gonugunta; D. Strand; R. Tekmal; J. Ahn*

Introduction: The majority of human breast cancer is estrogen receptor alpha (ER) positive. While anti-estrogens/aromatase inhibitors are initially effective, resistance to these drugs commonly develops. Therapy-resistant tumors often retain ER signaling, via interaction with critical oncogenic coregulator proteins. To address these mechanisms of resistance, we have developed a novel ER coregulator binding modulator, ERX-11. **Methods:** We have utilized multiple therapy sensitive and therapy-resistant BCa models with various genetic backgrounds. We tested efficacy using both acquired resistance and engineered models that express ER mutations or oncogenes. Efficacy of combination therapy was tested using established in vitro assays including, MTT, colony formation, apoptosis, and cell cycle progression. Mechanistic studies were conducted using reporter gene assays, gene expression, RNA-seq analysis and signaling alterations. Patient-derived BCa explant and Xenograft studies were used to determine the in vivo efficacy of the combination therapy **Results:** ERX-11 interacts directly with ER and blocks the interaction between a subset of coregulators with both native and mutant forms of ER. ERX-11 effectively blocks ER-mediated oncogenic signaling and has potent anti-proliferative activity against therapy-sensitive and therapy-resistant human breast cancer cells. ERX-11 is orally bioavailable, with no overt signs of toxicity and potent activity in both murine xenograft and patient-derived breast tumor explant models. Co-treatment of ERX-11 with palbociclib synergistically reduced cell viability and induced apoptosis of therapy sensitive and resistant BCa model cells. Importantly, combination therapy of ERX-11 and the palbociclib synergistically reduced the growth and induced apoptosis of tamoxifen and letrozole resistant xenograft tumors compared to either drug alone. **Conclusions:** This first-in-class agent, with its novel mechanism of action of disrupting critical protein-protein interactions, overcomes the limitations of current therapies and may be clinically translatable for patients with therapy-sensitive and therapy-resistant breast cancers.

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Poster Session B

A novel LSD1 inhibitor Seclidemstat as a promising candidate for the treatment of prostate cancer *Ruolan Han, Salarius Pharmaceuticals LLC; R. Vázquez; M. Riveiro; K. Rezai; S. Huguet; M. Bekradda; C. Catapano; B. Jimenez; J. Larson; R. Soldi*

Introduction: Lysine-specific demethylase 1 (LSD1) overexpression correlates with disease progression and castration resistance in prostate cancer. LSD1 is a coregulator of ligand-independent androgen receptor signaling. We examined the antitumor efficacy of LSD1 inhibition with Seclidemstat (SP-2577), a novel small molecule reversible inhibitor of LSD1 in several models of advanced-stage prostate cancer with various status of androgen receptor (AR) expression. **Methods:** A panel of prostate cancer cell lines with various AR status -DU145 and PC3 (AR-), LNCaP (AR-FL), 22RV1 and VCaP (AR-FL and AR-SV7)- and the normal prostate epithelial cell line RWPE-1, were used to examine the cell survival, colony formation, histone methylation, LSD1 expression, LSD1 and AR interaction upon treatment with Seclidemstat. Single-agent in vivo efficacy was examined in 22RV1 xenograft in nude mice in comparison with docetaxel. In vitro combination studies, using Seclidemstat with docetaxel or enzalutamide, were performed to assess the synergy. (AR-FL: full-length androgen receptor; AR-SV7: androgen receptor splice variant 7) **Results:** Seclidemstat potently inhibits the growth of all 5 prostate cancer cell lines tested regardless of AR status, while it has no effect in the proliferation of RWPE-1 cells. Seclidemstat also inhibits the colony formation of DU145, 22RV1and LNCap cells. Seclidemstat treatment causes a dose-dependent increase in H3K9me2 (histone H3lysine 9) levels and a decrease in LSD1 expression in both LNCap and PC3 cells. Seclidemstat treatment also caused a decrease of the LSD1-AR interaction in LNCap cells. Orally-administered Seclidemstat significantly reduced the tumor growth of 22RV1 xenografts in mice comparable to that of docetaxel with no apparent toxicity. Seclidemstat potentiated the anti-proliferative effect of enzalutamide in AR+ prostate cancer cell lines, whereas it is synergistic with docetaxel in both AR+ and AR- cell lines. **Conclusions:** LSD1 inhibition with Seclidemstat shows potent antitumor activity in vitro in both androgen-dependent and independent cell lines and inhibits tumor growth of castration-resistant 22RV1 xenograft in vivo. Seclidemstat also shows promise in combination therapy with standard of care enzalutamide and docetaxel.

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Poster Session B

Phase I trial evaluating genetically modified autologous T cells expressing a T-cell receptor recognizing a cancer/germline antigen in patients with squamous NSCLC or HNSCC (ACTengine® IMA201-101) *Steffen Walter, Immatics Biotechnologies; A. Bourgogne; A. Mohamed; Y. Bulliard; O. Schoor; N. Hilf; K. Sieger; J. Fritsche; A. Satelli; D. Maurer; C. Wagner; L. Alten; S. Bunk; N. Pawlowski; C. Reinhardt; T. Weinschenk; G. Blumenschein; P. Kebriaei; P. Hwu; H. Singh*

Introduction: Immunotherapy has dramatically changed the landscape of therapeutic options in oncology. Adoptive cellular therapy is one of the major drivers of this success, which includes the administration of autologous or allogenic anti-tumor T lymphocytes after ex vivo manipulation and expansion. IMA201-101 is a first-in-human clinical trial testing IMA201 product in patients with recurrent or refractory advanced squamous non-small cell lung cancer (NSCLC) or head and neck squamous cell cancer (HNSCC), whose tumors express the targeted antigen. IMA201-101 is an open-label dose-escalating phase 1 trial investigating safety, tolerability, and signs of biological and clinical activity in end-stage cancer patients. The IMA201 product are T cells engineered to express a naturally occurring (non-affinity maturated) T-cell receptor (TCR) specific to a cancer-germline peptide bound to HLA-A*02:01. The target peptide has been characterized in depth by Immatics' proprietary antigen discovery technology, XPRESIDENT®. The XPRESIDENT® platform applied two independent methodologies to confirm tumor selectivity of the target versus various healthy tissues: i) quantitative immunopeptidome analyses by mass spectrometry and ii) quantitative mRNA expression analyses by RNASeq. The TCR used for IMA201 shows an exceptional specificity profile. TCR-engineered T cells showed specific recognition of tumor cell lines and lack of recognition of healthy normal cells. **Methods:** Only HLA-A*02:01 positive patients expressing the specific target above a pre-defined threshold as determined from a tumor biopsy are eligible for the intended IMA201-101 clinical trial. If a patient meets the enrollment criteria, a leukapheresis is performed to manufacture the autologous, TCR-engineered IMA201 T-cell product. The ACTengine® T-cell manufacturing process uses cryopreserved peripheral blood mononuclear cells isolated from a patient's leukapheresis samples. After activation, the cells are transduced with a lentiviral vector encoding the specific TCR, then expanded before harvest and cryopreservation. The ex vivo expanded IMA201 T-cell product is infused into the pre-

conditioned (lymphodepleted) patient. Patients participate then in an extensive post-infusion biomarker program investigating i) the persistence and functionality of IMA201 T cells in vivo, ii) correlative biomarkers for clinical success, and iii) target expression levels in the tumor before and after the T-cell infusion. **Results: Conclusions:** Overall, the goal of the ACTengine® IMA201-101 is to determine if IMA201 T-cell treatment can safely and effectively manage the tumors of target positive patients with recurrent or relapsed advanced squamous NSCLC and HNSCC.

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Poster Session B

Phase I adoptive cellular therapy trial with autologous, multi-target CD8+ T-cells in patients with relapsed and/or refractory solid cancers (ACTolog®) *Steffen Walter, Immatics Biotechnologies; S. Kuttruff; C. Stewart; A. Mohamed; Y. Bulliard; O. Schoor; A. Satelli; N. Hilf; K. Sieger; J. Fritsche; D. Maurer; C. Reinhardt; H. Ma; T. Weinschenk; H. Singh; C. Yee; A. Tsimberidou; P. Hwu*

Introduction: Immunotherapy has dramatically changed the landscape of therapeutic options in oncology. Adoptive cellular therapy (ACT), which includes the administration of autologous or allogenic anti-tumor T lymphocytes after ex vivo manipulation and expansion, is one of the major drivers of this success. To date, only a relatively small proportion of patients has benefited from these advances due to i) heterogeneity of tumor antigen expression in cancer patients, ii) observance of significant side effects (e.g. expression of targets on normal tissues), or iii) tumor escape (e.g. only one target is addressed). The IMA101 (ACTolog®) concept, utilizing antigen specific T cells, is intended to address these limitations by introducing multiple novel tumor targets, identified by the Immatics' proprietary XPRESIDENT® technology, with an adoptive cellular therapy approach. ACTolog® is a personalized approach where autologous T-cell products are manufactured against the most relevant tumor target peptides (from a predefined target warehouse) for an individual patient whose tumor is positive for at least one target. **Methods:** IMA101-101 is a first-in-human clinical trial in patients with relapsed or refractory solid cancers including but not limited to ovarian, esophageal, gastric and NSCLC whose tumors express at least one (and up to 4) target(s) from a predefined warehouse of 8 cancer targets. Patients will be included depending on their HLA type and the expression of warehouse target(s). As the patients participating in this trial are expected to have a high unmet medical need (e.g. very poor prognosis and/or refractory or recurrent disease following multiple lines of established therapy), treatment with IMA101 T-cell products will take place when patients experience recurrence or progressive disease or if therapy is no longer warranted. Patients will receive their last line of established therapy during the production phase of the IMA101. **Results:** The primary goal of the trial is to assess the safety profile of the underlying concept of autologous T-cell therapy on the basis of targets identified by the XPRESIDENT® platform. **Conclusions:** The ACTolog® concept accounts for: 1) the individuality of each tumor, as a truly personalized warehouse approach, 2) intra-tumoral heterogeneity, as a multi-target approach intended to generate broad anti-tumor activity that is more likely to be effective and that prevents tumor escape or evasion, and 3) the scarcity of suitable tumor antigens for ACT by using novel tumor targets identified by XPRESIDENT®.

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Poster Session B

Optimization of reconstituted High Density Lipoprotein nanoparticles for short-interfering RNA Delivery *Linda Mooberry, University of North Texas Health Science Center at Fort Worth; N. Sabnis; S. Raut; A. Lacko*

Introduction: The objective of these studies was to characterize short-interfering RNA transporting rHDL nanoparticles (rHDL/siRNA NPs) and to evaluate their suitability for translation toward clinical applications. Previous studies have shown that rHDL NPs are capable of promoting the delivery and retention of short-interfering RNA (siRNA) by cancer cells and tumors (Shahzad et al., 2011). **Methods:** Two methods were used to formulate rHDL/siRNA, cholate dialysis, a chemical dispersion process or through the NanoAssemblr™ microfluidics instrument (Precision NanoSystems Vancouver Canada). Characterization of rHDL NPs was carried out using dynamic light scattering (DLS), compositional analysis, transmission electron microscopy, and agarose gel electrophoresis. Efficacy of the rHDL NPs was evaluated through transfection studies utilizing confocal microscopy and Western blotting. **Results:** The size of the rHDL/siRNA complexes by DLS was found to be 68.2 ± 3.0 nm for nanoparticles prepared by cholate dialysis and 35.2 ± 6.0 nm for nanoparticles prepared by microfluidics. However, transmission electron microscopy showed smaller uniform spherical nanoparticles with a diameter of 23.9 nm ± 2.9. The siRNA was encapsulated in a complex as shown by a mobility shift assay with agarose gel electrophoresis. The formulation showed good stability after lyophilization and reconstitution with minimal change in size or loss of RNA content. Knockdown of the target transcription factor STAT-3 was observed in the SKOV-3 ovarian cancer cell line. Evidence for a SR-B1 receptor-mediated uptake mechanism was supported by data from confocal microscopy. The payload uptake, was blocked by an anti-SR-B1 antibody. **Conclusions:** The optimized rHDL/siRNA formulation has a small diameter, good siRNA incorporation efficiency that is biologically active. Importantly for potential clinical applications, this formulation was found to be stable after lyophilization. This study is also the first to report the preparation of NPs with a protein component, using the NanoAssemblr instrument.

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Poster Session B

Clinical safety and efficacy of MDNA55: results of 3 studies in recurrent malignant gliomas *Martin Bexon, Medicenna Therapeutics, Inc.; R. Abi-Habib; R. Merchant; F. Merchant*

Introduction: MDNA55 is a targeted immunotherapeutic agent comprising a circularly permuted interleukin-4 (cpIL-4) fused to a truncated version of Pseudomonas exotoxin A (PE). MDNA55 binds to the interleukin-4 receptor (IL-4R), over-expressed by glioblastoma cells and by non-malignant cells of the tumor microenvironment (TME) such as myeloid-derived suppressor cells (MDSCs). **Methods:** Three clinical trials of MDNA55 (two Phase I and one Phase II) were carried out in patients with recurrent malignant gliomas. Most patients received a single dose of MDNA55 by direct intra-tumoral infusion over a period of 3 to 5 days. 2 patients received up to three doses of the drug. **Results:** A total of 72 patients treated with intratumoral doses of MDNA55 ranging from 6μg to 855μg. The highest concentration administered to patients was 15μg/ml and the highest infusion volume administered 185ml. In study 1, overall survival rates at 6 and 12 months were 71% and 57%, respectively with a median survival of more than 12 months for patients showing tumor response or disease control (68%). Pooled efficacy data from the other 2 studies showed overall survival at 6 months 51% and median survival 210 days, with rapid tumor necrosis observed in 50% of patients with a partial or a complete response. There were no evidence of systemic toxicity following intratumoral infusion nor detectable levels of MDNA55 systemically. There were no deaths attributed to MDNA55 and drug-related adverse events (AEs) were primarily neurological, mostly an aggravation of pre-existing neurological deficits characteristic of patients with GBM or related to cerebral edema following drug infusion. The maximal tolerated dose in GBM patients was 240μg. Approximately 40% of treated patients had elevated systemic titers of anti-MDNA55 IgG antibodies, mostly directed against the PE moiety, for several months following infusion. These were not associated with any clinical sequelae. **Conclusions:** These studies illustrate the tumor selectivity and safety of MDNA55 for the intratumoral treatment of malignant gliomas. They also appear to suggest robust efficacy with favorable response rates and survival compared to historical comparators and a strikingly higher number of subjects with sustained outcomes than might have been predicted. This may be partially due to the immunotherapy-like effects of MDNA55 mediated through its targeting of immunosuppressive MDSCs in the TME. Several features of MDNA55, make it a rational and attractive choice for the treatment of re-current GBM.

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Poster Session B

LSD1 inhibition alone and in combination with chemotherapy in Ewing's sarcoma cell lines *Ruolan Han, Salarius Pharmaceuticals LLC; D. Welch; E. Kahen; C. Cubitt; D. Reed*

Introduction: Ewing Sarcoma (ES) is the second most common primary bone cancer affecting children and young adults. Despite advances in treatment that have led to survival rates of approximately 73% for localized disease, outcomes for patients with metastatic or recurrent ES remain poor. A distinguishing feature of ES is the presence of the EWS/FLI1 fusion in 85% of cases. The fusion has been shown to alter expression of a number of oncogenic genes. Mechanistic studies have demonstrated that the NuRD co-repressor complex interacts with EWS/FLI1. The associated protein LSD-1 contributes to the repressive function by histone modifications. While reversible LSD1 inhibitors demonstrate single agent activity, in preclinical models, a system to evaluate combinations may be needed for optimizing effect in clinical trials. **Methods:** Here, we seek to confirm promising single drug activity and evaluate combination therapies using active chemotherapies currently utilized in ES care (4-HC, etoposide, SN-38, vincristine and doxorubicin) along with the LSD1 Inhibitors SP2509 and SP2577 and romidepsin, an HDAC inhibitor. We evaluated these combinations in high-throughput screening platforms and well-established cell line models for ES (A-673, TC-32, RD-ES, TC-71). Taking into consideration past lessons learned from in vitro experiments, we designed stringent screening conditions that assess the candidate compounds and combinations at clinically-relevant concentrations and exposure times that mimic the in vivo pharmacokinetics in an effort to maximize the translational potential of these results to the clinical setting.

All combinations of agents were studied in two-drug combinations to evaluate for synergy in addition to efficacy. **Results:** IC50 for SP2509 was found to be in the submicromolar range across cell lines with SP2577 being more potent. A-673 and TC-71 were 5-10 fold less sensitive than RD-ES and TC-32. Agents currently utilized in clinic were universally active at clinically achievable concentrations and exposure times. Combinations showed additivity frequently and demonstrated promising activity that can be used to inform further decision making once LSD1 inhibition toxicities are better known. **Conclusions:** These findings suggest potentially promising opportunities for developing combination clinical trials to maximize development of LSD1 inhibitors.

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Illuminating the Role of Kynurenine in Cancer Progression and Treatment *Joseph Dekker, The University of Texas at Austin; N. Ashora; T. Triplett; K. Garrison; J. Blazeck; C. Karamitros; Y. Tanno; C. Lamb; E. Stone; L. Ehrlich; M. Zhang; M. Manfredi; G. Georgiou*

Introduction: Cancer is the second leading cause of death in the United States and, despite progress in treatment options, there is a critical need for novel treatments that limit toxicity to healthy cells while targeting cancerous cells. Our immune system routinely identifies cancer cells and eliminates them prior to clinical intervention. To evade immune clearance, many cancers elevate tryptophan (Trp) catabolism in the tumor microenvironment (TME) by upregulating the enzyme indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3- dioxygenase (TDO). This change in metabolism generates immune suppression in the TME, but whether the cause arises from Trp depletion or the accumulation of the IDO1/TDO product kynurenine (Kyn) remains highly controversial. Kyn is known to induce immunosuppressive phenotypes through aryl hydrocarbon receptor (AhR) activation. However, the functional role of this binding is poorly understood. This work aims to (1) determine Kyn's effect on the immune system and (2) whether its depletion can relieve tumor burden. **Methods:** We observed the in vitro effects of Kyn addition on gene expression patterns and immune cell functionality in murine and human T lymphocytes. We tested the ability of a pharmacologically optimized enzyme, PEGylated kynureninase (Kynu) to safely degrade Kyn into multiple mouse cancer models to assess its effect on (1) tumor growth and (2) TME immune cell composition. **Results:** Exposing T cells to Kyn in vitro results in (1) gene expression changes consistent with T_{reg} generation (FoxP3+CD4+ expansion) and (2) an enhanced ability to repress naïve T cell proliferation, establishing Kyn as a key therapeutic target for relieving TME immune suppression. We next demonstrated that administration of Kynu potently inhibited tumor growth in several mouse models while also generating a significant increase in the infiltration and proliferation of polyfunctional CD8+ lymphocytes. In treated animals, Kynu reduces Kyn concentration in the TME without affecting the concentration of Trp. Notably, we show that Kynu synergizes with clinically approved immune-checkpoint inhibitors, and that Kynu administration alone results in superior efficacy compared to the IDO inhibitor clinical candidate, Epacadostat. **Conclusions:** Kyn accumulation in the TME independently plays a role in cancer's immune evasion and directly induces Foxp3+T_{reg} generation. Elimination of Kyn by an engineered human kynureninase, an ongoing project in our lab, will improve natural immune recognition of multiple tumor types, making it a promising therapeutic candidate. Finally, studying Kynu's efficacy will illuminate details of Kyn's mechanism of action, contributing critical information to diverse field of AhR-mediated immune regulation.

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Dissecting the effect of a novel synthetic retinoid-polymanine conjugate on mRNA and miRNA expression profiles of HaCaT cells *Konstantinos Theofilatos, InSyBio Ltd; K. Grafanaki; C. Kontos; A. Korfiati; S. Mavroudi; D. Anastasakis; I. Skeparnias; G. Kyriakopoulos; D. Papaioannou; A. Skordilas; D. Drainas; C. Stathopoulos*

Introduction: Recently, new synthetic retinoids with elaborate efficiency and minimum side effects have emerged as novel drugs. We have previously established that the novel synthetic N1,N12-Bis(all-trans-retinoyl)spermine (termed RASP) exhibits anti-cancer and anti-proliferative activity, as well as limited toxicity and teratogenicity in rats. The aim of the present study was to evaluate the effect of RASP on HaCaT cells, a model of human epidermis, at the molecular level. **Methods:** A RASP-rhodamine conjugate was used for intracellular localization studies. The RASP IC50 (1μM) supplemented HaCaT culture media. Total RNA was analysed using DNA microarrays (One Array) on a Perkin Elmer platform (ScanArray Express). The small RNAs fraction (<200 nt) was isolated with MiRVana (Ambion) and sequenced on the IonTorrent PGM platform. Bioinformatics analysis was performed using InSyBio Suite for the construction of miRNA mediated networks and functional enrichment. Apoptosis was monitored using confocal microscopy for mitochondrial integrity and DNA damage assays. FACS analysis verified the effect of RASP on apoptosis and cell cycle regulation. **Results:** 1437 downregulated and 416 upregulated genes were detected during the mRNA expression analysis. In addition, 35 upregulated miRNAs targeting 1159 of the downregulated genes and 25 downregulated miRNAs targeting 336 upregulated genes were identified after target prediction analysis. The analysis with InSyBio Suite offers a unique miRNA target-prediction pipeline, which results in scored miRNA target sites in mRNAs with over 95% accuracy. Protein-protein interactions analysis was performed using the miRNA target-predicted genes, resulting in 31 downregulated and 2 upregulated significant genes which are involved in the functional enrichment of important pathways like TRIF-dependent toll-like receptor signalling, positive regulation of G1/S transition of mitotic cell cycle, SMAD protein signal transduction, negative regulation of TGFb receptor signalling and negative regulation of cell growth. Several genes affect the induction of apoptosis and interfere with different cell cycle phases. FACS analysis showed significant cell cycle arrest in G2 phase and DNA damage. Cell cultures at various conditions showed extensive mitochondrial breakdown and DNA fragmentation which is also supportive for the apoptotic path of cells after exposure to RASP. **Conclusions:** RASP is a new synthetic retinoid-based compound with anti-proliferative and anti-cancer effects. Based on our previous studies and current results, we propose that RASP could be used further, in studies which could extend to melanoma and skin cancer treatment. RASP could provide the basis for further development of improved synthetic retinoid analogues without the deleterious effects of previous compounds in use.

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Tegavivint (BC2059), a novel Wnt/β-catenin pathway inhibitor, demonstrates significant anti-tumor activity for osteosarcoma *Motonari Nomura, Baylor College of Medicine; N. Rainusso; R. Shuck; L. Kurenbekova; J. Yustein*

Introduction: Osteosarcoma is the most common bone cancer in children and adolescents. While outcomes have improved through the use of high dose chemotherapy, patients with metastatic disease still have extremely poor prognosis. It has been reported that the activation of Wnt pathway is closely associated with osteosarcoma development and metastatic progression. Tegavivint (BC2059), a novel small molecule inhibitor of the Wnt/β-catenin pathway, has recently been reported to suppress the downstream activity of canonical Wnt signaling and induce apoptosis in AML cells. However, the evidence of its anti-tumor activity against solid tumors has not yet been reported. In this study, we investigated the anti-tumor activity of Tegavivint against human osteosarcoma cell lines and patient-derived xenograft (PDX) tumors in vitro and in vivo. **Methods:** In vitro: Human osteosarcoma cell lines (SaoS-2, LM7 and 143B) and PDX-derived cell lines (PDX22, PDX46, PDX54, PDX63 and PDX84) were treated with Tegavivint for 24 hours and the cell viability was evaluated by CCK-8 assay. In vivo: (1) Orthotopic placement of 1 x10^6 LM7 cells was performed by injecting them into tibia of NSG mice and they were randomized to receive 5x/week intraperitoneal injections of Tegavivint or placebo when tumor volume reached 100 mm^3. (2) PDX63 tumor, which showed inherent resistance to doxorubicin in vitro, was implanted subcutaneously into the right dorsal flank of NSG mice. When the tumor volume reached 100 mm^3, they were randomized to receive 5x/week intraperitoneal injection of Tegavivint and/or doxorubicin. (3) PDX84 tumor, which was derived from relapsed lung metastatic tumor, was dissociated into single cells and injected via tail vein into NSG mice. After one week, intraperitoneal injection of Tegavivint or placebo was initiated and lungs were extirpated after 4 weeks of treatment to evaluate metastasis. **Results:** In vitro: Tegavivint showed anti-proliferative activity against all osteosarcoma cell lines tested in vitro in a dose-dependent manner. In vivo: (1) Orthotopic LM7 tumors were completely eradicated and lung metastasis was significantly suppressed in Tegavivint treatment group. (2) PDX63 tumor growth was significantly suppressed by Tegavivint alone and Tegavivint enhanced the anti-tumor activity of doxorubicin. (3) Lung metastasis was significantly suppressed by the treatment with Tegavivint. **Conclusions:** In summary, our pre-clinical data demonstrate that Tegavivint has promising therapeutic potential for primary and metastatic osteosarcoma. *This work was partially supported by Beta Cat Pharmaceuticals through the Product Development Award CP130058 from the Cancer Prevention and Research Institute of Texas (CPRIT).

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Targeted granzyme B immunotherapy: A novel approach to deliver GrB to Fn14+ solid tumors *Linda Paradiso, Mirata BioPharma, LLC; L. DePalatis; Y. Tu; A. Cienfuego; L. Cheung; K. Mohamedali; J. Winkles; L. Inge; T. Whitsett; M. Rosenblum*

Introduction: All immune effector cells, including engineered T-cells and other immunotherapeutic approaches, rely on the delivery of the serine protease granzyme B (GrB) to target cells resulting in a potent cytotoxic (apoptotic) effect. We developed a platform of novel human constructs for targeted, tumor antigen-mediated delivery of GrB without the need for effector cells. These bivalent constructs incorporate scFv proteins

that bind to cell-surface antigens as Targeted GrB Immunotherapeutics (TGIs). Our initial focus is GrB-Fc-IT4 (MRT-101), a dimeric, bivalent construct that binds the TWEAK receptor fibroblast growth factor-inducible protein 14 (Fn14). This receptor is highly over-expressed in many solid tumors including non-small cell lung cancer. (NSCLC), triple-negative breast cancer (TNBC) and melanoma. High Fn14+ expression is a negative prognostic factor for disease recurrence and survival. **Methods:** MRT-101 (GrB-Fc-IT4), was expressed in HEK293E or Chinese hamster ovary (CHO) suspension cells, harvested under serum-free conditions and purified to homogeneity. Activated caspase cascades and cytochrome C-related pro-apoptotic mechanisms were assessed to confirm consistency with known intracellular functions of GrB. Human tumor xenograft studies were conducted in athymic mice with Fn14+ MDA-MB-231 (TNBC), 5/group, at doses of 4, 8 and 20 mg/kg, and in an Fn14+ NSCLC patient-derived xenograft (PDX) model at 20 mg/kg, 6/group; all doses administered IV every other day for 5 total doses. A pharmacokinetic (PK) study was conducted in mice at 10 mg/kg single-dose and a preliminary toxicology study was conducted in mice at 20 mg/kg x 5 doses. **Results:** Against a panel of >40 human cancer cell lines expressing Fn14, MRT-101 showed high affinity and selective cytotoxicity, with IC50s 4-284 nM and 2-100x greater potency than free GrB. MRT-101 activated caspase cascades and cytochrome C-related pro-apoptotic mechanisms consistent with the known intracellular mechanism of GrB. Dose-dependent TNBC tumor growth suppression was observed at all 3 dose levels versus vehicle controls, with complete tumor regression at 20 mg/kg ($p < 0.06$). The NSCLC PDX study demonstrated >50% tumor growth suppression versus saline controls. Plasma bi-exponential clearance was demonstrated with rapid initial clearance (t ½ alpha = 0.36 hours) followed by prolonged terminal-phase (t ½ beta = 35 hours). No toxicity was seen based on body weight changes, liver enzymes and histopathology. **Conclusions:** MRT-101 represents a new therapeutic class containing a human GrB domain identical to immune effector cells. MRT-101 is currently undergoing IND-enabling studies and GMP manufacturing in advance of a Phase 1 clinical trial in advanced solid tumors.

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Development of a precision oncology approach for the treatment of lymphomas and other cancers *Donald Stewart, Omm Scientific Inc; J. Mackey; R. Heit; L. Berthiaume*

Introduction: Myristoylation critically regulates membrane binding of numerous proteins and signal transduction. It is catalyzed by two ubiquitously expressed N-myristoyltransferases (NMT1 and NMT2) in mammalian cells. The current understanding is NMTs are overexpressed in cancer. **Methods:** Using bioinformatic tools, bisulfite sequencing, HDAC and DNA methylation inhibitors, rationale drug design on first-in-kind target (NMT), click chemistry, cancer cell toxicity assay in vitro using first-in-kind lead candidate and in vivo using xenografts, Western blotting and Wnt-luciferase reporter assays, we show: **Results:** that loss of NMT2 is common in numerous human cancers and occurs mainly through epigenetic mechanisms at especially high prevalence in lymphomas, where it is linked to a worse prognosis. We mechanistically link NMT2 loss to the loss of function of the known myristoylated tumour suppressor Nkd1, which is an obligate negative feedback regulator of the canonical Wnt pathway. Loss of Nkd1 functionality leads to derepression/activation of the Wnt pathway and explains in part the high prevalence of NMT2 loss in numerous cancers. We exploit this NMT2 loss to selectively kill NMT2-deficient lymphoma cells with a potent first-in-class NMT inhibitor, PCLX-001, in vitro and in three B-cell lymphoma xenograft models, and spare normal cells (which have two NMTs). In addition, we have developed a companion diagnostic test using proprietary monoclonal anti-NMT antibodies that enable the identification of patients with NMT2-deficient cancers using IHC and FACS analysis. **Conclusions:** Taking advantage of the epigenetically induced essentiality at one of two NMT loci to inhibit the remaining NMT1 with PCLX-001 represents a novel "synthetically lethal" approach to lymphoma therapy.

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329 **Poster Session B**

Deciphering the impact of radiation therapies at molecular level using biological network based bioinformatics *Konstantinos Theofilatos, InSyBio Ltd; K. Tatsi; S. Mavroudi; A. Georgakilas*

Introduction: Understanding the interaction of different types of ionizing radiation (IR) with healthy and cancer biological samples is an open problem in radiation biology whose solution could be a step towards personalized radiotherapy (RT) and could also contribute towards getting mechanistic insights on radiation-induced carcinogenesis and toxicity. However, using simple differentially expression techniques for the analysis of relative transcriptomics datasets generated after applying different types of IR therapies on cancer tissues results in a large number of genes including many false positive predictions. **Methods:** To overcome this problem, in the present work, we utilized InSyBio's Suite (https://www.insybio.com/pages/suite) in order to locate the genes whose role in the underlying biological networks is significantly altered after the application of different types of IR i.e. high-LET alpha particles and proton radiation (Gene Expression Omnibus Datasets: GSE23899 and GSE21059). These types of radiations are relative to the evolving use of particles for the efficient RT. We pre-processed all datasets to estimate missing values with the k-Nearest Neighbours imputation method, normalized the expression values and split the dataset into subgroups according to their biological condition, e.g. normal samples, cancer samples radiated low dose, etc. Next, for every biological condition, a gene-co-expression network was constructed using a Pearson correlation based method with adaptive threshold for adding edges between two nodes. As a next step, the different co-expression networks were compared using a Pagerank based method in order to identify network modules whose role in the biological networks is significantly altered in different radiation therapy setups. Finally, the uncovered genes were filtered to keep only differentially expressed ones and scored according to their importance. The uncovered gene lists were further analysed to generate their corresponding protein-protein interaction networks, and to functionally annotate them with Gene Ontology and KEGG terms. **Results:** The network-based bioinformatics analysis resulted in short lists of genes whose role in the underlying biological networks is significantly altered when applying alpha particles and proton radiation of various setups. These lists except from genes whose connection with ionizing radiation has already been studied such as RAB31, include other genes such as KLF5 and GP9. **Conclusions:** The identification of genes and their role(s) in a radiation response biological network and how it is altered after the application of different types of IR could be the first step towards deeper understanding the molecular mechanisms of radiation response including radiation-induced immune response and evolution of carcinogenesis.

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SaliPhe prodrugs with improved pharmacokinetics and immune oncology potential *Donald Stewart, Omm Scientific Inc; J. Garcia-Rodriguez*

Introduction: Invasive, metastatic, and therapy resistant cancers are responsible for most cancer deaths. SaliPhe is a potent inhibitor of H+ v-ATPase enzyme complex that is largely responsible for acidification of intracellular and extracellular environments of many aggressive cancers. SaliPhe has been shown to be active against such cancer phenotypes and acts synergistically with current chemo- and radiation-therapies. Acidification of the extracellular environment of a tumor has also been closely linked to suppression of the immune system that otherwise would kill or control cancer cells and tumors. **Methods:** SaliPhe has been prepared by a much more stereoselective and shorter synthesis. Prodrugs of SaliPhe have been prepared and their plasma PK determined with 3 mice/time point for 8 time points over 24h. Based on PK and release of SaliPhe, one prodrug was chosen for assisting antiPD2 immune therapy in a CT26 colon carcinoma syngenic model. BalbC/C57/SAM mice were used with 12-15 male or female mice per arm. A 6 arm study with vehicle, SaliPhe, SaliPhe-Prodrug, anti-PD1, SaliPhe/anti-PD1, and Prodrug/antiPD1. **Results:** Prodrugs had a longer plasma PK profile including one with 3x longer half-life. The activities of SaliPhe and one prodrugs alone and in conjugation with anti-PD1 will be reported. **Conclusions:** SaliPhe and its prodrugs show promise as single anticancer agents with potential to improve immune therapies

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Laser-Initiated Nanosyringes for intelligent chemotherapy *Ryan Deschner, NanoHybrids Inc; J. Kelvekar; J. Cook; K. Homan; S. Emelianov; K. Sokolov; J. Harris*

Introduction: There are over 3,000 cancer drugs currently in development, of which ~90% are classified as poorly water soluble and suffer from limited pharmacokinetics and in vivo stability. Furthermore, many of these drugs require cytosolic delivery. All too often these drugs are abandoned during testing because of poor efficacy resulting in ~$100 billion dollars wasted on failed attempts. To address these limitations, we are developing a nanocarrier system known as Laser-Initiated Nanosyringes (LINs), capable of solubilizing hydrophobic drugs and delivering them into the cytosol of cancer cells. **Methods:** We have constructed a nanoparticle capable of encapsulating hydrophobic drugs, consisting of a perfluorocarbon (PFC) core with an incorporated dye. The LINs are administered intravenously and after specific uptake by cancer cells, illuminated with a near-infrared laser to vaporize the PFC core, rupturing the endosome and delivering the drug into the cytosol. This technology avoids patient pretreatment and the side effects associated with adjuvant-enabled delivery. All components of the platform are biocompatible, modification of the drug molecule is not necessary, and the nanocarrier's lipid shell can be readily conjugated to several targeting moieties. **Results:** In in vitro cell cultures we have demonstrated efficient epidermal growth factor (EGFR) targeting of breast cancer cells, laser-initiated PFC vaporization, and subsequent endosomal

release of hydrophobic drugs, such as Paclitaxel. We have also achieved a high loading of Paclitaxel into the LINs, with low drug leakage and high stability over >2 months. MTS assays of cancer cells treated by Paclitaxel loaded LINs demonstrate effective cancer killing capability, while retaining low toxicity to healthy cells. **Conclusions:** The innovative LINs technology being developed by NanoHybrids, Inc. will allow more of the thousands of new cancer drugs in development to overcome solubility limitations and reach the clinic, giving cancer patients more treatment options and reducing side effects associated with common adjuvants. In addition, the LINs platform can be used to increase the efficacy of cancer drugs requiring cytosolic delivery for effective treatment.

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Impact of Post-Transplant Infusion of Donor T Cells Genetically Modified with Inducible Caspase 9 Safety Switch (BPX-501 Cells) on Outcomes of Children with Leukemia given Alpha Beta T-Cell Depleted HSCT *Vincent O'Neill, Bellicum Pharmaceuticals, Inc.; P. Merli; A. Bertaina; f. Galaverna; M. Algeri; F. Locatelli*

Introduction: HLA-haploidentical allogeneic hematopoietic stem cell transplant (haplo-HSCT) offers an option for children with acute leukemia who lack an HLA-identical donor. T cell depletion reduces the risk of GVHD, but leads to delayed immune reconstitution, predisposing to serious infections and leukemia relapse due to the lack of a graft-versus-leukemia (GvL) effect. To address these challenges, we have infused mature BPX-501 T cells (donor peripheral lymphocytes modified with the iCasp9 suicide gene) after αβ T-cell depleted haplo HSCT to facilitate immune reconstitution and GvL. BPX-501 T-cells are genetically modified with the iCasp9 safety switch and a truncated CD19 marker. In the event of GvHD, the switch is activated by an infusion of the drug rimiducid resulting in rapid T cell apoptosis and GvHD reversal **Methods:** A prospective Phase I-II study enrolling children with hematopoietic disorder who lack a matched donor. 38 patients have been enrolled and treated with αβ TCR depleted haplo HSCT after a myeloablative regimen followed by BPX-T cell infusion to date; 24 had ALL and 14 AML (21% CR1, 79% CR2). Median follow-up is 11 months (range 3-24). **Results:** All patients engrafted with no secondary graft failure. Median time to neutrophil and platelet recovery was 16 days (range 8-33) and 11 days (range 7-19), respectively. With a median follow-up of 11 months (range 3-24 months), the cumulative incidence of NRM and relapse was 3.7% and 12.0%. All aGVHD resolved (5 Grade I skin, 5 Grade II skin, 2 Grade III GI). One child received rimiducid to treat steroid-resistant grade II skin with complete resolution in 24 hours. There were 3 cases of chronic GvHD, 2 were mild; 1 severe and fatal in a patient whose donor had VZV reactivation during mobilization. **Conclusions:** Engraftment was brisk and T cell recovery normalized by 6 months. Overall incidence of severe aGVHD was low and rimiducid infusion successfully activated the safety switch. Cumulative incidence of NRM compares favorably to historic controls. The data suggest that BPX-501 T infused after αβ T-cell depletion, are safe and result in a rapid immune reconstitution and a potentially stronger GvL effect in children with high-risk leukemia who lack a matched donor.

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Antitumor activity of Bcl-2 DNAbilize™ antisense in non-Hodgkin's lymphoma *Ana Tari Ashizawa, Bio-Path Holdings, Inc.; Y. Gutierrez-Puente; R. Ford; G. Lopez-Berestein*

Introduction: Aggressive non-Hodgkin's lymphoma (NHL) progresses rapidly. It makes up about 60% of all NHL cases in the United States. The chemotherapy regimen R-CHOP could cure up to 70% of patients with aggressive NHL, but about 30% of patients relapse from R-CHOP within 2 years of initial treatment. Novel therapeutics are urgently needed for patients with relapsed, aggressive NHL. Bcl-2 is a potential therapeutic target because high expression of Bcl-2 has been correlated with adverse prognosis for NHL patients. The DNAbilize™ antisense technology platform was developed to overcome problems that have been associated with the clinical utility of DNA antisense: drug instability, drug delivery, and non-specific toxicity. The DNAbilize™ antisense, which is a combination of an uncharged P-ethoxy antisense backbone and a neutral liposome delivery vehicle, was utilized to develop BP1002 to inhibit Bcl-2 expression. **Methods:** First, we investigated the potential adverse effects of BP1002 in mice. Normal CD-1 mice were intravenously injected with BP1002 at doses of 7.5, 15 or 30 mg/kg, twice weekly for 4 weeks. Mouse body weight, hematological parameters, liver and kidney functions, and histopathology were used to examine BP1002 potential toxicity. Second, we studied the anti-tumor activity of BP1002 in NHL cell lines. The viability of NHL cells after incubation with BP1002 was determined by the sulforhodamine B cytotoxicity assay. Third, we studied the activity of BP1002 in extending the survival of severe combined immunodeficiency (SCID) mice implanted with NHL xenografts. SCID mice bearing NHL xenografts were intravenously injected with 20 mg/kg of BP1002 or liposome-incorporated control oligodeoxynucleotide twice weekly until they were moribund. **Results:** BP1002, even at 30 mg/kg, was not toxic to normal mice. BP1002 did not decrease mouse body weight, blood parameters, liver or kidney functions. Histopathology did not show drug-related toxicity in major organs examined. On the other hand, BP1002 exerted anti-tumor activity; BP1002 decreased the viability of NHL cells and extended the survival of mice bearing NHL xenografts. At 200 micrograms/mL, BP1002 decreased ≥50% viability in 10 of 13 NHL cell lines. All untreated mice and control mice were moribund in week 5, but only 40% of BP1002-treated mice were moribund. **Conclusions:** Similar to our other DNAbilize™ antisense drugs, BP1002 is safe and can be delivered systemically. Moreover, BP1002 suppresses the viability of NHL cells in vitro and in vivo, indicating that BP1002 is a novel potential therapeutic for aggressive NHL.

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Metallic ions: A promising platform technology against cancer *Zsolt Keresztessy, Ion Biotechnology (USA); D. Stone; J. Kennedy*

Introduction: Ionic metallopharmaceuticals have demonstrated anti-cancer activity, such as cisplatin in chemotherapy which uses the platinum ion. J. W. Kennedy invented a platform technology based on other ionic metals, which is theorized to exploit differences in metabolic cycles of healthy and cancer cells. The platform utilizes proprietary blends of metallic ion coordination complexes in aqueous solution. The first drug candidate, ION-ZC1, is based on copper (II) and zinc (II) coordinated compounds. A series of validations, including dosing, toxicity and efficacy, are currently underway in preclinical models by Ion Biotechnology. **Methods:** Anti-tumor efficacy of ION-ZC1 was tested in a syngeneic mouse melanoma model by subcutaneously injecting B16 metastatic melanoma cells in 30 C57BL/6 mice. Mice with established tumors were then randomized (n=10/group) and topically treated with 17% ION-ZC1 in a cream vehicle, Imiquimod, or control. Anti-tumor efficacy of ION-ZC1 was evaluated by tumor dynamics as presented by tumor volume over time. Measurement of acute toxicity of ION-ZC1 was performed by 0.2 mL tail-vein injection in mice (same strain) with five concentrations ranging from 0.78% to 12.5% using a baby branule system. Mice were monitored for 14 days post injection and analyzed for survival, body weight, blood composition, organ weight, and pathology. **Results:** ION-ZC1 suppressed tumor volume in B16 mouse melanoma more effectively than Imiquimod. ION-ZC1 was not toxic in the four lowest doses. At the highest dose, two mice died after injection (cause unknown), there was minor liver toxicity, and weight gain in liver, brain, and kidneys. **Conclusions:** These pilot studies suggest ION-ZC1 may be an effective and non-toxic treatment in B16 mouse melanoma. Ion Biotechnology, a company formed this year in Texas, is develop this and other metallic ion coordination complexes as candidates for novel anticancer therapies.

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Challenges in manufacturing scale-up of plasmonic gold nanorods: Bringing photothermal therapy to the clinic *Len Pagliaro, Siva Therapeutics Inc; J. Harris; B. Henson; J. Cook*

Introduction: Siva Therapeutics Inc. and NanoHybrids Inc. are developing a simple, safe, and effective cancer treatment - Targeted Hyperthermia™ -for photothermal therapy. Using systemically injected SivaRods™ precision gold nanorods coupled with a SivaLum™ infrared light engine, therapeutic heat is generated within solid tumors. Heat has several beneficial effects for solid tumors, including selective induction of apoptosis in cancer cells, stimulation of the immune system, inactivation of cancer stem cells, and improved drug efficacy through increased perfusion. Targeted Hyperthermia provides precision heating of tumors with minimal collateral damage, and promises to be a valuable adjunct to drug therapy. While awareness of the therapeutic value of hyperthermia has been in the cancer community for many decades, implementing practical, safe, and cost effective hyperthermic therapies has been challenging. Nanotechnology has provided key tools for targeting heat to tumors, and photohermal therapy has demonstrated efficacy in both animal models and recently in the clinic. **Methods:** An important hurdle for photothermal therapy has been scaling up the production of plasmonic gold nanorods to pilot batch size, while maintaining the ideal absorption spectra and uniformity. SivaRods are currently undergoing full characterization of pilot batches of material through a grant from the Nanotechnology Characterization Laboratory, which is supported by the National Cancer Institute, the FDA, and NIST. **Results:** The results of pilot batch scale-up studies, including full physico-chemical characterization, will be shown. Additionally, Siva is developing a second-generation infrared light engine with the ability to illuminate regions of ~10 cm in diameter with high intensity infrared light to excite nanorods that have concentrated in tumors. **Conclusions:** Together, these advances have made nanotechnology-enabled photothermal therapy more practical, safe, and cost-effective than was previously possible. Targeted Hyperthermia is currently in preclinical testing and unapproved by the FDA; it is anticipated that it will be a Class 3 PMA medical device.

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Postpartum HPV Vaccination of Young Women Delivering at a Healthcare Center in Southeast Texas: A Program Assessment *Abbey Berenson, The University of Texas Medical Branch at Galveston; J. Hirth; R. Rupp; K. Sarpong*

Introduction: Effective interventions are needed to address the low rate of human papillomavirus (HPV) vaccination in the United States, particularly among young women. Counseling and offering the vaccine to postpartum women could be an effective strategy to increase uptake among those who did not complete the 3-dose series at an earlier age. The purpose of this evaluation was to assess the effectiveness of a multi-component program designed for postpartum women that used patient navigators and reminders for follow-up visits to improve uptake and completion of the HPV vaccine series. **Methods:** All HPV vaccine-eligible women (N=1,832) were educated about it by specially trained vaccine coordinators within 24 hours of delivery. They were offered the opportunity to initiate or complete the series at no cost to them through CPRIT funding. Follow-up appointments to receive subsequent doses were coordinated with a postpartum visit or at the pediatrician's office where their newborn received care. Women who missed an appointment were called by a vaccine coordinator to reschedule. We evaluated completion rates among participants to determine the effectiveness of this approach. **Results:** A total of 1,340 (73.1%) eligible women agreed to receive the HPV vaccine on the postpartum unit. There were 1,144 women who received their first dose, 102 that received their second dose, and 94 that received their third dose during their hospitalization or shortly thereafter. Of the 999 women who initiated and were eligible to receive the third dose at the time of this analysis, the series completion rate was 84.8%. Only 9.2% of women were lost to follow-up and 6.0% were overdue for the final dose of the vaccine at time of analysis. **Conclusions:** This program achieved a HPV vaccine series completion rate much higher than reported averages for the US and Texas and may be an effective way to reach underserved women who did not get vaccinated at a younger age.

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Medical Student Willingness to Offer the HPV Vaccine by Vaccination Status *Abbey Berenson, The University of Texas Medical Branch at Galveston; J. Hirth; E. Fuchs; R. Rupp; Y. Kuo*

Introduction: The HPV vaccine is an underutilized tool for preventing cancers. Multiple studies have shown that provider recommendation is the best predictor of HPV vaccine uptake. Additionally, a provider's own attitude about the vaccine is a strong predictor of recommendation behaviors. We therefore sought to determine if a provider's personal vaccination status affects willingness to recommend the HPV vaccine. **Methods:** An anonymous, voluntary, 1-page survey was administered to multiple groups of third-year medical students from November 4, 2015 to November 23, 2016 during obstetrics/gynecology clinical rotations at the University of Texas Medical Branch in Galveston. The survey assessed knowledge and attitudes about HPV and the HPV vaccine. Results were analyzed using chi-square for bivariate analyses. Fisher's exact tests evaluated differences for any outcomes with cell counts ≤5. **Results:** A total of 231 students completed the survey and provided information about their personal HPV vaccination status. A higher frequency of students were ≤25 years old and female. Most (58%) were unvaccinated. Vaccinated students were more often ≤25 years old and female. Knowledge did not vary by vaccination status. Significant differences ($p<0.05$) in frequency were observed between vaccinated and unvaccinated students for: a preference to wait until a child is 15–16 years old to recommend the vaccine; willingness to discuss the vaccine when patients come in for other problems, including chronic conditions; and willingness to recommend the vaccine for 9–10 year olds. **Conclusions:** Even though medical students are a well-educated population involved in healthcare, there is still a need for interventions to increase HPV vaccine uptake among them. Vaccinated students appeared to have a stronger commitment to HPV vaccination at every eligible patient encounter than unvaccinated students. Campaigns focused on increasing HPV vaccination among medical students might be an effective way to increase the number of HPV vaccines administered at the CDC-recommended ages.

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Quitxt: A Text-Based Smoking Cessation Service for Young Adults in South Texas *Patricia Chalela, The University of Texas Health Science Center at San Antonio; A. McAlister; K. Gallion; E. Muñoz; C. Despres; D. Akopian; S. Kaghyan; A. Fernandez; R. Diaz; A. Ramirez*

Introduction: Smoking among Latino young adults (18-29) in South Texas is high (23.2% to 25.7%), representing a serious public health problem. Yet few are reached by services to help them quit smoking. Young adults are heavy users of mobile devices for texting and access to mobile media. These have an extraordinary potential for assisting smoking cessation by providing peer modeling and eliciting social reinforcement for behavior change. We present preliminary results of Quitxt a bilingual text messaging and mobile media service to help young adults quit smoking. **Methods:** We constructed a bilingual texting and mobile media system that was promoted in South Texas via social media advertising and other recruitment channels. The ads, which featured couples with different themes (disgust with cigarettes or confidence in quitting success) and styles (cowboy, metro/urban, geek, punk and graphic novel), asked potential participants who showed interest in quitting smoking to text a code to our system corresponding to the channel of recruitment. Text messages include links to web pages with additional content and YouTube videos with peer modeling of reasons and skills to quit smoking. **Results:** Results showed that enrollments were achieved for 798 participants with a mean age of 29.3 and 55% were below the age of 30. More men (57%) than women (43%) enrolled and 36% identified themselves as Hispanic or Latino. The mean number of cigarettes consumed per day was 11.5. Seven-month texted follow up found that 21% (171) of the enrollees reported abstinence at that point. This is consistent with high rates of success found in studies of telephone counseling for young adults and confirms that text and mobile media service specifically designed for young adults provide a feasible and cost-effective approach to promoting cessation. **Conclusions:** Results provide evidence that young adult smokers in South Texas can be reached via mobile media service. The anticipated outcome is a scalable, culturally relevant, evidence-based and cost-effective service with broad national reach to help young adult Latinos stop smoking, with the potential to reduce health care costs, reduce chronic disease burden and improve quality of life among this young, fast-growing, at-risk population.

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Tobacco Dependence Education for Staff and Clinicians at Behavioral Health Centers: Knowledge Gained and Lessons Learned *Bryce Kyburz, Austin Travis County Integral Care; S. Buoy; D. O'Connor; I. Martinez Leal; W. Wilson; V. Correa-Fernández; T. Stacey; L. Reitzel*

Introduction: Cigarette smokers significantly increase their cancer risk. Overall, 14% of adults in Texas smoke. However, smoking is more common among mental and behavioral health center clientele, with rates ranging from 40-75%. Many health clinicians in these settings lack the knowledge and resources to address tobacco use. Taking Texas Tobacco Free (TTTF) is a collaboration between the University of Houston (UH) and Integral Care (IC) to assist behavioral health clinics across Texas in the adoption of a multi-component program that includes providing education on tobacco dependence to all staff and clinicians; cessation resources; specialized training to clinicians and prescribers; and tobacco-free workplace policy development and implementation. This presentation focuses on the education provided to non-clinical staff (no direct clientele contact) and clinicians (direct clientele contact) by outlining knowledge gained via on-site vs webinar-based training and lessons learned in the transition between the modalities. **Methods:** Since 2013, 1- (staff) or 2- (clinicians) hour educational sessions have been provided to almost 5,000 employees working within hundreds of behavioral health clinics. Trainings were conducted by tobacco cessation specialists from UH and IC. A 10-item knowledge test was administered pre- and post-trainings. Initial funding (PP130032) allowed on-site trainings, and dissemination funding (PP160081) piloted live webinar-based administration of trainings. Training content was unchanged. **Results:** Knowledge increase from pre- to post-training was 24.1% for the on-site vs 23.9% for the webinar-based non-clinical staff trainings. Knowledge increase was 24.0% for the on-site vs 19.1% for the webinar-based clinician trainings. The difference between modalities in knowledge gained was statistically significant for clinician trainings ($p=0.040$); however, this difference was equivalent to <1 additional correct response on the knowledge test. Each presentation modality had challenges and benefits, which are reviewed in conjunction with knowledge gain results. **Conclusions:** TTTF has provided behavioral health stakeholders across Texas with an evidence-based tobacco control program that has evolved over time. Movement from on-site to on-line tobacco dependence education trainings for employee stakeholders was one modification. This change made training more efficient and less costly with little sacrifice to knowledge increases among non-clinical staff. Although there may have been potential compromises to knowledge gained by clinicians, the magnitude of the difference may not be significant in practice. This presentation covers the specifics of training implementation, pros and cons of on-site vs on-line trainings, and lessons learned from the transition.

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MHMR Tarrant County: Providing Nicotine Recovery Programs to Behavioral Health and the Community *Lawrence Carter, Mental Health Mental Retardation of Tarrant County; C. Johnson-Harris*

Introduction: MHMR Tarrant's Behavioral Health (BH) Division observed that the majority of individuals receiving mental health and substance use disorder services presented with a co-morbid nicotine dependency diagnosis. Three years ago (MHMRTC) BH Division introduced the successful No Butts/ New Opportunities Smoking Cessation program to its organization. We have revised the program, now called the Nicotine Recovery Program, to continue to address and reduce nicotine dependency throughout the agency. **Methods:** The Nicotine Recovery Program (NRP) was designed to prevent individuals from contaminating their bodies with nicotine and other compound chemicals that are found in non FDA approved nicotine sources. At MHMRTC we provide persons served, staff and the community with education on the effects of nicotine products and harm reduction with 4 to 8 week sessions. We offer the new NRP to these populations, staff, and our youth and young adults in the Tarrant County community. The nicotine user's individualized needs are determined upon entering treatment by administration of the Fagerstrom and NHANES smoking surveys which determine initial level of use. Both surveys are administered at the start and completion of treatment to measure decreased use of nicotine products. Individuals' Carbon Monoxide level in their lungs is tested throughout the 8 sessions, to determine actual decrease of CO in their system. Also, MHMR Tarrant's NRP provides education to the community by participating in community /health fairs. At these events, display tables with pamphlets and outside resources for the participants are set up to view and use. **Results:** Within the last year in the previous program, there were 3,988 self-reported nicotine/tobacco users in 16 clinics. This information was collected from 6,338 Fagerstroms administered by staff within the various clinics. Of the self-reported tobacco users 1,326 individuals reported a willingness to quit. During this reporting period 1,454 (37%) of the self-reported nicotine/tobacco users were enrolled as new program participants. These individuals received services in the form of individual sessions or group sessions—whichever was more convenient for the person. Of those entering the program, 60% (871) completed the smoking cessation program. **Conclusions:** Primary prevention with the NRP is helping those with nicotine addictions and health related issues caused by nicotine products. Our goal has been to encourage use of FDA approved Nicotine Replacement Therapies in Behavioral Health clinics and those in the communities. We provide patches, gum and lozenges to those who chose to refrain from using nicotine products.

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Poster Session B

Developing and Disseminating a Family Health History-based Cancer Genomics Training Program for Hispanic and English Speaking Community Health Workers *Lei Shih Chen, Texas A&M University; S. Zhao; Y. Yeh; K. Nimmons*

Introduction: Cancer, a genomic disease, is the second leading cause of death in Texas. According to the Centers for Disease Control and Prevention, collecting Family Health History (FHH) serves as an initial genomics tool for providers to identify clients' personalized cancer risk. Later, cancer prevention strategies can be tailored to clients based on their individualized cancer risk. Such FHH-based cancer genomics service has been shown to be an effective approach for cancer prevention. Due to the shortage of genetic specialists and difficulties in reaching underserved communities, community health workers (CHWs) are the ideal candidate to provide FHH-based cancer genomics services. Yet, CHWs have not been trained in this topic. To fill this gap, this CPRIT-funded study aimed to develop and disseminate the first FHH-based cancer genomics training program for CHWs in Texas. **Methods:** Our program has two phases. In the development phase, we proposed the FHH-based cancer genomics training curriculum for CHWs in Texas. In the implementation and dissemination phase, partnering with CHW training centers in Texas, we proposed to implement, evaluate, and disseminate the FHH-based program in both workshop and Web-based formats to all CHWs in Texas. **Results:** The cancer genomics training curriculum was developed and reviewed by a research team of health educators, a CHW instructor, geneticists, genetic counselors, and physicians. It was based on the Social Cognitive Theory, the Diffusion of Innovations Theory, and the Theory of Planned Behavior and addressed CHWs' education level, background, and work setting. Given that Texas has a large Hispanic population, the curriculum was translated to Spanish to reach out to more CHWs. The final version of the curriculum was approved by the Texas Department of State Health Services for six certified continuing education hours for CHWs. We plan to pilot both English and Spanish curriculum in early Fall 2017. Based on the findings, the curriculum will be revised, delivered, and disseminated to all CHWs in Texas. Data from the clients served by CHWs will be collected. **Conclusions:** This FHH-based cancer genomics training program is currently in the development phase. Program evaluation data will be presented at the conference. This study is anticipated to increase CHWs' competencies in cancer genomics, which will in turn, reducing cancer mortality and morbidity rates in Texas.

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Poster Session A

Evaluation of the First Family Health History-Based Colorectal Cancer Prevention Workshop for Chinese Americans in Texas: A Preliminary Analysis *Yulyu Yeh, Texas A&M University; M. Li; L. Chen*

Introduction: Cancer is the leading cause of death for Chinese Americans (more than 70% are immigrants) in Texas. Among all cancers, colorectal cancer (CRC) is the second leading cause of death and the most commonly diagnosed cancer among Chinese Americans. With recent developments in cancer genomics, utilizing family health history (FHH) in cancer prevention has shown to effectively promote behavior changes for the Whites, Hispanics, and Blacks. Yet, Asian (Chinese) Americans are underserved in FHH-based cancer prevention. Funded by the Cancer Prevention and Research Institute of Texas, we conducted the first FHH-based CRC prevention workshop for Chinese Americans. The aim of this study is to report the preliminary data regarding the effectiveness of the FHH-based CRC prevention workshop for Chinese Americans. **Methods:** Three hundred and seventy Chinese Americans attended the two-hour, face-to-face FHH-based CRC prevention workshop in Texas. Participants were asked to complete paper-and-pencil questionnaires in the beginning and end of the workshop. A paired sample t-test was used to analyze the data. **Results:** After the workshop, participants' intention, attitudes, and self-efficacy of collecting FHH of CRC from family members, CRC FHH communication with doctors, and knowledge of CRC and FHH significantly improved (ps < 0.01 for all variables). Participants also reported significant increases of perceived benefits of FHH of CRC collection ($p < 0.01$), perceived severity of CRC ($p < 0.01$), and perceived susceptibility of getting CRC ($p < 0.05$). **Conclusions:** The preliminary findings suggest that our FHH-based CRC prevention workshop is an effective way to enhance Chinese Americans' views in FHH of CRC collection and communication with doctors and family members. As collecting and communicating FHH of CRC is the first step in personalized CRC prevention, this study showed initial success of the workshops. Follow-up data will be needed to evaluate behavioral changes.

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Poster Session B

Qualitative Program Evaluation: What program practices and information promote pediatric HPV vaccination? *Jacqueline Hirth, The University of Texas Medical Branch at Galveston; L. Matsushita; L. Cofie; V. Brown; R. Rupp; Y. Kuo; A. Berenson*

Introduction: Texas has a high rate of cervical cancer. Vaccination with the human papillomavirus (HPV) vaccine is expected to greatly reduce the burden of cervical cancer cases. However, vaccination has been suboptimal in Texas. Therefore, a program utilizing patient navigators (PNs) was introduced to increase vaccination of patients at 2 pediatric clinics. The purpose of this study was to identify which program practices and information promoted pediatric HPV vaccination. **Methods:** We collected information on socio-demographic information and conducted semi-structured interviews with 23 caregivers whose children participated in the HPV vaccine program over the phone. Participants included caretakers who had participated in discussions with PNs or clinic providers about the HPV vaccine, and who had a child that initiated the vaccine series in one of the participating clinics. We asked parents to comment on what barriers they faced related to HPV vaccination, and how the program helped them to overcome these problems. Interview data were analyzed using thematic analysis. Nvivo software was used to code themes found in the data. **Results:** Solutions to barriers addressed by the HPV vaccine program that caretakers found to be helpful included: appointment scheduling, appointment reminders, help with cost, and getting information about the vaccine. Parents often mentioned that they would not have completed the vaccine series without the provided reminders. They appreciated that they could get the vaccine regardless of their child's insurance status. Parents also appreciated having someone to ask questions about the vaccine, and mentioned the pamphlets that were passed out by the PNs often. The parents also mentioned specific educational materials that helped them. For example, many said that without being approached, they wouldn't have known that it was available, or that their child was eligible for the vaccine. They also appreciated the chance to discuss vaccine effectiveness and safety with someone before asking their doctor about it or accepting the vaccine. However, some patients still felt that there was not enough research, and misconceptions about the vaccine continued to persist, particularly among parents whose children did not complete the HPV vaccine series. **Conclusions:** Overall, the PN program was perceived as a positive addition to the clinic by parents. They felt that it addressed barriers that they faced when trying to get their children vaccinated. This feedback shows that parents value this program, and indicate that it could be successfully adapted to other clinics.

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Factors Impacting Tobacco Cessation in Behavioral Health Facilities: A Qualitative Analysis *Isabel Martinez Leal, University of Houston; H. Okamoto; S. Shree; B. Kyburz; W. Wilson; V. Correa-Fernández; D. O'Connor; L. Reitzel*

Introduction: Tobacco use is the leading cause of preventable death worldwide and is linked to 40% of all diagnosed cancers. In particular, smoking rates are 2-3 times higher for behavioral health consumers in the US compared to the general population. To address this disparity, it is essential to identify the factors hindering the adoption of tobacco cessation interventions in behavioral health facilities. Taking Texas Tobacco Free (TTTF) is a collaboration between the University of Houston and Integral Care delivering a multi-component tobacco-free workplace program consisting of: education on tobacco dependence to all staff and clinicians, specialized training to clinicians and prescribers, tobacco-free policy development and implementation, integration of tobacco-use assessment and treatment resources, and community engagement and outreach to behavioral health clinics across Texas to treat tobacco use and address second-hand smoke exposure. Here, we identify the factors hindering the adoption of tobacco cessation interventions in participating behavioral health facilities to inform more effective intervention design and implementation efforts. **Methods:** An explorative qualitative study was undertaken between January and April 2017. Three focus groups (ns = 6, 9, and 13) were conducted with clinicians and managers at 3 facilities before program implementation. Thematic analysis and constant comparison were used to code, categorize and summarize data into themes. **Results:** Data analysis yielded 5 themes impacting tobacco cessation efforts: 1) policy parameters and applicability; 2) organizational culture: values and practices; 3) tailoring program to suit community center; 4) staff attitudes towards clients and tobacco-use; and 5) internal conflicts of addiction. These themes reflect factors on the socio-economic-political system, organizational, community, interpersonal and personal levels which interact across levels to either support or impede the implementation of tobacco cessation interventions. **Conclusions:** Because behavior change is both affected and affected by various levels of influence, tobacco control is a multidimensional issue. Reducing or quitting tobacco among behavioral health consumers requires addressing barriers across different levels of influence – systemic, organizational, community, interpersonal and personal levels. This study identified clinicians' perceptions of the various factors influencing tobacco cessation efforts at behavioral health centers. These findings contribute to the development of flexible strategies and tailored interventions that target the reciprocal, multilevel influences impacting tobacco dependence at these different centers, thus enhancing the effectiveness and sustainability of the TTTF program.

345 **CPRIT Grantee Poster Session B**

Implementation of a HPV Vaccination Program in UTMB Pediatric Clinics: What are patient navigator and provider perceptions of remaining barriers to vaccination *Jacqueline Hirth, The University of Texas Medical Branch at Galveston; E. Dinehart; L. Cofie; R. Rupp; Y. Kuo; A. Berenson*

Introduction: Human papillomaviruses (HPV) are the most common sexually transmitted infections in the US. Persistent infection can cause several cancers, including: oropharyngeal, cervical, vaginal, vulvar, anal, and penile cancers. Vaccination with the HPV vaccine is expected to reduce the burden of these cancers. In particular, Texas has experienced a high rate of cervical cancer cases, yet has had suboptimal rates of vaccination since it was introduced. In order to address the low vaccination rates, an HPV Vaccination Program utilizing patient navigators (PNs) was implemented in 2 pediatric clinics. The purpose of this study was to evaluate PN and provider perceptions of the program and remaining barriers to vaccination. **Methods:** We collected demographic information and conducted semi-structured, in-person, audio-recorded interviews with providers (n=14) and PNs (n=7) who participated in the HPV vaccination program between December 2016 and January 2017. Interviews were conducted in a private area in each of the 2 clinics. We asked providers and PNs to comment on barriers to vaccination that remained, as well as what program benefits they perceived. Interviews were analyzed using thematic analysis and co-investigators reviewed interview transcripts to identify major and minor themes. Transcripts were coded using NVivo software and checked for agreement by a second coder. **Results:** PNs and providers felt the vaccination program benefited the clinic by eliminating cost and scheduling barriers, aiding in coordination of follow-up for booster doses, improving provider recommendation, reducing clinic workload, and increasing education. PNs and providers identified a few remaining barriers to vaccination experienced by their patients. These included: concerns about side effects, refusal without giving a reason, and refusal due to the vaccine being not mandatory for school entrance. **Conclusions:** Overall, both PNs and providers perceived the HPV vaccine program as a beneficial addition to the clinic. PNs and providers felt the program addressed traditional barriers to vaccination in the adolescent population such as awareness, cost and lack of provider recommendation. Reduced clinic workload allowed for more time for providers to address questions about the vaccine with parents, or to spend time discussing other important health topics. PN-provided services were seen as a strong facilitator to vaccination. Future adjustments to the program should include providing updated evidence about side effects of the vaccine.

346 **CPRIT Grantee Poster Session A**

Patient and provider barriers to hepatocellular carcinoma prevention through hepatitis C screening and treatment in a county integrated safety net health system *Robin Higashi, The University of Texas Southwestern Medical Center; L. Quirk; S. Lee; M. Jain; B. Turner; A. Singal*

Introduction: Hepatitis C-related cirrhosis is the most common risk factor for hepatocellular carcinoma (HCC). Hepatitis C treatment is the most effective method for HCC primary prevention to reduce future HCC burden in Texas; however, effective implementation of an HCC prevention program through hepatitis C screening and treatment of baby boomers (born 1945-65) in a county integrated safety net system poses several challenges. Analysis of screening rates across 12 Parkland primary care clinics from 2015-2017 indicates uneven and suboptimal uptake of the intervention: overall, < 35% of eligible baby boomers were tested for hepatitis C despite intensive education, training, and electronic medical record (EMR) reminders. This qualitative study aims to identify intervention barriers and facilitators to identify strategies that can enhance implementation of HCC prevention. **Methods:** A multi-level data collection strategy, still in progress, consists of: (1) focus groups with primary care providers/staff; (2) interviews with Liver clinic providers/staff; (3) interviews with primary care providers based on high or low individual screening rates; and (4) interviews with patients at 3 different stages of the screening continuum: antibody (Ab)+ without confirmatory HCV RNA, RNA+ without a Liver Clinic appointment, and Liver Clinic patients. Interview and focus group domains include: knowledge of hepatitis C and available treatments, experiences with the testing and referrals, perceived and/or experienced stigma toward people with hepatitis C, and access to services and treatment. **Results:** Preliminary data reveal: (1) Primary care providers and staff are familiar with hepatitis C screening guidelines but lack understanding of specific procedural requirements, e.g. which tests are required before treatment evaluation; ignoring EMR reminder due to lack of knowledge and/or higher priority clinical concerns; and concerns about delays and rejection of referred patients. (2) Providers and staff at Liver Clinic report patients are eager to learn about hepatitis C and treatment; the vast majority of patients are medication compliant; negative patient experiences are primarily related to complexity and time involved in medication authorization from insurance providers (especially Texas Medicaid); and providers are pleased with clinic modifications to increase efficiency, e.g. expansion of clinic space and staffing. (3) Despite understanding about modes of hepatitis C transmission, Liver Clinic patients report fear of infecting family members, profound gratitude for access to medications, and relief about being cured. **Conclusions:** Qualitative evaluations of providers' and patients' experiences with hepatitis C screening and treatment reveal areas of success and opportunities to enhance prevention at patient-, provider-, and system-levels.

347 **CPRIT Grantee Poster Session B**

Using academic detailing to improve human papillomavirus vaccination rates in south Texas *Raquel Romero, The University of Texas Health Science Center at San Antonio; L. Crocker; B. Flores; E. Villarreal; D. Parra-Medina; D. Morales-Campos*

Introduction: Cervical cancer is the most common human papillomavirus (HPV) associated cancer among Hispanic women. Prevention of cervical cancer is possible through the HPV vaccine; however, HPV vaccination rates for Hispanic adolescents in Texas remain low. Studies show a strong provider recommendation is a factor influencing HPV vaccination. Academic detailing (AD), which uses brief, facilitator-led face-to-face evidence-based education sessions with providers, is one method for increasing provider recommendation for the HPV vaccine. Our two projects are using a Provider Directed Intervention (PDI) using AD sessions, which we designed to give providers key evidence-based messages to use with patients. The purpose of the PDI is to improve vaccination initiation and completion rates for adolescents aged 11-18 years old in five rural counties in south Texas. **Methods:** Research staff collected baseline data including clinic reports on HPV vaccination initiation and completion rates, clinic staff surveys on knowledge and attitudes regarding the vaccine,

and provider interviews about HPV vaccination. Additionally, the study team developed an AD booklet with supplemental materials using the Centers for Disease Control and Prevention's "You are the Key to HPV Cancer Prevention" curriculum, the Immunization Schedule for Preteens and Teens, and The Community Guide. Clinic facilitators will deliver four monthly AD sessions to providers followed by two sessions to develop a strategic plan. Each session will last 30-60 minutes and give providers Continuing Medical Education credits for their participation. The AD sessions cover the following themes: (1) understanding the burden of HPV infection and disease; (2) evidence-based strategies to HPV disease prevention; (3) talking about HPV vaccine to patients; and (4) strategies to improve HPV vaccine coverage. **Results:** Eleven clinics in five Texas counties are participating in the PDI. Two clinic facilitators are collecting baseline data and implementing the PDI in two distinct territories. Reports summarizing baseline data have been shared with the lead provider at four participating clinics, while baseline data is being finalized for four other sites. **Conclusions:** We expect that AD will empower providers to make a strong recommendation for the HPV vaccine and increase HPV vaccine initiation and completion rates in these rural clinic settings. Thus far, providers have been receptive to and interested in our findings, specifically showing interest in decreasing missed opportunities for vaccination, increasing the number of patients offered the vaccine, and developing strategies to remind patients to complete the vaccine series.

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Poster Session A

Increasing HPV vaccination rates in a U.S.-Mexico border community *Amir Hernandez, Texas Tech University Health Science Center at El Paso; J. Molokwu; N. Shokar*

Introduction: Tiempo de Vacunar is an evidence- based program which is designed to reduce HPV related cancer rates in a Hispanic, low-socioeconomic area. The program is tailored specifically to the needs of the community and reached individuals without access to care, HPV vaccines, and health navigation services. **Methods:** Participants were recruited at various events and sites throughout El Paso County by community health workers. Eligibility requirements were those between the ages of 9 and 26, who are Texas residents, who have limited or no insurance, and who have not completed the three dose HPV vaccination series. Eligible participants received a pre-education survey which contained questions on their awareness, knowledge, and intentions on HPV and the HPV vaccine. A brief educational session was then given to the participants; afterwards a post-education survey was administered containing the same set of questions as the pre-education survey in order to measure the changes in knowledge, awareness, and intentions. Finally, participants were administered the HPV vaccine at no cost. Navigation services were then offered to the participant to complete the three dose series over the 6 month dose schedule. Finally, a post program survey was given to assess changes in knowledge, awareness, and intentions since the beginning of the program. **Results:** A total of 1422 participants were recruited, 687 of whom were adults and 735 of whom were children. From these, 1190 (83.7%) completed one dose, 679 (47.7%) completed two doses, and 385 (27.1%) completed three doses. A total of 875 (61.5%) participants initiated the series within the study and 315 (22.15%) initiated outside the study. A total of 454 (31.9%) completed the vaccine series, including 295 (40.1%) children and 166 (24.2%) adults. **Conclusions:** Increasing community awareness and knowledge of HPV vaccine as a means to prevent cervical cancer and providing no-cost vaccine to those who otherwise would not have access to it will impact the community at large by reducing the burden of HPV infection in the community thereby reducing incident cervical cancer in the area.

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349 **CPRIT Grantee**
Poster Session B

Barriers to completion of HPV vaccination series among a mostly Hispanic population in El Paso county *Amir Hernandez, Texas Tech University Health Science Center at El Paso; J. Molokwu; N. Shokar*

Introduction: Published studies have identified numerous barriers to vaccination against the Human Papilloma Virus (HPV). Frequently cost is identified as a barrier; other deterrents reported were low knowledge of the HPV vaccine and HPV itself. A lack of health care provider recommendation of the HPV vaccine has proven to be an important barrier as well. **Methods:** Participants were recruited at various events and sites throughout El Paso County by community health workers. Eligibility requirements were those between the ages of 9 and 26, who are Texas residents, who have limited or no insurance, and who have not completed the three dose HPV vaccination series. A brief education session on HPV, the HPV vaccine, and HPV associated cancers was given. Participants were administered the HPV vaccine at no cost. Navigation services provided by the program allowed participants to complete the three dose series over the 6 month dose schedule. Navigation notes were kept to provide a history of each participant's case. Qualitative data from navigation notes were thematically analyzed. **Results:** Major barriers to HPV vaccination identified by participants included difficulty in getting out of work or school to receive the service. Both young adults and parents of children recognized the difficulty in scheduling the doses around school. Numerous participants stated that they had moved out of town and could no longer receive the vaccine series with the program. Various young women identified pregnancy as a barrier to vaccination; these women became pregnant after intake. The program does not vaccinate pregnant women or breastfeeding women. Some participants no longer wished to participate in the program due to their desire to complete the vaccine series with their primary care provider. Finally, countless participants could not be reached. Various barriers for this included, no answer and no call back, phone was disconnected, voice mailbox was full, and wrong number. **Conclusions:** Several actions were made to decrease the barriers to vaccination for participants. Home visits by the program staff was implemented in order to provide services to participants directly to their homes. Additionally, the program staff has worked on weekends and after work hours in order to accommodate the participant's schedules. A participant who wishes to complete the doses with their principal care provider was encouraged to do so since the program aims to increase HPV vaccine uptake regardless of where they receive the service.

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350 **CPRIT Grantee**
Poster Session A

Perceptions of a faith-based cancer primary prevention program in Hispanic faith communities *Summer Wilmoth, The University of Texas at San Antonio; E. Martinez; L. Carillo; M. Pan; E. Sosa; Z. Yin; D. Parra-Medina; L. Neira; A. Price; M. He*

Introduction: The Building a Healthy Temple (BHT) Program is a translation of the Body and Soul Program in predominately Hispanic church settings in San Antonio, TX. BHT aimed to reduce cancers risks through integrating spiritual and physical health promotion to facilitate lasting healthy lifestyle changes. **Methods:** BHT was a 4-month multi-component program including Health Ministry Committee (HMC), church environmental and policy changes, health sermons, health Bible study, nutrition education and cooking demonstration, Active Living Competition, and Peer Coaching. BHT was delivered by trained church health lay leaders. Focus groups were conducted to solicit insights about BHT feasibility, facilitators, barriers and impact. Using a semi-structured guide, two trained moderators facilitated the discussion. All sessions were audio-taped and transcribed verbatim. Inductive content analysis was performed with strategies e.g., member checking, debriefing, and team-analysis approach to enhance trustworthiness of data interpretation. **Results:** A total of 10 focus groups with 55 participants were conducted. Most participants were females, Hispanic, over the age of 40, employed or retired, and with some college education. 1. Training and support: Lay leaders perceived they received adequate training, though more refresher and online training were warranted. It was suggested that leaders would benefit from mandatory cross training in all components. BHT team's onsite support throughout the program was highly valued. 2. Program delivery: All intervention components were reportedly successfully implemented, except for Peer Coaching, which was only implemented in a few churches in a support group setting. HMC members valued the flexibility of program content and implementation pace. Support from HMC members and pastoral/clergy, leading by example, promotion, community partners and external funding were viewed as program facilitators. Perceived barriers are: heavy burden of paperwork, language and culture, a lack of church instrumental support, church leadership and volunteer transition, and loss of motivation over time. 3. Perceived BHT impact: The BHT was viewed as impactful. The faith-health connection was perceived as necessary in health programming in church settings. Program reception varied by church size, with a higher participation and larger impact reported in small to medium sized churches. Many churches reported healthy environmental and policy changes throughout the program. Participants were optimistic of BHT sustainability through continued HMC and future plans to broaden or re-implement the program. **Conclusions:** BHT took a holistic approach by integrating and promoting spiritual and physical health to reduce cancer risks. Program participants viewed BHT to be feasible, successful, and sustainable in the faith-communities.

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351 **CPRIT Grantee**
Poster Session B

Current efforts to increase human papillomavirus vaccination rates in Starr County, Rio Grande City, Texas *Ana Rodriguez, The University of Texas Medical Branch at Galveston; R. Rupp; K. Yong-Fang; S. Kaul; J. Baillargeon; G. Baillargeon; I. Tijerina; C. Martin; K. Schmeler; M. Edgerton; E. Baker; M. Lopez; S. Fisher-Hoch*

Introduction: Schools are a trusted institution within the community with access to both parents and children. School-based vaccinations are successful in delivering other vaccines and may increase HPV vaccine access and uptake. For our CPRIT funded project, an environmental scan

was used to develop a school-based HPV vaccination model targeting recommended age groups. This collaboration was between Rio Grande City Consolidated Independent School District (RGCCISD), Starr County Health Department, the University of Texas Health Science Center School of Public Health – Rio Grande Valley, the University of Texas MD Anderson Cancer Center, and the University of Texas Medical Branch. **Methods:** We analyzed baseline HPV vaccination rates reported by the RGCCISD and surveyed parents of eligible children aged ≥ 9 years about HPV. The parent survey included: (1) demographic information; (2) an assessment of parental knowledge about the HPV vaccine; and (3) information about their children and HPV vaccine experience, including reasons for not receiving the HPV vaccine, having children who graduated high school that received the HPV vaccine, and their children's current enrollment status in the Texas Immunization Registry (ImmTrac). A comparison between baseline HPV vaccination rates of RGCCISD and National Immunization Survey-Teen (NIS-Teen) was made. Descriptive statistics for the parent survey are in progress. **Results:** Based on vaccination data reported by RGCCISD, as of 09/01/2016 there were 7,606 students aged ≥ 9 years in RGCCISD, of which 12.2% completed the HPV vaccine. Baseline HPV vaccine completion rates were lower for RGCCISD students aged 12-14 years compared to students aged 9-11 and ≥ 15 years (6% versus 15%). Among RGCCISD students aged 12-14 years, 30% received 1 dose and 6% received 2 doses. RGCCISD HPV vaccine completion rates were higher among females aged 12-14 years than males (6.5% versus 4.9%). HPV completion rates for RGCCISD adolescent females and males at baseline was substantially lower than those reported in NIS-Teen (National completion rate: 42% and 28% versus Texas: 41% and 24% respectively). **Conclusions:** Baseline HPV vaccination rates in RGCCISD are far below national and state averages and do not meet the Healthy People 2020 goal of 80%. Using results from our environmental scan, we will pilot a school-based vaccination program at 1 middle school in August of 2017 and expand to 4 additional middle schools in 2018, with the goal of significantly increasing HPV vaccination rates in the region.

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Poster Session A

Effectiveness of hepatitis C therapy as a strategy for hepatocellular carcinoma prevention in difficult-to-treat patients in a safety-net health system *Mamta Jain, The University of Texas Southwestern Medical Center; C. Yek; C. de la Flor; J. Marshall; C. Zoellner; G. Thompson; L. Quirk; C. Mayorga; B. Turner; A. Singal*

Introduction: Hepatocellular carcinoma (HCC) has the fastest increasing incidence among all solid tumors in Texas, largely related to the large burden of patients with advanced hepatitis C virus infection. Hepatitis C therapy offers a key strategy for primary and secondary prevention of HCC, with significantly lower HCC rates for patients who achieve sustained viral response (SVR) than untreated patients. Direct-acting antivirals (DAAs) have revolutionized hepatitis C treatment, with far higher SVR rates than prior treatments, but evidence for real-world effectiveness is lacking among vulnerable populations. Because HCC prevention given HCC disproportionately affects racial/ethnic minorities and uninsured patient populations, studies in these groups are greatly needed. This study was conducted to characterize effectiveness of DAAs in a racially diverse and low income patient cohort. **Methods:** This retrospective observational study included all patients undergoing hepatitis C treatment with DAA-based therapy between April 2014 and June 2016 at a large urban safety-net health system (Parkland Health and Hospital System, Dallas, Texas). Many of these patients were diagnosed through a CPRIT supported infrastructure. The primary outcome was SVR defined as an undetectable viral load 12 weeks after end of treatment, with secondary outcomes including: treatment discontinuation, treatment relapse, and loss to follow-up. **Results:** DAA-based therapy was initiated in 512 patients who were mostly male (56%), Black (44%), median age 58 years, treatment experienced (16%), and cirrhotic (51%). The cohort was 56% uninsured and 13% Medicaid with high rates of homelessness (10%), alcohol and substance use (41% and 50%, respectively), and mental health disorders (38%). SVR was achieved in 94% of patients (n=459) with a follow-up SVR. SVR was significantly less likely in patients with decompensated cirrhosis (OR 0.37, 95%CI 0.16-0.85) but did not differ by insurance status (p=0.98), homelessness (p=0.77), alcohol/substance use (p=0.34), or mental disorders (p=0.57). Reasons for treatment failure included: loss to follow-up (n=26, 5.1%); viral relapse (n=16, 3.1%); non treatment-related death (n=7, 1.4%); and treatment discontinuation (n=4, 0.8%). Among the 16 patients with viral relapse, outcomes included: 6 non-compliant and not yet retreated; 5 retreated with SVR achieved; 4 had resistance testing but not yet retreated; and one lost to follow-up. **Conclusions:** Effective outcomes with DAA-based therapy can be achieved in difficult-to-treat low income, minority populations in resource-constrained safety-net health systems. This promising model of care has the potential to reduce HCC burden in Texas.

353 **CPRIT Grantee**
Poster Session B

Hepatocellular carcinoma prevention via hepatitis C screening and linkage-to-care is infrequent in safety net health systems *Mamta Jain, The University of Texas Southwestern Medical Center; B. Adamson; L. Quirk; B. Turner; A. Singal*

Introduction: Safety-net health systems disproportionately care for patients at high risk for hepatitis C with high associated incidence rates of hepatocellular carcinoma (HCC). Routine hepatitis C virus (HCV) screening is recommended in all baby boomers (born from 1945 to 1965) because 75% of cases are in this age group of whom roughly half are undiagnosed. Hepatitis C treatment is an effective HCC chemopreventive modality but relies on effective systems for hepatitis C screening, referral for management, and treatment. Few studies have examined hepatitis C screening in safety-net health systems. **Methods:** We conducted a retrospective study of baby boomers with a primary care visit between June 2013 and July 2015 without prior hepatitis C testing in our safety-net health system. We excluded those with decompensated cirrhosis, as hepatitis C testing was likely for diagnostic reasons. In a generalized linear mixed model with a nested structure, we examined predictors of hepatitis C screening among baby boomers. **Results:** Our cohort of 57,797 baby boomers was racially diverse (41.5 % Hispanic, 35.5% Black, 16.5% White) and low income (59.2% uninsured and 10.8% Medicaid). Hepatitis C screening was conducted in 10.7% (n=6200) of baby boomers. Of 1202 (19.4%) patients with a positive anti-HCV antibody, follow-up confirmatory testing with HCV RNA for chronic HCV was performed in 56.2% (n=681) of whom 520 (76.4%) were chronically infected. An additional 549 HCV RNA tests were performed among those with HCV antibody tests performed prior to the study period of whom 427 (77.8%) where chronically infected. Among 948 (14%) persons with chronic infection, 384 (40.5%) kept a liver clinic appointment. Hepatitis C screening was associated with having Medicare (adjusted odd ratio (AOR) [95% confidence interval] 1.29 [1.14-1.47] or Medicaid (AOR 1.37 [1.20-1.57) versus private insurance; having evidence of advanced liver disease such as cirrhosis (AOR 1.53 [1.10-2.12]), elevated AST (AOR 1.76 [1.51-2.06]), thrombocytopenia (AOR 1.35 [1.06-1.71]); and other conditions such as HIV co-infection (AOR [1.91-2.59]), or homelessness (AOR 4.46 [4.03-4.93). Linkage to liver clinic was less likely to occur for patients in HIV (AOR 0.56 [0.33-0.93]) and homeless clinics (AOR 0.38 [0.23-0.62]) compared to community-based primary clinics. **Conclusions:** Only 10% of baby-boomers in safety-net systems had hepatitis C screening, limiting effectiveness of HCC prevention efforts. Screening was primarily risk-based and not universal. Programs to increase universal screening and linkage in baby boomers are needed in order to identify those with chronic HCV infection and link them to HCV treatment.

354 **CPRIT Grantee**
Poster Session A

Preventing liver cancer in our booming and aging population *Roberto Villarreal, University Health System; A. Taranova; L. Fornos; D. Gonzales; A. McCracken; B. Taylor; A. McCracken*

Introduction: Infection with Hepatitis C Virus (HCV) is the most common risk factor for developing Hepatocellular Carcinoma (HCC), a primary malignancy of the liver. The majority of those infected with HCV were born between 1945 and 1965. Referred to as baby boomers, these individuals account for 75% of all patients with HCV. Unfortunately, South Texas has the highest incidence of HCC in the nation—about 5% higher than the national incidence. When compared to national prevalence estimates, University Health System baby boomers have more than twice the prevalence of HCV. Our program, Hepatitis Viral Infection and Systematic Treatment Alliance (HepVISTA), focuses on HCC prevention by expanding HCV screening efforts and linkage to care. We also perform comprehensive patient and provider education and tailored navigation services for Bexar County's underserved minority communities. **Methods:** HepVISTA, a three-year CPRIT funded program, focuses on expanding awareness of HCV screening guidelines through tailored advertisements targeting at-risk residents in Bexar County. To further improve HCV screening rates, an automatic laboratory order that uses an algorithm in the Health System's Electronic Medical Record will identify baby boomers never previously screened or diagnosed with HCV. The order initiates HCV testing after assessing eligibility in patients presenting to clinics for routine appointments. Upon a reactive HCV antibody result, the algorithm elicits a confirmatory HCV RNA PCR test on the same blood sample to confirm chronic active HCV infection. During follow-up visits, Patient Navigators conduct culturally tailored education for those newly diagnosed with chronic HCV. These patients complete a questionnaire to assess HCV knowledge and attitudes. They also receive a packet containing information about HCV risk reduction practices and assistance with linkage to care with the University Health System Gastroenterology and Hepatology Services. **Results:** HepVISTA supports cancer prevention efforts in Bexar County through HCV education, routine testing, linkage to care, and increased

access to treatment for the HCV positive patient population. Through the program we anticipate to reach 180,000 community members, screen at least 12,000 baby boomers in Bexar County and surrounding areas, and identify 480 new chronic HCV patients that will be counseled and linked to care. **Conclusions:** HepVISTA targets system-wide HCV screening and navigation to treatment and therefore prevents HCC. As a result, it will avoid unnecessary costs and high service utilization, reduce readmissions, and improve end-stage liver disease management.

355 **CPRIT Grantee**
Poster Session B

Effectiveness of best practice alert and provider education for hepatitis C screening among baby boomers *Mamta Jain, The University of Texas Southwestern Medical Center; B. Adamson; L. Quirk; B. Turner; A. Singal*

Introduction: Effective screening and treatment of hepatitis C virus (HCV) among baby boomers, born between 1945-1965, can reduce the incidence of hepatocellular cancer (HCC). We examined the effectiveness of a simple best-practice alert (BPA) within our electronic medical record coupled with provider education to increase HCV screening and linkage rates among baby boomers. **Methods:** We implemented a BPA in June 2015 coupled with provider education in a large urban safety net health system in Dallas County. We compared baby boomers without prior HCV screening with an outpatient appointment between 6/1/13-5/31/15 -before BPA- to a group of unscreened baby boomers with an outpatient appointment between 6/1/15-8/26/17- after BPA. Comparison of rates for HCV antibody (Ab), HCV RNA, and linkage-to-care (i.e. completing a liver clinic appointment after HCV diagnosis) were performed using generalized estimating equations controlling for gender, race/ethnicity, insurance, and clinic. **Results:** Of 56,727 at-risk baby boomers seen before BPA implementation, 10.3% had HCV screening performed. HCV RNA confirmatory testing was completed in 54.2% of the 1117 HCV Ab-positive patients, and 43.1% (n=201) of patients with confirmed HCV infection (RNA positive) completed a liver clinic appointment. Among the 39,351 baby boomers seen after BPA implementation, the BPA was not acted on by the provider for over half of patients (52.7%). For those patients with response to BPA, providers ordered HCV Ab for 36.3%, and turned the BPA off for 11%. HCV RNA confirmatory testing was performed in 74.7% of the 1205 HCV Ab-positive patients, and 45.7% (n=289) of patients with confirmed HCV infection (RNA positive) completed a liver clinic appointment. The intervention including BPA and provider education was associated with significantly increased odds of HCV antibody screening (AOR 5.42; 95%CI 5.22-5.62), confirmatory testing with HCV RNA (AOR 2.38; 95%CI 1.95-2.90); however, the linkage to care rates was not significantly improved (AOR 1.61; 95%CI 0.88-1.54). **Conclusions:** Implementation of a simple BPA and provider education significantly increased hepatitis C screening; however, linkage to care rates remain inadequate at only 50%. Further study is needed to understand reasons for turning the BPA off as well as interventions to improve linkage to care of patients with HCV infection are needed to reduce HCC burden in Texas.

356 **CPRIT Grantee**
Poster Session A

Development of Provider Training to Increase HPV Vaccination among 11-26 year olds in a Federally Qualified Health Clinic *Lara Savas, The University of Texas Health Science Center at Houston; J. Delaney; I. Valencia-Torres; K. Bundage; T. Megdal; M. Mims; L. Ramondetta; M. Fernandez*

Introduction: Multilevel interventions can increase HPV vaccination rates in community health clinics. Legacy Community Health (Legacy), a large Federally Qualified Health Center located in Harris and Jefferson Counties, implemented evidenced-based system level changes and provider education, to increase HPV vaccination initiation and completion rates among eligible patients aged 11 through 26. In 2013, 18.5% of eligible Legacy patients initiated the HPV vaccine and of those, 57% who received the second dose completed the third. Legacy collaborated with The University of Texas Health (UTHealth) Science Center at Houston and MD Anderson Cancer Center (MDACC) to develop targeted training for Legacy providers to improve provider HPV recommendation and increase HPV vaccination rates. **Methods:** Intervention Mapping, a systematic approach for developing theory and evidence-based multilevel interventions was applied to 1) identify sub-behaviors necessary for providers to deliver strong HPV vaccine recommendations; 2) specify determinants for these behaviors; 3) create matrices of change objectives; 4) select methods and strategies to influence determinants of behaviors; and 5) produce training materials incorporating these methods and strategies. UTHealth collaborated with MDACC to develop a comprehensive, targeted provider training. Legacy implemented the resulting in–person and Web-based training for pediatric, family medicine, and OB/GYN physicians; medical assistants; nurses; and care team assistants (providers) to improve communication skills regarding HPV vaccine recommendations, as well as reduce missed opportunities for vaccination. **Results:** An HPV vaccine advocate and gynecological oncologist from MD Anderson delivered the in-person training to 63 Legacy providers between March and May 2016. In January 2017, training materials were modified to incorporate revised CDC HPV vaccination recommendations and feedback from Legacy providers. For example, Legacy requested the inclusion of HPV vaccination recommendations for specific population groups including people with compromised immune systems (HIV positive); transgender people; and gay or bisexual men. To accommodate busy clinic and provider schedules, the revised training is delivered via webinar. This format offers a more flexible learning environment and reduces disruption to clinical service delivery. Between April and June 2017, 117 Legacy providers completed the Web-based training. **Conclusions:** Participatory and systematic planning processes were important for developing training components for Legacy providers. Intervention Mapping provided a systematic process for identifying and addressing specific needs, developing key messages and training materials to address them. Using Intervention Mapping facilitated the development of provider training to increase HPV vaccination, which goes beyond typical knowledge based education and enables practitioners to engage in best practice when providing HPV vaccine recommendations.

357 **CPRIT Grantee**
Poster Session B

An innovative social marketing strategy for increasing HPV vaccination *Efrat Gabay, The University of Texas Health Science Center at Houston; S. Vernon; D. Santa Maria; C. Healy; J. Wilkerson; M. Aguilar; G. Johnson; S. Misra; R. Atterstrom; K. Eldersveld; R. Addy; P. Cuccaro*

Introduction: Since the human papillomavirus (HPV) vaccine was introduced in 2006, vaccine-type HPV prevalence decreased 71% among female youth aged 14-19 years. The Advisory Committee on Immunization Practices (ACIP) recommends a 2-dose vaccination schedule for 11- to 14-year-old adolescents, but HPV vaccination rates are below the Healthy People 2020 goal of 80% completion. The goal of this project is to increase HPV vaccine uptake and completion among minority youth in medically underserved areas in Houston, Texas. To increase knowledge, positive attitudes, and intentions regarding the HPV vaccine, as well as vaccine initiation and completion, we are using a 3-prong strategy: 1) A parent-focused social marketing campaign, including culturally-appropriate messages; 2) Comprehensive school-based vaccination clinics (SBVCs) held in public middle schools, at which youth will be offered all ACIP-recommended adolescent vaccinations; and 3) Annual continuing school nursing education. **Methods:** To develop the social marketing campaign, we conducted an extensive discovery process. Discovery components included audience segmentation of parents of 11-14-year-olds in target schools, review of the relevant literature, in-depth surveys of team members regarding HPV and HPV vaccination, two half-day retreats to map out the intervention, and in-depth interviews with content experts in health communication, cervical cancer screening and treatment, and adolescent medicine. **Results:** We developed “All for Them”, an innovative social marketing strategy targeting parents of 11-14 year olds. “All for Them” provides parents with the message that to fully protect their child, it is important for parents to make sure their child gets all of the recommended adolescent vaccinations, including HPV vaccine. Creative collateral illustrates concepts such as “You wouldn’t give your child half an umbrella” and includes the tagline “It’s All for Them, Because All is Better than Some.” Materials in the campaign will include posters at schools prior to the school-based vaccination clinics, a cover letter and fact sheet included with the vaccination clinic consent packets sent home to all parents, a website, and targeted social media ads for parents whose children attend target schools. As we are in the preliminary stages of this project, results are not yet available for presentation. **Conclusions:** This project can reduce the prevalence of vaccine-type HPVs, reduce future HPV-related cancer morbidity and mortality rates, increase access to immunization services for youth in Houston MUAs, and establish a program of SBVCs in public middle schools that can continue once funding has ended.

358 **CPRIT Grantee**
Poster Session A

Entre Familia: Evidenced-based Services Program *Edna Villarreal, The University of Texas at Austin; D. Morales-Campos; L. Crocker; M. Morales; N. Silva; C. Rohr-Allegrini; L. Trevino; A. Lopez; C. Leal; I. Garcia*

Introduction: Cervical cancer is the most common HPV-associated cancer among Hispanic women. In Hidalgo County, women experience higher incidence and mortality from cervical cancer compared to the state and nation. Prevention of cervical cancer is possible using the HPV vaccine, which the Advisory Committee on Immunization Practices recommends for males and females ages 11-26 years. Despite this

recommendation, uptake of the HPV vaccine remains low for Hispanics adolescents and young adults in Texas. The Entre Familia (EF) program integrates a community education component (public education and health professional training/education) and clinic component (provider-directed intervention and healthcare systems-based intervention) to increase HPV vaccine initiation and completion rates in Hidalgo County. **Methods:** Community health workers (CHWs) at community and clinic sites recruit parents of Hispanic adolescents (ages 11-17) and young adults (ages 18-26) who have not initiated or completed the vaccine series. As part of the community component of EF, CHWs engage in county-wide outreach activities, delivering group health education sessions using a flipchart and one-on-one sessions with an educational brochure. This component also provides education and training for community-based healthcare providers. The clinic component of EF will educate and train healthcare providers to implement evidence-based strategies to increase vaccination rates and to make strong recommendations for the HPV vaccine to their patients. CHWs will implement healthcare systems-based interventions (e.g., clinic-based patient education and patient reminders) selected by the lead clinical provider at each site to increase vaccination rates. **Results:** The EF program is currently underway. We expect EF to increase HPV immunization rates (initiation and completion) through implementation of clinic and community components in Hidalgo County. From 3/2017 to 5/2017, we: (1) reached 1,157 adult residents of Hidalgo County through outreach; (2) educated 349 adult residents of Hidalgo County using EF's evidence-based education sessions and brochures; (3) educated 109 healthcare professionals; (4) served 46 vaccine-eligible clinic patients through the clinic CHWs. We also plan to (5) educate 60 health care providers on evidence-based HPV vaccination practices; (6) increase over baseline the proportion of healthcare providers that routinely offer the HPV vaccine; and (7) meet or exceed Texas' vaccine initiation (39%/16%) and completion (20%/8%) rates for adolescents and young adults using clinic electronic medical records. **Conclusions:** By increasing vaccine initiation and completion among adolescents and young adults, EF has the potential to reduce cervical cancer incidence and mortality among Hispanic women in Hidalgo County.

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Poster Session B

"Dancing, Not Wrestling": Promoting Patient Behavior Change By Exemplifying the Change *Johanna Becho, Cancer Prevention and Research Institute; W. Calmbach*

Introduction: Obesity is a major health care problem for patients in Texas, and is an independent risk factor for several cancers. Designed with obese patients in mind, the South Texas Ambulatory Research Network (STARNet) developed an evidenced based- educational intervention utilizing Motivational Interviewing (a counseling style) to assist STARNet primary care physicians, physician assistants, nurse practitioners, and staff help overweight and obese patients reduce or stabilize their weight. This presentation invites attendees to consider the value of academic detailing coupled with a simple counseling approach, to promote screening and prevention. **Methods:** "Motivational Interviewing" (MI) is a goal-oriented, patient-centered, counseling style for eliciting behavior change. MI positions patients to resolve ambivalence associated with behavior change. Key skills of MI include: 1.) Open ended questions, Affirmations, Reflective statements, Summaries (OARS); 2.) Agenda Setting; 3.) Scaling, and 4.) Recognizing Change Talk. Trainings include a brief PowerPoint presentation incorporating short videos, 5-minute practice sessions, and group discussion. STARNET clinics participate in 4 Motivational Interviewing training sessions and a "Research 101" (Human Subjects Protection) training, prior to study launch. Participants complete a modified version of the Motivational Interviewing Knowledge and Attitudes Test (MIKAT) to determine content knowledge/retention, and complete session evaluations. Participants are highly encouraged to debrief about patient experiences between training sessions, share ideas or express concerns through the process. **Results:** To date, we have successfully enrolled 19 clinics. Practice trainings thus far have taught our team new lessons about viewing each clinic as an individual system; each with their own "personality" and each with their own set of strengths and weaknesses, as they contend with competing demands central to busy primary care practices. **Conclusions:** Variables enhancing each clinic's capacity to adopt Motivational Interviewing and enroll/track 50 patients include: A.) training intervals B.) Emphasis on cultivating and maintaining key relationships, C.) collective participation D.) Diffusing power differentials E.) Cultural considerations, F.) considering "Zip Code" advantages/disadvantages G.) Modeling the "Spirit of MI" H). Research as a form of "investing" in clinic staff. This study reveals potential to incite change at the micro level (clinic dynamics) in order to produce change on the macro level (target population). Field observations suggest busy primary care practices may benefit from participating research initiatives with potential to reduce obesity rates and foster research appreciation.

360 **CPRIT Grantee**
Poster Session A

Establishing a clinic-community collaboration to promote HPV vaccination in South Texas *Raquel Romero, The University of Texas Health Science Center at San Antonio; D. Parra-Medina; L. Granado; D. Morales-Campos; J. Botello; P. Winkler; J. Bazan; O. Garcia*

Introduction: Every year in the US, doctors diagnose an estimated 19,200 women and 11,600 men with a cancer caused by HPV (human papilloma virus) infection. The HPV vaccine offers a potentially powerful primary prevention strategy to decrease the incidence of HPV related cancers. Yet, the initiation and series completion rates, particularly among Texas adolescents, remain extremely low. This project aims to decrease the morbidity and mortality associated with HPV-related cancers by increasing HPV vaccination among adolescents ages 11-17 in rural primary care settings using community outreach and education, a Provider Directed Intervention (PDI) and Health Care System (HCS) strategies. **Methods:** This Quality Improvement program targets six clinics from a Federally Qualified Health Center in four medically underserved rural counties (Frio, Medina, LaSalle, and Dimmit). For community outreach and education, two trained outreach coordinators engage in county-wide outreach activities and deliver health education in group sessions using a flipchart or one-on-one with a brochure. They also provide education and training activities to healthcare professionals in the community. For the PDI, a practice facilitator (PF) delivers continuing medical education sessions to health care providers focusing on evidence-based strategies to increase HPV vaccination rates in their practice. The PF also provides training to Clinic Immunization Champions regarding the HCS strategies (e.g., clinic-based patient education, scheduling vaccination appointments, and patient reminders and recalls). We used descriptive statistics to summarize process data (e.g., # persons contacted, # education sessions, and # participants educated) and provide preliminary baseline and 6-month follow-up vaccine initiation and completion rates. **Results:** The program is currently ending its second year. We expect the program will increase HPV immunization rates (initiation and completion) through implementation of clinic and community components. From 3/2016 to 5/2017, we (1) reached 18,097 adult residents, (2) educated 3,797 adult residents using evidence-based education sessions and brochures; (3) educated 452 healthcare professionals; and (4) 192 adolescents received a vaccine. Baseline data show that 5% of eligible patients receive one or more doses of the HPV vaccine. **Conclusions:** By increasing awareness and education throughout community events and clinic interactions, we have been seeing a remarkable increment in the number of people that receive HPV vaccine, which offers the benefit of potentially reducing HPV–related cancer and associated diseases.

361 **CPRIT Grantee**
Poster Session B

Interim Results of a Tiered Patient Recall/Reminder Program for Human Papillomavirus Vaccination in a Safety Net Healthcare System in Houston, Texas *Jane Montealegre, Baylor College of Medicine; L. McGee; M. Daheri; H. Sangi; M. Mallory-McRae; L. Hanser; K. Kline; M. Anderson; J. Boom; M. Scheurer; M. Jibaja-Weiss*

Introduction: Each year, there are 26,900 cases of human papillomavirus (HPV)-associated cancer in the US. Despite the HPV vaccine's safety and efficacy, vaccination rates remain low. We implemented a tiered patient tracking, reminder/recall, and navigation program as part of multicomponent intervention to improve HPV vaccine initiation and completion rates in a large, urban safety net healthcare system. Here we present interim results from Year 1 of the program. **Methods:** The tiered program involves creating and managing a registry of age-eligible pediatric patients. Patients' vaccination status is categorized as unvaccinated, partial (1 dose), or complete (2 or 3 doses, according to age-specific guidelines). Patients are prospectively tracked and receive reminder/recalls for doses 2 and 3. Clinics (n=23) were randomly assigned to an 'early' (Group 1, G1) or 'delayed' implementation group (Group 2, G2) for staggered role out. To date, G2 clinics have not received the intervention. Among G1 clinics, implementation is currently focused on 11-12 year olds who have received 1 dose of the vaccine. We assessed clinic-level baseline and Year 1 initiation and completion rates among 11-12 and 13-18 year olds. The Wilcoxon sign rank test was used to compare Baseline versus Year 1 among G1 and G2 clinics. Baseline and Year 1 rates were based on patients whose last visit was between 01/01/15 - 12/31/16 (n =11,581) and 04/01/16 - 04/30/17 (n=7,254), respectively. **Results:** Baseline initiation and completion rates were respectively 58.4% and 32.8% among 11-12 year olds and 74.0% and 52.1% among 13-18 year-olds. Year 1 rates were respectively 65.4% and 38.2% among 11-12 year-olds and 76.0% and 56.0% among 13-18 year-olds. Baseline completion rates were lower in G2 versus G1. Increase in initiation rates between baseline and Year 1 was similar among G1 and G2, overall and by age group. Increase in completion rates was statistically significant among 11-12 year olds in G1 (8.6% increase, p =0.02), but not those in G2 (2.7%

increase, p =0.37). Increase in completion among 13-18 year olds was similar among G1 and G2 clinics. **Conclusions:** Over the assessment period, the tiered program was targeted to 11-12 year olds in G1 clinics. Completion rates significantly improved for 11-12 year-old patients in clinics that received the intervention (G1) while remaining unchanged in clinics that did not (G2). Our results indicate that tiered patient tracking, reminder/recall, and navigation is effective at increasing HPV vaccine completion rates in a safety net healthcare system.

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362 **Poster Session A**

Using best practices to promote HPV vaccination among adolescents in rural health care settings in south Texas *Laura Crocker, The University of Texas at Austin; R. Romero; C. Rohr-Allegrini; E. Villarreal; D. Parra-Medina; D. Morales-Campos*

Introduction: The incidence of cervical cancer in Health Services Region (HSR) 8 (10.5) and 11 (10.6) continue to be the highest in the state, but HPV-immunization rates remain low among Texas adolescents. The most significant indicator for adolescent vaccination is provider recommendation. Therefore, provider education and support staff training is critical. Other barriers to HPV vaccination include infrequent healthcare visits, missed opportunities for vaccination, and lack of health insurance and/or a medical home. **Methods:** We have implemented two HPV-specific Immunization Champions programs in seven rural clinics in HSR8 and four clinics in HSR11 to improve adolescent HPV vaccination rates in these areas. The "champion" is empowered to promote vaccination through improved clinic systems and patient and provider education. Staff conducted chart reviews using the Comprehensive Clinical Assessment Software Application (CoCASA) and collected baseline data for 336 and 100 randomly selected patients between the ages of 11 and 17 in HSR8 and HSR11, respectively. In HSR8, staff trained Champions to communicate with parents, contact patients overdue for their HPV vaccine to schedule an appointment, and prompt providers to offer the vaccine to eligible patients in the clinic, thereby avoiding a missed opportunity. In HSR11, staff will begin similar efforts upon completion of the needs assessment. **Results:** In HSR8, 15 patients (4.46%) had initiated the HPV series with at least one dose. Of these, just one eligible patient (0.30%) had completed the three dose series. Three patients (0.89%) had received two doses and 11 patients (3.27%) had received only one dose. After six months, HPV-vaccine initiation nearly doubled to 29 (8.61%). Three patients (0.89%) completed the series, while nine patients (2.67%) received the 2nd dose. Missed opportunities dropped from 7.74% at the start of the project to 2.08%. In HSR11, 40% of eligible 11-17 year olds had completed the appropriate HPV vaccine series at the start of the study, with 28 missed opportunities. Follow-up data will be available during subsequent stages of the project. **Conclusions:** The efforts of the Immunization Champions have led to an increased uptake of the HPV vaccine in the clinics in HSR8 through reminder/recall and avoiding missed opportunities. We expect to see a similar improvement in HPV vaccination rates in the HSR11 clinics.

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363 **Poster Session B**

Be Well Communities: A place-based approach to cancer prevention and control *Ruth Rechis, The University of Texas M.D. Anderson Cancer Center; A. Brewster; E. Caballero; K. Oestman*

Introduction: A broad range of scientific evidence indicates that more than 50% of cancers can be prevented by focusing on areas such as diet, physical activity, preventive care, UV radiation, and tobacco control. A critical step is to identify and implement the most effective means of putting this knowledge into action in the community. This presentation will highlight how a cancer center, in partnership with a corporate partner, developed and implemented a community action plan for a place-based approach to cancer prevention and control. **Methods:** After receiving significant support from ExxonMobil, a rigorous process was followed to develop a place-based approach for implementation and to create an enabling environment for implementation. Specifically, interviews, a literature review and program assessments were conducted both to identify components of Healthy Community approaches that could be applied to cancer and to identify scientifically-supported interventions which would be relevant in a cancer prevention and control context. Baytown, Texas was selected for this project (population: ~76,000) based on a community assessment and proximity to the corporate partners' location. The community assessment was conducted to understand the current state of health, strengths of the community, areas of need and to identify key stakeholders for a Steering Committee. The Steering Committee (SC) was led through a consensus process to prioritize scientifically-supported strategies from those that had been identified. Based on the chosen strategies, interventions were modified based on the needs and capacity of the community. The SC organizations submitted work plans which were organized into a comprehensive community action plan. **Results:** Five components of successful approaches for implementing a Healthy Community which could be applied to cancer were identified. A database of approximately 100 strategies focused on cancer prevention and control was developed. The Steering Committee, the funder and the lead institution approved the community action plan and subsequently funding was allocated to the collaborating organizations to carry out the interventions. MD Anderson Cancer Center will continue to serve as the backbone organization to support the work and provide cancer prevention expertise. In Baytown, 9 organizations will carry out 17 interventions focused on diet and physical activity initially and will address additional high impact areas over time. **Conclusions:** Modeled on several decades of Health Community approaches, this initiative has successfully yielded a place-based resident-driven, cancer prevention community action plan to be implemented over the next five years. Using this place-based approach, cancer centers and similar health systems could have a significant impact on addressing cancer prevention and control by engaging the community.

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Collaborative Cancer Prevention Partnership that Addresses the Social Determinants of Health *Norberto Gonzalez, MHP Salud; M. Arjona Jr.*

Introduction: Introduction: According to the American Cancer Society, Hispanics are more likely to die from cancer than are non-Hispanic whites. These disparities begin in communities with existing social determinants of health long before a diagnosis is ever reached. Disparities such as these are particularly acute in the Rio Grande Valley, a four-county region located in the southernmost tip of Texas with high levels of Hispanic residents. Incidences and mortalities related to cancer in this region have exceeded state averages, indicating a significant need for outreach, education, screening and diagnostic services. **Methods: Methods:** Organizations have struggled to adequately provide these services due to their inability to reach the source of the problem; the distinct social, behavioral, and environmental determinants of health unique to this region. To address these issues at their source, resources must first be channeled to address community level determinants of health, a key ingredient most clinical interventions lack. Recognizing that this cannot be done without an expert in the local area and culture, the Cada Paso del Camino project utilizes Promotores(as), as a bridge from the community to clinical services. The Promotores(as) offer outreach, one-on-one education, referrals, and follow-up, but they are only part of the overall strategy of this project. Cada Paso del Camino is a unique collaboration between a health center provider that provides preventive, diagnostic, and treatment services to the underserved, uninsured residents in this region. **Results: Results:** MHP Salud and Nuestra Clinica del Valle, in Hidalgo County, Texas have worked together to serve the local community with cancer screening, diagnostic and detection services. To date, MHP Salud has reached through door-to-door outreach, health fairs and waiting rooms a total of 4,092 individuals to determine eligibility for cancer screening services, 100% of the individuals that met the requirements for cancer screening received referrals from the Promotoras to received screening services. Specific metrics were determined for breast, cervical and colorectal screenings, however, there have been a combined total of 2,688 screenings provided surpassing the goal to increase baseline by a total of 1,705. It has been proven to be effective for the Promotoras de Salud and local health center to work together in reaching individuals to screen for cancer, both new patients and returning patients. **Conclusions:** Conclusion: Cada Paso del Camino offers a unique partnership model that could be used to inform similar future efforts within and beyond Texas's Rio Grande Valley.

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Importance of Distance to Screening Facility for Colorectal Cancer Screening Method in Rural East Texas *Carlton Allen, The University of Texas Health Science Center at Tyler; G. Orsak; E. Caldwell; M. Collier; P. McGaha*

Introduction: Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. Colonoscopy and fecal immunochemical tests (FIT) are two CRC screening methods. While colonoscopy has become the standard for CRC screening, FIT provides a more convenient option for patients. Patients living in rural regions are less likely to undergo CRC screening with colonoscopy due to travel distances and other barriers. The current project provided colonoscopy and/or FIT testing at a Health Science Center located in Smith County. It was hypothesized that patients living in Smith County would be more likely to choose colonoscopy over the FIT, that patients living in Smith County would be more likely to receive a follow-up colonoscopy following a positive FIT, and that this follow-up would occur sooner than for patients living outside of Smith County. **Methods:** Patients were counseled regarding their two screening options: FIT and colonoscopy. Patients (N = 1014) were mostly female (69.7%) and did not live inside Smith County (66.9%). The sample was 29.3% Hispanic, 17.8% non-Hispanic Black, and 52.4% non-Hispanic White. More patients preferred the FIT as their first choice of testing (54.3%). A total of 69 patients had positive FIT result warranting further action. **Results:** As expected, patients living in Smith County were 6.49 times more likely to choose a colonoscopy over a FIT, $B = 1.87$, $p < .001$. As expected, when assessing the duration of time between positive FIT and colonoscopy, patients living in Smith County were 2.22 times more likely to follow-up and receive a colonoscopy after a positive FIT, $B = .80$, $p = .015$. Patients received a colonoscopy 14 weeks sooner when living in Smith County ($M = 8.36$, $SE = 2.19$) as compared to not living in Smith County ($M = 22.96$, $SE = 3.041$), χ^2 (1), $p = .009$. Finally, out of the 18 patients who did not follow-up with a colonoscopy, 17 were living outside of Smith County. **Conclusions:** Rural settings present unique challenges for their residents. Individuals in these settings usually have to travel a greater distance to seek care from specialists for medical treatment, and have longer waiting times for appointments. These barriers may prevent individuals from seeking care. The results suggest that additional interventions targeting rural areas, such as increased follow-up or additional transportation targeting patients living outside of Smith County, are warranted in order to have a truly successful rural outreach program.

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Empower Her To Care Expansion: Increasing Access to Breast Cancer Screening and the Continuum of Care for Underserved Texas Women *Bernice Joseph, The Rose*

Introduction: Rural Texas counties have a greater cancer burden than their urban counterparts due to access-to-care barriers (being uninsured, poor and with limited transportation) and lack of infrastructure to carry out prevention programs. With more than 80% of Texas designated rural by federal government standards, 3.3 million people live in rural communities. Despite healthcare reform, Texas still has the highest number of uninsured, non-elderly adults in the nation at just over 23%. Access to health care for the uninsured in Texas is a growing, long-term problem. The Empower Her ® to Care Expansion project will continue to increase the delivery of breast cancer screening, diagnostic procedures and patient navigation services to 3,700 underserved women in 34 southeast Texas counties. **Methods:** The two-year project serves 3,700 underserved/uninsured women, age 40 and above, who have not had a mammogram within the last five years or are not regularly receiving mammograms and live within 34 Texas counties. The Rose's digital Mobile Mammography Program provides services through partnerships with established community clinics, physicians and other organizations that offer education/outreach efforts and clinical breast exams to recruit eligible women needing screening. Diagnostic testing, coordinated care and access to breast cancer treatment are provided at either of The Rose's two locations. The Empower Her ® to CARE Expansion project involves removing barriers, offering services, and building levels of trust that result in medically underserved women making the time to CARE for their health. All outcomes depend on our ability to provide the environment, education and access to care that allows her take action. **Results:** By addressing transportation, financial and system barriers, the Empower Her ® to Care Expansion project has increased access to breast health services while offering a continuum of care unique to these communities. Over 22 months (September 2015 to July 2017), this project served 4,109 women with 33% (1,358) of those women receiving their first-ever (baseline) mammogram. Of the women served, 76 women were diagnosed with breast cancer with 32 (42%) resulting from a first-ever screening mammogram and 60 (79%) women diagnosed at early stages. **Conclusions:** The Empower Her ® to Care Expansion project is significantly impacting Texas, saving lives and improving safety-net systems for long-term community health, by increasing breast cancer screening awareness, promoting the CPRIT program funding to increase access to care, delivering services and coordinated care, and strengthening (or creating) safety-net systems.

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Cervical cancer screening and patient navigation (X-SPAN): increasing capacity for rural and medically underserved women *Melanie Carithers, The University of Texas Southwestern Medical Center Moncrief Cancer Institute; K. Argenbright; E. Berry; A. Rodriguez*

Introduction: Recent legislative decisions in Texas have restricted eligibility for Medicaid and funding for clinical services affiliated with Planned Parenthood, leaving many low income women without access to affordable health care. As a result, the demand for preventative services, like cervical cancer screening, currently outpace capacity, fostering disparities in screening participation, incidence, and mortality, particularly among the uninsured and medically underserved. Moncrief Cancer Institute is addressing these access barriers by expanding its prevention and early detection efforts to include cervical cancer screening and follow-up care. **Methods:** Leveraging infrastructure from its successful Breast Cancer Screening and Patient Navigation (BSPAN) program, Moncrief is expanding clinical service delivery to include cervical cancer and HPV screening through co-testing, as well as colposcopy with biopsy and loop electrosurgical excision procedures (LEEP) where required as follow-up care. Fundamental to the program are its core components: a) Outreach & Health Promotion to reach rural and underserved women across the 35 county service area; b) Delivery & Navigation to guide patients through comprehensive screening and follow-up care; and c) Centralized Reimbursement to fund clinical services with awards from CPRIT and BCCS. Using its innovative program design, Moncrief is further increasing access to screening. Program nurses have undergone training approved by the Texas Department of State Health Services (DSHS) and are providing Papanicolaou (Pap) testing with physician oversight, while follow-

up, including colposcopy with biopsy and LEEP, are being performed by a board certified gynecologist. **Results:** The program team has provided co-testing to 481 women, and follow-up care, like colposcopy with biopsy and/or LEEP, to 57 women. Of those undergoing follow-up, 28 have been diagnosed and treated for dysplasia, while two have been diagnosed with cancer, one squamous cell and the other adenocarcinoma. The program continues to grow with support from the outreach team. Meetings have been held with 26 providers, resulting in 22 contracts across the rural service area for the provision of provide clinical services for eligible clients. **Conclusions:** Moncrief Cancer Institute is addressing access barriers to improve cervical cancer screening participation among rural and medically underserved women across North Texas through its comprehensive program. Training nurses to elevate their scope of practice within the confines of their license, Moncrief is able to increase provider capacity within the region, reducing disparities in care.

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Results from a large mailed outreach program to promote colorectal cancer screening within a safety-net health system *Stacie Miller, The University of Texas Southwestern Medical Center Moncrief Cancer Institute; E. Berry; S. Gupta; M. Koch; F. Irving; H. Pozos; R. Mercado; A. Rodriguez; B. Balasubramanian; K. Argenbright*

Introduction: Colorectal cancer (CRC) screening rates are suboptimal among underserved populations such as the uninsured and minorities. While mailed outreach offering non-invasive tests like the fecal immunochemical tests (FIT) has been shown to increase one time screening rates, several challenges remain, including ensuring diagnostic colonoscopy after abnormal FIT, and repeat testing after normal FIT. Here we report outcomes of a large mailed FIT outreach program, inviting 15,017 individuals to complete at least one FIT over a 3-year period. **Methods:** Uninsured individuals, age 50 to 64, not up to date with screening from a large safety-net health system were selected for mailed FIT outreach conducted over a 3 year period. Outreach included a mailed invitation in English and Spanish with an enclosed FIT, and automated and "live" telephone reminders to complete screening. Patients with normal FIT results were re-invited annually, those with abnormal tests were navigated to complete no-cost colonoscopy, and those not responding were not offered further testing. In this analysis, we report the proportion completing: a) FIT after first invitation; b) repeat FIT after 1st FIT with normal results; c) repeat FIT after 2nd FIT with normal results; d) diagnostic colonoscopy after abnormal FIT. In addition, we report the number of patients diagnosed with CRC, advanced adenoma, or non-advanced adenoma. **Results:** Over 3 years, a diverse group of 15,017 individuals received > 1 FIT invitation. Return rates increased from initial to first re-invitation and again for second re-invitation. Of those with abnormal FIT, 54.0% completed diagnostic colonoscopy. Patients diagnosed with CRC, advanced adenoma, or non-advanced adenoma were 11, 110, and 296, respectively. **Conclusions:** Through our mailed FIT outreach program, 5,837 patients completed at least one FIT. Approximately one-third responded to initial FIT, and nearly two-thirds completed a repeat FIT. Among individuals completing 2 FITs, almost 80% complete a 3rd, suggesting a significant proportion of individuals who find FIT acceptable will repeat the test in response to mailed outreach. A significant number of patients with CRC, advanced adenoma and non-advanced adenomas were diagnosed as a result of outreach, but only 54% of patients with abnormal FIT completed diagnostic colonoscopy, suggesting more patients with neoplasia could be diagnosed by improving colonoscopy follow up.

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369 **CPRIT Grantee Poster Session B**

Colorectal Cancer Screening and Patient Navigation Coalition: Colonoscopy Capacity in a Rural Service Area *Stacie Miller, The University of Texas Southwestern Medical Center Moncrief Cancer Institute; E. Berry; S. Gupta; M. Koch; F. Irving; H. Pozos; R. Mercado; A. Rodriguez; B. Balasubramanian; K. Argenbright*

Introduction: Screening reduces colorectal cancer (CRC) incidence and mortality. System-level mailed outreach using fecal immunochemical test (FIT) has demonstrated effectiveness for increasing screening completion in underserved populations (PP100039), particularly when widely implemented among the diverse patients served by the safety-net health system for Tarrant County (PP120229). Fundamental to program success is colonoscopy capacity, as those receiving abnormal results must be navigated for follow-up. As a result, transition from a closed system to an open system has required an evaluation of colonoscopy capacity across the expanded 21 county service area (PP150061). **Methods:** Uninsured individuals age 50 to 74 not current with screening are identified and invited to participate in colorectal cancer screening using mailed FIT. Outreach efforts include: 1) a 1-page bilingual invitation letter, 2) a FIT kit, 3) 2 automatic and up to 2 "live" reminder phone calls, and 4) telephone-based navigation to colonoscopy after positive FIT. The program team includes two nurses and three medical assistants, and is supported by the community outreach team. This team not only raises awareness for the program and the services available, but also work with the nurse manager to identify providers within the community to collaborate with for clinical service delivery, including pre- and postoperative appointments and diagnostic colonoscopy. **Results:** The program team has invited 53,871 patients through organized outreach to participate in CRC screening. Approximately 13% of patients have completed screening at initial invitation, but this rate increases to 45% at annual re-invitation. More than 6% of patients (n=425) have had positive FIT results, requiring diagnostic colonoscopy. Nearly 40% (n=163) have already completed colonoscopy; precancers have been identified in 49 patients and another eight patients have been diagnosed with CRC. Colonoscopy providers have been identified in 18 of the 21 counties, and include gastroenterologists (45.8%), general surgeons (25%), and family practice endoscopists (29.2%). With increased colonoscopy capacity through coalition growth, the colonoscopy completion rate is expected to improve further. **Conclusions:** Colonoscopy capacity is fundamental to the success of the large scale implementation of CRC screening through organized outreach. As the program continues to grow both in volume and geography, targeted outreach specific to provider recruitment has enabled the study team to navigate patients to geographically convenient clinical services and as a result improve colonoscopy completion rates. The next step is to analyze metrics collected as part of colonoscopy documentation to evaluate quality across the service area.

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370 **CPRIT Grantee Poster Session A**

Establishing a comprehensive cancer prevention and support program within Asian American communities in Houston and Austin areas *Furjen Deng, Light and Salt Association; H. Sun*

Introduction: There are a total of 398,342 Asian Americans (AAs) living in the Houston and Austin areas (49% of AA in Texas) and cancer is the leading cause of death among AA populations in the US and Texas. With the funding from CPRIT (2015-2018), this project targets Chinese, Vietnamese, Korean and Filipino communities, which have large foreign-born populations with higher rates of illiteracy and experience greater cultural, linguistic and structural barriers in accessing quality health care. Lack of coordinated efforts and resource shared among local AA community-based organizations further contribute to these gaps. Thus, this project establishes culturally and linguistically cancer prevention and support programs within each AA community to effectively reducing service gaps and disparities in diagnoses and deaths among different AA populations. **Methods:** The proposed project is a joint effort of 12 AA community-based organizations, clinics and universities targeting Vietnamese, Chinese, Filipino and Korean communities in the Houston and Austin areas. Its four major components include: prevention/education; screening; survivorship services; and capacity building. The cancer prevention and screening components address colon, breast, cervical and liver cancer, and healthy eating. Methods of service delivery include: seminars, workshops, health fairs, newspaper articles, and TV programs, one-on-one education, and curriculum-based nutrition classes. The screening services include mammogram, Hepatitis B and C, FOBT, and Pap Smear/HPV tests. The survivorship program provides group-based interventions, patient navigation, and one-on-one support for cancer patients and the capacity building component develops a network to strengthen the capacities of local AA community organizations that address cancer disparities. **Results:** The project is a 3-year project. By the end of project, it is expected that 77,786 AAs will be educated about breast, colorectal, cervical, and liver cancer prevention; risk factors; the importance of screening and early detection; and healthy lifestyle behaviors. An additional 600 individuals will attend curriculum-based nutrition classes and 3,015 AAs will receive screening services. At least 430 cancer patients and survivors will receive support services including navigation services, transportation and language assistance, and psychological consultations. After 1.5 years of implementation, the outcomes have met the target goals except screenings for cervical cancer and hepatitis B. **Conclusions:** Through coordinated efforts, resource sharing, staff and volunteer training, and using various culturally- and linguistically-appropriate outreach mechanisms, the project will significantly enhance AA communities' capacities to address cancer disparities and reach more targeted populations and generate more behavioral changes within AA communities. Lessons learned and challenges faced by AA communities will also be discussed.

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The El Paso & Hudspeth County Breast Cancer Education, Screening and NavigaTion Program (BEST) *Navkiran Shokar, Texas Tech University Health Science Center at El Paso; C. Martin; A. Alomari; R. Salaiz; A. Ayyappan; A. Dwivedi; T. Byrd*

Introduction: Breast cancer is the leading cause of cancer among women in the US (excluding non-melanomic skin cancers), is the second commonest cause of cancer death in women, and is the leading cause of cancer death among Hispanic women. Rates of late stage diagnosis and mortality are higher among Hispanic women on the border, compared to Hispanics elsewhere in the US. Screening for breast cancer is widely recommended, yet rates among border women are low. We sought to address this through the development of a program that targets barriers to screening identified from analysis of local data, key informant interviews and focus groups. **Methods:** We developed and implemented a culturally tailored, bilingual evidence-based breast cancer screening program between 2014 and 2017. The program was designed to be culturally tailored, bilingual and addressed key barriers identified in this predominantly Hispanic, Border Region of far West Texas. Program components included: 1) community health worker delivered theory-based and culturally tailored breast cancer education; 2) Outreach through targeted media and a network of geographically dispersed community partners serving the target region; 3)) Creation of an enhanced access mammography network for program participants; 4)Provision of no-cost breast cancer screening and diagnostic testing; 5) Patient navigation to facilitate screening, diagnosis, health insurance coverage, access to a PCP, and treatment; and, 6) A rigorous process and outcomes evaluation. **Results:** By the end of the three year program, 2121 women were recruited into the BEST program and offered services, 1971 qualified for screening, 143 for education-only and 7 for navigation-only services. Among the 1971 women eligible for screening: mean age was 56 years; 14% (n=282) had never had a mammogram and 52% (n=1044) had a mammogram greater than 3 years previously. 1721 of 1971 (85%) of eligible women completed a screening mammogram and 19.5% (n=327) of these women required further testing. 85.2% (551/647) of follow-up diagnostic mammograms and ultrasound tests were completed. 51 biopsies were indicated (2.5% of the total number screened) and 46 (90.2%) were completed. Eleven patients (0.6% of those screened) had cancers diagnosed (n=2 stage 0, n=1 stage 1, n=6 stage 2, n=1 stage 3 and n=1 unknown) and all were navigated into treatment. **Conclusions:** A comprehensive breast cancer screening program has achieved a high screening and diagnostic test completion rate in a Border population with low prior test completion rates and has the potential to significantly impact breast cancer outcomes in this population.

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Poster Session A

A Retrospective Analysis of Breast Cancer Incidence Detected by Expanded Access to Screening in Rural West Texas *Kacci Jacoby, Angelo State University Center for Community Wellness; K. Stewart; L. Ross*

Introduction: Access to Breast and Cervical Care for West Texas (ABCC4WT) is a CPRIT funded breast and cervical cancer prevention project serving in West Texas. The ABCC4WT Project arranged breast cancer screening for more than 2,200 high risk adult female residents of 21 counties between 2012 and 2017. Women had access barriers due to rural residence, and a combination of low household income with inadequate insurance coverage. Hispanic women comprised 59%; 37% were Non-Hispanic Whites; average age was 49.2 years and 87% were age 40 and over. **Methods:** Epidemiological studies show female breast cancer incidence rates rapidly increased in correlation with better access to mammography screening in the 1980s (Breast Cancer Facts & Figures, American Cancer Society, 2015-2016, p. 6). This poster updates a similar link between breast cancer incidence and access to mammography in rural West Texas. Mounting evidence that Community Health Workers (CHWs) improve prevention is also supported by detailing effective strategies to remove barriers and increase screening among vulnerable rural women (County Health Rankings and Roadmaps, What Works for Health, Community health workers, Accessed August 1, 2017: http://www.countyhealthrankings.org/policies/community-health-workers). A retrospective analysis of mammography and breast cancer detection in a 5 year CPRIT supported project documents a high incidence of breast cancer resulting from expanded access to screening in the Concho Valley of West Texas. The retrospective results are combined with TCR, BRFSS, and selected demographic data in assessing the possibility of reducing the future risk pool. **Results:** It is expected that the retrospective analysis will reveal a significantly higher incidence rate of breast cancer in a high risk population experiencing new access to screening. It is further expected that the assessment of reducing the future risk pool will reveal a need for long-term commitment to eliminating barriers to screening. Effective strategies for CHW intervention to facilitate screening and detection will be identified. **Conclusions:** The results are expected to suggest: 1) Obstacles to mammography screening mask incidence rates of breast cancer among vulnerable rural women that are significantly higher than revealed in normal annual epidemiological reporting required by the Texas Health and Safety Code. 2) Future reductions in breast cancer incidence are dependent upon removing obstacles to screening for vulnerable populations in rural areas. 3) Strategies employed by CHWs are effective means of reducing access barriers in rural populations.

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Poster Session B

Against Colorectal Cancer in our Neighborhoods 2 (ACCION 2) *Navkiran Shokar, Texas Tech University Health Science Center at El Paso; T. Byrd; R. Salaiz; P. Guevara; A. Dwivedi*

Introduction: Although colorectal cancer (CRC) screening is universally endorsed, screening rates in the US remain suboptimal, particularly among the poor, the uninsured, recent immigrants and Hispanics. In order to address this disparity, we implemented a bilingual comprehensive, theory-based CRC screening intervention (ACCION) that we previously developed and tested. For this second phase of intervention, we added new components based on our prior program experience **Methods:** Evidence-based core program components are: 1)Outreach through a community network covering El Paso and Hudspeth County; 2) Bilingual education program delivery by certified community health workers (CHWs) in either video-only, or CHW-only versions; 3)Provision of no-cost fecal immunochemical tests (FIT), colonoscopy, and a fast track referral system; 4)Patient navigation to facilitate testing uptake, address barriers, and facilitate health coverage, diagnosis and treatment. New components include an education/partial navigation pathway to facilitate screening among those with health coverage, in-reach to promote repeat screening and expansion to new target areas through direct service provision in new target areas, through support of new CPRIT funded programs and through wider dissemination strategies. **Results:** Between March 2015 and July 2017, 6,030 participants were recruited for screening. So far, overall screening test uptake has been 67.5%. 5,554 were eligible for FITs, and 3,723/5,558 (67.0%) completed the FIT test; the uptake among repeat program screeners was 80.8%. The FIT positive rate was 3.0%; so far 140 have qualified for a screening colonoscopy and 82.9% (116/140) completed their screening colonoscopy; 77.39% (89/115) completed a diagnostic colonoscopy; 71 patients were diagnosed with adenomatous polyps, 4 with colorectal cancer, 1 with anal cancer and 2 with carcinoid tumors. All patients were navigated into treatment. An additional 295 insured participants were provided with education/navigation services to facilitate testing with their own doctor and the completion rate in those followed up so far is 54% (86/160). The program is also currently being implemented in a 19 county largely rural area of West Texas through two new CPRIT funded programs, and program staff are providing implementation support. **Conclusions:** The ACCION program has been successfully implemented in a 21 county area of West Texas. Data suggest that significant barriers exist even among those with health insurance.

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Poster Session A

De Casa En Casa: Preventing Cervical Cancer in El Paso County and Hudspeth County *Navkiran Shokar, Texas Tech University Health Science Center at El Paso; T. Byrd; J. Molokwu; S. Winters; J. Calderon-Mora; R. Salaiz; A. Alomari; A. Dwivedi*

Introduction: Women on the US-Mexico border have a higher cervical cancer incidence rate, are diagnosed at later stages, and have higher mortality compared to non-Border women in the US. In addition, Hispanic women have almost double the incidence of all race/ethnicities and are twice as likely to die from cervical cancer compared to non-Hispanic women. We identified key barriers to screening through an analysis of local data, key informant interviews and focus groups and have designed a program that addresses the needs of our community, addresses gaps in services, and creates a coordinated program of education, outreach, service delivery, navigation and capacity building for the future. **Methods:** A multicomponent, culturally tailored, bilingual, evidence-based cervical cancer screening program was developed at Texas Tech University Health Sciences Center (TTUHSC) - El Paso, Paul L Foster School of Medicine. The program is being implemented in two Border counties (El Paso and Hudspeth County), in partnership with multiple community and university partners. Key program components are: 1) theory-based and culturally tailored cervical cancer education delivered by bilingual, certified promotoras; 2) Provision of no-cost pap and HPV screening to eligible women; 3) On-site diagnostic and treatment colposcopy; 4) Patient navigation and tracking to facilitate screening, diagnosis, health insurance coverage, access to a PCP, and treatment, and 5) Enhanced resident and faculty colposcopy training to increase colposcopy capacity. A rigorous program evaluation is in process. **Results:** A total of 2,318 women were recruited into the program and offered services. 2,114 women were eligible for screening: mean age of the population was 44.8 years, 4.7% (n=108) had never had a pap smear and 40.8 % (n=945) last received a pap over 5 years previously. Screening uptake was 75.4% (n=1594); 8.0% (n=116) of those tested were positive for high risk HPV. 7.0% (n=111) of screening tests

required follow up with colposcopy and 92.0% (n=102) were completed. Six cancers were diagnosed. **Conclusions:** A comprehensive cervical cancer screening program can achieve significant screening uptake rates in a high risk population with historically low screening uptake and has the potential to significantly impact cervical cancer incidence and mortality in this border region.

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Poster Session B

Impact of Targeted Single Service Events *Sharon Felts, Texas Tech University Health Science Center at Amarillo; R. Layeequr Rahman; L. Santos; B. Talamantes; T. Baker*

Introduction: Texas Panhandle has one of highest rates of cervical cancer in the United States. Public Health Department of Amarillo's 2013 Community Assessment reported 29.9% women, ages 21-64, in Potter and Randall counties were out of compliance with cervical cancer screening recommendations. TTUHSC Breast Center of Excellence received CPRIT funds on 9/1/2014 to expand breast cancer outreach, education and services program with a goal of performing 525 cervical cancer screening services by 8/31/2017. On 1/22/16, Access to Breast and Cervical Care for West Texas (ABC24WT) reported 127 Pap smears completed. **Methods:** An inter-professional team of public, private and community partners met to review data and seek alternative approaches for connecting women with services and increasing Pap smears provided. One proposal received universal team approval - a Saturday morning single service walk-in clinic event, promoted as "Amarillo's First Annual Pap Day" to be scheduled during January's Cervical Cancer Awareness Month, allowing for focused, targeted traditional and social media linked to cervical cancer awareness. Strategic planning tools, such as Six Thinking Hats, Team Task Lists, Marketing Plans and Post Event Evaluations, were used for planning, execution and evaluation of results. The team's goal - perform 50 Pap smears in 5 exam rooms in 4 hours. **Results:** Traditional and social media resulted in 202,000 indirect contacts the week prior to the event, 100 direct contacts with women for ABC24WT eligibility for services, and resulting in 80 pre-scheduled appointments. Sixty women kept appointments for Pap smears. Another 40 women were served as walk- in appointments. Of the 100 seen on Pap Day, 67% were out of compliance with current recommendations, with 19% reporting abnormal results requiring additional services. Additionally, 57 women were scheduled to have Pap smears between 1/25/16 and 3/31/16. At the half-way point of ABC24WT, 54% of goal was accomplished and ABC2 4WT is on target to exceed program goals. **Conclusions:** Targeted single service events are highly effective in reaching risk eligible population; this success is attributable to: • careful analysis of data and re-strategizing when current methods are not meeting goals • inter-professional team use of specific strategic planning tools and processes to develop new approaches, document team input, track accountability, timelines and activities and identify strengths and weaknesses for future planning. The success of the initial single service event in 2016 resulted in three similar events in 2017.

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Poster Session A

Change in breast cancer knowledge is associated with a change in intention to be screened in Mexican-origin women after a breast cancer education intervention *Jennifer Salinas, Texas Tech University Health Science Center at El Paso; T. Byrd; C. Martin; A. Alomari; R. Salaiz; A. Dwivedi; N. Shokar*

Introduction: : Mexican American women have low rates of mammogram screening. The aim of this study was to determine the relationship between breast cancer knowledge and intent to receive a mammogram within six months in a sample of Mexican-origin women living in El Paso, Texas. **Methods:** A total of 489 uninsured Mexican-origin women 50 to 75 years of age who were assigned to treatment or control had complete data at pre and post intervention. Pre-post analysis was conducted using descriptive statistics and logistic regression to determine if a change in knowledge was associated with a significant change in intent between baseline and follow-up data collection. **Results:** Participants were 56.7 years of age and spoke primarily Spanish (92.6). The majority of the sample had not had a mammogram in three or more years (51.6%) and 14.6% had never had a mammogram. At baseline, the majority intended to be screened for breast cancer within the next 6 months (93.4%). At post-intervention, nearly half of the intervention group had changed their 6-month intent to be screened for breast cancer from likely to unlikely. The change in intent was strongly associated with a change in knowledge of risk of having a first child by the age of 30 and breast cancer being rare after the age of 70. **Conclusions:** The intent to be screened for breast cancer in Mexican-origin women may depend on the type of knowledge they have. Change in knowledge may influence perceived risk that contributes to intention to be screened.

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Poster Session B

Evaluation of a community-based breast and cervical cancer screening prevention program delivered among underserved Hispanic women *Lara Savas, The University of Texas Health Science Center at Houston; E. Figueroa; M. Fernandez; P. Moralez; A. Valdes; K. Hernandez*

Introduction: Hispanic women in El Paso County have higher breast and cervical cancer mortality rates than women's rates nationally. The Cancer and Chronic Disease Consortium (CCDC), a Breast and Cervical Cancer Services (BCCS) program provider, and University of Texas SPH-Houston collaborated to deliver an evidence-based breast and cervical cancer screening education program, Cultivando La Salud, originally developed for Hispanics in rural communities. We adapted CLS to increase screening among low-income women residing in El Paso, and to increase repeat mammography and cervical cancer screening among CCDC BCCS program participants. Evaluation of the adapted CLS program, called Unidas Por Vida Y Salud, will inform future program expansion. **Methods:** Community Health Workers (CHWs) invited women in community settings to participate in the Unidas Por Vida Y Salud program. Eligibility criteria included: Hispanic ethnicity, older than 21 years of age, no mammogram within the last 2 years, no Pap smear in the last 3 years, not currently pregnant, no personal history of breast or cervical cancer, and did not have a hysterectomy. Participants were assigned to intervention and delayed intervention groups. Data collectors administered baseline and 6-month follow-up electronic questionnaires to assess potential covariates: demographic and socioeconomic characteristics, health care-related factors, knowledge, and psychosocial factors related to screening and cancer. We compared outcomes among women in the intervention group versus delayed intervention (comparison). **Results:** During the 31-month program period, 5,541 women participated in the program. The evaluation group included 654 participants. Among the 404 women in need of a mammogram, overall 40% completed at mammogram at 6 months follow-up. Intention-to-treat (ITT) analysis indicate that at 6 months follow-up significantly more women completed a mammogram in the intervention group compared with the control group (49.3% vs. 37.7%; p = .019). Among the 544 women in need of a Pap test, 46% completed a Pap screening test; however, no significant Pap screening differences were found between the intervention and control groups. **Conclusions:** CHWs successfully reached and delivered this evidence-based program to 5,541 women in need of screening, reaching more women than originally planned (n=4,100). This program evaluation establishes effectiveness of the CHW-delivered program for mammography screening among low-income Hispanic women with unmet breast cancer screening needs. While we found increased Pap screening rates among participants, overall screening rates did not differ significantly by intervention group assignment. Future efforts should focus on strengthening the cervical cancer prevention intervention to increase the effect among vulnerable Hispanic women.

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Poster Session A

Effects of program scale-up on time to resolution for patients with abnormal screening mammography results *Simon Lee, The University of Texas Southwestern Medical Center; R. Higashi; B. Adamson; H. Zhu; S. Inrig; C. Mejias; K. Argenbright; J. Tiro*

Introduction: The National Breast and Cervical Cancer Early Detection Program (NBCCEDP) established federal funding for state-administered programs to improve breast cancer screening among underserved women. While patient navigation programs have increased screening outcomes such as diagnostic follow-up of abnormal results and reducing time to resolution (TTR), little is known about the impact of program expansion to large rural areas. Rural-related disparities in breast cancer screening are especially concerning in Texas where, 46% of the 254 counties are rural. Objective: Determine whether TTR varied significantly by (a) service delivery time period [before vs. after expansion], (b) location [original vs. expansion county], and (c) participant characteristics, in a cohort of 2,860 women with abnormal screening results who participated in the community-based Breast Screening and Patient Navigation (BSPAN) program between Oct. 1, 2012 – May 1, 2015. **Methods:** We calculated the proportions undergoing diagnostic follow-up and resolved within 60 days. We used Kaplan-Meier plots calculated median TTR for each program expansion/service delivery time period and abnormal result type. Cox proportional hazards regressions estimated the effect of service delivery period and patient characteristics on TTR. Wilcoxon rank sum tests evaluated a priori whether TTR differs between women who received all services in one county versus transferred among counties for services. **Results:** Most of the 2,860 women who received an abnormal screening result were uninsured (93%), Hispanic (52%), asymptomatic at intake (73%), and received services in an expansion county (64%). Almost all

(91%; n=2,599) completed diagnostic follow-up during the study period with a median TTR of 16 days. Across service delivery time periods, TTR was similar (range: 14-18 days). Overall, 92% of those completing follow-up were resolved within 60 days – well above the NBCCEDP quality metric of 75%. However, follow-up was significantly lower for women with a BI-RAD 3 result (59%). Only a small proportion of women needed to transfer to a different county for resolution (n=293; 12.4%). Median TTR was longer for women who had to transfer for services (26 vs. 16 days; $p < .001$). **Conclusions:** BSPAN's outreach and patient navigation screening program maintained timely service delivery during expansion and increased access to high-quality screening services among indigent rural populations. Programs should monitor follow-up among women with BI-RAD 3 results as our data showed much lower completion rates and longer TTR. Policies that add a separate quality metric for BI-RAD 3 outcomes could encourage monitoring.

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Poster Session B

Colorectal Cancer Prevention in a Minority Population via Personalized Education and Navigation Services *Roberto Villarreal, University Health System; L. Meraz; A. McCracken; D. Pineda; V. Mika*

Introduction: In Bexar County, colorectal cancer (CRC) is the third leading cause of cancer death. Incidence and mortality rates over 10 years show that Texas is experiencing a significant decline in CRC rates, except in Hispanics. An estimated 60% of CRC deaths are preventable if everyone over age 50 were routinely screened. Early cancer detection can effectively reduce morbidity and mortality by removing precancerous lesions. Given the disparities that exist for minority populations in cancer morbidity and mortality, it is important for University Health System to expand the success of the navigation program to address documented barriers and improve CRC screening rates for Hispanic women as well as men. We aim to motivate, initiate, and sustain health-seeking behavior changes through increasing patient knowledge about CRC and the benefits of preventive care, addressing cultural factors, and reinforcing a relationship of trust with University Health System. **Methods:** We are using our provider referral system (Access Plus), electronic health records, and patient navigation services to increase the number of first time CRC screenings in low-income, uninsured, Bexar County adults, age 50 and older. This program will overcome cultural, social, and system barriers by providing financial and transportation assistance, as well as bilingual patient navigator (PN) services tailored by gender. During the initial face to face interaction the PN delivers medication for the procedure and relevant CRC prevention information provided by the American Cancer Society and University Health System. The face to face interaction allows the PN to educate on properly preparing for the procedure and gives the patient a familiar face to alleviate anxiety when coming in for the procedure. PNs eliminate the gender specific barriers and provide individual level care. **Results:** Between January 2016 and May 2017, we reached 1,152 uninsured adults and provided navigation services and CRC screenings to 574. Of those that completed screenings, 210 (37%) had polyps and 1 had localized cancer. We provided additional navigation services to 210 insured patients and transportation services to 35 insured patients. Program satisfaction has been high, with 98% indicating that the navigator worked with them to overcome challenges to receiving care and that they are satisfied with the navigator program. **Conclusions:** The Colorectal Cancer Prevention Screening Program addresses financial, system, cultural, and gender-specific barriers to CRC screening for Hispanic men and women. Our patient navigators have provided invaluable support and assistance to low-income, uninsured patients in need of CRC screenings.

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Poster Session A

Prevalence and characteristics of colorectal polyps among Texas C-STEP colonoscopy recipients *David McClellan, Texas A&M University System Health Science Center; M. Akinlotan; K. Pekarek; R. Pope; V. Nguyen; J. Bolin*

Introduction: The U.S. Preventive Services Task Force recommends that adults age 50-75 be screened for colorectal cancer (CRC) through either fecal occult blood tests, stool DNA tests, or colonoscopies. Colonoscopy is regarded as the gold standard for CRC screening because it allows for visualization of the entire colon, as well as detection and removal of polyps which have the potential to become cancerous. The objective of this study was to determine the prevalence and characteristics of colorectal polyps among persons who received screening colonoscopies through the Texas Cancer Screening Training Education and Prevention (Texas C-STEP) program. **Methods:** We retrospectively reviewed colonoscopy pathology reports for 895 individuals who received colonoscopy between December 2013 and May 2017 and extracted data of patients with polyp findings. Patients were primarily residents of seven counties comprising the Brazos Valley region of Texas, with 7.8% coming from outside the region. Descriptive statistics were conducted to calculate number, size, type, and location of polyps by age, sex, race, and ethnicity. **Results:** Of the 895 persons who received one or more colonoscopies over a 42-month period (63.5% female, 36.5% male), 241 had a polyp finding (26.9%). Of these, 49.8% were female, and 45% were male. Men with polyp findings were significantly older on average compared to their female counterparts (mean age: 58 vs. 55.5 years). The highest proportion of those with polyps were between ages 60-69 (32.4%), followed by the 50-59 age group (26.8%). 30.7% of Whites had polyp findings compared to 24.9% of Hispanics, and 22% of Blacks. Majority of the polyps were located in the proximal colon (65%), 35% in the distal colon, and about 5% in multiple locations. Tubular adenomas were the most common polyp finding (59%), followed by tubulo-villous adenomas (9%). On average, polyp size was larger in males (0.46cm) compared to females (0.43cm); about the same size across Whites and Blacks (0.47cm), and smallest among Hispanics (0.44cm). The average polyp size was highest among those below age 50 (0.59cm), but lowest among those aged 50-59 (0.42cm), and increased with increasing age (60-69: 0.43cm; 70-75: 0.46cm). **Conclusions:** Fewer men received colonoscopies; however, such men were older and constituted a significant proportion of those with polyp findings. Screening recipients younger than age 50 were more likely to have larger polyp sizes, possibly due to their high risk. Contrary to much of the literature, Whites had the highest proportion of polyps detected rather than Blacks.

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Poster Session B

Knowledge and confidence of residents and nurse practitioner students before and after interprofessional simulation training in women's cancer diagnostic procedures *Marvellous Akinlotan, Texas A&M University System Health Science Center; C. Weston; A. Lichorad; J. Bolin; C. Ojinnaka; B. Holland; D. McClellan*

Introduction: Women's cancer prevention is predicated on individualized counseling about cancer risk to increase the likelihood of healthy behaviors and screening for early detection. High functioning interprofessional teams with shared knowledge, awareness, and collaboration have been shown to contribute to increased cancer screening. The objective of this study was to determine baseline risk factor knowledge of cancers affecting women and then report the effect of a high-quality interprofessional education (IPE) simulation training for family medicine residents and family nurse practitioner (FNP) students utilizing standardized patients (SPs). Outcome variables include self-reported confidence in counseling a woman to receive appropriate screening and evaluation for breast and cervical cancer. **Methods:** Between 2014 to 2016, a convenience sample of 76 family medicine residents and FNP students participated in a baseline survey of risk factor knowledge of breast and cervical cancers. Thereafter, an interprofessional education (IPE) simulation utilizing standardized patients in a primary care practice setting was implemented. A questionnaire which assessed FNP students' and family medicine residents' self-reported confidence levels in counseling a woman who is reluctant to have a breast or cervical cancer screening procedure was administered before and after the IPE simulation. The questionnaire also assessed confidence in performing and interpreting results of a clinical breast examination. **Results:** There were knowledge deficits in breast and cervical cancer risk factors in both disciplines with the average risk factor knowledge score of 8.6 points out of 12 points for breast cancer, and 7.9 out of 12 points for cervical cancer. Following IPE simulation, confidence in counseling women reluctant to have breast or cervical cancer screening improved across both disciplines ($p<0.01$) and qualitative findings suggest improved attitudes toward collegiality, communication, and understanding of interprofessional roles amongst both disciplines. **Conclusions:** Knowledge gaps exist among both nurse practitioner students and family medicine residents in breast and cervical cancer risk factors. This study suggests IPE simulation is useful in building health provider confidence in cancer screening or evaluation and team collegiality.

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Poster Session A

Engaging community health workers for cancer education and navigation *Katharine Nimmons, Texas A&M University System Health Science Center; J. Bolin; J. Helduser; B. Macareno; M. Sanchez*

Introduction: The 2015-2017 ACTION (Access to Cancer Training, Information, Outreach, and Navigation) project promotes the use of Community Health Workers (CHWs) to disseminate culturally competent cancer education messages to vulnerable populations across Texas. The project equips CHWs and CHW organizations to deliver information related to Colorectal, Cervical, and Breast Cancer prevention, detection, treatment, survivorship, and navigation. **Methods:** The ACTION project reaches CHWs directly by providing training on cancer topics in person and online. The CHW training modules were originally developed and

implemented in earlier CPRIT projects (Texas C-STEP and EPICO), and the ACTION project team revised, updated, and packaged these modules for in-person and online delivery, in English and in Spanish. To date, ACTION CHW Instructors have delivered these modules in person to CHWs in Harlingen, Rio Grande City, Corpus Christi, Tyler, Bryan, Austin, and Houston. The same modules are available online at no charge to CHWs across the state through the ACTION project website. All ACTION modules are approved for continuing education credit by the Texas Department of State Health Services. Additionally, the ACTION project supports other CHW organizations in implementing cancer education and navigation training in their own communities. By providing technical assistance, promoting an affiliation model for CHW instructors and programs, and sharing existing educational resources, the ACTION project builds the capacity of CHW organizations across the state to disseminate Colorectal, Cervical, and Breast Cancer prevention, detection, treatment, and survivorship messages. **Results:** Through July 2017, the ACTION project has directly delivered online training to 740 CHWs, and in-person training to 51 CHW instructors and 237 CHWs. These training modules are also available to CHW instructors and programs to deliver to CHWs in their service areas, expanding the reach of the ACTION project. MOUs and affiliation agreements have been signed with three partner organizations as of July 2017, and the project team is providing technical assistance and support to other organizations across the state as well. Finally, the ACTION website, http://chwaction.tamhsc.edu, contains training modules and toolkits for CHWs, as well as information for CHW organizations about best practices, available resources, and technical assistance. **Conclusions:** Disseminating CHW resources and training through a combination of in-person and online training, web-based resources, and technical assistance and programmatic support represents a successful model for engaging CHWs and partner organizations in community-based cancer education, navigation, and training across Texas.

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Poster Session B

Factors associated with navigation failure among medically underserved women screened for cervical cancer *Tracilyn Hall, Baylor College of Medicine; J. Montealegre; M. Daheri; L. Hanser; M. Jibaja-Weiss; M. Anderson*

Introduction: Patient navigation has been widely adopted as a standard of care intervention to improve the uptake of cancer screening and evaluation. However, it remains unclear how best to optimize navigation programs to address the needs of specific at-risk populations. Here, we have utilized our experience with navigating medically underserved residents of Harris County, Texas as a platform for understanding how best patient navigation programs can be organized to improve their impact. The specific goal of this project was to identify factors associated with the ability of a comprehensive real-time patient navigation system developed in collaboration with Harris Health to ameliorate health disparities inherent to cervical cancer screening. **Methods:** After obtaining IRB approval, demographics and clinical outcomes were abstracted for all women navigated for abnormal cervical cytology by Harris Health, the nation's 3rd largest safety net health system, between September 1, 2014 and August 31, 2015. All data elements were abstracted from a prospective database used by program navigators to insure appropriate follow up. Navigation failure was defined as >1 missed appointments following enrollment. Chi-squared and Mann-Whitney tests were used to evaluate statistical significance. **Results:** A total of 3,526 women were diagnosed and navigated for abnormal cervical cytology (>ASCUS) within the defined study window. When compared to successfully navigated patients (n=3,298), women with >1 missed appointment (n=228, 6%) disproportionately self-identified as African-American (44% vs. 22%, $p<0.0001$) and current tobacco users (30.0% vs. 13%, $p<0.0001$), They were also more likely to have a public source of external funding for their health care ($p<0.0001$) and have been diagnosed cytologically with low grade dysplasia. Median time to diagnostic resolution among unsuccessfully navigated women was 166 days (Range: 8-1271), significantly longer than women without missed appointments (75 days; Range: 1-472, $p<0.001$). Median time from referral to colposcopy was also longer (58 days (Range: 0-383) vs. 45 days (Range: 1-513), $p<0.01$). No differences in age, prior history of dysplasia, distance traveled, or acknowledged exposure to intimate partner violence were observed between successfully and unsuccessfully navigated women. **Conclusions:** Our results suggest that African-American women may be disproportionately vulnerable to navigation failure. If confirmed, potential causes for this disparity should be carefully delineated and addressed as part of CPRIT-supported navigation projects.

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Poster Session A

Champions for Women's Healthcare: A Navigator-led Breast Health Program *Roberto Villarreal, University Health System; L. Meraz; M. Martinez; A. McCracken; V. Mika; E. Carlson*

Introduction: Breast cancer is the most commonly diagnosed cancer in women and the second leading cause of cancer deaths in Texas women. Underserved and uninsured women are disproportionately affected by cancer, with higher incidence and mortality rates. Access to mammography services is particularly difficult for uninsured and underinsured Hispanic women, who experience barriers to care such as transportation, financial coverage, fear, cultural concerns, and system issues. The A Su Salud Breast Health Program addressed the need for increased education about breast cancer, the importance of regular screening and early detection, and how to navigate the Health System to obtain a mammogram. **Methods:** This CPRIT-funded health promotion and clinical services program was comprehensive, community-based, and culturally appropriate. It was tailored to Hispanic women in Bexar County and those who live in zip codes designated as high risk for breast cancer mortality and late stage diagnoses. Health promotions designed to support behavior changes included mass mail outs, newsletters, television and radio Public Service Announcements, social media and telephone reminders. Patient Navigators removed barriers to screening and motivated women socially and emotionally. Those with no prior mammograms received the most intensive intervention consisting of navigation, barrier assessment and personal follow-ups to ensure appointments were kept. Women who received abnormal results were referred to the Women's and Preventive Health Department for biopsy appointments and treatment. **Results:** From 2014 to 2016, 3,107 women were scheduled for mammograms and navigated by Patient Navigators. Seventy-eight percent (2,435) completed screenings with 1% (25) displaying abnormal results. In addition to those navigated through our program, we funded 7,210 mammograms, reducing the financial barrier for many women in our community. Overall, our program provided 9,645 mammograms, with 2,475 (26%) from high risk zip codes. Health promotion outreach and education efforts served 557,700 community members through billing inserts, handouts, newsletters, phone reminders, and outreach events. **Conclusions:** The A Su Salud Breast Health program improved upon current services by reducing barriers to mammograms, improving screening service coordination and increasing awareness of breast cancer screening and early detection. A system change evaluation was conducted using staff interviews, patient focus groups, and cost-effectiveness. Results indicate that the program was cost-effective, integrated suitably into University Health System, improved the Health System's ability to serve its patients, and earned high patient satisfaction. It provided champions for underserved minority women to navigate the health system who would otherwise not have had access.

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Poster Session B

Bridge Breast Network: Bridging Access to Healthcare Services *Terry Wilson-Gray, The Bridge Breast Network*

Introduction: The Bridge Breast Network (BBN) is an innovative organization reducing disparities in breast cancer mortality through early detection and early treatment. Even after the implementation of the Affordable Care Act, approximately one out of every six Texans lack health insurance and even those that are insured may be underinsured, and/or face crippling deductibles or out-of-pocket costs. BBN provides breast health services to low income, uninsured, and underinsured individuals in 28 counties in North Texas, with an emphasis on Dallas County. BBN has provided mammography screenings, diagnostic evaluations, biopsies, breast cancer treatment, survivorship services and clinical referrals for over 5,500 unduplicated women since 2014. **Methods:** The project plans to: 1) increase mammography screenings using facilities and Mobile Mammography units from Methodist Dallas Medical Center , Harris Methodist Hospital Fort Worth, Hunt Regional Medical Center, and Baylor Scott & White Healthcare to reduce structural and geographical barriers to care by providing free mammography services to women in rural and underserved areas; 2) increase community partnerships in the Eastern/Southern counties of North Texas to identify medically underserved population groups in the area; 3) conduct education sessions about breast health awareness and the availability of free mammography services utilizing age, language and culturally appropriate materials; and 4) provide diagnostic care and patient navigation services through treatment for women with abnormal findings. **Results:** Since 2014, BBN has provided mammograms to 2,400 women per year, on average. Roughly 44% of the malignant cancers diagnosed by BBN were discovered at stage 0 or 1, indicating the cancers were caught in very early stages; another 40% were diagnosed at stage 2, demonstrating that approximately 84% of all malignant cancers found by BBN were discovered at a stage that often responds well to treatment. **Conclusions:** 2014-2017 data demonstrate that Bridge Breast Network is meeting its goals of expanding screening, diagnostic, education, and supportive services to un- and under-insured women in North Texas counties, as well as increasing the number of minority women who are receiving first-time mammograms. Malignant cancers are being caught early, and the expansion of county reach indicates that BBN is meeting an ever-present community need.

386 **CPRIT Grantee Poster Session A**

Project REACH (Rural Education and Awareness for Community Health): Experiences and Process Evaluation Outcomes to a Community Screening for Breast and Cervical Cancer Program *Alison Johnson, Coastal Bend Wellness Foundation; G. Pacheco; H. Werfelli*

Introduction: According to the Centers for Disease Control and Prevention (CDC), cervical cancer is the number one cause of cancer death for women in the United States, with Hispanic women disproportionately affected. Similarly, breast cancer is the most common cancer in all women, but the most common cause of cancer death in Hispanic women. The Coastal Bend Wellness Foundation (CBWF) is a community-based, non-profit organization that serves the residents of Corpus Christi and surrounding counties. CBWF provides a myriad of health-related screenings, outreach, and educational activities throughout the area. The Rural Education and Awareness for Community Health initiative (Project REACH) was launched in December of 2015 with the purpose of delivering evidence-based and culturally tailored education and navigation services for breast and cervical cancer early detection among Hispanic women. The evaluation goals are: 1) to improve the overall performance of the project; 2) to improve the overall design of the project; and 3) to determine the level of effectiveness and impact of the project as a whole. Project REACH is currently in Year 2 of implementation. The aims of this study will be to illustrate the challenges, barriers, and experiences related to the implementation of the program and provide preliminary process outcome data related to the evaluation of the program. **Methods:** The focus of Project REACH has been in providing outreach services via community presentations, to encourage participation in brief education program, and to invite participants as a peer health advocate. Participants were asked to complete a pre and post survey, as well as provide demographic information. Key informant will be scheduled in early fall with Project REACH program coordinators to identify potential barriers, challenges, and experiences learned thus far. A sampling frame will be created to contact past program participants to invite them in a focus group session to follow-up regarding their experiences regarding the intervention and to identify ways to better target the population and improve the early detection messaging. **Results:** A total of 439 have been outreached and 276 women have participated in Project REACH and completed both pre and post surveys through July 31, 2017. Less than 11% (n= 30) have participated in a previous CBWF program. **Conclusions:** We hypothesize that this program will be invaluable to the community residents, especially for women in rural areas.

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Building Bridges Initiative: Results of an Outreach, Education and Cancer Screening Refugee Health Project *Amy Raines Milenkov, University of North Texas Health Science Center at Fort Worth*

Introduction: Resettled refugees, like many immigrant groups, have been shown to have low cancer screening rates thus increasing the chances for higher cancer incidences and mortality rates. The Building Bridges Initiative (BBI) at the University of North Texas Health Science Center is a Cancer Prevention and Research Institute of Texas (CPRIT) funded prevention program that provides breast, cervical and liver cancer education and screening to refugee women and links them into appropriate health services. The purpose of this poster is to describe the results of the first three years of the BBI intervention on adherence to recommended breast and cervical cancer screenings among enrolled participants at baseline and resulting from the intervention. **Methods:** Trained bicultural and bilingual lay health educators from four refugee communities/regions, (i.e., Bhutanese, Karen, Somali and Central Africa) provide group and individual education to women enrolled in the Building Bridges program in 10 different languages. Data for this analysis comes from baseline enrollment and service records. Uptake rates, date of last screen, and prevalence of abnormal screens were analyzed among program participants. **Results:** From September 2014 – May 2017, the lay health educators enrolled 433 refugee women and 115 refugee men participants. Cancer prevention education classes were attended by 502 participants. The uptake rate of screenings was 93% (511/548). The large majority had never been previously screened or were not following recommended guidelines (75% needed a pap exam, 85% needed a mammogram, 70% did not know their hepatitis B status). Of those screened, navigation services were provided for 11 abnormal cervical screens (n=168 cervical screens completed), 15 abnormal mammograms (n=128 mammograms completed), and 22 positive Hepatitis B screens (n=215 Hepatitis B screens completed). Among 100 age appropriate women, 47 women started the HPV vaccine, and 23 (49%) completed the entire series. We also had 59 youth who received the HPV vaccine and 31 (53%) completed the series. **Conclusions:** As a result of CPRIT funding, we were able to reach a population of underserved individuals, many who had never received a cancer screening. The lay health worker model, which focuses on natural systems in the community setting, was effective in overcoming many of the system-level, cultural, linguistic and structural barriers that prevent refugees from receiving timely and life-saving cancer screenings.

388 **CPRIT Grantee Poster Session A**

Population Screening for Hereditary Colon Cancer Syndromes: Program Experience to Date *Jillian Huang, The University of Texas Southwestern Medical Center; S. Pirzadeh-Miller; E. Berenson; T. Ross*

Introduction: Although hereditary colon cancer syndromes, like Lynch syndrome (LS), account for 3-5% of all colon cancers, it is estimated that less than 2% of individuals with a cancer predisposition syndrome have been identified. Most identification strategies employed to date have focused on testing individuals who have been diagnosed with colon or uterine cancer. Underserved patients are even less likely to have been tested for LS, or received genetic counseling, highlighting this as an important public health issue. **Methods:** We use a multipronged approach to identify individuals at increased risk for hereditary colon cancer syndromes, primarily LS, and provide them with genetic counseling and testing. We incorporated family history screening of colon cancer questions into mammography and GI clinics at several institutions. We partnered with the CPRIT-grant-funded CSPAN Coalition to send educational cards to individuals receiving a fecal immunochemical test (FIT) from CSPAN, and to use family history screening for individuals who have a positive FIT kit. We are using cascade testing, where one tests other family members when a patient's mutation is found. We will promote education among patients and providers through a media awareness campaign, a Lynch Leadership Committee, and educational videos. Patient navigators actively guide patients to genetic counseling. To address barriers to access to genetic counseling, such as transportation or time constraints, we are providing telephone-based counseling. Patients are mailed a saliva-based genetic testing kit for 18 genes associated with hereditary colon cancer syndromes, which they can complete at home. **Results:** During the first year of the program, we screened 29,554 individuals. We identified 1,565 individuals at increased risk for hereditary colon cancer based on their family history. We provided telephone-based counseling to 108 individuals, and offered genetic testing to 89 individuals. Of the 62 saliva tests that have been completed, we found 5 genetic mutations (3 MSH2, APC, MUTYH), for a mutation positive rate of 8.1%. We also identified an additional 23 individuals (37%) with negative genetic testing results who, based on their family history of colon cancer, would benefit from high-risk colon cancer screening. **Conclusions:** This program is a novel and effective way to identify individuals with hereditary colon cancer syndromes such as LS. Telephone counseling is an efficient way to address some of the barriers to genetic counseling for underserved populations. We continue to refine the processes associated with this population screening, such as re-contacting patients to ensure they complete testing kits.

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Use of a Genetic Patient Navigator to Improve Cancer Surveillance Compliance in Underserved Gene Mutation Carriers *Jillian Huang, The University of Texas Southwestern Medical Center; K. Pratt; S. Pirzadeh-Miller; T. Ross*

Introduction: The goal of identifying individuals with Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome (LS) is to reduce cancer incidence in these populations. However, there are known deficits in compliance with cancer surveillance in underserved populations. This study sought to determine whether a dedicated genetic patient navigator (GPN), in place to identify and reduce barriers to care, would increase these high-risk patients' compliance to National Comprehensive Cancer Network (NCCN) guidelines, and thus reduce cancer incidence. **Methods:** The GPN re-established contact with 177 underserved HBOC and LS mutation carriers at two county hospitals from 2011-2015. The GPN provided additional information, scheduled appointments, and identified financial resources. Compliance with NCCN guidelines was measured as having had age-appropriate breast or colon surveillance within the past 2 years, or having had prophylactic bilateral mastectomy (PBM) or bilateral salpingo-oophorectomy (BSO) with or without hysterectomy. **Results:** Compliance with HBOC guidelines improved from 22-74% to 44-86% (8/18 and 79/91) for each respective hospital site. Uptake of PBM improved from 20% to 22-53% (4/18 and 46/87). Uptake of BSO improved from 22% to 60-67% (12/18 and 52/87). Compliance with LS colonoscopy guidelines decreased from 81% to 61-69% (8/13 and 18/26). Patients had completed initial colonoscopy screening after their initial diagnosis of LS, but some did not return for additional follow-up. Uptake of TH-BSO in LS patients improved from 19-23% to 58-72% (7/12 and 13/18). Adherence to cancer risk-reduction strategies in our underserved

population is projected to result in a 64% reduction in breast cancer, a 54% reduction in ovarian cancer, and a 37% reduction in colon cancer based on previously published risk models. Common barriers identified included insurance problems, transportation, a lack of time, or an inability to navigate healthcare systems. **Conclusions:** Dedicating a genetic navigator to perform long-term follow-up for underserved patients had a largely positive impact on cancer surveillance compliance and projected cancer incidence. This type of role may be an important consideration for other programs seeking to enhance the effectiveness of their cancer genetics screening programs.

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Poster Session A

Integrating Cancer Prevention Services into Substance Abuse Treatment Centers *Martha Felini, University of North Texas Health Science Center at Fort Worth; I. Oluwatosin; S. Gupta; A. Prykhodko; K. Ukpaka; P. Dokpesi; S. Bakre*

Introduction: Women in residential and out-patient substance abuse treatment programs represent a broad range of criminally affected indigent uninsured women and sex workers at high risk of cervical cancer. Using preliminary data collected through a nontraditional partnership with law enforcement and over 30 community organizations (Dallas Prostitute Diversion Initiative), we capitalized on an opportunity to create a cancer screening prevention program targeting this population that is more likely to not be adhering to recommended screening guidelines. **Methods:** Focus groups conducted among the target population informed the development of an evidence-based and trauma sensitive cancer prevention education that was subsequently integrated into Nexus Recovery Center, the largest female substance abuse center in North Texas, and Salvation Army. Cervical screenings were provided at PRISM Health of North Texas which specializes in providing trauma-informed medical care to poor and vulnerable populations. Other screenings provided included anal, breast, HIV / sexually transmitted infections, and hepatitis. A follow-up clinic visit was provided 7 days from the initial screen as a second opportunity to continue prevention messaging, explain screen findings, and navigate abnormals to diagnostic care. **Results:** We served 3278 uninsured women residing across 119 Texas counties while attending residential treatment for substance use disorders in Dallas. A total of 5974 women (including repeaters) attended trauma sensitive cancer prevention classes, where knowledge scores improved 40%. The uptake rate of cervical cancer screenings was 97%, nearly double the rate reported in similar populations (54%). Nine out of ten women participated in all four screenings offered, of which 40% were not compliant with pap screening guidelines. Twelve percent of cervical screens were abnormal, as were 7% of anal screens, and 13% of hepatitis screens. A total of 6067 HIV and STD screens were funded by alternate sources and HIV+ screens were linked to a medical home. Screening abnormals presented unique challenges to successful delivery of diagnostic services. Despite a dedicated experienced navigation team and advocate, ten percent of abnormal screens completed a diagnostic exam. Reasons for poor completion rates included structural barriers, immediate needs (housing, food, shelter) which took precedence after leaving recovery, and unusable contact information due to migratory status. **Conclusions:** Substance abuse treatment centers provide an exceptional window of opportunity to engage high risk uninsured women receptive to cancer screening programs. Key elements to success depend on providing trauma-sensitive services and completing diagnostic services before women leave recovery centers.

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Poster Session B

Provider Baseline Survey Results from the Alliance for Colorectal Cancer Testing Program *Amanda Sintes-Yallen, The University of Texas Health Science Center at Houston; K. McGauhey; L. Ibekwe; M. Fernandez; P. Cuccaro*

Introduction: Colorectal cancer (CRC) is the second leading cause of cancer deaths in the U.S., yet around 63% of deaths in 2010 were attributable to a lack of screening. Mass screening is critical in preventing CRC deaths as survival rates decrease dramatically when diagnosed later. CRC screening occurs through several methods, including fecal immumochemical tests (FITs) and fecal occult blood tests (FOBTs), with a much lower cost than colonoscopy for those paying out-of-pocket. Disparities in screening exist for the uninsured, lower educated, recent immigrants, and racial/ethnic minorities. Through the Alliance for Colorectal Cancer Testing (ACT), MD Anderson, the UTHealth School of Public Health, and the American Cancer Society are collaborating with community health centers to reduce CRC screening disparities. **Methods:** ACT is in 11 clinic systems, providing medical services to 26 Texas counties. The program provides clinic-level training on CRC screening guidelines and program logistics, provides FITs at no cost to the clinic or patients, and trains clinic staff on evidence-based approaches to increase CRC screening. We administered an online survey to providers who see patients aged 50 years or older regarding the clinic setting and provider practices. The survey assesses knowledge, attitudes, best practices, barriers and implementation readiness. **Results:** Baseline survey results (n= 79) revealed that 77.9% of providers believed that FOBT/FIT alone or any other screening method is a preferred method to use for average risk patients. When looking at attitudes towards FOBT/FIT, 95.9% felt these methods were somewhat to very effective in reducing CRC mortality in average risk patients. As clinic best practices, 92% of providers indicated referrals for diagnostic workup of abnormal FIT results, while 89% indicated referrals to specialists for patients with abnormal colonoscopies. Regarding barriers to screening recommendations, 95.9% indicated patient reluctance, while 88% indicated a lack of endoscopy services. In regards to implementation readiness factors, 75% felt that their clinic supported learning new information and skills; 68% felt that clinic staff were receptive to change after receiving feedback and 69% felt that clinic leadership built an environment where tasks could be completed. **Conclusions:** Most providers indicated use of FIT/FOBT as a preferred CRC screening method in their current practice and use referrals for diagnostic work up of abnormal results, and almost two-thirds of providers track diagnostic workup of abnormal results. Providers who worked in productive environments with work cultures supportive of change were more prepared to implement change.

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Poster Session A

Genetic risk assessment for cancer in all South Texas: Facilitating early detection and screening for breast and colon cancer through a competency-based framework for training primary care providers and physicians-in-training *Judith Livingston, The University of Texas Health Science Center at San Antonio; L. Mette; M. Thomas; C. Aguilar; B. Pollock; J. Tysinger; G. Tomlinson*

Introduction: With the increasing integration of genetics/genomics into healthcare, there is a growing need to ensure primary care health professionals (PCPs) can competently deliver genetic services. Yet, medical education programs have had limited success in educating physicians. Recent studies indicate that PCPs continue to have low levels of genetic testing-related knowledge, uncertainty about testing, and inadequate patient communications skills. The situation is more pronounced in South Texas where there is a large underserved population, few genetic resources, and a dearth of PCPs prepared to provide appropriate genetic services. To address these challenges, GRACIAS Texas (Genetic Risk Assessment for Cancer In All South Texas) focused on preparing PCPs, physicians-in-training, and faculty educators to facilitate early detection of breast and colon cancer in high-risk persons unaware of their risks and options for genetic testing and cancer screening. The goals were to assess the educational needs and increase the numbers of PCPs in South Texas trained in early detection and intervention for breast and colon cancer. **Methods:** PCP baseline knowledge of cancer genetic risk and screening was evaluated using a 25-item instrument to assess educational needs and guide curriculum implementation. We structured the curriculum using the Accreditation Council for Graduate Medical Education (ACGME) core competencies for residency training including medical knowledge, patient care, practice-based learning and improvement, interpersonal and communications skills, systems-based practice, and professionalism, tailored to cancer genetics. Training was implemented through interactive, small group teaching using clinical vignettes developed with questions aligned to the core competencies and integrated into the expert-led discussion. **Results:** Data from the baseline knowledge assessment confirmed the need for cancer genetics education. In a sample of 113 PCPs assessed, 30% were unable to recognize the inheritance pattern of autosomal dominance, 66% answered incorrectly to a question of sibling risk for testing positive for BRCA1 mutation, and 81% responded incorrectly to the question of when to begin breast cancer surveillance in a 19-year-old female with a BRCA2 mutation. During the project period, March 2012–February 2016, direct education to address learning needs was provided to 4,768 PCPs. **Conclusions:** The ACGME core competencies, familiar to graduate medical educators and increasingly to practitioners, provided a useful conceptual framework for cancer genetics education and may help residency program directors evaluate their trainees. Implementing the GRACIAS Texas curriculum strengthened cancer genetic services in South Texas. The curriculum is transferable to other settings to help address PCP cancer genetics educational needs.

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393 **CPRIT Grantee**
Poster Session B

Predictors of cirrhosis diagnosed through baby boomer cohort-based hepatitis C screening: Data from 31 Texas primary care practices *Barbara Turner, The University of Texas Health Science Center at San Antonio; T. Melhado; L. Quirk; B. Adamson; J. Guerrero; M. Jain; L. Tenner; A. Singal*

Introduction: Chronic hepatitis C virus (HCV) infection is the leading cause of hepatocellular carcinoma (HCC). In the U.S., HCC has the fastest rising incidence rate of all cancers and Texas has the highest mortality rate from HCC in the nation. The risk of HCC is substantially greater for persons with HCV-related advanced fibrosis or cirrhosis. National guidelines recommend screening adults born from 1945-65 (baby boomers or BBs) for HCV because treatment with direct-acting, anti-HCV drugs can reduce risks of both HCC and liver-related mortality. With CPRIT funding, universal BB HCV testing was implemented in 31 primary care practices serving low-income patients in north and south Texas. We examined risk factors for advanced fibrosis/cirrhosis among BBs diagnosed with chronic HCV in this program. **Methods:** From 6/1/2015 to 08/26/2017, never-tested BBs were screened for anti-HCV antibody and, if positive, tested for HCV RNA. To assess disease severity in BBs with chronic HCV (RNA+), the FIB-4 index was calculated from age, alanine aminotransferase, aspartate aminotransferase, and platelet count. The dependent variable was a FIB-4 >3.25, indicative of advanced fibrosis/cirrhosis. Predictors included: demographics, body mass index (BMI), alcohol abuse/dependence, diabetes mellitus (DM), and insurance status. A series of logistic regression models were estimated and results reported from a reduced model which shows similar significant associations to a full model. **Results:** Of 1,273 anti-HCV positive BBs, 968 (76.0%) were tested for HCV RNA. Of these, 700 (72.3%) BBs were RNA+ and 608 (86.9%) had FIB-4 data. These 608 subjects characterized by: mean age 58.3 (SD 4.7); 66% men; 56% Black; 27% non-Hispanic White [NHW]; 14% Hispanic; and 31% obese (BMI >30). DM was diagnosed in 31% and alcohol abuse/dependence in 22%. Most were uninsured (63%). Overall, 139 (22.9%) had FIB-4 >3.25. Adjusted odds ratios (AORs) for FIB-4 >3.25 were: age per year (1.05, 95% CI 1.00-1.10, P=.033); Hispanic (1.92, 95% CI 1.08-3.40, P=0.026) and NHW (1.38, 95% CI 0.84-2.26, P=0.20) vs. Black; and alcohol abuse/dependence (2.37, 95% CI 1.51-3.72, P<.001). Sex, DM, BMI, and insurance were not associated (P>0.10). **Conclusions:** In this BB universal HCV screening program, 23% had a high FIB-4 >3.25, indicating higher risk for HCC due to advanced fibrosis or cirrhosis. A high FIB-4 was nearly two-fold more likely for Hispanics versus Blacks. Older persons and persons with a history of alcohol dependence were also at increased risk of advanced fibrosis/cirrhosis.

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Poster Session A

Reducing Racial/Ethnic Disparities in Colorectal Cancer Screening: A Comprehensive EMR-Based Patient Navigation Program Including Technology-Driven Colorectal Cancer Outreach and Education Program *Ajeesh Sunny, Baylor College of Medicine; L. Rustveld; S. Nash; V. Varghese; J. Salemi; L. Hanser*

Introduction: The main objective of this analysis is to present key findings for the time period August 2016 through May, 2017 of a CPRIT-funded project that was borne out of the need to improve systems efficiency for navigating and coordinating timely completion of Colorectal Cancer (CRC) screening at two major medical institutions (Baylor College of Medicine and Harris Health System) in Harris County, Texas. The approach taken by this project involves: 1) A CRC screening registry in the Electronic Medical Record (EMR) that includes age-eligible and high-risk patients targeted for navigation; 2) An EMR-based patient navigation work bench that includes capturing CRC screening data, outcomes of patient navigation; 3) An interactive CRC education App featuring a standardized colonoscopy preparation guide, modifiable CRC risk factors, and links to existing resources. **Methods:** Structured Query Language (SQL) program extracted pertinent medical record data (socio-demographics including zip code and county data, CRC screening information, FIT and colonoscopy orders, FIT results, scheduled colonoscopies, Boston Bowel Preparation Scale scores), which was subsequently populated in the EMR patient navigator work bench. This work bench also included pertinent variables necessary for patient navigation including documentation and tracking of telephone encounters, and outcome of navigation (CRC screening referrals, scheduled and completed colonoscopies, cancellations, reschedules, and no-shows). The principal intervention during the initial phone call to the patient was discussion of the colonoscopy preparation guide, reviewing details about ingesting the preparation solution, dietary and medication restrictions, and what to do on the day of the procedure. **Results:** Calls made to patients resulted in relatively compliant interactions, consisting primarily of appointment reminders, clear liquid diet instructions, instructions for taking the prep solution, and answering questions that arose. So far, a total of 5,559 age-appropriate (Mean age, 53.9 ± 6.3 years) patients received navigation services (30.4% White, 26.2% Black, 29.1% Hispanic, 7.6% Asian, and 6.7% Other race). Out of the navigated patients, 4,402 went on to complete CRC screening tests (2,868 colonoscopies, 1,450 FITs, and 84 sigmoidoscopies). **Conclusions:** Results suggest that the EMR-based patient navigation program is having a positive impact on overall CRC screening completion and a significant impact on timely follow-up of those at high risk for CRC (FIT positive, iron deficiency anemia, and rectal bleeding). The multi-faceted approach taken with the current project provides patients with individualized patient navigation services that are sensitive to their needs and more likely to result in successful completion of CRC screening.

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395 **CPRIT Grantee**
Poster Session B

Universal baby boomer HCV screening a safety net health care system: Who is at risk of HCV infection? Barbara Turner, The University of Texas Health Science Center at San Antonio; A. Singal; T. Melhado; L. Quirk; B. Adamson; J. Sanders; L. Tenner; M. Jain

Introduction: Screening and linkage to care for hepatitis C virus (HCV) infection can prevent advanced liver disease and hepatocellular carcinoma (HCC). Persons born 1945-65 (baby boomers, BBs) comprise 75% of persons with HCV nationally and are recommended for one-time HCV screening by national guidelines. Yet rates of BB screening in the U.S remain low. With CPRIT funding, an infrastructure for BB screening in primary care practices serving low-income patients offers a valuable model for HCV screening implementation. **Methods:** Starting in 6/1/15, HCV screening and linkage to care in 12 primary care practices in a Dallas safety-net system included: electronic medical record modification; clinician/staff education; patient education; referral to specialty care; disease staging; and treatment of chronic HCV. HCV screening metrics through 8/31/17 include: % of eligible BBs tested for anti-HCV antibody; % anti-HCV positive (+); % tested for HCV RNA (chronic HCV); and % RNA+. In logistic regression models, we examined associations with anti-HCV+ and RNA+ (among HCV+). Predictors include: demographics; body mass index (BMI); diabetes (DM); alcohol abuse/dependence; insurance status. **Results:** Of 35,040 eligible BBs, 14,164 (40.4%) were tested for anti-HCV and 1,205 (8.5%) were positive. RNA testing in 1,023 (85.0%) of anti-HCV+ BBs identified 632 as RNA+ (61.8% of RNA tested; 4.5% of all screened). Adjusted odds ratios (AORs) for anti-HCV+ were higher (P<0.001) for men (2.04, 95%CI 1.80-2.32) and alcohol abusers (2.07, 95%CI 1.70-2.50) but lower (all P<0.02) for: Hispanics (0.23, 95%CI 0.19-0.28) vs non-Hispanic whites (NHWs); Medicare (0.44, 95%CI 0.35-0.56), private insurance (0.24, 95%CI 0.17-0.36), and uninsured (0.61, 95%CI 0.51-0.73) vs. Medicaid; BMI >30 (0.53, 95%CI 0.32-0.90) vs <25; and those with diabetes (0.66, 95%CI 0.58-75). AORs for RNA+ (among HCV+) were higher (P<0.05) for men (2.25, 95%CI 1.68-3.02); alcohol abusers (1.57, 95% CI 1.02-2.42) and Blacks (2.01, 95%CI 0.1.40-2.88) vs NHWs but lower (all P<0.05) for: Hispanics (vs NHW); Medicare or private insurance (vs Medicaid); BMI 30-34 (vs <25). **Conclusions:** This program screened 40% of eligible BBs for HCV, far higher than nationally. Of tested BBs, 8.5% were anti-HCV+ and 4.5% had chronic HCV (RNA+), both rates over twice those nationally. Men and alcohol abusers were significantly more likely to test anti-HCV+ and Blacks more likely to test RNA+ than NHWs. Hispanics were less likely to test anti-HCV+ or RNA+ than NHWs. Medicaid enrollees were more likely to have chronic HCV, but restrictive eligibility limits access to HCV treatment and effectiveness of HCC prevention efforts.

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396 **CPRIT Grantee**
Poster Session A

The Effect of A Multifaceted Colorectal Cancer Patient Navigation Program on Quality of Colonoscopy Preparation *Luis Rustveld, Baylor College of Medicine; A. Sunny; S. Nash; M. Horsfield; J. Salemi; V. Varghese; L. Hanser*

Introduction: The effect of patient navigation on completion of CRC screening has been evaluated in both community- and hospital based interventions, and most recently in a comprehensive review of the literature. The overwhelming evidence from these studies indicate a positive impact of patient navigation programs on CRC screening completion. However, little is known whether patient navigation improves quality of colonoscopy. The main objective of this analysis is to present preliminary findings on quality of colonoscopy for a CRC CPRIT-funded project at Baylor College of Medicine. **Methods:** Intervention group included adults aged 50-75, who completed a colonoscopy between August 2016 and May 2017, and who had complete Boston Bowel Preparation Scale (BBPS) data recorded in the Electronic Medical Record (EMR). All patient navigation occurred as part of a comprehensive EMR-based patient navigation module with real time CRC screening registry and Graphical User Interface (GUI) embedded in the EMR as a reporting workbench. Directly from this GUI patient navigators viewed and documented all patient navigation outcomes such as telephone encounters (scheduled, canceled, completed, and rescheduled) for CRC screening. Intervention patients received colonoscopy preparation education, and reminder calls. The usual care group consisted of patients who completed colonoscopies a year prior to start of the project, and who received standard CRC care, but no dedicated navigation services. Continuous variables

were summarized by means and standard deviations, and statistically significant differences determined by the Student's t-test, and Analysis of Variance (ANOVA). **Results:** Analysis included 240 usual care and 435 intervention patients. Significant differences were observed in mean BBPS between intervention and usual care patients (mean BBPS 8.0 ± 1.45 vs. 7.6 ± 1.5, respectively, p = 0.03). Significant intervention impact was evident as well across racial ethnic groups. Mean BBPS scores for African American and Hispanic patients who received dedicated patient navigation services were significantly higher compared to usual care (Blacks: Intervention BBPS 8.0 ± 1.6 vs. Usual Care BBPS 7.5 ± 1.5, p = 0.03; Hispanic: Intervention BBPS 8.2 ± 1.2 vs. Usual Care 7.5 ± 1.2, p = 0.01). No significant intervention impact on mean BBPS scores were observed for Whites and Other racial/ethnic groups. **Conclusions:** These preliminary findings suggest the EMR-based patient navigation program significantly improved quality of completed colonoscopies compared to usual care. As the project continues to fully implement its patient navigation program in the coming years, analysis of its effectiveness in improving quality of colonoscopies will be evaluated further.

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397 **CPRIT Grantee**
Poster Session B

Hepatocellular carcinoma prevention in the high-risk region of South Texas through baby boomer screening for hepatitis C and linkage to care. *Trisha Melhado, The University of Texas Health Science Center at San Antonio; R. Bobadilla; L. Tenner; M. Jain; A. Singal; J. Guerrero; B. Turner*

Introduction: Texas has the highest age-adjusted incidence of hepatocellular carcinoma (HCC) in the U.S. One-time screening of baby boomers (BBs, born 1945-65) has been endorsed by the U.S. Preventive Services Task Force to prevent HCC and liver disease. Over half of incident HCC cases in Texas are in South Texas (S TX) where most residents are Hispanic and many uninsured. Because treatment of hepatitis C infection (HCV) reduces the risk of HCC, S TX is a priority location for novel approaches to implement HCV screening and linkage to care. **Methods:** From 6/1/2016-5/31/2017, a program for HCV screening and treatment was operationalized in 19 primary care practices within 4 S TX clinic systems. The program includes: electronic medical record (EMR) modification; clinician/staff training; patient education; coverage of testing for uninsured; reflex HCV RNA testing; case management; and telehealth specialty support for onsite direct-acting antiviral (DAA) therapy. We compare results of anti-HCV screening and RNA testing for chronic HCV across the 4 systems. **Results:** The highest performing clinic system had 1,103 eligible BBs and tested 575 (52%) while the lowest had 1,894 eligible BBs and tested 447 (24%). Across the 4 clinic systems, mean monthly eligible BBs ranged from 18 to 158 and mean monthly BBs with anti-HCV testing ranged from 13 to 48. Anti-HCV+ rates for screened BBs ranged from 6% to 19%. Across all 4 systems, 80% of anti-HCV+ BBs received follow-up RNA testing. Of all 1,462 RNA tested BBs, 91 (6%) were RNA+, ranging 3% to 9% by system. Of the 91 BBs with chronic HCV, 68 (75.0%) were uninsured and eligible for telehealth specialty support for onsite anti-HCV treatment in the primary care practice. Among these 68 BB, the mean age was 57 (SD=3.9), 44 (65%) were men and 36 (57%) Hispanic. As of 8/31/17, 12 BBs completed onsite DAA therapy, 14 are on treatment, 13 have had telehealth review, and 29 are being staged for review. **Conclusions:** In 4 S TX clinic systems serving low income patients, 24% to 52% of eligible HCV BBs were screened for HCV, far higher than the reported national rate (13%). The yield of screening has been high, with 6% of all screened patients diagnosed with chronic HCV. With telehealth specialty support, 26 uninsured BBs have been or are being treated for HCV by the primary care practice and 42 are in various stages of gaining access to treatment.

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Poster Session A

Evaluation of a comprehensive intervention to improve colorectal cancer screening and diagnostic follow-up in a safety-net healthcare system *Jane Montealegre, Baylor College of Medicine; P. Allred; M. Suarez; L. Hanser; M. Daheri; R. Chenier; B. Musher; L. Scott; M. Jibaja-Weiss*

Introduction: Colorectal cancer (CRC) screening rates among eligible adults in the U.S. are far below the national 2018 goal of 80%. This is especially true of medically underserved populations. We implemented a multimodal intervention to address low screening and diagnostic follow-up in a high-volume, urban safety-net healthcare system. Here we evaluate the program's impact on CRC patient screening and diagnostic outcomes. **Methods:** Harris Health System (HHS) is the safety-net healthcare system for Harris County, Texas, which has one of the highest levels of un- and under-insured in the nation. Over the period of analysis (2010 to 2015), a 3-collection Fecal Immunochemical Test (FIT) was used to screen average-risk, age-eligible patients (males and females age ≥ 50 years). Colonoscopy was used for diagnostic follow-up. Using the Quality in the Continuum of Cancer Care framework, intervention strategies were developed to address system failures related to detection and diagnosis of disease. The primary interventions were 1) patient education (linguistically- and culturally-targeted videos viewed in primary care exam rooms and a low-literacy FIT kit); and 2) a tiered patient tracking and navigation system to ensure diagnostic follow-up among FIT-positive patients. Screening, diagnostic, and cancer staging outcomes were compared between 2010 (baseline) and 2015. **Results:** Between 2010 and 2015, HHS experienced a 29% increase in the number of age-eligible patients, from 87,941 to 113,023. During this interval, the proportion of age-eligible patients who received a FIT increased from 24% to 59% (p<0.001). The average return rate was 45.3%. Accounting for the return rate, FIT screening coverage increased from 22% to 34% (p<0.001). Loss-to-diagnostic follow-up decreased from 50% to 5% (p<0.001). Compared to 2010, there was a non-statistically significant decrease in stage IV diagnoses in 2015 (prevalence ratio= 0.77, p=0.076) and a significant increase in stage III (PR = 1.37, p=0.029). **Conclusions:** Implementing patient education and patient navigation interventions may be effective in addressing low CRC screening and follow-up in a high-volume safety-net healthcare system. At HHS, these interventions were associated with a 2.5-fold increase in the distribution of FITs, resulting in a significant increase in FIT screening coverage. Loss-to-diagnostic follow-up also decreased dramatically. Tumor staging data are suggestive of possible stage migration from stage IV to stage III disease, a diagnosis associated with a 6 to 7-fold increase in five-year survival. Further interventions are needed to address the low return of FITs needed to achieve the 2018 goal of 80% screening coverage.

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399 **CPRIT Grantee**
Poster Session B

Improving cervical cancer screening and prevention in the Rio Grande Valley through patient education and navigation and increasing provider capacity *Ana Rodriguez, The University of Texas Medical Branch at Galveston; M. Lopez; M. Munsell; A. Ogburn; R. Gowen; A. Milbourne; M. Mallory; L. Guerra; P. Toscano; E. Hawk; L. Campos; M. Gasca; L. Valdez; N. Esquivel; J. Morales; N. Burkhalter; E. Robles; M. Pontremoli; E. Marin; C. Perez; K. Doughtie; B. Reininger; S. Fisher-Hoch; K. Schmeler; E. Baker; M. Daheri*

Introduction: Cervical cancer is a preventable disease; however in low-resource settings, in the US and globally, a higher proportion of women die from cervical cancer due to lack of access to screening and treatment of pre-invasive disease. The Rio Grande Valley (RGV) along the Texas-Mexico border represents such a region where cervical cancer mortality rates are approximately 30% higher than the rest of Texas. The goal of this program is to increase the number of women undergoing cervical cancer screening in the region and to increase provider capacity to manage abnormal results. **Methods:** This program consists of two complementary interventions. The first is community education and navigation to facilitate access to cervical cancer screening services offered at the participating sites. The second intervention is to increase providers' clinical capacity to manage abnormal cervical cancer screening tests through hands-on training courses and ongoing telementoring using Project ECHO® (Extension for Community Health Outcomes). ECHO is a well-established telementoring model connecting specialists at academic centers with providers in lower resource regions, expanding access to specialty medical care for underserved areas using videoconferencing, case-based learning and patient co-management. Our program consists of biweekly one hour videoconferences to discuss management of cervical dysplasia. **Results:** Since November of 2014, a total of 9,510 women have been educated on cervical cancer prevention, cervical cancer screening and HPV vaccination. In addition, 13,436 women have been screened (Pap and/or HPV), and 1,785 have undergone colposcopy for abnormal results. A total of 346 were treated with LEEP (Loop Electrosurgical Excisional Procedure) or surgery. Ninety-four patients have been diagnosed with CIN2/3 and five have been diagnosed with invasive cervical cancer. Five additional local providers have been trained to perform colposcopy, cervical biopsies and/or LEEP. Eighty ECHO telementoring videoconference sessions have been held with an average of 23 participants per session. **Conclusions:** Our initial experience suggests that improving cervical cancer screening rates and patient outcomes require a multi-pronged approach that includes community outreach and education, patient navigation within existing systems offering these services and training of providers to provide care locally. The outcomes of this program will help support an expansion initiative to deliver similar programs in Laredo and Northeast Texas.

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400 **CPRIT Grantee**
Poster Session A

Eliminating Cancer Disparities in Medically Underserved Immigrant and Refugee Populations in Houston Texas *Shane Chen, Asian American Health Coalition of Greater Houston (dba Hope Clinic); A. Caracostis; K. Dunn*

Introduction: The Asian American Health Coalition dba HOPE Clinic has worked diligently in facilitating access to prevention screenings to eliminate cancer disparities in the medically underserved immigrant and refugee community, and for the last 10 years has worked addressing breast, cervical and liver cancer through preventative and early detection initiatives. "Eliminating Cancer Disparities in Medically Underserved Immigrant and Refugee Populations in Houston, TX" program targeted the Asian immigrants living primarily in Southwest Houston, as well as other foreign born and refugees that may come from elsewhere in the city. Other underserved populations impacted include uninsured and low-income minorities of all races. **Methods:** The main goal of reducing the cancer burden in the medically underserved immigrant and refugee populations of Houston was achieved utilizing best practice methods bridging affordable and accessible cancer screenings and prevention services to vulnerable population in a culturally and linguistically appropriate processes to address breast, cervical, colorectal, lung, and liver cancer. Preventative services are closely integrated with primary care so that comprehensive care may be delivered in a community health center setting with patients partnering with their primary care provider and medical support team. In addition, HOPE expanded services to include health nutrition education to address obesity and malnutrition which impact various forms of cancer. **Results:** Within last three years, HOPE Clinic has bridged prevention services to more than unique 7,321 individuals delivering with more than 36,610 cancer prevention encounters that are accessible and timely. Low income and uninsured women are able to receive comprehensive breast and cervical cancer prevention services, whereas 8,706 pap smears and 3,058 screening mammograms were provided. In addition to screening 4,443 for hepatitis B and 4150 for hepatitis C, HOPE Clinic's implementation of in house viral hepatitis B and C treatment empowered the medically underserved patients to take charge of their health and partner with HOPE providers, so that by controlling and eliminating viral hepatitis B or C, these individuals are offered better health and more optimal futures. **Conclusions:** To reduce barriers for among medically underserved immigrant and refugee populations, HOPE Clinic has strengthened its own capacity to screen, follow up, and address detected abnormalities so that patients receive timely care. HOPE Clinic serves a unique patient population that is usually underrepresented in large research studies. Collecting cultural, social, and economic data through HOPE's electronic health record eClinicalWorks has shown to be useful in understanding the needs of this population and possibly impact care.

401 **CPRIT Grantee**
Poster Session B

Health is Happiness – A breast and cervical cancer prevention program targeting Vietnamese nail salon workers *Frances Nguyen, The University of Texas Health Science Center at Houston; V. Schick; T. Huynh; Y. Le; M. Fernandez-Esquer*

Introduction: Vietnamese women have the highest cervical cancer rate in the United States (43.0/100,000) and the lowest rate of Pap test receipt among ethnic/ racial groups in Houston, Texas (47.9%). Additionally, breast cancer is the third leading cause of cancer death among Vietnamese women nationally, and Vietnamese women had the lowest rate of mammography among racial/ ethnic groups in Houston (58.4%). Among Vietnamese women, nail salon workers' (NSW) cancer risk is amplified by work-related barriers that increase their difficulty in getting cancer screening. The purpose of the Health is Happiness (HiH) program was to promote breast and cervical cancer screening among NSW employed by local establishments in Houston. **Methods:** Nail salon establishments in the Chinatown neighborhood of Houston were recruited into the HiH program. NSW at these establishments were approached by a community outreach team consisting of interviewers and lay health educators. NSW were consented, interviewed, and educated prior to being offered culturally appropriate cancer screening navigation services for breast and cervical cancer screening. A second educational session was conducted prior to the post-test interview conducted three months later. **Results:** Of 276 NSW observed at sixty-two participating salons, 187 NSW (67.8%) completed the pre-intervention survey. Sixty-eight NSW (36.6%) were non-compliant with Pap smear guidelines, and thirty-three (25.8%) were non-compliant with mammography guidelines. Of those available for follow-up, 71.2% of NSW had accepted Pap smear navigation and 63.3% had accepted mammography navigation. Four-fifths of women (78.6%) were compliant with Pap guidelines at follow-up compared to 52.9% who did not accept navigation (p=.049). Four-fifths (78.9%) of these women were compliant with mammography guidelines at follow-up compared to 27.3% who did not accept navigation (p=.005). **Conclusions:** Results indicate that NSW participating in a program tailored to their cultural and work needs can be navigated for breast and cervical cancer screening successfully. Community based programs have the potential to reduce underutilization of cancer screening among Vietnamese women in need of these services.

402 **CPRIT Grantee**
Poster Session A

Using Intervention Mapping to Adapt a Breast and Cervical Cancer Education Prevention Program *Andrea Siceluff, The University of Texas Health Science Center at Houston; E. Adlparvar; P. Cuccaro; M. Fernandez; L. Savas*

Introduction: Hispanic women experience higher cervical cancer incidence rates and are diagnosed with breast cancer at a later stage compared to non-Hispanic whites. We used Intervention Mapping Adapt (IM Adapt) to adapt Cultivando la Salud – Houston (CLS-Houston), an evidence-based cancer prevention education program delivered by community health workers (CHW) to increase mammography and Pap screening. The adapted program aims to increase breast and cervical screening and HPV vaccination uptake among Hispanics in the Houston and Corpus Christi Gulf Coast area. This work describes the application of IM Adapt steps 1, 3 and 4 to incorporate theory and evidence to guide adaptation for urban and suburban Hispanic populations. **Methods:** We applied a participatory approach throughout the IM Adapt process. For IM Adapt step 1, we conducted a needs assessment, including a literature review and review of evidence from the previous program evaluations to inform our logic models of change for screening and HPV outcomes. In step 3, we planned adaptations by evaluating the fit of the original program with our new population. This included adapting matrices of behavior change, design and cultural adaptions for the target population, and changing the design of the education program implementation. In step 4, we developed program materials using evidence-based activities adapted for the target population and new community setting. **Results:** We developed a logic model of change based on the needs assessment (step 1). We identified performance objectives for new determinants, particularly related to overcoming access barriers (step 3). To increase self-efficacy, we identified theoretical methods, such as problem solving, skill building, and goal setting with counseling. For step 4, we created new education materials to facilitate group presentations delivered by CHWs. The Prezi presentation, with updated education on HPV screening and vaccination, replaced the original one-on-one delivered flip chart and video. We developed a one-on-one coaching call to provide a personalized, goal setting-approach to increase self-efficacy, skills and support to overcome personal barriers, in addition to a brief telephone-based screening/HPV vaccination education for women who cannot attend in-person education. **Conclusions:** IM adapt provided a systematic process to guide adaptation of a breast and cervical cancer screening education program to include HPV vaccination, and to meet the needs of underserved Hispanic women disconnected from the healthcare system. A strength of this work is the use of the IM adapt approach, leading to a more comprehensive intervention to meet the needs of medically underserved Hispanic women.

403 **CPRIT Grantee**
Poster Session B

Improving adenoma detection rates: The role of fecal immunochemical test *Eugene Nwankwo, Texas Tech University Health Science Center at Amarillo; S. Trehan; J. Lines*

Introduction: There is limited knowledge about Adenoma Detection Rate (ADR) rates on patients with positive fecal immunochemical test (FIT) that detects for human blood from the lower intestines. We hypothesized that colonoscopy done on patients with a positive FIT test should yield higher ADR rates. **Methods:** We reviewed ADR rates for colonoscopies done after a positive FIT test and compared them to ADR rates for routine colonoscopy done without an initial FIT test over the last 20 months at multiple endoscopy sites. **Results:** Of the 979 patients that underwent FIT test as part of the Cancer Prevention and Research Institute of Texas (CPRIT) grant for reducing colorectal cancer in the Texas Panhandle, 119 patients (12.1%) were found to be positive. Majority were females 78/119 (65.5%). Caucasians had a slight majority 56/119 (47.1%). Of the 119 colonoscopies that were done after a positive FIT test, thirty-nine patients (32.8%) were found to have one or more tubular adenomatous (TA) polyps on final pathological examination. Of patients with TA's, majority were females 25/39 (64.1%). Fifty-eight patients (48.7%) had no polyps, 19 patients were found to have a hyperplastic polyp (15.9%), two patients (1.7%) had findings consistent with ulcerative colitis and one patient (0.8%) was found to have adenocarcinoma. In the control group of 2603 patients in whom routine colonoscopy was done as the initial tool for screening, 715 patients were found to have one or more tubular adenomas, an ADR rate of 27.5%. In this group, colon cancer rate was found to be 1%. **Conclusions:** Although there is a similar detection rates for cancer in both groups, there is an expected statistically significant increase in the Adenoma Detection Rates if colonoscopy is done after a positive FIT test. Recommending colonoscopies after a positive FIT test. This will not only improve ADRs significantly, but also lower the overall healthcare cost for screening colon cancer in this era of escalating healthcare costs.

404 **CPRIT Grantee Poster Session A**

Innovations in Cancer Prevention and Research Conference V *Lewis Foxhall, The University of Texas MD Anderson Cancer Center; R. Kingston; E. Furlan; R. Blake*

Introduction: Colorectal cancer (CRC), the second leading cause of cancer deaths in the United States and the State of Texas, is curable if detected in its early stages, but often fatal when diagnosed later. Studies have shown that CRC screening (CRCS) for the detection and treatment of early cancer, as well as the removal of precursor adenomatous polyps, is effective in reducing CRC incidence and mortality. According to the Agency for Healthcare Research and Quality (AHRQ), only half of all adults aged 50-75 have ever received age-appropriate CRCS, and in minority populations, that number drops to 30%. The project utilizes an evidence-based approach to increase CRCS through clinical practice changes that engage primary care clinicians to discuss the importance of CRCS with patients. Practices are encouraged to pair CRCS with the annual flu shot, an approach with demonstrated effectiveness (Flu FIT) as a Research Tested Intervention Program (RTIP). Our goal is to increase adherence to CRCS recommendations in CPRIT's priority populations served through primary care clinics, thus reducing colorectal incidence and mortality disparities. **Methods:** We have implemented the Alliance for Colorectal Cancer (ACT) Testing, a CRCS coalition involving MD Anderson and community clinics serving the RFA priority population. The coalition supports the delivery of a program offering take-home fecal immunochemical tests (FIT) to CPRIT priority populations in north, east and southeast Texas. These priority populations include, but are not limited to, underinsured and uninsured individuals, those in rural areas, medically unserved or underserved, racial, ethnic, and cultural minority populations and those with low screening rates, high incidence rates and high mortality rates. **Results:** The project partners with FQHCs and community clinics and has distributed 3999 FIT as of September 2017. The positive rate is 7.4% and all of those patients have received navigation services to colonoscopy. 6 cancers have been diagnosed and all are receiving or have completed treatment. **Conclusions:** The program will continue to widen its network of community gastroenterologists to increase the number of positive patients who complete their colonoscopies.

405 **CPRIT Grantee Poster Session A**

FluFIT on the Frontera project: Interim results *Thelma Hurd, The University of Texas Health Science Center at San Antonio; M. Garcia; C. Lozano; R. Rodriguez; S. Sotelo; T. Sunil*

Introduction: Colorectal cancer (CRC) screening prevalence is only 30% among Border Hispanics and community specific screening data is lacking. FluFIT on the Frontera, a comprehensive, CRC screening program for average risk people, was implemented in Del Rio Texas, a rural/frontier Border community, to increase screening and awareness and characterize CRC screening practices. **Methods:** Community and clinic participants received CRC education from trained clinic-based providers and community based promotores from Val Verde Regional Medical Center (VVRMC) and QUAD Counties Promotoras Program, respectively, and were invited to testing and navigation. Demographic, risk factor and screening history were collected. Participants who did not have a primary care provider were assigned to a provider at VVRMC. All test results were given to participants by their assigned/private providers and those requiring colonoscopy were navigated. **Results:** In the first 21 months of programming, 286,773 education/awareness encounters were delivered via media, and social networking, and 6810 community members were educated in group/individual settings. A cohort of 4404 adults (1740 males, 40%; 2664 females) aged 50-75 years were evaluated and offered screening. Seventy six percent were Hispanic and 28.6% were uninsured. There were 1699 (38.5%) participants who met average risk screening criteria; an additional 2702 were ineligible. Within the screening ineligible group, there were 1581 average risk and 1,121 high risk participants. Of these, 1581 average and 635 high risk participants reported prior screening. Among ineligible people, CRC screening prevalence increased from 33.6% in year 1 to 60.2% in year 2. FIT kits were accepted by 1284 (74.3%) eligible participants. The FIT test completion was 80.8% in the promotora navigated community and 43.1% in the clinic settings. Among 777 kits (60.5%) that were returned, 105 (13.5%) were positive. Thirty-four people declined colonoscopy or had medical contraindications. Colonoscopy was completed in 69/71(97.2%) patients, polyps identified in 11 and no cancers were diagnosed. Among 190 participants offered annual re-screening 29 (15.3%) reported recent CRC screening, 34 declined and 113 participated. Eighty-one percent have completed FIT re-screening and 12% are positive. **Conclusions:** The FluFIT intervention was successfully implemented and experienced robust male recruitment. The prevalence of CRC screening has increased 1.8 fold over the project period in this cohort and indicates a change in community screening practices. FIT test completion was 2-fold higher among community navigated compared to clinic based screening participants. The unexpectedly elevated proportion of high risk individuals merits broader community wide screening initiatives.

406 **Poster Session B**

Lung cancer screening guidelines in primary care: A survey on Knowledge of, Attitudes toward, and Practices *Maria Mejia de Grubb, Baylor College of Medicine; S. Gonzalez; R. Levine; R. Zoorob*

Introduction: Screening with low-dose computed tomography (LDCT) is one tool that may increase the early detection and reduce lung cancer mortality. Most family physicians report discussing US Preventive Services Task Force (USPSTF) screening guidelines with patients at high risk for lung cancer (LC); however, referrals remain low. We conducted a needs assessment survey regarding smoking cessation and lung cancer screening practices and services in our clinics. **Methods:** A 10- item electronic questionnaire was distributed to members of the Baylor College of Medicine, Department of Family and Community Medicine who provide services in a private practice and community health centers in Houston, Texas, between April-May, 2016. All responses were anonymous and confidential. Descriptive statistics were calculated. **Results:** There were 61 responders within the targeted provider population and the majority were Family Medicine practitioners (70%). Although over 80% of providers asked patients about their smoking behavior and were familiar with the USPSTF LC screening guidelines, less than half had ever referred a patient to a smoking cessation program and only 16% reported having a formal LC screening program in their practice. Most providers discussed the risks/benefits of screening with their patients in some capacity (85%); however, only 42% reported having patients ask if they can or should be screened for lung cancer in the past year. Concerns regarding the implementation of a lung cancer-screening program in their practice included cost, EMR integrated screening tools, referral process, and access to smoking cessation programs. **Conclusions:** The findings reflect a likely lack of knowledge about smoking cessation services available to patients and a lack of consistent protocols for engaging in shared decision-making activities with patients who are identified at high risk for LC. Our findings support previous reports that showed gaps in physician knowledge about screening guidelines and reimbursement, and the need for further educational outreach.

407 **Poster Session A**

The Witness Project of Texas: Cancer Health Disparities *Myra Michelle DeBose, The Witness Project of Texas; M. Caldwell*

Introduction: Despite the advances in cancer screening, African American women continue to lag behind in screening efforts. There is evidence that early detection and screening of cancer has increased survival in this population across the country. In Texas, however, outreach initiatives have fallen short in engaging African American women in cancer screening. The relative low numbers of outreach may be due to access, affordable health care, cultural differences, biases and biological factors. Education and income have been shown to be powerful predictors of screening behavior than race and ethnicity alone. This project will utilize expert nurse educators to recruit and train cancer survivors and lay health advisors to share their cancer experiences and share community resources available for screening and treatment. **Methods:** Utilizing cancer survivors as role models and community members as lay health advisors to increase screening in African American women, The Witness Project, has been successfully replicated across the United States. The theoretical framework is based in adult learning, anthropology and health eduction. African American cancer survivors are able to share their cancer experiences with other African American women, who look like them. African American community members committed to early detection and prevention of cancer deaths serve as trained health advisors who provide accurate health information related to cancer. The survivors and health advisers are culturally appropriate role models who can directly relate to the value of screening and provide impactful testimony of surviving cancer. The expert nurse educators are credible resources who have a long history of promoting public health. **Results:** The use of culturally appropriate role models and lay health advisors are well documented in the literature. Recruitment and training of these individuals, along with skilled and trained professional nurse educators can be an effective way to increase screening of cancer. Nurses are charged with educating the public through evidence-based recommendations while encouraging community members to participate in screening that will improve their health. **Conclusions:** The Witness Project has been successfully implemented in 25 sites delivering cancer education and screening programs to over 10,000 women. It is one of the 183 Evidenced-Based Intervention Programs supported by the National Cancer Institute.

408 **Poster Session B**

Effect of colonoscopy outreach versus fecal immunochemical test outreach on colorectal cancer screening completion: A randomized clinical trial *Amit Singal, The University of Texas Southwestern Medical Center; S. Gupta; C. Skinner; C. Ahn; N. Santini; D. Agrawal; C. Mayorga; C. Murphy; J. Tiro; K. McCallister; B. Adamson; W. Bishop; A. Loewen; E. Halm*

Introduction: Effectiveness of colorectal cancer (CRC) screening is limited by underuse, particularly in underserved populations. We previously reported a fecal immunochemical test (FIT) outreach program was more effective than colonoscopy outreach and usual care for increasing one-time CRC screening in a racially diverse and socioeconomically disadvantaged cohort of patients; however, long-term effectiveness may be challenged by need for repeat testing and timely follow-up of abnormal results. **Methods:** We conducted a pragmatic randomized clinical trial from March 2013 to July 2016 among 5999 participants aged 50-64 years who were receiving primary care in an urban safety-net health care system and not CRC screen up-to-date. Effectiveness of FIT outreach and colonoscopy outreach to increase completion of the screening process (screening initiation and follow-up) during a 3-year period was compared. Patients were randomly assigned to mailed FIT outreach (n=2400), mailed colonoscopy outreach (n=2400), or usual care with clinic-based screening (n=1199). Primary outcome was screening process completion, defined as adherence to all guideline-recommended screening steps: colonoscopy completion, annual testing if normal FIT, diagnostic colonoscopy for abnormal FIT, and/or treatment evaluation if CRC detected. Secondary outcomes included detection of any adenoma and/or advanced neoplasia including CRC. **Results:** All 5999 participants were included in intention-to-screen analyses. Screening process completion was achieved in 38.4% ((95%CI 36.5-40.4) of persons randomized to colonoscopy outreach, 28.0% (95%CI 26.2-29.8) receiving FIT outreach, and 10.7% (95%CI 9.1-12.6) receiving usual care. Screening process completion was 27.7% (95%CI 25.1-30.4) and 17.3% (95%CI 14.8-19.8) higher in outreach groups than usual care ($p<0.001$ for both) and 10.4% (95%CI 7.8-13.1) higher for colonoscopy outreach compared with FIT ($p<0.001$). Adenomas were detected in 344 (14.3%) colonoscopy outreach, 128 (5.3%) FIT outreach, and 48 (4.0%) usual care participants. Advanced neoplasia was detected in 105 (4.4%) colonoscopy outreach, 49 (2.0%) FIT outreach, and 16 (1.3%) usual care participants. Adenoma and advanced neoplasia detection were 10.3 (95%CI 9.5-12.1) and 3.1% (95%CI 2.0-4.1) higher for colonoscopy outreach and 1.3% (95%CI -0.1-2.8) and 0.7% higher (95%CI -0.2-1.6) for FIT outreach than usual care (differences between outreach arms: 9.0% (95%CI 7.3-10.7) and 2.4% (95%CI 1.3-3.3), respectively). **Conclusions:** Among persons aged 50-64 receiving primary care at a safety-net institution, mailed outreach invitations offering FIT or colonoscopy, compared with usual care, increased the proportion completing CRC screening process within 3 years. The rate of screening process completion was higher with colonoscopy than FIT outreach.

409 **Poster Session A**

Project DERM: skin cancer health education, screening services and outcomes in an underserved population in Harris County, TX *Mary Tripp, The University of Texas M.D. Anderson Cancer Center; Y. Rivera; D. Benson; C. Bernard; S. George; A. Ciurea*

Introduction: Five million patients receive treatment for skin cancer annually in the United States. The incidence rate of melanoma has doubled over the past 30 years. In 2017, 87,110 new cases of invasive melanoma are expected. Melanoma incidence is highest in non-Hispanic whites (NHW). Hispanics are more likely than NHW to have thicker melanoma tumors, more advanced stage at diagnosis and higher mortality. Lower socioeconomic status (SES) is associated with thicker melanoma tumors, advanced stage at diagnosis and poorer survival. **Methods:** Project DERM provides skin cancer health education and screening to an underserved, low-SES population. Educational sessions (36 groups, 612 attendees) on skin cancer prevention and early detection were conducted with community partners. Dermatologists conducted 45 screenings at community clinics and Federally Qualified Health Centers. **Results:** Of 1251 patients screened, most were female (75.2%) and identified as Hispanic/Latino (82.9%) or white (70.6%). Average age was 46.2 (SD = 13.8) years. Skin cancer family or personal history was reported by 13.5% and 3.0%. Almost half reported at least one sunburn in the past year (41.4%) and moles that recently changed in size, color or shape (48.2%). Patients reported "most of the time" or "always" using sunscreen (17.9%); wearing a wide-brimmed hat (12.4%), sleeved shirts (24.2%) or sunglasses (35.7%); and staying in shade (40.7%). Skin biopsy was recommended for 183 (14.7%) and completed for 169 (13.5%) of screened patients. Pathology results indicated 42 skin cancers (29 basal cell carcinomas, 9 squamous cell carcinomas and 4 melanomas) in 33 patients (2.6% of patients screened, 19.5% of patients with completed biopsy, 6.1% of patients with family history of skin cancer and 22.2% of patients with personal history of skin cancer). Men were more likely to be recommended for biopsy and diagnosed with skin cancer ($p<.001$). Skin cancers were diagnosed in 14.4% of NHW and 1.7% of Hispanic patients screened. Half (50.0%) of patients diagnosed with skin cancer were Hispanic. **Conclusions:** To our knowledge, this is the largest observational study of skin screening in an underserved population in the US. Project DERM results so far demonstrate that skin cancer health education and screening of an underserved population is feasible and warranted. Outreach may increase screening in men. Outcomes, including skin cancer diagnosis in clinically meaningful proportions of NHW and Hispanic patients who were screened and had biopsies, support the rationale for skin cancer screening in this population.

410 **Poster Session B**

Hispanic males and cultural norms: critical elements in cervical cancer prevention among Hispanic women *Bertha Flores, The University of Texas Health Science Center at San Antonio; M. Martinez; L. Arevalo-Flechas; M. Tobar; D. Patel; M. Goros; J. Gelfond; D. Parra-Medina*

Introduction: Cervical cancer incidence and mortality are higher for Hispanic women in Texas compared to non-Hispanic whites (13.9 vs. 8.2 per 100,000). The majority of deaths are preventable through early detection and screening. Cervical cancer screening is recommended every 3 years for women 21 to 65 years old and HPV co-testing starting at age 30 every 5 years. However, Hispanic women in Texas are under screened. Reported barriers to cervical cancer screening among Hispanic women include cultural beliefs, socioeconomic status, education level, limited English proficiency, health literacy and perceived lack of male-partner support. We seek to investigate the links between health literacy, socio demographic variables, access and utilization of care, culture and language related to cervical cancer screening practices among Hispanic women. **Methods:** A mixed-method community-based study using focus group interviews and survey data with Hispanic males and females is being conducted. Using the Paasche-Orlow & Wolf (2007) model linking health literacy to health outcomes, we aim to identify individual level factors that influence cervical cancer screening behaviors. Focus group discussions were led by bilingual/ bicultural researchers, audio-recorded and transcribed verbatim. Survey data, includes cervical cancer knowledge, attitudes, beliefs, self-efficacy, health literacy and acculturation. **Results:** Eleven focus groups and 100 surveys (n= 74 females and n=26 males) have been collected thus far with Hispanic males and females in South Texas. The majority were Mexican-American (50%) and Mexican (35%), the mean age was 51 (SD 13). The majority (93%) of females reported having a Pap smear, however 50% of these same women had not had a Pap smear in 3 years or more, potentially exceeding the recommended interval. In addition, participants did not know if they had HPV co-testing (45%). A majority of participants (55%) reported primarily receiving medical information from the doctor's office. Focus group narratives were analyzed using thematic content analysis. The preliminary theme from female focus group interviews is: "include males" in cervical cancer prevention education. The overreaching theme from male focus group is a "clash of cultures" or navigating between scientific knowledge and expected Hispanic cultural norms. **Conclusions:** These results suggest the need for concerted efforts to improve consistent, regular recommended cervical cancer screening and the importance of provider recommendation for cervical cancer screening. Community-based, culturally competent cervical cancer screening intervention strategies including male partners are needed to decrease Hispanic cervical cancer health disparities in Texas.

411 **CPRIT Grantee Poster Session A**

Promoting Activity in Cancer Survivors: The PACES program *Chad Rethorst, The University of Texas Southwestern Medical Center; C. Skinner; B. Haley; K. Argenbright; M. Trivedi*

Introduction: Physical activity is an effective, safe, and evidence-based behavior that improves physical and psychosocial functioning, and potentially improves recurrence and survival among breast cancer survivors. Multiple organizations, including the American Cancer Society, the National Comprehensive Cancer Network, and the American College of Sports Medicine, recommend cancer survivors engage in at least 75 minutes intense or 150 minutes moderate activity per week. Despite the significant benefits of physical activity, at least two-thirds of breast cancer survivors do not meet these recommendations. Evidence-based strategies for increasing physical activity range from brief physical activity education and self-monitoring, to more intensive lifestyle counseling and on-site supervised activity. However, such interventions are rarely covered by insurance or offered within standard oncologic care, making them out of reach for cancer survivors. In addition, although multiple strategies have proven efficacious, little is known about the optimal intervention strategies for breast cancer survivors. **Methods:** We aim to achieve 3 goals: 1) Provide education and evidence-based interventions to Increase physical activity among breast cancer survivors treated at the Simmons Cancer Center, 2) Rigorously evaluate changes in physical activity and identify the optimal intervention or combination of interventions for increasing physical activity in breast cancer survivors who are not meeting physical activity guideline recommendations, and 3) Assess factors related to dissemination and implementation of the PACES program. **Results:** A pilot trial of the proposed intervention demonstrates feasibility for the program as we observed very good adherence to education sessions (82%) and use of Fitbit devices (80%). Preliminary evidence from the pilot trial indicates increases in physical activity and improvements in psychosocial functioning. We have also conducted focus group work to gather input from survivors prior to program initiation. Survivors identified many motivators for participation in PACES, including opportunity for social support and programs designed specifically for breast cancer survivors. Survivors also expressed interest in a program that supports their efforts to be physically active by providing "accountability" either through self-monitoring tools or frequent communication with program staff. **Conclusions:** The PACES program is designed to provide physical activity resources to breast cancer survivors and to evaluate the most effective and efficient strategies for increasing physical activity in this population.

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Active Living After Breast Cancer: Combining physical activity and survivorship navigation to improve quality of life of breast cancer survivors *Lizette Rangel, The University of Texas M.D. Anderson Cancer Center; K. Basen-Enquist; E. Shinn; L. Gatus*

Introduction: Physical activity is associated with improved quality of life and increased disease-free survivor in breast cancer survivors. Active Living after Breast Cancer (ALABC) is a program funded by the Cancer Prevention and Research Institute of Texas to improve breast cancer survivors' quality of life through increasing physical activity and providing survivorship information. The evidence-based program was developed and tested at MD Anderson, and adapted for delivery in the Houston community. **Methods:** We hypothesized that breast cancer survivors who participate in the ALABC program would show improvements in physical activity, physical functioning, and quality of life. Participants for ALABC were recruited from the Houston community, including a local multi-specialty care provider, the public hospitals, and area support groups. The program was delivered in 12 group sessions. Each session covered behavioral skills for increasing physical activity (40-50 minutes), 10 minutes of physical activity, and 30 minutes on a survivorship topic. The program emphasized increasing physical activity through incorporating short bouts of activity throughout the day. At the first and last sessions, participants completed questionnaires (IPAQ, PROMIS Global health short form), performance tasks (6-minute walk, 30-second sit-stand), and anthropometric assessments. **Results:** The first group began November, 2014. Since then we have conducted 34 groups (25 in English, 8 in Spanish and 1 in English/Mandarin). We have screened a total of 489 survivors; 199 have started the program and 132 have completed the program (66% completion rate). Mean age of participants was 59.7 years (SD=10.6, range 34-84). Participants were 31% African-American, 34% white, 9% Asian, 2% other; 24% were Hispanic. Participants report increases in their weekly minutes of walking (p<.000) and moderate to vigorous physical activity (p<.003). Changes in six-minute walk and sit-stand tests improved (p< .000 for both), demonstrating that physical functioning objectively improved. Self-reported quality of life also improved in both the physical health (p<.000) and mental health (p=.000) domains. There were no significant changes in waist circumference or BMI. **Conclusions:** Data from the ALABC program evaluation indicated that the program was effective at increasing physical activity and improving quality of life. Furthermore, it is feasible to deliver to a diverse survivor population, including Spanish-speaking survivors. Participants in the program showed mastery of the program content and indicated they were using the behavioral strategies for increasing physical activity. Future efforts should expand to other cancer survivors and also address disparities among minority cancer survivors.

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Childhood cancer survivors and parents with regular follow-up have limited understanding of treatments and risks for late effects *Jason King, Baylor College of Medicine; P. Lupo; M. Scheurer; M. Gramatges; E. Shohet; M. Fordis; M. Horowitz; D. Poplack*

Introduction: The Passport For Care Survivor Website (PFCSW) is a patient-centered decision support tool that provides survivors and/or their parents with a cancer treatment summary, an individualized Survivorship Care Plan (in English or Spanish) with recommendations for follow-up screening based on COG LTFU Guidelines, and related educational content. **Methods:** Childhood cancer survivors in Texas were invited to enroll in the PFCSW during a survivorship clinic visit or were contacted with information about the PFCSW after being identified through the Texas Cancer Registry. At time of enrollment, survivors and parents were asked to participate in a research study assessing self-reported knowledge of prior cancer history/treatments, potential late effects, and means for receiving follow-up care. **Results:** A total of 528 participants completed the baseline survey (response rate = 35%), including 213 survivors and 315 parents. Although 92% reported regular follow up for their cancer diagnosis, 28% of survivors and 24% of parents reported moderate to no knowledge of their treatment exposures. Furthermore, 32% of survivors and 38% of parents reported moderate to no knowledge of potential late effects of their cancer therapy. Survivors reported barriers to receiving follow-up care including: busy schedule (27%), poor insurance coverage (17%), perception that follow-up is not needed (8%), and distance to clinic (7%). Parents also reported considerably more fear of late effects or cancer recurrence, with 20% expressing that they were very afraid or extremely afraid, versus 7% of survivors. **Conclusions:** Our findings stress the importance of distributing a Survivorship Care Plan to childhood cancer survivors, a population who may have an incomplete understanding of the diagnoses and treatments they received as children, and may be unprepared to manage related health risks of treatments. Enrollment in the PFCSW has the potential to reduce some of the barriers to receiving follow-up care that were identified in this study by survivors and their parents.

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Improving Service Delivery to Cancer Survivors in Primary Care Settings *Maria Rodriguez, The University of Texas M.D. Anderson Cancer Center; L. Shay; L. Foxhall*

Introduction: An estimated 14 million cancer survivors live in the U.S., with up to 18 million expected by 2020. Innovative educational programs to teach primary care providers (PCPs) about the specific needs of long-term cancer survivors are limited. **Methods:** We established a partnership with three Texas family medicine training programs to provide interactive educational sessions focused on survivors' needs for primary prevention and lifestyle counseling, surveillance and screening, and prevention of psychosocial and long-term effects. In Project ECHO, cancer center faculty and partners led interactive tele-mentoring sessions following a systematic curriculum to share best practices and facilitate case-based problem solving. Surveys assessing resident and PCP knowledge, self-efficacy, and practices regarding survivorship care management were administered through REDCap in July 2016 and 2017. Paired t-tests evaluated differences from baseline to follow-up. **Results:** Baseline response rates were 64% (60/94) and 59% (55/93) at follow-up. Compared to baseline, providers at follow-up were significantly more likely to report being "very confident" in their knowledge about: appropriate surveillance to detect recurrent breast cancer (5% vs 24%; p=0.01); long-term physical effects of colon cancer and its treatment (8% vs 18%; p=0.04); potential adverse psychosocial outcomes of colon cancer treatment (24% vs 44%; p=0.01); appropriate screening for new primary breast (29% vs 61%; p<0.001) and colon cancers (27% vs 51%; p=0.01); and preventive lifestyle/behavioral counseling for breast (39% vs 59%; p=0.03) and colon cancers (37% vs 59%; p=0.01). Participants were also more likely to "strongly agree" that they have the skills necessary to: provide follow-up care related to the colon cancer and its treatment (10% vs 28%; p=0.02); initiate appropriate screening for other new primary cancers for breast (28% vs 56%; p<0.01)

and colon cancer survivors (28% vs 58%; p<0.01); and conduct lifestyle/ behavioral counseling to prevent cancer for breast (33% vs 53%; p=0.03) and colon cancer survivors (34% vs 55%; p=0.02). Finally, providers were more likely to report "always" or "almost always" having a specific discussion with cancer survivors regarding recommendations for future care and surveillance (5% vs 20%; p=0.08). **Conclusions:** Preliminary results suggest our project has improved provider knowledge, self-efficacy, and practices regarding survivorship care management, with the highest levels in areas pertaining to screening and prevention. While significantly improved, knowledge and self-efficacy around surveillance for cancer recurrence remains low. We aim to continue this trajectory of improvement in subsequent project years and disseminate the project to other primary care training sites in Texas and beyond.

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Poster Session A

Interactive patient-centered website to prevent dysphagia in irradiated pharyngeal cancer patients *Eileen Shinn, The University of Texas M.D. Anderson Cancer Center; R. Trevino-Whitaker; E. Kamunyo; J. McLaughlin; A. Garden*

Introduction: While cancer of the throat is highly curable, up to 39% of survivors experience serious permanent swallowing problems. Targeted swallowing exercises performed during radiation have demonstrated efficacy in preventing dysfunction. However, patients find the preventive swallowing exercises to be extraordinarily difficult due to significant side effects from radiation. **Methods:** During the first two project periods, we have developed a full-scale responsive web-based application program to deliver an effective intervention program to help patients adhere to preventive swallowing exercises and cope with radiation side effects. The website features tracking logs for weight loss, trismus and swallowing exercises, how-to-videos, patient stories and an all-inclusive search bar. The website is also available in Spanish. Patients at Texas Health Care in Fort Worth are receiving the preventive program; due to slower accrual than expected, we have expanded the program to include head and neck cancer patients at UTMB Galveston and at Kelsey Seybold, Houston. All patients will receive 10 weekly behavioral modules with coping strategies, practical side-effect information, and psychological skills training during radiation and during the four week post-radiation period. All participants are asked to create a log-in and password, taught how to navigate the program and asked to log in to the website at least once a week during and after radiation. **Results:** Ninety-four patients have been enrolled onto the prevention program; 52 who received a non-interactive, pilot version of the web-based program and 42 who have received the full-scale interactive program. Accrual rates are approximately 95%, with the most common reason for refusal is dislike of a computer-based platform. Approximately 52 (38%) of the enrolled patients are either uninsured or low SES patients. Fifteen mobile tablets with monthly data plans have been distributed to patients without access to computers or smartphones. All 92 patients have received preventive and diagnostic speech pathology services, including fiberoptic endoscopic swallowing tests. Of the 42 patients who have been enrolled onto the full-scale interactive website, 75% have logged in at least once and over 50% log in regularly throughout the course of their radiation. Patients who have logged into the website have rated the program highly on helpfulness in coping with radiation side effects and helpfulness with adhering to preventive swallowing and trismus exercises. **Conclusions:** Head and neck cancer patients are willing to use internet-based intervention programs to learn how to cope with radiation and prevent long-term swallowing dysfunction.

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416 **CPRIT Grantee**
Poster Session B

Improving Electronic Documentation of Disease History Among Colorectal Cancer Survivors at UTMB *Christian Alch, The University of Texas Medical Branch at Galveston; P. Lavere; J. Islam*

Introduction: Cancer survivors represent a diverse population with a variety of needs in primary care settings. As treatment and management has improved, life expectancy of cancer survivors has increased, leading to a transition of disease-specific follow-up care out of the offices of specialists and into family medicine clinics. Unfortunately, currently no standardized documentation form exists in the UTMB Electronic Medical Record, EPIC. Providers are forced to perform laborious, often futile, searches through the electronic documentation system to obtain data relevant to survivorship care. **Methods:** The UTMB Epic Database was surveyed for patients with a known diagnosis of breast, colorectal, lung, or prostate cancer. Colorectal cancer survivors were chosen as documentation subjects, with breast, prostate and lung cancer to be updated at a later time. Exclusion criteria included patients no longer receiving care at UTMB and patients exclusively receiving cancer-related care at other facilities. The "social documentation" field of EPIC was filled with the following information for colorectal cancer survivors:

Cancer type:
Date of diagnosis:
Age when diagnosed:
Pathology report:
Stage:
Surgery:
Surgery Date:
Radiation:
Last day of radiation:
Chemotherapy:
Completed chemo?:
Last date of chemotherapy:

Chemotherapy agent: **Results:** Out of 156 patients identified through the database search, 74 met criteria to be included in intervention. Reasons most often found for not qualifying included death and patients no longer receiving care at UTMB. Full pathologic history (TNM staging) was identified from database review in 86% of male colorectal cancer survivors and 64% of female colorectal cancer survivors. **Conclusions:** Documentation of cancer survivors can be performed in a primary care settings through meticulous search of EMR records. Further studies can demonstrate how clear documentation of disease history among colorectal cancer patients improves clinical decision making and time restraints in the clinics.

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417 **CPRIT Grantee**
Poster Session A

A Statewide Tele-Mentoring Medical Education Program to Improve Survivorship Care *Maria Rodriguez, The University of Texas M.D. Anderson Cancer Center; G. Palos; L. Foxhall; L. Shay; K. Gilmore; R. Harris; P. Lewis-Patterson*

Introduction: Education and guidance on the clinical management of cancer survivors is needed to standardize survivorship care for this growing population. To address this need, a tele-mentoring educational curriculum utilizing Extension for Community Healthcare Outcomes (ECHO) methodology was developed to deliver evidence-based recommended cancer survivorship care and preventive services. Here we present findings from a survey to address satisfaction with the curriculum and program. **Methods:** The curriculum consisted of hybrid educational sessions provided by the Project ECHO platform. Tele-mentoring video conference sessions combined didactic lectures and case studies discussions. Sessions were held twice a month and led by an interdisciplinary team of faculty and providers assigned to clinics of the Survivorship Program of M. D. Anderson Cancer Center. Content focused on the principles and practices of survivorship care, prevention, and management of late effects related to cancer or its treatment. Study investigators developed an evaluation tool to assess: 1) satisfaction with ECHO operations, 2) self-efficacy in clinical management of survivors, and 3) barriers towards distribution of treatment summaries and delivery of survivorship care. REDCap, a secure, web-based application, and was used to build, distribute and manage all survey data. **Results:** In June 2017, electronic surveys were distributed to 116 faculty and medical residents from 3 collaborating Texas-based institutions. There was a 46.4% response rate and the majority of respondents attended the ECHO sessions (81.5%). The most common reason for non-attendance related to scheduling conflicts with the ECHO sessions (77.8%). Respondents were split in their ratings of the organization of the clinic, with just over half rating the organization as good or very good (54.5%). Reasons for ratings of fair or poor included: session did not provide information on guidelines, having the learning topics and case studies match and planned the topics in advance, providing handouts with information on where to look for resources on cancer survivorship, have specialist present to answer questions. Almost all respondents reported being interested in continuing participation in ECHO sessions to improve their knowledge and skills (81.8%), and reported that participation in ECHO clinics increased their ability to offer more complete comprehensive care (88.6%). The majority of respondents endorsed the ECHO sessions as an effective way for their clinic to enhance its expertise (77.3). **Conclusions:** Overall, participants found the sessions helpful in improving cancer survivors' care, despite feedback from half reporting there were limitations in the curriculum's format. Efforts will be made to integrate their suggestions into future program improvements.

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418 **CPRIT Grantee**
Poster Session B

Preserving Hope: Results from the 2017 LIVESTRONG Survey on Fertility Concerns *Kendall Bergman, LIVESTRONG; A. Narayan; C. Bann; K. Treiman; C. Soloe*

Introduction: According to the 2009 Behavioral Risk Factor Surveillance Survey, 16% of the more than 24.7 million Texans diagnosed with cancer are under 45 years (reproductive years). Research shows that infertility

affects a cancer survivor's long-term quality of life by causing unresolved grief and depression, as well as reduced life satisfaction and increased anxiety. Addressing fertility concerns has emerged as a major component of survivorship care. Fertility preservation is often possible in people undergoing cancer treatment. Despite the American Society for Clinical Oncology's guidelines for oncologists to disclose risks of infertility, health care professionals (HCPs) are not routinely offering fertility information and referrals to their patients. CPRIT awarded LIVESTRONG funds to create a cancer and fertility training to increase awareness of this issue among Texas HCPs, and to increase the number of survivors who receive information about infertility risks and preservation options. **Methods:** In 2017 LIVESTRONG launched a survey to assess the number of cancer survivors who were informed of infertility risks due to cancer. A total of 123 people diagnosed with cancer between ages of 15-39 during 2006 to 2017 in Texas responded to the survey. **Results:** Seventy-five percent of respondents reported that a doctor or HCP discussed fertility issues related to cancer treatment with them. Of these respondents, 26% reported that they raised the topic themselves. The majority (76%) reported that they discussed fertility issues with a HCP before starting treatment. Respondents reported that discussion topics included possible risks to fertility (85%), methods for fertility preservation (63%), timing for fertility preservation (43%), and costs of fertility preservation (34%) among other topics related to fertility. However only 40% reported being referred to a fertility specialist. Respondents who did not take steps to preserve their fertility (55%) cited cost, a desire to start treatment right away, and not knowing it was a possibility as reasons for not doing so. Among respondents who did take steps to preserve their fertility (43%), 68% reported receiving financial assistance to cover costs of fertility preservation. **Conclusions:** Receiving a cancer diagnosis can be overwhelming and cause fear and anxiety. A patient may not be aware of all questions to discuss with a HCP. LIVESTRONG strongly recommends that all HCPs who interact with cancer patients during their reproductive years inform them of any potential risks to their fertility so patients can make informed decisions about taking protective or preservation measures to have hope for a biological family after cancer.

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A Bio-Psychosocial Intervention Program for Improving Quality of Life in Breast Cancer Survivors - Final Outcome of a Prospective Randomized Trial *Sharon Felts, Texas Tech University Health Science Center at Amarillo; J. Pettiford; E. Wischkaemper; D. Miller; S. Crawford; R. Layeequr Rahman*

Introduction: Given the 3.1 million breast cancer survivors in America, quality of life (QoL) is a vital issue. Bio-psychosocial milieu of survivorship is increasingly important. This study assesses the impact of Bio-psychosocial Intervention (BPSI) on the QoL of breast cancer survivors utilizing Functional Assessment of Cancer Therapy – Breast (FACT-B) instrument. The objective of the study was to determine the impact of a bio-psychosocial intervention on the quality of life of breast cancer survivors. **Methods:** A prospective randomized trial was designed; intervention arm included a 4-hour BPSI coping skills class; control arm received standard of cancer and follow up care (SOC). Women diagnosed within 2 years of study initiation were eligible. Sample size was based on 8-point difference in FACT-B score, 90% power, 5% type I error, and 20% attrition. FACT-B questionnaire was administered to all patients at baseline and at 6-month intervals. SAS 9.3 software was used to analyze data using Chi-square test for categorical and Wilcoxon rank sum for ordinal data; linear mixed modeling was used for longitudinal analysis. **Results:** One-hundred-three of 120 (86%) patients were available for analysis. Forty-seven patients were in BSPI arm, and 56 received SOC. For BPSI arm vs. SOC arm, the median (interquartile) age [60 (52,68) vs. 58 (52,68)yrs. p=0.9135], cancer-stage [0:1:2:3=11%:41%:35%:13% vs. 18%:46%:22%:15%-p=0.4645], and biology [ER+:triple negative:HER2+ = 74%:9%:16% vs. 72%:7%:20%-p=0.8454], respectively, was similar. Median (25th-75th centile) FACT-B scores in BPSI vs. SOC arms at baseline were 109 (95,121) vs. 112 (95, 122) [p=0.6125]; mean (SE) change since baseline at 6, 12, 18, and 24 months was: 7.42 (2.22) vs. 7.04 (1.97) [p=0.8862]; 17.0 (2.64) vs. -6.09 (2.37) [p<0.0001]; 16.03 (2.53) vs. 3.58 (2.29) [p=0.0004], and 15.48 (1.89) vs. 16.4 (1.71) [p=0.7966] respectively. The inter-group differences remained after adjusting for confounding variables at baseline. The p-value for interaction amongst groups over two years remained <0.0001 except for breast cancer specific concerns. **Conclusions:** BPSI coping skills class significantly improved the QoL of breast cancer survivors by one year post-intervention time point; this difference narrowed at 18 months and disappeared at 24 months.

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Numerals refer to abstract numbers

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