Recommendations for Scientific Research Peer Review Panels

- Steve Altschuler, Ph.D.
- Paul A. Bunn, M.D.
- Arion Chatziioannou, Ph.D.
- Michael A. Hollingsworth, Ph.D.
- David A. Mankoff, M.D., Ph.D.
- Alexander Meissner, Ph.D.
- Carolyn D. Runowicz, M.D.
- Kristin R. Swanson, Ph.D.
- Cameron Turtle, M.D., Ph.D.
- Eliezer M. Van Allen, M.D.
- Henry VanBrocklin, Ph.D.
- Lani Wu, Ph.D.

Recommendation for Prevention Peer Review Panels

- Bob Riter

Recommendations for Product Development Peer Review Panels

- C. Glenn Begley, Ph.D.
- Renzo Canetta, M.D.
- Terence Porter, Ph.D.
- Sandra Silberman, M.D., Ph.D.

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OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: Altschuler, Steven J.

eRA COMMONS USER NAME (credential, e.g., agency login): SALTSC

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania	B.A.	06/85	Mathematics
University of California, San Diego	MA	06/86	Mathematics
University of California, San Diego	PhD	06/90	Mathematics

A. Personal Statement

Over the past decade, my laboratory, in collaboration with the laboratory of Dr. Lani Wu, has pioneered multiple approaches for quantifying and interpreting cancer heterogeneity in normal and diseased tissues. Traditionally, this phenotypic heterogeneity, whether arising from microenvironment, epigenetic or genetic sources, has been viewed as an impediment to understanding and treating cancer. We were therefore very surprised by our ability to identify biological and clinical information hidden within patterns of heterogeneity. Our cancer research program is focused on: 1) accelerating the path of early cancer drug discovery; 2) identifying clinically important information from cellular and tissue heterogeneity; and 3) understanding heterogeneity arising from drug resistance.

I take an active role in helping to train the next generation of young scientists. In my own lab, I meet frequently with students to discuss all aspects of research projects. I am very active in the UCSF graduate programs, teaching an intensive bootcamp to incoming graduate students and a minicourse on systems biology, guest lecturing in numerous other graduate classes and retreats, and meeting after hours to talk about science or the process of doing science. I am an active participant in both national and international programs aimed at teaching/mentoring the next generation of young scientists. These activities include founding and directing courses on quantitative image analysis for the past five years at MBL and a summer school for mathematical biology graduate students in MSRI at UC Berkeley as well as teaching at workshop in Italy, Switzerland and China.

a) Ramirez M, Rajaram S, Steininger RJ III, Osipchuk D, Roth MA, Morinishi LS, Evans L, Ji W, Hsu C-H, Thurley K, Wie S, Zhou A, Koduru PR, Posner BA, Wu LF*, Altschuler SJ*, Diverse drug-resistance mechanisms can emerge from drug-tolerant cancer persister cells, Nature Communications, 2016 to appear.
b) Kang J, Hsu CH, Wu Q, Liu S, Coster AD, Posner BA, Altschuler SJ*, Wu LF*.; Improving drug discovery with high-content phenotypic screens by systematic selection of reporter cell lines. Nature Biotechnology. 2015. PMCID in process.
c) Thorne CA, Wichaidit C, Coster AD, Posner BA, Wu LF*, Altschuler SJ*. GSK-3 modulates cellular responses to a broad spectrum of kinase inhibitors. Nat Chem Biol. 2014 Nov 17. PMCID: PMC4270937.
d) Singh DK, Ku C-J, Wichaidit C, Steininger RJ, Wu LF*, Altschuler SJ*, Patterns of basal signaling heterogeneity can distinguish cellular populations with different drug sensitivities. Molecular Systems Biology 2010 May 11;6:369. PMCID: PMC2890326.

(* = co-senior author)

B. Positions and Honors

Positions and Employment

1990-1991	Research Fellow, **University of Minnesota**, Institute for Mathematics and its Applications Minneapolis, MN.
1991-1992	Research Associate, **Australian National University**, Centre for Mathematics and its Applications, Canberra, Australia.
1992-1993	Research Fellow, **Institute for Advanced Study**, Princeton, New Jersey.
1993-1994	Instructor, Mathematics Department, **Princeton University**, Princeton, New Jersey.
1994-2000	Group Manager and Senior Researcher, **Microsoft Corporation**, Redmond, WA.
2000-2001	Director Research, Informatics, **Rosetta Inpharmatics**, Kirkland, WA.
2001-2005	Fellow, Bauer Center for Genomics Research, **Harvard University**, Cambridge, MA.
2005-2009	Assistant Professor, **U.T. Southwestern Medical Center**, Dallas, TX.
2009-2014	Associate Professor, **U.T. Southwestern Medical Center**, Dallas, TX.
2014-	Professor, **University of California at San Francisco**, San Francisco, CA.

Other Experience and Professional Memberships

Scientific Advisory Panels

2009	Site Visit Committee (SVC) for evaluation of the Department of Cell Biology and Infection, Institute Pasteur, Paris, France, March
2011-2013	External Scientific Panel, NIH Library of Integrated Network-based Cellular Signatures (LINCS)
2011-2015	Scientific Advisory Board, European Systems Microscopy Network of Excellence
2012	Editorial board, Developmental Cell
2012	Editorial board, Quantitative Biology, open access journal

Conferences/Classes

2008	Organizer, Institute for Mathematics Annual Program Year Workshop, Organization of Biological Networks, Minneapolis, MN
2008	Organizer, American Society of Cell Biology (ASCB) Minisymposium on Information Technology for Cell Biology, San Francisco, CA
2010	Organizing Committee, Bioimage Informatics, Carnegie Mellon University, Pittsburgh, PA
2010	Chair, Days of Molecular Medicine, Systems Biology Approaches to Cancer and Metabolic Disease, Karolinska Institutet, Stockholm, Sweden

2010	Program committee, ISMB, Bioimaging session, Boston, MA
2011	Instructor, Yeast Systems Biology International Course, Institut Pasteur de Montevideo, Uruguay
2011	Instructor, Concepts in Developmental Biology, Summer School, Karolinska Institutet, Sweeden
2011	Co-director & instructor, MBL CIAN course (10 day class), Woods Hole, MA
2011-2012	Theme organizer on Systems Biology, Annual Meeting of the American Society for Biochemistry and Molecular Biology (ASBMB), San Diego, CA
2011-2015	Chair, co-chair, Gordon Conference on Stochastic Physics in Biology, Santa Monica, CA
2014	Program committee for the 2015 ASCB Annual Meeting in San Diego, CA
2015	Co-organizer, EMBO-EMBL Symposium on Cellular Heterogeneity, Heidelberg, Germany
2015	Co-director & instructor, Mathematical Topics in Systems Biology (2 week class), Mathematical Sciences Research Center, UC Berkeley, CA

Other

1997	Visiting Researcher, Mathematical Sciences Research Institute, Berkeley, CA.
1998-	Awarded 12 U.S. Patents
2003	Advanced Bacterial Genetics, Cold Spring Harbor, NY.
2005-2009	F1000 Reviewer, Faculty Member of Chemical Biology

Honors

1985	B.A. Magna Cum Laude, Departmental Honors
1989	Alfred P. Sloan Doctoral Dissertation Fellowship
1997	AMS Profiled Industrial Mathematician of the Month
2005	UTSW endowed scholar: W. W. Caruth, Jr. Scholar in Biomedical Research
2008	Rita Allen Foundation Scholar: Milton E. Cassel Scholar

C. Contribution to Science

1. Spatial patterning and cellular decision making. A major theme in our lab has been to understand how normal and diseased cells process information and make decisions, often involving spatial organization. Our approach combines experiment, image analysis, and mathematical modeling. My contributions to this research area include: the discovery that endocytosis rates can tune the precision of spatial patterning (a); the discovery of a fundamentally new polarity mechanism by which cells can break symmetry (or "polarize") through the use of positive feedback, which challenges a paradigm established 60 years ago by Alan Turing (b); a new approach for understanding the dynamics of crosstalk in complex signaling networks (c); and the ability to infer network topology by analysis of natural cell-to-cell variability, which allows cellular behaviors to be studied in unperturbed conditions (d).

a) Marco E, Wedlich-Soldner R, Li R, Altschuler SJ*, Wu LF*. Endocytosis optimizes the dynamic localization of membrane proteins that regulate cortical polarity. Cell 2007 Apr 20;129(2):411-22. PMCID: PMC2000346.
b) Altschuler SJ*, Angenent SB, Wang Y, Wu LF*. On the spontaneous emergence of polarity. Nature 2008 Aug 14, 454:886-890. PMCID: PMC2562338.
c) Ku C-J, Wang Y, Weiner OD, Altschuler SJ*, Wu LF*, Evolving cross-talk in neutrophil polarity network. Cell 2012 May 25; 149(5):1073-1083. PMCID: PMC3614011.
d) Wang Y, Ku C-J, Zhang ER, Artyukhin AB, Weiner OD, Wu LF*, Altschuler SJ*, Identifying network motifs that buffer front-to-back signaling in polarized neutrophils, Cell Reports 2013 May 6. pii: S0955-0674(13)00067-7. doi: 10.1016/j.ceb.2013.04.004. PMCID: PMC3674638.

2. Cellular heterogeneity. Recent studies have revealed that populations of seemingly identical cells exhibit a bewildering array of phenotypic and genetic differences. These differences challenge traditional classifications of cell types, raise profound questions about how living systems can give rise to reliable behaviors and present impediments to treating disease. To address these challenges, our lab developed experimental and analytical methodologies for studying cellular heterogeneity (a-b). Our work demonstrated that patterns of cellular heterogeneity are robust readouts of cellular populations, and can be used to reveal surprising insights into the biological networks that control cells, tissues, and diseases (c-d). Understanding the role of heterogeneity will ultimately have profound implications to all fields of biology, including understanding emergent behaviors of living systems, developing improved approaches for tissue engineering and cancer treatment.

a) Slack MD, Martinez ED, Wu LF, Altschuler SJ*. Characterizing heterogeneous cellular responses to perturbations. Proceedings of the National Academy of Sciences USA, 2008 December 9; vol. 105, no. 49, 19305–19310. PMCID: PMC2614757.
b) Loo LH, Lin HJ, Steininger RJ, Wang YQ, Wu LF*, Altschuler SJ*, On an Approach for Extensibly Profiling the Molecular States of Cellular Subpopulations. Nature Methods 2009, vol. 6, 759-765. PMCID: PMC2779244.
c) Loo LH, Lin HJ, Singh, DK, Lyons, KM, Altschuler SJ*, Wu LF*, On Heterogeneity in the physiological states and pharmacological responses of differentiating 3T3-L1 preadipocytes. Journal of Cell Biology 2009 Nov 2;187(3):375-84. PMCID: PMC2779244.
d) Singh DK, Ku C-J, Wichaidit C, Steininger RJ, Wu LF*, Altschuler SJ*, Patterns of basal signaling heterogeneity can distinguish cellular populations with different drug sensitivities. Molecular Systems Biology 2010 May 11;6:369. PMCID: PMC2890326.

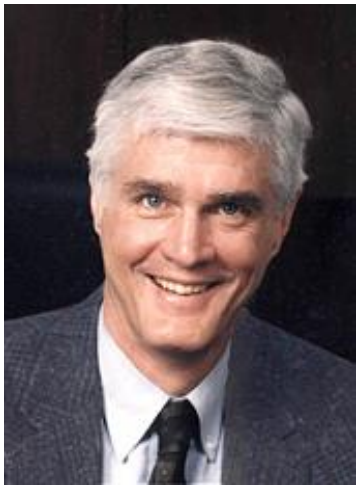
3. Cytological profiling. Recent advances in high-content fluorescence microscopy have accelerated progress in many areas of cell biology. Approaches from computer vision are essential for analyzing image data sets that are too large to examine by human eye. Over the last decade, our lab pioneered machine-learning approaches for extracting informative signatures of cellular perturbations and identifying stereotyped subpopulations. Our work helped to start the field of high throughput cytological profiling and set standards in both academics and industry (a-b). We released to the research community a software tool, called "PhenoRipper," that vastly simplified and accelerated the process for cell biological laboratories to make use of automated phenotypic profiling (c), as well as tools, "Simucell," to facilitate development and comparison of new tools. Additionally we have developed a computational and experimental approach to identify optimal reporter cell lines for annotating large compound libraries across diverse drug classes (d).

a) Perlman ZE, Slack MD, Feng Y, Mitchison TJ, Wu LF*, Altschuler SJ*. Multi-dimensional drug profiling by automated microscopy. Science 2004 Nov 12;306(5699):1194-8. PMID: 15539606.
b) Loo LH, Wu LF, Altschuler SJ. Image-based multivariate profiling of drug responses from single cells. Nature Methods 2007 May;4(5):445-53. PMID: 17401369.
c) Rajaram S, Pavie B, Wu LF*, Altschuler SJ*, PhenoRipper: an approach for rapid analysis and exploration of high content microscopy images. Nature Methods 2012 July Vol. 9, No. 7: 635-637. PMCID: PMC3842428.
d) Kang J, Hsu CH, Wu Q, Liu S, Coster AD, Posner BA, Altschuler SJ*, Wu LF*.; Improving drug discovery with high-content phenotypic screens by systematic selection of reporter cell lines. Nature Biotechnology. 2015. PMCID in process.

4. Mathematics. In my early work, I developed approaches to use nonlinear partial differential equations to solve problems in differential geometry and topology. My work on curve shortening provided the first classification of singularities (a), answered a conjecture of Calabi for about how to pass through singularities (b), and developed a theory for self-similar solutions (c). This work played a role in the recent solution of the Poincare conjecture and has been applied to unexpected areas of engineering, including computer graphics and robotics. My work on evolving one-form fields on 3D manifolds helped start a new area of mathematics research, now called "confoliations" (d).

a) Altschuler SJ*. Singularities of the curve shrinking flow for space curves. Journal Differential Geometry 1991; 34 (2):491-514.
b) Altschuler SJ*, Grayson MA*. Shortening space curves and flow through singularities. Journal Differential Geometry 1992; 35(2):283-98.
c) Altschuler DJ, Altschuler SJ, Angenent SB, Wu LF, The zoo of solitons for curve shortening in n-dimensions. Nonlinearity 2013 Vol. 26, No. 5: 1189-1226. DOI:10.1088/0951-7715/26/5/1189.
d) Altschuler SJ*. A geometric heat flow for one-forms on three-dimensional manifolds. Illinois Journal of Mathematics 1995; 39 (1):98-118.

List of Published Biological Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40629613/?sort=date&direction=ascending



OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Paul A. Bunn Jr.

eRA COMMONS USER NAME (credential, e.g., agency login): PAUL_BUNN

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date	FIELD OF STUDY
Amherst College, Amherst, MA	BA	1967	Biology
Cornell University Medical Center, New York, NY	MD	1971	Medicine
University of California, San Francisco, CA, Moffitt Hospital National Cancer Institute, Medicine Branch, Bethesda, MD		1971-1972 1972-1973 1973-1976	Medical Internship Medical Residency Medical Oncology Fellowship

A. Personal Statement

Dr. Bunn is Distinguished Professor and the James Dudley endowed Professor of Lung Cancer research at the University of Colorado Cancer Center and School of Medicine. Dr. Bunn and his laboratory have studied the role of growth factor signaling in lung cancer since he moved to the University of Colorado in 1984. Over this period Dr. Bunn has been involved in clinical trials of novel therapies and biomarkers for lung cancer. Dr. Bunn has mentored many fellows and young faculty who continue in lung cancer careers. Dr. Bunn has been the Principle Investigator of the University of Colorado Lung Cancer SPORE grant since 1992. Dr. Bunn has served on the external Scientific Advisory Boards for several Cancer Centers and SPOREs. Dr. Bunn is committed to diversity and will help in recruiting and training minority investigators.

B. Positions and Honors (past to present)

List in chronological order previous positions, concluding with the present position. List any honors. Include present membership on any Federal Government public advisory committee.

Positions and Employment

1976-1981 Sr. Investigator, NCI, Washington VA Hospital, Washington, D.C.
1978-1981 Assistant Professor of Medicine, Georgetown University Medical School
1981-1984 Head, Cell Kinetic Section, NCI, Naval Hospital, Bethesda, MD

1981-1984	Assoc. Prof. Medicine, Uniformed Services University of Health Sciences, Bethesda, MD
1984-present	Professor of Medicine, University of Colorado Health Sciences Center, Aurora, CO
1984-1994	Head, Division of Medical Oncology, University of Colorado Cancer Center, Aurora, CO
1987- 2009	Director, University of Colorado Cancer Center, Aurora, CO
1997-2006	Grohne-Stapp Endowed Professor of Oncology
2003-2013	Executive Director, International Association for the Study of Lung Cancer (IASLC)
2006-present	James Dudley Endowed Professor of Lung Cancer Research
2013-present	Distinguished Professor, University of Colorado Health Sciences Center, Aurora, CO.

Other Experience and Professional Memberships

1976-1986	Cell Kinetic Society
	Nominating Committee 1981-1983, Chair 1983
	Finance Committee 1983-1984
1976-2005	American Society of Hematology
	Scientific Subcommittee on Neoplasia 1989-1992
1977-present	American Society of Clinical Oncology (ASCO)
	Board of Directors 1995-1999
	President-Elect 2001-2002
	President 2002-2003
	Past President 2003-2004
	Chair, Program Subcommittee 1985, 1990
	ACRA (Advanced Clinical Research Award) Subcommittee, 2006-present
	Real Estate Task Force Committee, 2005-2006
	ASCO Foundation, Board of Directors 2004-2010, Chair 2006-2007
1977-present	American Association for Cancer Research (AACR)
	Grants Review Committee, 2006-2007
1978-present	American Federation for Clinical Research
1979-present	International Association for the Study of Lung Cancer (IASLC)
	Board of Directors 1988-2000
	President-Elect 1991-1994
	President 1994-1997
	Past President 1997-2000
	Executive Director 2003-2013
1983-present	American Association for the Advancement of Science
1985-1990	Lung Cancer Study Group
1985-present	Western Association of Physicians
1986-present	Southwest Oncology Group
1987-2009	American Association of Cancer Institutes (AACI)
	Board of Directors 1994-1997, 2000-2003
	President-Elect 1994-1995
	President 1995-1996
	Past President 1996-1997
1994-1998	International Society for Cutaneous Lymphomas
1998-present	American College of Physicians Fellow
2002-present	National Dialogue on Cancer Collaborating Partner
2003-present	European Society of Medical Oncology

Honors

1967	Howard Hill Mossman Award, Amherst College
1971	Alpha Omega Alpha, Cornell University Medical College
1971	Sondra Lee Shaw Research Award, Cornell University Medical College
1984	PHS Medal of Commendation
1991-present	The 400 Best Doctors in America, Good Housekeeping
1992	Scientist of the Year Award, ARCS - Denver Chapter
1996	UCHSC Faculty Council, Award for Excellence

1998	James F. Mitchell-Paul C. Kiernan Foundation Scholar Award
2001	James Addison Sewall Award, University of Colorado
2002	American Italian Cancer Research Foundation Award
2003	IASLC Merit Award
2004	Claude Jacquillat Award
2004	SPORE Leadership Award
2005	Fellow AAAS
2005-present	America's Top Doctors for Cancer, Castle Connolly Medical Ltd.
2006	American Association for the Advancement of Science Fellow
2008	Addario Foundation Award
2012	Uniting Against Lung Cancer "Caine Halter Hope Now Award for Lung Cancer Research"
2012	World Class Care Award, University of Colorado Denver
2013	Distinguished Professor, Univ. of Colorado
2016	ASCO Karnofsky Award

C. Contribution to Science

1.0 The role of the epidermal growth factor receptor (EGFR) in lung cancer pathogenesis, progression and therapy. Our SPORE group (on which I am PI) showed that EGFR overexpression occurs early in the pathogenesis (PMID:11894009). Some lung cancer cell lines were sensitive to EGFR tyrosine kinase inhibitors (TKIs) and sensitivity and response to EGFR TKIs in patients was related to EGFR gene copy number but not protein expression (PMID:17145836, PMID:17551144, PMCID: PMC3368372). Subsequent studies showed a relationship between EGFR gene copy number and activating mutations and the latter was the best predictor of sensitivity. We showed that resistance to EGFR TKIs developed through overexpression of alternative signal pathways such as FGFR, through epithelial to mesenchymal transition and through survival maintenance pathways such as the Wnt/Bcatenin pathway (PMCID: PMC3673784 Combinations of EGFR TKIs pus FGFR inhibitors or Wnt inhibitors were superior to TKIs alone). Cooperative studies of the Lung Cancer Mutation consortium (of which I am PI) demonstrated that EGFR mutation are present in about 20% of lung adenocarcinomas and that those with EGFR mutations who are treated with EGFR TKIs have longer survival than those who do not receive a TKI (PMCID: PMC4163053). The LCMC studies also described the frequency, and clinical characteristics associated with KRAS, NRAS, BRAF mutations and ALK fusions (PMCID: PMC 3643999, PMCID: PMC4305000, PMCID: PMC3370097). Our group also described the use of FISH to identify ALK, ROS and NTRK fusions and mechanisms of resistance to ROS1 and ALK TKIs.

2.0 Chemoprevention of lung cancer and markers of risk. Our SPORE group demonstrated that patients with atypical sputum cytology were at increased risk of lung cancer and that bronchial dysplasia can be used as a surrogate marker for chemoprevention studies (PMID:10626810, PMID:14578133). A chemoprevention trial evaluating 13-dis-retinoic acid showed no effect of the agent on bronchial dysplasia which is also a risk factor for development of lung cancer. A subsequent chemoprevention study showed that oral iloprost improved bronchial dysplas and follow-up studies are now ongoing.

3.0 Neoadjuvant chemotherapy studies. Dr. Bunn was involved in the design, implementation and completion of neoadjuvant chemotherapy studies prior to surgical resection in patients with early stage NSCLC. These studies demonstrated that the approach was feasible and safe and improved survival to a similar extent as post-operative adjuvant chemotherapy (PMID:10694600, PMCID: PMC2860367, PMID:24576776).

4.0 Small cell lung cancer biology and treatment. Dr. Bunn's laboratory demonstrated that small cell lung cancers express neuropeptide receptors that are intimately involved in autocrine. growth. Among these are the gastrin releasing peptide receptor and bradykinin receptor that transmit signals through their g-protein coupled receptors. We developed a dimeric long acting peptide antagonist that inhibited the growth of SCLC cell lines in vitro and in vivo. We defined the pharamocokinetic properties, toxicity and efficacy parameters of the agent and took the agent through the IND process (PMCID: PMC53646, PMID:1309227, PMID:1727271, PMID:7516822, PMID:8550585, PMID:8856150, PMID:11258669, PMCID: PMC123695, PMID:12489792).

5.0 Development of new lung cancer therapies. Dr. Bunn was the principal investigator on a phase III randomized study showing that pemetrexed was as active as docetaxel in the second line therapy of NSCLC

setting. The study results led to FDA approval of pemetrexed for this indication. Br. Bunn was the PI on the phase I trial of the combination of paclitaxel and carboplatin and continued study of this combination through a SWOG randomized trial that established the combination as a standard of care regimen.Dr Bunn was the lead investigator on a phase III randomized trial showing that the combination of chemotherapy with chest radiotherapy was superior to chemotherapy alone for early stage SCLC. This combined therapy approach remain the standard approach to this day (PMID:15117980, PMID:11432888, PMID:3032033).

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/paul.bunn.1/bibliography/42000224/public/?sort=date&direction=ascending
There are more than 320 peer reviewed articles, 20 editorials, 40 reviews, and 40 book chapters. See Pubmed for the complete list.

D. Research Support (For past three years, Active and Completed in last three years)

List both selected ongoing and completed research projects for the past three years (Federal or non-Federally-supported). *Begin with the projects that are most relevant to the research proposed in the application.* Briefly indicate the overall goals of the projects and responsibilities of the key person identified on the Biographical Sketch. Do not include number of person months or direct costs.

Active (during past three years)

Free to Breathe
2012-LCMC-02 Bunn (PI) 08/01/2012 – 12/01/2015
Title: Lung Cancer Mutation Consortium
Goals: Lung cancer is the leading cause of cancer death in men and women in the U.S., accounting for about 30% of all cancer deaths. About half of all lung cancer patients present with advanced disease for which standard chemotherapy combinations produce only modest survival improvement with the associated high toxicity rates, inconvenience of intravenous administration and high costs. Recent molecular studies showed that as many as 50% of lung cancer have activating mutations in known oncogenes to which novel therapeutic agents have been developed. Early clinical trials suggest that targeted oral agents have less toxicity and greater benefit than chemotherapy but only when administered to patients with the specific mutated oncogene. The new technologies in this application will allow a large number of lung cancer patients to have molecular tests for these newly described oncogenes so that we can understand their frequency, relevance and importance as predictors to benefit from the new targeted agents. This proposal will hasten the development of personalized medicine for lung cancer and other cancers as well.
Role: PI

NIH/NCI
P50 CA05817 Bunn (PI) 05/20/1997 – 04/30/2019
Title: SPORE in Lung Cancer. Project 2: Growth Factor Inhibitors for Lung Cancer Therapy and Prevention (Project Principal Investigator). Core 5: Administration (Core Director)
Goals: The goal of the Colorado Lung Cancer SPORE program is to conduct translational research studies that will lead to a reduction in the lung cancer mortality rates through improved early detection, prevention, and treatment. This goal is accomplished through four novel projects, a developmental research program, and a career development program all of which are supported by four interacting shared core resources. The future impact of the program will be to hasten translation of scientific discoveries from their development to approved human use of products and services benefiting patients.
Role: PI

NIH/NCI
1T32CA174648-01 Xiao-Jing Wang (PI) 04/01/2013 – 03/31/2018
Title: Training in Translational Research of Lung, Head, and Neck Cancers
Goals: This project funds postdoctoral fellows and graduate students engaged in lung, head and neck cancer research.
Role: Co-PI

EISAI, Inc. Bunn (PI) 2/11/2013 – 2/11/2016
AWD-140534

Title: Pre-clinical in vitro evaluation of Halaven in a panel of small cell lung cancer (SCLC) cell lines with affymetrix gene expression profiles
Goals: Specific aims are to determine the potential synergy between concurrent Halaven and radiation; and determine clonogenic survival in combination of Halaven and radiation.

Completed (within the last three years)

NONE

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Chatziioannou, Arion-Xenofon F.	Professor of Molecular and Medical Pharmacology
eRA COMMONS USER NAME (credential, e.g., agency login) ARIONC2	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
National and Capodistrian University of Athens	B.S.	06/1989	Physics
UCLA School of Medicine, Los Angeles, CA	M.S.	12/1993	Biomedical Physics
UCLA School of Medicine, Los Angeles, CA	Ph.D.	06/1996	Biomedical Physics

A. Personal Statement

I have a background in Imaging Physics, while my research is focused on the development of molecular imaging technologies. Starting as an Assistant Professor in the Department of Molecular and Medical Pharmacology in 2001, I have been the PI and Co-PI of several NIH, DOE and DTRA funded projects that involve detection and imaging by using ionizing radiation and visible light photons. Over this time, my lab has developed a number of technologies, from tools that support multimodality image registration and animal physiology, to integrated multimodality tomographic imaging systems (including PET, optical and x-ray CT), to detectors suitable for the detection and imaging of radionuclides in microfluidics. Several of these technologies have found their way as commercially available tools for research. Since 2009, I have been the Associate Director of the Crump Institute for Molecular Imaging and Vice Chair of the Department of Molecular and Medical Pharmacology at UCLA. My research continues its focus on the development of instrumentation, methodologies and mathematical algorithms for high resolution, quantitative imaging. In this project, over the past 10 I have been chairing M248, the introductory course on “Molecular Imaging”. I also am a member of the Admissions Committee, and I am also the Molecular Imaging Track representative in the graduate program. Over the past 5 years, in addition to chairing the PhD Disseration for 4 students of the graduate program I have also been a member of the Dissertation Committee for 6 additional students who received their PhD degrees from the Physics in Biology and Medicine IDP.

B. Positions and Honors

Positions and Employment

2001-2007 Assistant Professor, Department of Molecular and Medical Pharmacology, UCLA School of Medicine

2007- Associate Professor, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA.

2009- Associate Director, Crump Institute for Molecular Imaging, David Geffen School of Medicine at UCLA.

2009- Vice Chair, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA.

2012- Professor, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA.

Other Experience and Professional Memberships

2003 European 6th Framework Program for Research and Demonstration Activities study section
2004 NIH, National Heart Lung and Blood Institute, study section ad-hoc reviewer
2005-2008 National Electrical Manufacturers Association, Committee on Standards for Preclinical PET
2005-2012 UC Discovery Grant Program study section (Study Section Chair and Council Member 2009-2012)
2007- Editorial Board, Physics in Medicine and Biology
2009 NIH - NIBIB, Challenge Grants ad-hoc reviewer
2011-2012 NIH – NCI, Academic Industrial Partnerships Study Section reviewer (ongoing)
2012- NIH – MEDI Study section
2013- NIH Shared Instrumentation Proposals Reviewer.
2014- Ad-hoc reviewer for several NIH study sections

Honors

1992 Hortense Fishbaugh Memorial Scholarship
1997 Instrumentation and Data Analysis Young Investigator Award, Society of Nuclear Medicine
1998 First place Scientific Exhibit, Society of Nuclear Medicine Annual Meeting
2006 Springer Prize for top cited paper in the Eur. J. Nucl. Med.
2007 Alavi-Mandell Award for publication "Noninvasive Measurement of Cardiovascular Function in Mice with High-Temporal-Resolution Small-Animal PET", J. Nucl. Med. 2006
2009 Rotblat Medal from the Institute of Physics, for highest number of citations over 5 years in Physics in Medicine and Biology "GATE: A Simulation Toolkit for PET and SPECT" Phys Med Bio 49, 2004.
2010 Rotblat Medal from the Institute of Physics for highest number of citations received over 5 years in Physics in Medicine and Biology, "Tomographic Bioluminescence Imaging by Use of a Combined Optical-PET Imaging System: A Computer Simulation Feasibility Study", Phys Med Bio, 50, 2005.

C. Contribution to Science

1. My early contributions to science started with the development of the prototype microPET preclinical PET tomograph as a member of Simon Cherry's research group at UCLA. My efforts focused on the integration of the microPET system into a relevant tool for use in biological research. Prior to this work, longitudinal in-vivo imaging of preclinical models with PET was precluded due to limitations in the spatial resolution of available technology. Therefore research on drug biodistribution, pharmacokinetics, pharmacodynamics and interactions of drugs with mouse mammalian biology were restricted to ex-vivo samples of tissues with autoradiography. This work led to the creation of several generations of commercially available preclinical tomographs that today span across the globe. This by extension has enabled the pharmaceutical industry and research centers around the world to develop better diagnostic and therapeutic tools. The publications below illustrate the impact of the work.
   a. Cherry, Shao, Silverman, Meadors, Siegel, Chatziioannou, Young, Jones, Moyers, Newport, Boutefnouchet, Farquhar, Andreaco, Paulus, Binkley, Nutt, Phelps, "*MicroPET: A* High *Resolution PET Scanner for Imaging Small Animals*", IEEE Trans. Nucl. Sci., 44:1161-1166, 1997. (cited: 562)
   b. A Chatziioannou, S Cherry, Y Shao, R Silverman, K Meadors, T Farquhar, M Pedarsani, M Phelps, "Performance Evaluation of microPET: A High Resolution LSO PET Scanner for Animal Imaging", J. Nucl. Med., 40:1164-1175, 1999. (cited: 376)
   c. Qi, Leahy, Cherry, Chatziioannou, Farquhar, "High-resolution 3D Bayesian image reconstruction using the microPET small-animal scanner", Phys in Med and Biol, 43:1001-1013. 1998. (cited: 550)
   d. A Chatziioannou, J Qi, A Moore, A Annala, K Nguyen, R Leahy, S Cherry, "Comparison of 3D Maximum A Posteriori and Filtered Backprojection Algorithms for High Resolution Animal Imaging with microPET", IEEE Trans. Med. Imag. 19:507-512, 2000. (cited: 120)
   e. A. Chatziioannou, "Molecular imaging of small animals with dedicated PET tomographs", European Journal of Nuclear Medicine and Molecular Imaging 29: pp. 98-114, 2002. (cited: 298)
2. After the development of proof of principle first generation imaging systems, new generations of imaging technologies required a more sophisticated and optimized approach. The tools to enable this approach were based on Monte Carlo methods used in high energy physics experiments, such as GEANT. These

tools required development and extensive validation and this was undertaken by an international collaboration under the openGATE umbrella. In this collaboration, my research group developed the dosimetry aspect as well as methodologies to include voxelized models of subjects. This tied into the work of my UCLA research group on the development of an anatomically accurate volumetric model of a mouse, called DIGIMOUSE, that has been used extensively in the field of preclinical molecular imaging.

a. S. Jan, et. al. (author 15 of 53), "GATE Geant4 Application for Tomographic Emission: a simulation toolkit for PET and SPECT", Physics in Medicine and Biology, 49: 4543-4561, 2004. PMC3267383. (cited 1049)
b. G. Alexandrakis, F.R. Rannou, A.F. Chatziioannou, "Tomographic bioluminescence imaging by use of a combined Optical-PET (OPET) system: A computer simulation feasibility study", Physics in Medicine and Biology 50: 4221-4245, 2005. PMC1317109. (cited 368)
c. R. Taschereau, P.L. Chow, A.F. Chatziioannou, "Monte Carlo Simulations of dose from microCT imaging procedures in a realistic mouse phantom", Medical Physics, 33: 216-224, 2006. PMC3005289. (cited 86)
d. R. Taschereau, AF Chatziioannou, "Monte Carlo simulations of dose in a mouse phantom from 18-Fluorine compounds", Medical Physics, 34: 1026-1036, 2007. PMC3006169. (cited 68)
e. B Dogdas, D Stout, AF Chatziioannou, RM Leahy, "Digimouse: A 3D whole body mouse atlas from CT and cryosection DATA", Physics in Medicine and Biology, 52: 577-587, 2007. PMC3006167. (cited 272)

3. The development of new radiolabeled probes for imaging, as well as the development of new applications of these, requires extensive validation at all stages and scales of the process. New microfluidic based technologies that enable digital control of cell cultures down to a single cell level, as well as synthetic chemistry with digital precision, created new challenges for the detection of radiolabeled probes at very small quantities and very small scales. My laboratory has developed two enabling technologies that span a dynamic range of more than ten orders of magnitude, and can quantitatively image the distribution of radiolabeled compounds in microfluidics. These technologies have been used at one end of the range for the detection and imaging of synthesis quantities of positron emitting probes via imaging of Cerenkov radiation, and at the other end for the detection and imaging of radiolabeled probes in single cells, via direct charged particle imaging with a silicon avalanche photodiode detector.

a. JS Cho, S Olma, K Liu, Y Chen, C Shen, RM Van Dam, A Chatziioannou, "Cerenkov Radiation Imaging as a method for quantitative measurements of beta particles in a microfluidic chip", Physics in Medicine and Biology, 54: 6757-6771, 2009. Editors Choice. PMC2794558. (cited 64)
b. C Fang, Y Wang, NT Vu, W Lin, Y Hsieh, L Rubbi, ME Phelps, M Muschen, Y Kim, AF Chatziioannou, HR Tseng, TG Graeber, "A kinase activity radio assay for minute patient cancer samples using an integrated microfluidic and solid- state beta camera platform", DOI: 10.1158/0008-5472.CAN-10-0851, Cancer Research, 70 (21):8299-8308, 2010. PMC3989903. (cited 25)
c. NT Vu, ZT Yu, B Comin-Anduix, JN Søndergaard, C Chang, A Ribas, HR Tseng, AF Chatziioannou, "A microfluidic beta camera for real-time radioassay imaging of glycolysis in small cell populations", Journal of Nuclear Medicine, 52:815–821, 2011. PMC3270819. (cited 18)
d. PY Keng, S Chen, H Ding, S Sadeghi, GJ Shah, A Dooraghi, ME Phelps, N Satyamurthy, A Chatziioannou, CJ Kim, RM van Dam, "Micro-chemical synthesis of molecular probes on an electronic microfluidic device", PNAS, 109: 609-695, 2012. PMC3271918. (cited 66)
e. AA Dooraghi, NT Vu, RW Silverman, R Farrell, KS Shah, and AF Chatziioannou, "Betabox: a beta particle imaging system based on a position sensitive avalanche photodiode", Physics in Medicine and Biology, 58: 3739-3753, 2013. PMC3706465. (cited 5)
f. YS Shin, J Kim, D Johnson, AA Dooraghi, WX Mai1, L Ta, AF Chatziioannou, ME Phelps, DA Nathanson, JR Heath, "Quantitative assessments of glycolysis from single cells", DOI: 10.1142/S2339547815200058, Technology, 2015

D. Research Support

ACTIVE

21509 (2907)

D Huffaker and A Chatziioannou (Hadjioannou) 7/1/2014 - 6/30/2017 0.50 calendar (4%)
Defense Threat Reduction Agency
Nanostructured III-V Detectors for High Resolution WMD Sensing at 300K (Huffaker, Diana)
The goal of this project is to create an x-ray avalanche photodiode (APD) based on a nano-structured interfacial misfit array (IMF). This device will offer energy resolution of 0.3% at 662 keV, operating at room temperature, and could replace bulky, cryogenically cooled high-purity Germanium detectors. This will be achieved with an IMF-based APD that will enable monolithic integration of a high Z absorber and low Z multiplication region, eliminating spurious signals typically found in solid state x-ray avalanche photodiodes.
Role: Co PI

P30 CA016042 (Gasson) 3/7/2014 - 11/30/2018 0.60 calendar (5%)
National Institutes of Health Cancer Center Support Grant
The University of California, Los Angeles' Jonsson Comprehensive Cancer Center (JCCC) is an NCI designated matrix center conducting a wide range of translational research in the areas of laboratory, clinical and population sciences integrating the activities of 244 members. The goals of the JCCC are the integration of clinical activities to provide patient-centered care; research infrastructure improvement through technology and shared resources; increased communication within JCCC and to our many audiences; faculty support and development at all levels; and the advancement of emerging areas of research. Of 3,489 total publications in the reporting period, 35% were published in high-impact journals, 15% were inter-programmatic and 21% were intra-programmatic. Continuing support is requested for the eight Programs Areas and six Shared Resources. Programs: Cancer and Stem Cell Biology, Cancer Molecular Imaging, Cancer Nanotechnology, Gene Regulation, Healthy and At-Risk Populations, Patients and Survivors, Signal Transduction and Therapeutics, Tumor Immunology. Shared Resources: Biostatistics, Analytical Support and Evaluation, Genomics, Flow Cytometry, Translational Pathology, Molecular Screening Shared Resource, Small Animal Imaging Shared Resource.
Role: Director of the Shared Resource

Completed Research Support

DE-FG02-06ER64249 Phelps (PI) 6/1/2006 - 9/14/2012
Institute for Molecular Medicine Research Program
The objectives of the project are the development of the new Positron Emission Tomography (PET) imaging instrumentation, chemistry technology platforms and new molecular imaging probes to watch living biology within the body and examine its transformation to disease. These examinations can be used to: 1. To study the biology of disease in the living subject - mouse to patient; 2. For molecular imaging diagnostics in disease; 3. To guide and improve the processes for discovering new drugs; 4. To judge the impact of drugs on the biology of disease; 5. To select the right drug for the right patient.
Role: Investigator

U54 CA151819 (Phelps) 9/3/2010 - 7/31/2015 0.60 calendar (5%)
CalTech (NIH Prime)
Nanosystems Biology Cancer Center 2 (Heath, James)
Project 3: We propose to develop and use in vitro and in vivo molecular imaging technologies to study metabolic switches that happen in malignant transformation and to determine the importance of these metabolic switches for tumor proliferation, survival, and recognition/rejection by the immune system. Using a novel microfluidic device called the BetaBox for high throughput in vitro molecular imaging, we will quantitatively record transport and phosphorylation rates of [18F]fluorodeoxyglucose (FDG) as well as other metabolic probes in cancer cells grown on microfluidic chips. We will study the effects bidirectional metabolic switching has on uptake of these metabolic probes and proliferation rates of cancer cells in vitro in the BetaBox as well as in vivo using PET imaging, and on T cell recruitment to the tumor microenvironment using bioluminescence optical imaging.
Role: Investigator

DE- SC0001234 Chatziioannou (PI) 9/1/2009 - 8/31/2011
Development of a dual modality tomographic imaging system, for bioluminescence and PET. New technology for the integration of a high resolution, high sensitivity quantitative radiation imaging detector with optical imaging capabilities. This technology enable higher sensitivity spatially co-registered imaging of dual labeled

molecular imaging probes (optical and PET). It should help facilitate, validate and enhance bioluminescence imaging tomography.
Role: PI

U24 CA092865 (Phelps) 2/19/2001 - 1/31/2012
NIH-National Cancer Institute
The UCLA Imaging Resource for Mouse Cancer Models
In addition to providing service and support to more than 24 principal investigators, the roles of the small animal imaging resource are to: (a) educate students, postdoctoral scholars, physicians and other biology researchers from within and outside UCLA in the tools, technologies and applications of imaging, and (b) foster collaborations and develop new technologies and methodologies that will improve the quantitative capabilities of non-invasive imaging.
Role: Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contr butors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Michael A. (Tony) Hollingsworth

eRA COMMONS USER NAME (credential, e.g., agency login): MAHOLLIN

POSITION TITLE: Professor

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Wake Forest Univ., Winston-Salem, NC	B.A.	05/1978	Biology
Bowman Gray – Wake Forest Univ., NC	Ph.D.	05/1982	Microbiology/Immunology
Duke University Medical Center, Durham, NC	Postdoc	10/1985	Microbiology/Immunology

A. Personal Statement

Michael A. Hollingsworth, Ph.D., is a Professor in the Eppley Institute, and holds joint appointments in the Department of Pathology and Microbiology, and in the Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center.

I received a PhD from the Bowman Gray School of Medicine of Wake Forest University in 1982. Following a postdoctoral fellowship with Richard Metzgar at Duke University from 1982-1986, I was appointed to the faculty of the Department of Immunology at Duke from 1987-1991. I decided in 1985 to commit my research career to pancreatic cancer, and have worked on translational research projects in that subject area since that time, continuously maintaining R01 and other NCI funding (as Principal Investigator) for projects related to pancreatic cancer since 1987. The decision to work on pancreatic cancer was an important factor that contributed to my move to the Eppley Institute in 1991, where I have led the group effort in pancreatic cancer research for the past 15 years. I serve as the Principal Investigator of a GI SPORE in GI and pancreas cancer. I am the PI of an Early Diagnostic Research Network (EDRN) Biomarker Discovery Laboratory (U01) that focuses on biomarkers for pancreatic cancer, and I am a project leader on our U54 Tumor Microenvironment Network Grant. Over the past 12 years we have amassed a unique resource of longitudinal patient samples coupled to a rapid autopsy program, which is used to study progression and metastasis of pancreatic cancer. I have served on numerous review panels at the NIH and for other granting agencies, including recent service (2011-2012) as Chair of the Cancer Biomarkers Study Section (CBSS). I was appointed by NIH Director Dr. Francis Collins in July 2013 to serve as a member of the Center for Scientific Review Advisory Council. I have served as a member of the Gastrointestinal Steering Committee and currently serve on the Pancreas Cancer Task Force, which is organized by the Coordinating Center for Clinical Trials at the National Cancer Institute. I have participated in almost every major initiative from NIH related to pancreatic cancer since 1985.

B. Positions and Honors

Positions and Employment

1979-1982 Teaching Assistantship, NIH Predoctoral Fellowship, Department of Microbiology/Immunology, Bowman Gray School of Medicine, Winston-Salem, NC

1982-1985 NIH Postdoctoral Fellowship, Division of Immunology, Department of Microbiology and Immunology, Duke University Medical Center, Durham, NC

1985-1986	Research Associate, Division of Immunology, Department of Microbiology and Immunology, Duke University Medical Center, Durham, NC
1987-1991	Asst. Medical Research Professor, Div. of Immunology, Duke Univ. Med. Center, Durham, NC
1991-1995	Assistant Professor, Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE (UNMC)
1994-1999	Assoc. Prof., Eppley Inst. for Research in Cancer and Allied Diseases, UNMC, Omaha, NE
2000-Present	Professor, Eppley Institute for Research in Cancer and Allied Diseases, UNMC, Omaha, NE
2004-Present	Director, Pancreatic Cancer Research, Eppley Institute

Other Experience and Professional Memberships (selected)

2013-	NIH Center for Scientific Review Advisory Council (CSRAC), 3 year term
2011-2014	Gastrointestinal Cancer Steering Committee, NIH, NCI
2010	NCI Special Emphasis Panel, NCI Centers of Nanotechnology Excellence 1, Chair
2001-present	PanCAN (Pancreatic Cancer Action Network) Scientific and Medical Advisory Board
2008-2009	Ad Hoc member – Subcommittee A – Cancer Centers review panel
2007-2008	Review Panel Member – Cellular & Tissue Biology panel (SEP)
2007-2011	Cancer Biomarkers Review Panel (CBSS). Member and Chair (2009-2011)
2005-present	Review Panel – SPORE panels (Breast Cancer, Lung & Genitourinary, Prostate & Skin)

Honors

2006	University of Nebraska Medical Center Distinguished Scientist
2007	UNMC Eppley Cancer Center Carol Bell Distinguished Scientist Award
2010	University of Nebraska Medical Center Distinguished Scientist
2012	University of Nebraska Medical Center Scientist Laureate
2013	UNMC Outstanding Mentor of Graduate Students (awarded April 2014)

C. Contributions to Science.

1) Biomarkers of Pancreatic Cancer. I initially (1980s) contributed to the molecular characterization of biomarkers of pancreatic cancer by using molecular and biochemical techniques to identify glycoproteins recognized by monoclonal antibodies that identified markers of transformation and progression of pancreatic cancer. This included the discovery that mucins were the core proteins recognized by CA19-9 and related antibodies. This work has extended to the current time, where we continue to identify and characterize mucin based biomarkers of pancreatic cancer disease progression, and to develop improved assays that directly detect mucins and that evaluate immune responses (autoimmune and in response to vaccination).

a. Lan, M.S., Batra, S.K., Qi, W-N, Metzgar, R.S. and Hollingsworth, M.A. Cloning and sequencing of a human pancreatic apomucin cDNA. J. Biol. Chem. 265:15294-15299, 1990. PMID:2394722
b. Remmers N, Anderson JM, Linde E, DiMaio DJ, Lazenby A, Hans W, Mandell U, Clausen H, Yu F, Hollingsworth MA, Aberrant expression of mucin core protein and O-linked glycans associated with progression of pancreatic cancer. Clinical Cancer Research, 2013 Apr 15;19(8):1981-93. PMCID:PMC387363
c. Burford B, Gentry-Maharaj A, Graham R, Allen D, Pedersen JW, Nudelman AS, Blixt O, Fourkala EO, Bueti D, Dawnay A, Ford J, Desai R, David L, Trinder P, Acres B, Schwientek T, Gammerman A, Reis CA, Silva L, Osório H, Hallett R, Wandall HH, Mandel U, Hollingsworth MA, Jacobs I, Fentiman I, Clausen H, Taylor-Papadimitriou J, Menon U, Burchell JM. Autoantibodies to MUC1 glycopeptides cannot be used as a screening assay for early detection of breast, ovarian, lung or pancreatic cancer. Br J Cancer. 2013 May 28;108(10):2045-55. doi: 10.1038/bjc.2013.214. Epub 2013 May 7. PMCID:PMC3670483
d. Mirus, JE, Zhang, Y, Hollingsworth, MA, Solan, JL, Lampe, PD, Hingorani, SR. Spatiotemporal proteomic analyses during pancreas cancer progression identifies serine/threonine stress kinase 4 (STK4) as a novel candidate biomarker for early stage disease. Mol Cell Proteomics. (2014)13(12):3484-3496. PMCID:PMC4256499

2) Biology of Mucins in Pancreatic Cancer Progression. My laboratory has contributed significantly to our understanding of the biology of mucins in pancreatic disease progression, including seminal findings related to the manner in which altered glycosylation of mucins affects tumor cell adhesion, motility, the tumor microenvironment, and metastasis. We have also contributed to significantly to our understanding of how

membrane bound mucins engage in signal transduction and serve to directly reprogram gene expression in response to conditions encountered at the cell surface.

a. Hollingsworth, M.A., and Swanson, B.J. Mucins in Cancer: Protection and Control of the Cell Surface. Nature Reviews Cancer 4:45-60, 2004. PMID:14681689
b. Singh, P.K., Wen, Y., Swanson, B.J., Shanmugam, K., Kaslauskas, A., Cerny, R.L., Gendler, S.J., Hollingsworth, M.A. Platelet-Derived Growth Factor Receptor beta-Mediated Phosphorylation of MUC1 Enhances Invasiveness in Pancreatic Adenocarcinoma Cells. Cancer Research 67(11):5201-10, 2007. PMID:17545600
c. Behrens ME, Grandgenett PM, Bailey JM, Singh PK, Yi C-H, Yu F, Hollingsworth MA. The reactive tumor microenvironment: MUC1 signaling directly reprograms transcription of CTGF. Oncogene 29(42):5667-77, 2010. PMCID:PMC3412169
d. Liu X, Yi C, Wen Y, Radhakrishnan P, Tremayne J, Dao T, Johnson KR, Hollingsworth MA. Interactions between MUC1 and p120 catenin regulate dynamic features of cell adhesion, motility and metastasis, Cancer Res. 2014 Mar 1;74(5):1609-20, Published OnlineFirst December 26, 2013; doi: 10.1158/0008-5472.CAN-13-2444. PMCID:PMC4076167

3) Establishment of Rapid Autopsy Program for Pancreatic Cancer for study of matched sets of primary and metastatic tissues. We were the first to establish a rapid autopsy program for pancreatic cancer (our first rapid autopsy for pancreatic cancer was performed at Duke University in the late 1980's) and the first to institute a regular program of tissue acquisition through this mechanism (University of Nebraska Medical Center, August 2002). The program continues today, having performed 99 autopsies and collected well over 100,000 tissue samples). We were the first to couple this program of tissue acquisition with longitudinal sampling of patient samples (linked to resections and with interim collection of patient samples), and we freely distribute these samples for meritorious projects, along with clinical annotation, to investigators around the world. These samples have and will continue to contribute to seminal publications and studies of the translational biology of pancreatic cancer in humans.

a. Acharyya, S., Butchbach, M.E., Sahenk, Z., Wang, H., Saji, M., Carathers, M., Ringel, M.D., Skipworth, R.J., Fearon, K.C., Hollingsworth, M.A., Muscarella, P., Burghes, A.H., Rafael-Fortney, J.A. and Guttridge, D.C. Dystrophin glycoprotein complex dysfunction: a regulatory link between muscular dystrophy and cancer cachexia. *Cancer Cell*, 8(5): 421-432, 2005. PMID:16286249
b. Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, Rashid NU, Williams LA, Eaton SC, Chung AH, Smyla JK, Anderson JM, Kim HJ, Bentrem DJ, Talamonti MS, Iacobuzio-Donahue CA, Hollingsworth MA, Yeh JJ. Virtual dissection identifies tumor and stroma specific subtypes of pancreatic ductal adenocarcinoma. Nat Genet. 2015 Oct;47(10):1168-78. doi: 10.1038/ng.3398. Epub 2015 Sep 7 PMID:26343385
c. Ruiz C, Lenkiewicz E, Evers L, Holley T, Robeson A, Kiefer J, Hollingsworth, MA, Shen M, Prunkard D, Rabinovitch PS, Zellweger T, Mousses S, Trent JM, Carpten JD, Bubendorf L, Von Hoff D, Barrett MT. Advancing a clinically relevant perspective of the clonal nature of cancer. Proc Natl Acad Sci USA 2011 Jul 19, 108(29):12054-9. Epub 2011 Jul 5. PMCID:PMC3141975
d. Hoshino, A., Costa-Silva, B., Shen, T. L., Rodrigues, G., Hashimoto, A., Tesic Mark, M., Molina, H., Kohsaka, S., Di Giannatale, A., Ceder, S., Singh, S., Williams, C., Soplop, N., Uryu, K., Pharmer, L., King, T., Bojmar, L., Davies, A. E., Ararso, Y., Zhang, T., Zhang, H., Hernandez, J., Weiss, J. M., Dumont-Cole, V. D., Kramer, K., Wexler, L. H., Narendran, A., Schwartz, G. K., Healey, J. H., Sandstrom, P., Labori, K. J., Kure, E. H., Grandgenett, P. M., Hollingsworth, M. A., de Sousa, M., Kaur, S., Jain, M., Mallya, K., Batra, S. K., Jarnagin, W. R., Brady, M. S., Fodstad, O., Muller, V., Pantel, K., Minn, A. J., Bissell, M. J., Garcia, B. A., Kang, Y., Rajasekhar, V. K., Ghajar, C. M., Matei, I., Peinado, H., Bromberg, J., and Lyden, D. (2015) Tumour exosome integrins determine organotropic metastasis, *Nature 527*, 329-335.

4) Immunology and Immunotherapy of Pancreatic Cancer. As my PhD was in tumor immunology, I have long-standing interests and published studies into the role of the immune response in pancreatic cancer progression, especially with respect immunosuppression. We have used animal models since the early 1990s to characterize the nature of immune responses to pancreatic cancer, to study the role of tolerance and immunosuppression in tumor escape from immune destruction, and we have developed and tested new vaccination strategies (including novel molecular adjuvants) in these models, and we have carried these efforts

into the clinic (we initiated an immunotherapy clinical trial as part of our SPORE program in 2012 that is ongoing).

a. Rowse, G.J., Tempero, R.M., VanLith, M.L., Hollingsworth, M.A., and Gendler, S.J. Tolerance and Immunity to MUC1 in a human MUC1 transgenic murine model. Cancer Res. 58:315-321 1998. PMID:9443411
b. Tempero, R.M., VanLith, M., Morikane, K., Rowse, G.J., Gendler, S.J., and Hollingsworth, M.A. CD4+ lymphocytes provide MUC1-specific tumor immunity *in vivo* that is undetectable in vitro and is absent in MUC1 transgenic mice. J. Immunol. 161:5500-5506, 1998. PMID:9820526
c. Sivinski, C.L., Kohlgraf, K.G., VanLith, M.L., Morikane, K., Tempero, R.M., and Hollingsworth, M.A. Molecular requirements for CD8 mediated rejection of a MUC1-expressing pancreatic carcinoma: Implications for tumor vaccines. Cancer Immunol. Immunother. 51: 327-340, 2002. PMID:12111121
d. Bunt SK, Mohr AM, Bailey JM, Grandgenett PM, Hollingsworth MA. Rosiglitazone and Gemcitabine in combination reduces immune suppression and modulated T cell populations in pancreatic cancer. Cancer Immunol Immunother 2013 Feb;62(2):225-36. doi: 10.1007/s00262-012-1324-3. Epub 2012 Aug 5. PMCID:PMC3873637

5) Tumor Microenvironment of Pancreatic Cancer. My lab has published seminal findings with respect to the biology of the tumor microenvironment of pancreatic cancer, including the role of mucins in perineural invasion, the unexpected amplification and activity of CDK5 in perineural invasion, and the role of paracrine signaling by sonic hedgehog produced by pancreatic cancer in driving desmoplasia.

a. Swanson, B.J., McDermott, K.M., Singh, P.K., Eggers, J.P., Crocker, P.R., and Hollingsworth, M.A. MUC1 is a Counter-Receptor for Myelin-Associated Glycoprotein (Siglec-4a) and Their Interaction Contributes to Adhesion in Pancreatic Cancer Perineural Invasion. Cancer Research 67(21):10222-9, 2007. PMID:7974963
b. Eggers, JP, Grandgenett, PM, Collisson, EC, Lewallan, ME, Tremayne, J, Singh, PK, Swanson, BJ, Andersen, JM, Caffrey, TC, High, RR, Ouellette, M, Hollingsworth, MA. CDK 5 is amplified and over-expressed in pancreatic cancer and activated by mutant k-Ras. Clinical Cancer Res Oct 1 2011; 17(19):6140-6150; Published OnlineFirst August 8, 2011. PMCID:PMC3425449
c. Bailey, J.M., Swanson, B.J., Hamada, T., Eggers, J.P., Caffrey, T.C., Ouellette, M.M. and Hollingsworth, M.A. Sonic Hedgehog promotes desmoplasia in pancreatic cancer. Clinical Cancer Research 14(19):5995-6004, 2008. PMCID:PMC2782957.
d. Bailey, J.M., Mohr, A.M. and Hollingsworth, M.A. Sonic Hedgehog Paracrine Signaling Regulates Metastasis and Lymphangiogenesis in Pancreatic Cancer. Oncogene. 28(40):3513-25. Epub July 27, 2009. PMCID:PMC2910592.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/michael.hollingsworth.1/bibliography/40344558/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2 P50 CA127297-06A1 Hollingsworth 9/05/08 – 8/31/19
NIH/NCI
SPORE in Pancreatic Cancer
Focus is on translational studies that address basic and clinical issues of importance to improving outcome of patients with pancreatic cancer.
Role: SPORE Director, Project PI

5 U01 CA 111294-10 Hollingsworth/Batra (MPI) 9/10/10 - 6/30/16
NIH/NCI
Early Diagnosis of Pancreatic Cancer
The goal of this project is to develop early diagnostic tests for pancreatic cancer.
Role: PI

5 U54 CA163120-04 Batra (PI) 9/26/11 – 7/31/16
NIH/NCI

Tumor Microenvironment Network (TMEN)
Role: Core Director and Project Leader

5 P30 CA036727-28 Cowan (PI) 8/5/11 – 7/31/16
NIH/NCI
UNMC Fred & Pamela Buffett Cancer Center Support Grant
Role: Co-Investigator

(Hollingsworth) 1/07/15 – 7/31/16
Quest Pharma Tech, Inc.
Tumor Antigen Redirected IgE Constructs for Treating Cancer and Other Diseases
Role: PI

(Hollingsworth) 7/01/2014- 6/30/2016
GlycoMimetics, Inc.
Effects of GMI-1271 and New CXCR4/E-selection Dual Targeting Agent on the Motility and Adhesion of Fluorescent Pancreatic Cancer Cells.
Propose to test the new compound that targets CXCR4 and E-selection to evaluate effects on tumor growth, with particular reference to the tumor microenvironment

Completed Research Support

5 P50 CA127297-05 Hollingsworth 9/05/08 – 8/31/13
NIH/NCI No cost extension – 8/31/14
SPORE in Gastrointestinal Cancer
Role: PI

5 R03 CA149857-02 Hollingsworth 9/15/11 – 8/31/14
NIH/NCI
A Novel Combination Therapy for the Treatment of Pancreatic Adenocarcinoma
Role: PI

5 R03CA169953-02 Solheim (PI) 7/1/12 – 6/30/14
NIH
Effect of Beta-secretase Inhibitors on Pancreatic Cancer Cells
Role: Co-Investigator

5 R01 CA057362 Hollingsworth 6/10/08 – 4/30/13
NIH/NCI No cost extension – 4/30/14
Studies on the Post-Translational Processing of MUC1
Role: PI

5 UO1 CA 128437-02 Hollingsworth 9/21/07 – 8/31/12
NIH/NCI No cost extension – 8/31/13
Autoantibodies Against Glycopeptide Epitopes as Serum Biomarkers of Cancer
Role: PI

(Hollingsworth) 12/01/11 – 11/30/13
Eppley Cancer Center No cost extension – 11/30/14
Inhibition of CDK5 as a Treatment for Pancreatic Cancer
Role: PI

1 R01 CA133774 Batra (PI) 3/1/08 – 12/31/13
NIH/NCI No cost extension – 12/31/14
Smoking and Pancreatic Cancer
Role: Co-Investigator
(Hollingsworth) 3/01/14 – 2/28/15
Eppley Pilot Project

Pancreatic Ductal Adenocarcinoma Study Phase I (year 2)
Role: PI

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contr butors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: **MANKOFF, David, A., MD, PhD**

eRA COMMONS USER NAME (credential, e.g., agency login): MANKOFFD

POSITION TITLE: Gerd Muehllehner Professor of Radiology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Yale University	BS	1981	Physics
University of Pennsylvania	PhD	1988	Bioengineering
University of Pennsylvania	MD	1988	Medicine

A. Personal Statement

I am currently Vice Chair for Research and PET Center Director at University of Pennsylvania. Over my career, my research has included a variety of topics focused on imaging – from basic imaging technology and methodology development, to early translation of methods and imaging probes to patient studies, to imaging clinical trials (examples below). My current research focuses on the application of quantitative molecular imaging to cancer treatment, with a focus on breast cancer, and with the overarching goal of guiding more effective cancer therapy. Am important focus of my work has been on the relationship of breast cancer metabolism, measured by imaging, to therapeutic response. I continue to work on the translation of novel methods from pre-clinical studies to patient studies, with a focus on image analysis and kinetics. In addition to expertise in imaging methodology, including kinetic analysis, I also have extensive experience in cancer imaging clinical trials, both through my own research at Penn, but also as the Chair of the Experimental Imaging Sciences Committee and Scientific Program Co-Chair for ECOG-ACRIN.

1. Mankoff DA, Tewson TJ, Eary JF. Analysis of blood clearance and labeled metabolites for the estrogen receptor tracer, [F-18]-16α-fluoroestradiol (FES). *Nucl Med Biol.* 24: 341-348, 1997. (PMID: 9257333)
2. Mankoff DA, Shields AF, Link JM, Graham MM, Muzi M, Peterson L, Eary JF, Krohn KA. Kinetic analysis of 2-[C-11]-thymidine PET imaging studies: validation studies. *J Nucl Med*. 40:614-624, 1999. (PMID: 10210220)
3. Peterson LM, Mankoff DA, Lawton T, Yagle K, Schubert EK, Stekhova S, Gown A, Link JM, Tewson, Krohn KA. Quantitative imaging of estrogen receptor expression in breast cancer using PET and [^{18}F]-fluoroestradiol: comparison of tracer uptake and in vitro assay of ER expression by immunohistochemistry. *J Nucl Med* 49: 367-374, 2008. (PMID: 18287268)
4. Muzi M, Mankoff DA, Link JM, Shoner S, Collier AC, Sasongko L, Unadkat JD. Imaging of cyclosporine

5. inhibition of P-glycoprotein activity using ^{11}C-verapamil in the brain: studies of healthy humans. *J Nucl Med* 50: 1267-1275, 2009. PMCID: PMC2754733

B. Positions and Honors

Professional Experience

1989 - 1990	**Research Scientist**, UGM Medical Systems, Philadelphia, PA
1988 - 1990	**Research Associate** in Nuclear Medicine, University of Pennsylvania, Philadelphia, PA
1989 - 1990	**Director of Engineering**, UGM Medical Systems, Philadelphia, PA
1990 - 1992	**Resident**, Department of Internal Medicine, UW Affiliated Hospitals, Seattle, WA
1992 - 1994	**Resident**, Division of Nuclear Medicine, UW Affiliated Hospitals, Seattle, WA
1994 - 1995	**Chief Resident**, Division of Nuclear Medicine, UW Affiliated Hospitals, Seattle, WA
1995 - 1996	**Acting Instructor**, Division of Nuclear Medicine, University of Washington
1996 - 2001	**Assistant Professor**, Division of Nuclear Medicine, University of Washington
2001 - 2006	**Associate Professor**, Division of Nuclear Medicine, University of Washington
2002 - 2006	**Adjunct Associate Professor**, Division of Endocrinology, University of Washington
2005 - 2006	**Adjunct Associate Professor,** Department of Bioengineering, University of Washington
2005 - 2012	**Lead,** Seattle Cancer Care Oncology Translational Research Program for Radiology
2006 - 2012	**Professor**, of Radiology, Medicine, and Bioengineering, University of Washington
2012 - 2013	**Professor and Chief,** Division of Nuclear Medicine and Clinical Molecular Imaging and PET Center, University of Pennsylvania, Philadelphia, PA
2013 - 2015	**Gerd Muehllehner Professor and Chief,** Division of Nuclear Medicine and Clinical Molecular Imaging and PET Center, University of Pennsylvania, Philadelphia, PA
2016 -	**Gerd Muehllehner Professor and Vice-Chair for Research,** Department of Radiology, University of Pennsylvania, Philadelphia, PA

Honors and Responsibilities

1980	Phi Beta Kappa, Yale University
1981	Summa Cum Laude from Yale University with distinction in Physics, Yale University
1981	Howard L. Schultz Prize in undergraduate physics, Yale University Physics Department
1983	Selected for Medical Scientist Training Program (MSTP)
1986	I.E.E.E. Nuclear and Plasma Sciences Section Graduate Student Award,
1988	Dr. O.H. Perry Pepper Award, University of Pennsylvania School of Medicine
1994	Mallinckrodt Fellowship Award, Society of Nuclear Medicine
1994	Norman D. Poe Memorial Award, Western Regional Society of Nuclear Medicine
2005	Distinguished Scientist Award, Western Regional Society of Nuclear Medicine
2005-2009	Member, NIH Cancer Biomarkers Study Section (CBSS)
2007-	Chair, ACRIN Experimental Imaging Sciences Committee
2008-	American Board of Nuclear Medicine, Chairman, 2011
2011	University of Washington Department of Radiology Faculty Mentor Award
2015	Taplin Memorial Lecture, Western Regional Society of Nuclear Medicine
Other	Editorial Boards: *Nuclear Medicine and Biology, Breast Cancer Research, Journal of Nuclear Medicine, Clinical Cancer Research, The Breast Journal;* Associate Editor, *Journal of Nuclear Medicine, Breast Cancer Research* External Advisory Boards: Ontario Institute for Cancer Research, University of Wisconsin Carbone Cancer Center, Washington University Siteman Cancer Center

C. Contribution to Science (**including over 180 published manuscripts and chapters)**

1. My research has centered on the development application of novel methods for measuring in vivo cancer biology using molecular imaging. This includes translating basic science knowledge and pre-clinical methodology into early human studies. Research has covered a variety of process important to cancer, including metabolism, proliferation, hypoxia, and receptor expression.
   a) Shields AF, Mankoff DA, Link JM, Graham MM, Eary, JF, Kozawa SM, Zheng M, Lewellen B, Lewellen TK, Grierson JR, Krohn KA. Use of [C-11]-thymidine and FDG with Positron Emission Tomography (PET) to measure response to therapy. *J Nucl Med*. 39: 1757 - 1762, 1998. (PMID: 9776283).

b) Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Charlop A, Lawton TJ, Schubert EK, Tseng J, Livingston RB. Blood flow and metabolism in locally advanced breast cancer: relationship to response to therapy. *J Nucl Med* 43: 500-509, 2002. (PMID: 11937594).
c) Rajendran JG, Mankoff DA, O'Sullivan F, Peterson LM, Schwartz DM, Conrad EU, Spence AM, Muzi M, Farwell DG, Krohn KA. Hypoxia and glucose metabolism in malignant tumors: evaluation by FMISO and FDG PET imaging. *Clin Cancer Res*, 19: 2245-2252, 2004. (PMID: 15073099).
d) Linden HM, Stekhova S, Link JM, Gralow JR, Livingston RB, Ellis GK, Peterson LM. Schubert EK, Dunnwald LK, Krohn KA, Mankoff DA. Quantitative fluoroestradiol (FES) PET imaging predicts response to endocrine treatment. *J Clin Oncol* 24: 2793-2799, 2006. (PMID: 16682724)

2. Much of my research has focused on breast cancer, using molecular imaging to elucidate breast cancer clinical biology, direct treatment selection, evaluate response, and identify factors mediating therapeutic resistance. This has largely been accomplished through early-phase imaging clinical studies and more recently through multi-center trials.
   a. Specht JM, Tam SL, Kurland BF, Gralow JR, Livingston RL, Linden HM, Ellis GK, Schubert BA, Dunnwald LK, Mankoff DA. Serial 2-[18F] Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) to monitor treatment of bone-dominant metastatic breast cancer predicts time to progression (TTP). *Breast Cancer Res Treat*, 105: 87-94, 2007. (PMID: 17268819)
   b. Dunnwald LK, Gralow JR, Ellis GK, Livingston RB, Specht J, Doot RK, et al. Tumor metabolism and blood flow changes by PET : relation to survival in patients with neoadjuvant chemotherapy for locally advanced breast cancer. *J Clin Oncol* 26: 4449-4457, 2008. PMCID: PMC2653115
   c. Linden HM, Kurland DF, Peterson LM, Schubert EK, Gralow JR, Specht JM, Ellis GK, Lawton T, Livingston RB, Petra PH, Link JM, Krohn KA, Mankoff DA. Fluoroestradiol (FES) positron emission tomography (PET) reveals differences in pharmacodynamics of aromatase inhibitors, tamoxifen, and fulvestrant in patients with metastatic breast cancer, *Clin Cancer Res* 17: 4799-4805, 2011. PMCID: PMC3139698
   d. Peterson LM, Kurland BF, Schubert EK, Link JM, Gadi VK, Specht JM, Eary JF, Porter P, Shankar LK, Mankoff DA, Linden HM. A phase 2 study of 16α-[^{18}F]-fluoro-17β-estradiol positron emission tomography (FES-PET) as a marker of hormone sensitivity in metastatic breast cancer (MBC). *Mol Imaging Biol* 16: 431-470, 2014. PMCID: PMC4169237

3. From the time of my PhD in PET instrumentation and data analysis, I have focused on the PET imaging methodology. My recent focus on methods for quantitative image analysis, with a focus on quantitative imaging biomarkers.
   a. Mankoff DA, Shields AF, Graham MM, Link JM, Krohn KA. Graphical analysis method for estimating blood-to-tissue transfer constants for tracers with labeled metabolites. *J Nucl Med.* 37: 2049-2057, 1996. (PMID: 8970533)
   b. Mankoff DA, Shields AF, Graham MM, Link JM, Eary JF, Krohn KA. Kinetic analysis of 2-[C-11]-thymidine PET imaging studies: compartmental model and mathematical analysis. *J Nucl Med.* 39: 1043-1055, 1998. (PMID: 9627342)
   c. Krohn KA, Mankoff DA, Muzi M, Link JM, Spence AM. True tracers: comparing FDG with glucose and FLT with thymmidine. *Nucl Med Biol* 32: 663-671, 2005. (PMID: 16243640)
   d. Doot RK, McDonald ES, Mankoff DA. Role of PET quantitation in the monitoring of cancer response to treatment: Review of approaches and human clinical trials. *Clin Transl Imaging* 2(4):295-303, 2014. (PMID: 25229053) PMCID: PMC4163151

4. An emerging theme of my research is the development of a framework for using imaging biomarkers to guide more effective individualized treatment. This includes concepts for the use of molecular imaging to guide drug testing and development and developing a framework for the integration of quantitative molecular imaging biomarkers into clinical trials, both locally and nationally.
   a. Hartwell L, Mankoff D, Paulovich A, Ramsey S, Swisher E. Cancer biomarkers: a systems approach. *Nature Biotechnology* 8:905-908, 2006. (PMID: 16900126)
   b. Mankoff DA, O' Sullivan F, Barlow WE, Krohn KA. Molecular imaging research in the outcomes era: measuring outcomes for individualized cancer therapy. *Acad Radiol* 14: 398-405, 2007. (PMID: 17368207).
   c. Pryma DA, Demichele A, Mankoff DA. Evaluating the impact of new imaging tests: promises and pitfalls. *J Natl Cancer Inst* 104(24):1858-9, 2012. (PMID: 23243197).

d. Mankoff DA, Pryma DA, Clark AS. Molecular imaging biomarkers for oncology clinical trials. *J Nucl Med* 55:525-8, 2014. (PMID: 24772217)

Complete list of publications at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1Jqq6B_da1_AH/bibliograpahy/46404239/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

ECOG-ACRIN (Mankoff) 1/1/07 – 12/31/15
NCI/ACRIN
ACR Imaging Network Sciences Committee Chairmanship 4/07 –
The major goal of this project is to undertake clinical trials and other cooperative studies in an endeavor to advance knowledge in the curative and palliative management of cancer through the cooperative group mechanism of the ACR Imaging Network (ACRIN)

Komen Grant AC140060 (Mankoff) 1/17/14 – 1/17/18
Susan Komen Foundation
Molecular Imaging of Breast Cancer Metabolism to Predict Vivo Cancer Behavior
We hypothesize that PET imaging of breast cancer metabolism can characterize in vivo breast cancer biology and help direct individualized breast cancer treatment. This funding helps to support a breast molecular imaging program at Penn.

NIH/NCI 1R01CA174976 (Lin, Mankoff co-investigator) 4/1/14 -3/31/19
NIH/NCI
Using ^{18}F-EF5 PET to measure hypoxia modulation by Nelfinavir in larynx cancer
This project will perform a clinical trial in which patients with laryngeal cancer will be treated with nelfinavir in combination with standard chemotherapy and radiation. The study will also obtain noninvasive imaging and serum markers as surrogates for changes in oxygen and glucose metabolism and correlate with patient outcome, along with correlative laboratory studies to better understand the mechanism through which nelfinavir modulates tumor oxygen and glucose metabolism.

DE-SE0012476 (Mankoff) 9/1/14 – 8/31/16
Department of Energy
Multi-Disciplinary Research and Training Program in Breast Cancer Molecular Imaging and Targeted Radiochemistry
The goal of this program is to (1) develop and sustain a training program in translational nuclear medicine and radiochemistry research based on multi-disciplinary teams of trainees; (2) develop and test radiopharmaceuticals for imaging glutamine metabolism as an indicator of aggressive cancer and as a target for overcoming therapeutic resistance; and (3) develop and test methods for assessing cancer proliferation and quiescence based on a combination of thymidine analogs and sigma-2 binding radiopharmaceuticals, including theranostic compound pairs that target sigma-2 binding in quiescent cancers.

2R01-CA113941-10 (Karp, Mankoff co-investigator) 5/1/2015-4/30/2020
NIH/NCI
Time-of-Flight PET for Improved Whole-Body Imaging
The goal of this study is to develop and evaluate technology for the next generation of PET imaging instruments: development and evaluation of electronics and calibrations, as well as data correction and image reconstruction algorithms.

1U01CA190254-01 (Schnall, Mankoff co-PI) 3/20/2015-2/28/2020
NIH, American College of Radiology
ECOG-ACRIN-Based QIN Resource for Advancing Quantitative Cancer Imaging in Clinical Trials
Dr. Mankoff will collaborate with other at ECOG-ACRIN to direct activities related to Specific Aim 2, coordinating with the ACR Clinical Research Center headquarters staff, statistical contributors, NCI CIP, TCIA,

and QIN investigators to define, develop, make known, and make available datasets of images and outcomes metrics from completed legacy ACRIN

R21-CA-198563-01 (Zhou, Mankoff co-investigator 7/1/2015-6/30/2017
NIH/NCI
Metabolic Imaging Marker for Triple Negative Breast Cancer
In this proposal, we will test the utility of this imaging probe against a panel of human triple negative breast cancer lines encompassing a wide range of preference for glutamine utilization. We will also determine if this probe is suitable for predicting therapies that target cancer cell's glutamine metabolism. Completion of this grant will pave the way for further development of this imaging probe for clinical translation.

U24-CA189523-01A1 (Davatzikos, Mankoff co-investigator) 7/1/2015-6/30/2020
NIH/NCI
Cancer imaging phenomics software suite: application to brain and breast cancer
This project will develop advanced computer analysis methodology for interpretation of radiologic images of cancer, emphasizing brain and breast cancer. The functionality of the software will substantially transcend limitations of current analysis of cancer images, and will open the way for more precise and effective surgical planning as well as for more specific diagnosis of cancer based on its imaging characteristics, eventually leading to individualized medicine.

2-U01-CA148131-06 (Kinahan, Mankoff mPI) 12/1/2015-11/30/2020
NIH/University of Washington subcontract
Quantitative imaging for evaluation of response to cancer therapies
While quantitative PET imaging is a uniquely powerful tool to assessing response to more effective cancer therapies, it is also subject to several sources of bias and variability that degrade study power. In addition, multi-center studies are needed to increase patient accrual rates, even in early-phase studies. These multi-center studies in general confound quantitative accuracy and thus further reduce study power, leading to missed opportunities in evaluating new therapies

Completed Research Support
1U01 CA148131 (Kinahan, Linden, Mankoff) 4/1/10 – 3/31/15
NIH
Advanced PET/CT Imaging for Improving Clinical Trials
The major goal of this study is to improve cancer clinical trials by enhancing the effectiveness of quantitative PET/CT. Role, co-PI I multiple PI grant, transferred on move to Penn.

P50CA138293-01A1 (Porter) 10/1/10 – 9/30/15
NIH
Project 3: Metabolic Alterations in Locally Advanced Breast Cancer and Response to Systemic Therapy (PHCRC/UW Breast SPORE) (Multiple PI for Project, Hockenbery, Mankoff)
The project goal is to relate breast cancer by imaging and metabolomics to treatment response, disease relapse and patient survival. Role: Project Co-PI, transferred upon move to Penn.

P01 CA042045-18 (Krohn) 05/10/04 – 12/31/12
Molecular Imaging of Cancer and Its Response to Therapy
The major goals of this program project grant are to investigate ways of imaging cancer with PET. Role: PI of Project 4 and Data Analysis Core, transferred upon move to Penn.

5 R01 CA 124573-02 (Mankoff) 7/1/07 – 6/30/13
NIH
PET to Measure Breast Cancer Bone Metastasis Response
The major goal of this project is the study of FDG and fluoride PET in patients with bone-dominant breast cancer undergoing systemic therapy. Role: PI transferred upon move to Penn.

OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Alexander Meissner

eRA COMMONS USER NAME (credential, e.g., agency login): AMEISSNER

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Technical University Berlin, Germany	Dipl.-Ing.	1996-2002	Medical Biotechnology
Saarland University, Germany	Ph.D.	2003-2006	Biology
Whitehead Institute for Biomedical Research	postdoc	2006-2008	Stem cell biology

A. PERSONAL STATEMENT

Over the past decade, I have pursued two fundamental, but exceedingly complex, questions: how do cellular states change identities and what are the underlying epigenetic principles that guide these stable transitions?

Our description of the transcriptional and epigenetic impact of reprogramming on somatic cells has spurred numerous follow-ups from my group and others to assign specific molecular landmarks, providing substantial clarity to the underlying mechanisms and interpretation of this process, as well as an improved methodology for its study. We also pioneered the utility of gene expression signatures to accurately and efficiently determine the functional differentiation potential of pluripotent cells by their molecular signatures (Bock et al. *Cell* 2011, Tsankov et al. *Nature Biotech* 2015). In parallel to the reprogramming efforts, I worked to develop genomic strategies to advance our understanding of DNA methylation as it functions during mammalian development. My group has applied novel technologies to better understand the complete dynamic range of this modification, at the nucleotide level and across organismal life, from zygote through adult lineages (Smith et al. *Nature* 2012 and 2014, Ziller et al. *Nature* 2013), refining decades old models of its regulatory contributions at every developmental stage. Much of my past work has focused on questions of mammalian development and pluripotency, particularly their unique modes of epigenetic regulation. Within these fields, I have frequently sought to clarify lingering questions by pioneering tractable systems and technologies that permit robust interpretation from otherwise complicated processes. These efforts have resulted in many high impact publications (see below), but far more importantly have provided a continuous resource of new questions. Our highly successful research program will continue in these areas with some notable expansions that will continue push the boundaries of technical feasibility to obtain novel biological insights.

B. POSITIONS AND HONORS

Selected Positions and Employment

2015-current Professor (tenured), Harvard University (Dept. SCRB)
2012-2015 Associate Professor, Harvard University (Dept. SCRB)
2010-current Senior Associate Member, Broad Institute of MIT and Harvard

2008-2010 Associate Member, Broad Institute of MIT and Harvard
2008-current Principal Faculty Member, Harvard Stem Cell Institute (HSCI)
2008-2012 Assistant Professor, Harvard University (Dept. SCRB)

Professional Memberships

2013-current International Society for Stem Cell Research (ISSCR), Member
2012-current Editorial Board, Genome Biology (BMC)
2011-current Editorial Board, Scientific Reports (Nature Publishing Group)

Selected Study Sections/Grant Reviews

2016 New Jersey Governor's Council for Medical Research, CIRM Discovery program
2015 New Jersey Governor's Council for Medical Research
2014 New Jersey Governor's Council for Medical Research, *Ad hoc* reviewer NIH GCAT
2013 CIRM Genomics Centers of Excellence Awards, CIRM Basic Biology Awards V, New Jersey Governor's Council for Medical Research, ANR-BMBF Epigenomics 2013
2012 RFA 11-03: CIRM Basic Biology IV, Reviewer, *Ad hoc* reviewer, NIH R21 applications, Genes, Genomes and Genetics, New Jersey Governor's Council for Medical Research, NIH CRM, Intramural pilot program review
2011 *Ad hoc* reviewer, NCI SBIR, NHLBI, Intramural program review, *Ad hoc* reviewer, NIH Emerging Technologies and Training in Neurosciences IRG, Welcome Trusts, External reviewer
2010 RFA 10-04: CIRM Basic Biology III
2009 *Ad hoc* reviewer, NCI SBIR, *Ad hoc* reviewer, German Federal Ministry

Other

Peer-reviewer for journals (only most frequent journals are listed): Nature, Science, Cell, Cell Stem Cell, Nature Genetics, Nature Biotechnology, Nature Cell Biology, Genome Research, PLoS Genetics, PNAS

2014 Editor, Special Issue "Epigenomic Approaches", Methods (Elsevier)
2014 Editor (w/ Jörn Walter), "Epigenetic Mechanism in Cellular Reprogramming" Book, Springer (publication in 2014)
2012 Editor, Special Issue "Epigenomics", Genome Biology (BMC)
2009-current Abstract review (annually) for ISSCR Meeting

Selected Honors (Scholarships and Prizes)

2013 NYSCF Robertson Investigator
2009 GeneExpression Systems Epigenomics Young Innovator Award
2009 Pew Scholarship awarded
2003 Boehringer Ingelheim PhD fellowship
1999 Weizmann Institute of Science, Karyn Kupcinet Summer fellowship

C. CONTRIBUTION TO SCIENCE

June 2015 citations include 100 publications (of 111 total in May 2016):
Google Scholar 27144 | Web of Science 19557

All publications in Pubmed:
http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Search&db=pubmed&term=Meissner%20Alex%20OR%20Meissner%20Alexander

1. Cellular reprogramming: I began studying cellular reprogramming as a graduate student, first using comparatively intractable nuclear transfer and, following the groundbreaking work of Dr. Yamanaka, through directed reprogramming using ectopic transcription factors. At the outset, virtually nothing was immediately transparent in this new field: when confronted with a cocktail of inducing factors, somatic cells exhibited a wide range of behaviors and, after weeks, pluripotent cells would emerge seemingly at random. While many initially accepted this randomness as an inherent attribute, we alternatively utilized a clonally inducible model through which different components of this process could be dissected with experimental rigor. Our 2008 publication describing the transcriptional and epigenetic impact of reprogramming on somatic cells has spurred numerous follow-ups from my group and others to assign specific molecular landmarks, providing substantial clarity to the underlying mechanisms and interpretation of this process, as well as an improved methodology for its study. We have been at the forefront of several key transitions in the field, including the molecular equivalence of

induced pluripotency to ES cells, the fundamental contributions of epigenetic regulators, and the interplay of stochastic and deterministic transitions. We also pioneered the utility of gene expression signatures to accurately and efficiently determine the functional differentiation potential of pluripotent cells by their molecular signatures. Early and more recent work also showed the impact of various small molecules on the reprogramming process.

a) Mikkelsen TS, Hanna J, Zhang X, Ku M, Wernig M, Schorderet P, Bernstein BE, Jaenisch R, Lander ES, **Meissner A*.** Dissecting direct reprogramming through integrative genomic analysis. ***Nature***. 2008 Jul 3;454(7200):49-55. PMCID: PMC2754827
b) Smith ZD, Nachman I, Regev A, **Meissner A*.** Dynamic single-cell imaging of direct reprogramming reveals an early specifying event. ***Nature Biotechnol***. 2010 May;28(5):521-6. Epub 2010 May 2. PMCID: PMC2908494
c) Koche RP, Smith ZD, Adli M, Gu H, Ku M, Gnirke A, Bernstein BE, **Meissner A*.** Reprogramming factor expression initiates widespread targeted chromatin remodeling. ***Cell Stem Cell.*** 2011 Jan 7;8(1):96-105. PMCID: PMC3220622
d) Bock C, Kiskinis E, Verstappen G, Gu H, Boulting G, Smith ZD, Ziller M, Croft GF, Amoroso MW, Oakley DH, Gnirke A, Eggan K*, **Meissner A*.** Reference Maps of human ES and iPS cell variation enable high-throughput characterization of pluripotent cell lines. ***Cell.*** 2011 Feb 4;144(3):439-52. PMCID: PMC3063454

2. DNA methylation in development. In parallel to reprogramming efforts, we worked to generate genomic strategies to advance our understanding of DNA methylation as it functions during mammalian development. My group has developed (below) and applied several genome-scale and other approaches to better understand the complete dynamic range of this modification, at the nucleotide level and across organismal life, from zygote through adult lineages, refining decades old models of its regulatory contributions at every developmental stage.

a) Smith ZD, Chan MM, Mikkelsen TS, Gu H, Gnirke A, Regev A, **Meissner A*** A unique regulatory phase of DNA methylation in the early mammalian embryo. ***Nature***. 2012 Mar 28;484(7394):339-44. PMCID: PMC3331945
b) Bock C, Beerman I, Lien WH, Smith ZD, Gu H, Boyle P, Gnirke A, Fuchs E, Rossi DJ, **Meissner A*.** DNA methylation dynamics during in vivo differentiation of blood and skin stem cells. ***Molecular Cell.*** 2012 Aug 24;47(4):633-47. Epub 2012 Jul 26. PMCID: PMC3428428
c) Ziller MJ, Gu H, Müller F, Donaghey J, Tsai LT, Kohlbacher O, De Jager PL, Rosen ED, Bennett DA, Bernstein BE, Gnirke A, **Meissner A*.** Charting a dynamic DNA methylation landscape of the human genome. ***Nature***. 2013 Aug 22;500(7463):477-81. Epub 2013 Aug 7. PMCID: PMC3821869.
d) Smith ZD, Chan MM, Humm KC, Karnik R, Mekhoubad S, Regev A, Eggan K, **Meissner A*.** DNA methylation dynamics of the human preimplantation embryo. ***Nature*** 2014 Jul 31;511(7511):611-5. PMCID: PMC4178976

3. Technology Development, A key factor in our dramatically increased understanding of DNA methylation has been a revolution in technologies to map it comprehensively. For the past several years my lab has been a world leader in the development and application of the most advanced DNA methylation profiling approaches. Currently the most widely used ones include whole genome bisulfite sequencing (WGBS), reduced representation bisulfite sequencing (RRBS) and the Illumina Bead arrays. We initially developed the RRBS approach that is now widely used (Meissner et al. 2005 and 2008) and over the years we have improved the sensitivity down to now single cell resolution and as a result have been able to profile some of the most interesting cell types throughout *in vivo* development (early pre-implantation embryos, rare hematopoietic stem cells, individual neurons and many more).

a) **Meissner A**, Mikkelsen TS, Gu H, Wernig M, Hanna J, Sivachenko A, Zhang X, Bernstein BE, Nusbaum C, Jaffe DB, Gnirke A, Jaenisch R, Lander ES. Genome-scale DNA methylation maps of pluripotent and differentiated cells. ***Nature***. 2008 Aug 7;454(7205):766-70. Epub 2008 Jul 6. PMCID: PMC2896277
b) Bock C, Tomazou EM, Brinkman AB, Müller F, Simmer F, Gu H, Jäger N, Gnirke A, Stunnenberg HG, **Meissner A*.** Quantitative comparison of genome-wide DNA methylation mapping technologies. ***Nature Biotechnology*** 2010 Oct;28(10):1106-14. Epub 2010 Sep 19. PMCID: PMC3066564

c) Boyle P, Clement K, Gu H, Smith ZD, Ziller JM, Fostel JL, Holmes L, Meldrim J, Kelley F, Gnirke A, **Meissner A*.** Gel-free multiplexed reduced representation bisulfite sequencing for large-scale DNA methylation profiling. ***Genome Biology*** 2012 Oct 3;13(10):R92. PMCID: PMC3491420

d) Ziller MJ, Hansen KD, **Meissner A***, Aryee MJ*. Coverage recommendations for methylation analysis by whole-genome bisulfite sequencing. ***Nature Methods.*** 2015 Mar;12(3):230-2. PMCID: PMC4344394

4. Regulation of human pluripotent stem cells, Another major area in the lab has focused on dissecting the epigenetic mechanisms underlying pluripotency and differentiation. Human pluripotent stem cells possess the ability to self renew *in vitro* while maintaining a developmental plasticity that is similar to that exhibited by progenitor cells of the very early embryo. We continue to dissect how various transcription factors are able to access silent heterochromatin and gain insights on the individual steps during the transition to both primed and active states. We have made significant progress in differentiating human ES cells into all three germ layers and have extensively studied these early progenitor stages. We are now complementing these with several consecutive stages within selected lineages. Using epigenetic dynamics and footprints combined with computational modeling we began to derive regulatory hierarchies that control these cell state transitions. We have and continue to perform genetic manipulations to provide functional support for the various (presumably) regulatory events.

a) Gifford CA, Ziller MJ, Gu H, Trapnell C, Donaghey J, Tsankov A, Shalek AK, Kelley DR, Shishkin AA, Issner R, Zhang X, Coyne M, Fostel JL, Holmes L, Meldrim J, Guttman M, Epstein C, Park H, Kohlbacher O, Rinn J, Gnirke A, Lander ES, Bernstein BE, **Meissner A*.** Transcriptional and epigenetic dynamics during specification of human embryonic stem cells. ***Cell.*** 2013 May 23;153(5):1149-63. Epub 2013 May 9. PMCID: PMC3709577

b) Tsankov AM, Gu H, Akopian V, Ziller MJ, Donaghey J, Amit I, Gnirke A, **Meissner A*.** Transcription factor binding dynamics during human ES cell differentiation. ***Nature.*** 2015 Feb 19;518(7539):344-9. PMCID: PMC25693565

c) Ziller MJ, Edri R, Yaffe Y, Donaghey J, Pop R, Mallard W, Issner R, Gifford CA, Goren A, Xing J, Gu H, Cacchiarelli D, Tsankov AM, Epstein C, Rinn JL, Mikkelsen TS, Kohlbacher O, Gnirke A, Bernstein BE, Elkabetz Y, **Meissner A*.** Dissecting neural differentiation regulatory networks through epigenetic footprinting. ***Nature.*** 2015 Feb 19;518(7539):355-9. PMCID: PMC4336237

d) Liao J, Karnik R, Gu H, Ziller MJ, Clement K, Tsankov AM, Akopian V, Gifford CA, Donaghey J, Galonska C, Pop R, Reyon D, Tsai SQ, Mallard W, Joung JK, Rinn JL, Gnirke A, **Meissner A*.** Targeted disruption of DNMT1, DNMT3A and DNMT3B in human embryonic stem cells. ***Nature Genetics*** 2015 Mar 30. PMCID: PMC4414868

5. Cancer/aging epigenetics. My interest in cancer epigenetics goes back to my early graduate studies aimed at understanding the complex role of DNA methylation in carcinogenesis. Some of the first studies that I was involved in supported the notion of a dual role for DNA hypomethylation in suppressing later stages of intestinal tumorigenesis, but promoting early lesions in the colon and liver. Subsequent work using inducible overexpression that we still continue in the lab showed that Dnmt3b promotes tumorgenesis *in vivo*. More recently, we described several similarities between alterations in cancer and aging. Our most recent study (Landau et al) notably changed our view of cancer as it highlights the global deregulation in CLL through discordant methylation patterns that have strong implications for the clinical outcome.

a) Gu H, Bock C, Mikkelsen TS, Jäger N, Smith ZD, Tomazou E, Gnirke A, Lander ES, **Meissner A**. Genome-scale DNA methylation mapping of clinical samples at single-nucleotide resolution. ***Nat Methods.*** 2010 Feb;7(2):133-6. PMCID: PMC2860480

b) Huh SJ, Clement K, Jee D, Merlini A, Choudhury S, Maruyama R, Yoo R, Chytil A, Boyle P, Ran FA, Moses HL, Barcellos-Hoff MH, Jackson-Grusby L, **Meissner A***, Polyak K*. Age- and pregnancy-associated DNA methylation changes in mammary epithelial cells. ***Stem Cell Reports.*** 2015 Feb 10;4(2):297-311. PMCID: PMC4325231

c) Landau DA, Clement K, Ziller MJ, Boyle P, Fan J, Gu H, Stevenson K, Sougnez C, Wang L, Li S, Kotliar D, Zhang W, Ghandi M, Garraway L, Fernandes SM, Livak KJ, Gabriel S, Gnirke A, Lander ES, Brown JR, Neuberg D, Kharchenko PV, Hacohen N, Getz G, **Meissner A***, Wu CJ*. Locally disordered methylation forms the basis of intratumor methylome variation in chronic lymphocytic leukemia. ***Cancer Cell.*** 2014 Dec 8;26(6):813-25. PMCID: PMC4302418

D. RESEARCH SUPPORT

Ongoing Research Support

1P01GM099117 (Meissner) 08/01/2011-07/31/2017
NIH (NCE)
Dissecting the Establishment and Regulation of Human Pluripotency
This project aims to provide a detailed mechanistic understanding of the key protein factors that influence the cell state transitions (somatic to pluripotent) as well as the subsequent maintenance of the pluripotent state.

1R01HL128172 (Kotton/Meissner) 09/15/2015-06/30/2019
NIH
Epigenenomic and Transcriptonic Networks in Normal and Defective Lung Development
The project aims to perform comprehensive, integrative analysis of regulatory networks during normal and defective lung development.

NYCEF-R-I16 (Meissner) 01/01/2013-12/31/2017
The New York Stem Cell Foundation
Using phenotypic and genomic characterization of primary hepatocytes to facilitate the generation of mature, functional hepatocytes in vitro
Completion of this project will allow the routine generation of large quantities of patient-specific *in vitro* derived mature human hepatocytes.

1R01DA036898 (Meissner) 09/30/2013-05/31/2018
NIH/NIDA
Generation and characterization of tools for target-specific de novo DNA methylation
To design an innovative approach for targeted manipulation of DNA methylation in a unique cellular system that also enables accurate measurements of such performance.

3R01DA036898-03 (Meissner) 08/01/2015-07/31/2016
NIH/NIDA (Administrative supplement)
Generation and characterization of tools for target-specific de novo DNA methylation
The project goal is to overcome the inability to manipulate DNA methylation by designing an innovative approach for targeted manipulation of DNA methylation in a unique cellular system that also enables accurate measurements of such performance.

1R01HD078679 (McCarrey/Meissner) 09/01/2014-08/31/2019
NIH
Epimutations in Offspring Produced by Assisted Reproductive
The goals of this project are to determine the genome-wide extent and functional impact of epimutations induced in offspring of different ages produced by ICSI and to determine the timing of induction of epimutations in ART (assisted reproductive technologies) offspring.

BC134001P1 (Polyak/Meissner) 09/30/2014-09/29/2016
DoD/CDMRP
Epigenetic subtypes of triple negative breast cancer
The aims of this project are to: 1) define epigenetic heterogeneity in Triple negative breast cancer (TNBCs) and 2) investigate the role of histone demethylases (HDMs) in defining epigenetic heterogeneity in TNBCs.

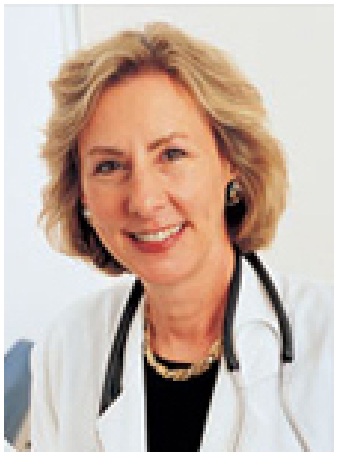
Completed Research Support

A18567 (Meissner) 09/01/2012-01/01/2015
Life Technologies Inc.
Scorecard 2.0
The goal of this project is to demonstrate that the ScoreCard approach reported with array methods can be adapted to current TaqMan qPCR-based and Next Gen Ion Torrent analysis platforms from Life Technologies.

No Award No. (Meissner/Nachman) 06/01/2011-05/31/2015
Human Frontier Science Program
Studying dynamics of cell state transitions during reprogramming using a live imaging approach
We aim to advance our understanding of the dynamics and mechanisms of cell state transitions during mammalian cell reprogramming using a combined high-resolution live cell imaging and probabilistic modeling approach.

U01HG007610 (Kellis/Meissner) 06/02/2014-03/31/2016
NIH
Epigenomic variation atlas across human tissues and individuals in GTEx
The goal is to characterize inter-individual variation of DNA methylation and its impact on gene expression.

P50HG006193 (Regev/Hacohen) 07/09/2011-04/30/2016
NIH
Reconstruction of the Protein and Non-coding RNA circuits that control and maintain ES cell chromatin
The overall goal of this program is to use two cellular systems, ES cells and dendritic cells, to reconstruct the dynamic regulatory circuits.



OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contr butors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Carolyn D. Runowicz, M.D.

eRA COMMONS USER NAME (credential, e.g., agency login): crunowicz

POSITION TITLE: Executive Associate Dean for Academic Affairs, Professor of Obstetrics & Gynecology
Herbert Wertheim College of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Connecticut	B.A.	05/1973	Biology
Jefferson Medical College, PA	M.D.	05/1977	Medicine
Mt. Sinai School of Medicine, NY	Residency	06/1981	Ob/Gyn
Mt. Sinai School of Medicine, NY	Fellowship	06/1983	Gyn/Oncology

A. Personal Statement

I have the expertise, knowledge, leadership, training and experience to successfully participate in the proposed research project. My research has focused on the development, initiation and conduct of clinical trials in gynecologic cancer and in cancer prevention. I have been treating patients with ovarian cancer for more than 30 years. I have served in leadership roles in the major cancer organizations: first woman president of the Society of Gynecologic Oncologists (2000), President of the American Cancer Society (2005) and Chair for 4 years (2006-2010) of the National Cancer Advisory Board (NCAB), appointed by President George W. Bush. I finished my term in June 2015 on the Board of Directors of the American Society of Clinical Oncology (2011-2015). I am currently serving as Vice President of the American Gynecological and Obstetrical Foundation Board. I am a leading expert in ovarian cancer.

1. Runowicz CD, Dottino PR, Shafir MK et al (1986). Catheter complications associated with intraperitoneal chemotherapy. Gynecol Oncol 24(1):45-50.
2. Runowicz CD, Wadler S, Rodriguez-Rodriguez L et al (1989). Concomitant cisplatin and radiotherapy in locally advanced cervical cancer. Gynecol Oncol 34(3);395-401.
3. Runowicz CD, Costantino JP, Wickerham DL et al. (2011) Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR) Am J Obstet Gynecol 205: 535.e1-5.

B. Positions and Honors

Positions and Employment

1983-1985	Instructor, Department of Obstetrics & Gynecology Division of Gynecologic Oncology, Mount Sinai School of Medicine, New York, NY
1985-1990	Assistant Professor, Director, Division of Gynecologic Oncology, Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, NY
1990-1995	Associate Professor, Director, Div. of Gynecologic Oncology, Dept. of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, NY
1995-2001	Professor, Director, Division of Gynecologic Oncology, Dept. of Obstetrics, Gynecology and Women's Health, Albert Einstein College of Medicine, Bronx, NY
1985-2001	Member, Albert Einstein College of Medicine Cancer Center, Bronx, NY
2001-2002	Clinical Professor, Dept. of Obstetrics, Gynecology and Women's Health, Albert Einstein College Albert Einstein College of Medicine, Bronx, NY
2002-2003	Professor, Clinical Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, NY, NY
2001-2003	Vice Chairman, Dept. of Obstetrics & Gynecology, St. Luke's Roosevelt Hospital Ctr, New York Director, Gynecologic Oncology Research, Continuum Health Partners, Inc., NY, NY
2003-2011	Professor of Obstetrics & Gynecology, Division of Gynecologic Oncology, UConn School of Medicine, Farmington, CT
2003-2011	Director, The Carole and Ray Neag Comprehensive Cancer Program, Northeast Utilities Chair in Experimental Oncology, University of Connecticut Health Center, Farmington, CT
2010	Lila Wallis Distinguished Professor, NY Hospital; Sanford Weill College of Medicine
2011-2012	Associate Dean for Women in Medicine and Science, Florida International University, Herbert Wertheim College of Medicine, Miami, FL
2011- present	Professor Department of Obstetrics and Gynecology, Florida International University, Herbert Wertheim College of Medicine, Miami, FL
2012- present	Executive Associate Dean for Academic Affairs, Professor Department of Obstetrics and Gynecology, Florida International University, Herbert Wertheim College of Medicine, Miami, FL

Other Experience and Professional Memberships (Abridged)

National Cancer Institute (Abridged)

2000-2004	Scientific Review Group – Subcommittee H
2002	Co-Chair, Early Reproductive Events and Breast Cancer Risk Workshop-Planning Committee
2004-2010	Member, National Cancer Advisory Board
2006-2010	Chair, National Cancer Advisory Board
2007-2010	Clinical Trials Advisory Committee
2012-	External Advisor to the NCI Clinical Proteomic Tumor Analysis Consortium
2012-	NIH Advisory Committee Reviewer: NCI Special Emphasis Panel (R25):ACA1R7RB-E(01) Manpower and Training Grants

American Cancer Society (Abridged)

2000- present Member, Gynecologic Cancers Advisory Group
2001- present Member, Health Promotions Advisory Workgroup
2005-2006 President
2008- present International Advisory Task Force
2012- present Honorary Life Member

American Society of Clinical Oncology (Abridged)

2011-2015 Board of Directors
2011- Cancer Policy and Clinical Affairs Board Liaison
2011- Research, Policy & Practice Subcommittee
2011-2013 Audit Committee
2011-2013 Clinical Practice Committee Liaison
2013- Health Disparities Committee Board Liaison

American Gynecological and Obstetrical Society (Abridged)

2010-2013 Foundation Board, Vice President American Association of Obstetricians and Gynecologists Foundation

Honors

Summa Cum Laude, University of Connecticut
Alpha Omega Alpha, Jefferson Medical College
Felix Rutledge Lecturer, M.D. Anderson Cancer Center, Houston, Texas
University of Connecticut "Distinguished Alumni", 2004
Phi Beta Kappa
Guest Speaker: President's Cancer Panel "Living Beyond Cancer: Meeting the Challenges of Older Adult Survivors", 2004
American Medical Women's Association "Local Legend" Award, 2004
Remarkable Individual Award, University of Connecticut Health Center, 2006
American Cancer Society/Society of Gynecologic Oncologists 2nd Annual Lecture, 2007
University of Connecticut Distinguished Honor Program Alumni Award, 2007
Cancer Care Award, Cancer Support Team, 2007
ASCO Statesman Award, 2008
American Cancer Society Star of Hope Award, 2008
Lila Wallis, Distinguished Professor, NY Hospital: Sanford Weill College of Medicine, 2010
Florida Dept. of Health, Miami Dade County, Breastfeeding Friendly Worksite Award, 2012

C. Contribution to Science

1. My publications have focused on novel clinical trials in gynecologic cancer, including ovarian cancer. A phase II trial of paclitaxel in ovarian cancer resulted in larger phase III cooperative group clinical trials and this drug was established as first line therapy in ovarian cancer. The early observation that concomitant chemotherapy in advanced cervical cancer resulted in improved responses which formed the basis for the larger randomized phase III cooperative group studies that changed the clinical treatment of cervical cancer. This treatment is now standard as a result of the earlier trials and the confirmation in the larger randomized studies.
    a. Runowicz CD, Wadler S, Rodriguez-Rodriguez L et al. (1989). Concomitant cisplatin and radiotherapy in locally advanced cervical cancer. Gynecol Oncol 34(3);395-401.
    b. Einzig AI, Wiernik PH, Sasloff J, Runowicz CD et al. (1992). Phase II study and long-term follow-up of patients treated with taxol for advanced ovarian adenocarcinoma. J Clin Oncol 10(11):1748-1753.

2. As a fellow and junior attending, I participated in the early clinical trials of intraperitoneal chemotherapy for ovarian cancer. These trials provided the preliminary data for the larger randomized trials establishing intraperitoneal chemotherapy as a standard in the first line chemotherapeutic management of ovarian cancer. Because of catheter complications, the use of intraperitoneal chemotherapy has been limited in clinical use. This limiting factor was an impetus to work with the engineers in designing the magneto-electric delivery of drug-nanoparticles to specific areas, e.g. the peritoneum in ovarian cancer. Our preliminary data forms the basis of this application.

    a. Runowicz CD, Dottino PR, Shafir MK et al. (1986). Catheter complications associated with intraperitoneal chemotherapy. Gynecol Oncol 24(1):45-50.
    b. Guduru R, Liang P, Runowicz CD et al. (2013). Magneto-electric nanoparticles to enable field controlled high-specificity drug delivery to eradicate ovarian cancer cells. Sci Rep3:2953.

3. I led the gynecologic committee in the NSABP breast cancer prevention trials and was important in describing the gynecologic effects of tamoxifen and raloxifene.

    a. Chalas E, Constantino JP, Wickerham DL, Wolmark N, Lewis GC, Bergman C, Runowicz CD (2005). Benign gynecologic conditions among partipants in the Breast Cancer Prevention Trial. Am J Obstet Gynecol192 (4): 1230-7.
    b. Runowicz CD, Costantino JP, Wickerham DL et al. (2011) Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR) Am J Obstet Gynecol 205: 535.e1-5.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/pubmed/?term=runowicz

D. Research Support

Ongoing Research Support

NSF Award Number 1408063 Khizroev (PI) 06/2014-05/2017
High-specificity drug uptake using magneto-electric nanoparticles for cancer treatment
A new nanotechnology is proposed to take advantage of (i) the difference between the membrane electric properties of cancer and healthy cells, and (ii) the capability of magneto-electric nanoparticles (MENs) at body-temperature to serve as localized converters of a remotely supplied magnetic field into the MENs' intrinsic electric fields that can trigger local nano-electroporation effects.
Role: Runowicz (Co-PI)

Completed Research Support

IRG-06-002-04 Runowicz (PI) 01/2006 – 03/2011
National Cancer Institute of Canada Phase II Exemestane in breast cancer prevention
NCI Phase II consortium: NYCC
Role: PI

American Cancer Society – Institutional Research Grant (IRG) Runowicz (PI)
01/2009-03/2011
Role: PI

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **Kristin Rae Swanson, PhD**

POSITION TITLE: **Professor and Vice Chair of Research of Neurological Surgery, Mayo Clinic Arizona**

eRA COMMONS USER NAME (credential, e.g., agency login): **krswanson**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tulane University, New Orleans, LA	BS	1996	Mathematics/Physics
University of Washington, Seattle, WA	MS	1998	Mathematical Biology
University of Washington, Seattle, WA	PhD	1999	Mathematical Oncology
University of California, San Francisco, CA	Postdoc	1999-2000	Mathematical Medicine

A. Personal Statement

My research group has pioneered the development of novel mathematical modeling techniques that allow for patient-specific quantification of brain tumor growth and invasion. I have been dedicated to pursuing clinically-derived questions in neuro-oncology emboldened by the belief that only through patient-specific mechanistic mathematical modeling (PSM^4) can we revolutionize patient care. My work in PSM^4 (Swanson 2000) has paved the way for bridging from Chalk-to-Bedside by allowing us to unveil a deeper mechanistic understanding of this disease from both a biological and a theoretical perspective. Specifically, we have developed techniques for translating changes seen on routinely available clinical imaging (MRI) into tissue-level estimates of rates of net proliferation (ρ) and net dispersion (D) rates for individual patients. These techniques allow for the generation of patient-specific simulations of the diffuse glioma cell distribution peripheral to the imaging abnormality seen on imaging. This has helped clinicians identify which patients have an (un)favorable prognosis (Wang, 2009; Baldock, 2014) and which patients will respond to resection (Baldock, 2014), radiation (Rockne 2010) and other treatments (Hawkins-Daarud, 2013) We have also applied these mathematical modeling techniques to optimize tumor control and minimize radiation dose to normal tissue based on model-derived metrics of radiosensitivity (Corwin, 2012). Further, we have developed develop novel metrics of treatment response which account for PSM^4-informed tumor growth kinetic (Neal 2013). Our PSM^4 methods are providing novel tools for bridging biology and medicine by elucidating biological mechanisms underlying clinical and experimental data. Thus, my background is ideal to lead this work, in which we will incorporate information from clinical imaging for discovering key biological drivers that quantitatively underpin intra- and inter- patient heterogeneity, identifying patients that benefit from novel therapies, and tailoring localized treatments to the patient.

1. A. L. Baldock, R. Rockne, A. Boone, M. Neal, M. M. Mrugala, J. K. Rockhill, **K. R. Swanson**. From Patient-Specific Mathematical Neuro-Oncology Towards Precision Medicine. *Frontiers in Molecular and Cellular Oncology*, 3:62. doi: 10.3389/fonc.2013.00062 PMID: 23565501, PMCID: PMC3613895.
2. R. A. Morshed, M. Gutova, J. Juliano, M. E. Barish, A. Hawkins-Daarud, D. Oganesyan, K. Vazgen, T. Yang, A. Annala, A. U. Ahmed, K. S. Aboody, **K. R. Swanson**, R. A. Moats, M. S. Lesniak. Analysis of glioblastoma tumor coverage by oncolytic virus-loaded NSCs using MRI-based tracking and histological reconstruction. Cancer Gene Ther. 2015 Jan;22(1):55-61. doi: 10.1038/cgt.2014.72. Epub 2014 Dec 19 PMID: 25525033 PMCID: PMC4293243
3. **K. R. Swanson,** R. Rockne, J. Claridge, M. A. J. Chaplain, E. C. Alvord, Jr, A. R. A. Anderson. Quantifying the role of angiogenesis in malignant progression of gliomas: In silico modeling integrates imaging and histology. *Cancer Research,* 71(24):7366-7375, Dec 15, 2011 *doi: 10.1158/0008-5472.CAN-11-1399* 21900399 PMCID: PMC3398690
4. **K. R. Swanson**, E. C. Alvord Jr, J. D. Murray: A quantitative model for differential motility of gliomas in grey and white matter. *Cell Proliferation*, 33(5):317-29, 2000 PMID: 11063134

B. Positions and Honors:

Professional Appointments:

2002-2008 Assistant Research Professor of Pathology, U of Washington, Seattle, WA
2002-2008 Adj Assistant Research Prof of Applied Mathematics, U of Washington, Seattle, WA
2004-2005 Shaw Research Asst Professor in Neuropathology, U of Washington, Seattle, WA
2008-2012 Associate Research Professor of Pathology, U of Washington, Seattle, WA
2009-present Affiliate Member Computational Biology, Fred Hutchinson Cancer Center, WA
2012-present Affiliate Professor of Applied Mathematics, U of Washington, Seattle, WA
2012-2015 Professor and Vice Chair of Research of Neurosurgery, Northwestern University, Chicago, IL.
2013-2015 Professor of Engineering Sciences & Applied Math, Northwestern U, Evanston, IL
2014-2015 Professor of Radiology, Northwestern University, Chicago, IL
2015-present Professor and Vice Chair of Research of Neurosurgery, Mayo Clinic, Phoenix, AZ
2015-present Professor of Mathematics, Arizona State University, Tempe, AZ
2015-present Professor of Cell & Cancer Biology and Neurogenomics, Phoenix AZ

Select Honors and Advisory Board Membership:

2012-present Advisory Board, James S. McDonnell Foundation Mathematical and Complex Systems Approaches to Brain Cancer Program
2011-2012 James D. Murray Endowed Chair of Applied Mathematics in Neuropathology
2009 William E. Schiesser Lecture, Lehigh University (Bethlehem, PA)
2008 Undergraduate Research Mentor of the Year, University of Washington
2007-2010 Board of Directors, Society for Mathematical Biology
2005-2010 James F. McDonnell Foundation 21st Century Research Award
2004-2005 Shaw Endowed Professorship, University of Washington
1999-2003 NSF Mathematical Sciences Postdoctoral Research Fellowship
2001 Burroughs Wellcome Fund Career Awards at the Scientific Interface Finalist
1999 Landahl/Busenberg Travel Grant
1998 NSF Mathematical Biology Training Grant
1997 Boeing Graduate Research Fellowship
1996 Kappa Kappa Gamma Prize in Math; Elsie Field Dupre Memorial Prize in Physics
1995-1996 Mortar Board Honor Society Treasurer

Patents

"Method and system for characterizing tumors" **K. R. Swanson**. E. C. Alvord, Jr, J. D. Murray, R. Rockne. File date: 2/19/2010 Application #: US 12/709,367 Publication Date: October 29, 2013

Peer Review Involvement:
International**:** Royal College of Surgeons in Ireland (2014), Swiss National Science Foundation (2014), French Aix-Marseille Excellence Initiative, A*MIDEX (2013), Ontario Cancer Institute 4th Investigator Award Retention and Promotion Committee (2013), Italian Association for Cancer Research (2011), French Insitut National du Cancer (2010), French National Research Agency (2009) National Natural Sciences and Engineering Research Council of Canada (2006, 2013)
National: NCI Bridging the Gap Between Cancer Mechanism and Population Science (2014), NSF Mathematical Biology and the Computational Mathematics (2011), NIH Modeling and Biological Systems (MABS) (2011), NSF Research Training Groups Enhancing the Mathematical Sciences Workforce in the 21st Century (2010), NSF Mathematical Biology 2006

C. Contribution to Science

I. Predictive patient-specific mechanistic minimal models of tumor growth: Patient-Specific Mathematical Oncology Gliomas, and particularly the most aggressive grade IV glioblastoma (GBMs), are heterogeneous, aggressive, and highly invasive primary brain tumors associated with dismal prognoses. Although clinical imaging (such as magnetic resonance imaging, MRI, and positron emission tomography, PET) are routinely used to assess tumor growth, these methods only actually serve as an obscuring lens to the underlying tumor biology. My lab has generated a series of mathematical models of brain tumor growth (of varying degrees of complexity) that, with patented calibration methods, can be used to quantify each patient's' tumor in terms of net phenotypic rates of proliferation and invasion. We continually refine our models to incorporate key elements of how clinical imaging may or may not reflect the tumor biology at play in the patient. Using extended patient-specific models of tumor growth and physiology, we have begun to incorporate more of a realistic connection between tumor biology and the component that manifests on imaging, c.f. edema formation on MRI. Further, we have begun to simulate the physics behind both PET and MR imaging to generate simulated clinical images that provide direct insight into the (dis)connect between patient imaging and the tumor biology underlying each image.

1. **K.R. Swanson**, E.C. Alvord, J.D. Murray, R. Rockne. Method and system for characterizing tumors. US 8571844 B2, 2013.

2. **K. R. Swanson**, R. Rockne, J. Claridge, M. A. J. Chaplain, E. C. Alvord, Jr, A. R. A. Anderson. Quantifying the role of angiogenesis in malignant progression of gliomas: In silico modeling integrates imaging and histology. *Cancer Research*, 71(24):7366-7375, 2011 PMID: 21900399; PMCID: PMC3398690
3. S. Gu, G. Chakraborty, K. Champley, A. Alessio, J. Claridge, R. Rockne, M. Muzi, K. A. Krohn, A. M. Spence, E. C. Alvord Jr, A. R. A. Anderson, P. Kinahan, **K. R. Swanson**. Applying A Patient-Specific Bio-Mathematical Model of Glioma Growth to Develop Virtual [18F]-FMISO PET Images. *Mathematics in Medicine and Biology*, 29(1): 31-48, 2011 PMID: 21562060.
4. **K. R. Swanson**, C. Bridge, J. D. Murray, E. C. Alvord Jr.: Virtual and Real Brain Tumors: Using Mathematical Modeling to Quantify Glioma Growth and Invasion. *Journal of the Neurological Sciences*, 216(1):1-10, 2003 PMID: 14607296

II. Novel treatment response metrics Clinicians are routinely questioning the efficacy of any given treatment and, to date, have very few tools for assessing treatment response in a clinically relevant timeframe. Under the current paradigm, glioma patients are considered to have failed a new treatment protocol if their imaging abnormality has increased by at least 25%. Due to the vast heterogeneity in growth rates brain cancer patients, this could lead to up to 3 months of practically untreated growth while an ineffective therapy is being administered. Thus, small-scale Phase I and II studies are hindered statistically by glioma heterogeneity and by the fact that current response metrics fail to predict prognosis. Thus, the ability to predict whether promising therapies will have success in larger Phase III studies is limited, further hindering the advancement of potentially valuable treatments into advanced phase clinical trials. We have demonstrated that PSM^4 tuned to clinical MRIs can be used to define a baseline simulated untreated virtual control (UVC) against which therapeutic response can be assessed. “Days Gained”, our UVC-based response metric, is defined as the number of days the treatment deflected the growth of the tumor when comparing against the UVC growth curve. The incorporation of patient-specific kinetics into metrics of response would allow clinical trials the opportunity to separate out treatment effect from GBM heterogeneity, even in small cohort studies. That is, we believe UVC-based response rates measured in Phase I/II data for new therapies will be more predictively aligned with the future outcomes in overall survival in later phase studies, allowing for more efficient decisions of which therapies should move on to Phase III studies.

1. M. L. Neal, A. D. Trister, S. Ahn, A. L. Baldock, C. A. Bridge, L. Guyman, J. Lange1, R. Sodt, T. Cloke, A. Lai, T. F. Cloughesy, M. M. Mrugala, J. K. Rockhill, R. C. Rockne, **K. R. Swanson**. Response classification based on a minimal model of glioblastoma growth is prognostic for clinical outcomes and distinguishes progression from pseudoprogression. *Can Res*, 2013;73(10):2976-86.PMID: 23400596.
2. M. L. Neal, A. D. Trister, T. Cloke, R. Sodt, S. Ahn, A. L. Baldock, C. Bridge, A. Lai, T. Cloughesy, M. M. Mrugala, J. K. Rockhill, R. Rockne, **K. R. Swanson**. Discriminating survival outcomes in patients with glioblastoma using a simulation-based, patient-specific response metric. *PLOS One*, Jan 2013 PMID: 23372647; PMCID: PMC3553125
3. C.H. Wang, J. K. Rockhill, M. Mrugala, D. L Peacock, A. Lai, K. Jusenius, J. M. Wardlaw, T. Cloughesy, A. M. Spence, R. Rockne, E. C. Alvord, Jr, **K. R. Swanson**. Prognostic Significance of Growth Kinetics in Glioblastoma: Novel Insights from Combining Serial MR Imaging with a Bio-mathematical Model for Glioma Growth and Invasion. *Cancer Research*, 69:9133-9140, 2009 PMID: 19934335; PMCID: PMC3467150.

J. E. Adair, S. K. Johnston, B. C. Beard, L. A. Guyman, A. L. Baldock, C. A. Bridge, A. Hawkins-Daarud, D. Born, J. K. Rockhill, D. L. Silbergeld, M. Mrugala, R. C. Rockne, ***K. R. Swanson,** *H-P. Kiem. (*co-senior authors) Gene therapy enhances chemotherapy tolerance and efficacy in glioblastoma patients. *Journal of Clinical Investigation,* Aug 8, 2014, PMID:25105369.

III. Patient-specific optimized treatment protocols The current standard-of-care for GBM consists of resection followed by conformal radiation therapy (RT) with concomitant and adjuvant temozolomide chemotherapy. Despite decades of effort, little progress has been made in determining an optimal treatment protocol that dramatically improves outcomes. For resection, there has been a long-standing debate as to the optimal use of a localized treatment strategy of resection for removing an unknown fraction of an intrinsically diffusely invasive disease. For surgical resection, using our PSM^{4}s to predict the patient-specific diffuse invasion of gliomas peripheral to the abnormality seen on routine clinical MRI, we were able to determine who received a median 75% increase in survival if they received extensive resection (versus less extensive resection). This suggests patient-care can be significantly improved that by combining existing neurosurgical technologies with our PSM^{4}s to reinterpret existing clinical imaging. For RT, the clinical challenges of delivering the right dose to the right patient at the right time is becoming increasingly complicated as technological advances provide new opportunities to spatially and temporally sculpt RT dose. As gliomas are known to extend diffusely into the normal-appearing tissue surrounding the imaging abnormality, the current standard-of-care includes dosing to standard margins beyond the enhancing area in an attempt to capture subclinical disease. Yet, depending on the patient-specific degree of diffuse invasion of areas peripheral to the imaging abnormality, the amount of normal tissue irradiated in these one-size-fits-all margins may or may not correlate with the extent of tumor cell burden found in the margin. For RT, we have developed framework to test and improve treatment protocols that minimize exposure to normal tissue and maximize impact to the tumor. For systemic therapies, my group has also begun exploring differential responses to anti-angiogenics, such as bevacizumab, based on the patient specific growth kinetics.

1. A. Hawkins-Daarud, R. Rockne, A. R. A. Anderson, **K. R. Swanson**. Modeling glioma-associated edema during anti-angiogenic therapy. *Frontiers in Molecular and Cellular Oncology*, 3:66 PMID: 23577324, PMCID: PMC3616256.
2. R. Rockne, J. K. Rockhill, I. Kalet, E. C. Alvord, **Jr, K. R. Swanson**. Predicting Efficacy of Radiotherapy in Individual Patients with Gliomas*. Physics in Medicine and Biology*, 55:3271-3285, 2010 PMID: 20484781– **Awarded Top 10 Best Publication in PMB for 2010; Finalist for Roberts' Prize from Institute of Physics and Engineering in Medicine**
3. D. Corwin, C. Holdsworth, R. Rockne, A. D. Trister, M.M. Mrugala, J.K. Rockhill, R. D. Stewart, M. Philips, **K. R. Swanson**. Toward Patient-Specific, Biologically Optimized Radiation Therapy Plans for the Treatment of Glioblastoma. *PLOS One*, 12 Nov 2013 PMID:24265748, PMCID: PMC3827144
4. A. L. Baldock, S. Ahn, R. Rockne, M. Neal, D. Corwin, H. Malone, V. Ebaina, A. Sonabend, M. M. Mrugala, J. K. Rockhill, R. Rostomily, D. L. Silbergeld, A. Lai, T. Cloughesy, G. McKhann, J. Bruce, P. Canoll, **K. R. Swanson**. Patient-specific metrics of invasiveness reveal significant prognostic benefit of extensive resection in a subset of less diffuse malignant gliomas. *PLOS One*, 2014 Oct 28;9(10):e99057. doi: 10.1371/journal.pone.0099057. eCollection 2014. PMID: 25350742 PMCID: PMC4211670

IV. Connecting Static Experimental and Clinical Data to Elucidate Biological Mechanisms PSM^4 provides a conduit for connecting mechanisms discovered at the genetic, cellular or experimental model level with the overall human disease. Although there are ongoing and dramatic advances in our molecular understanding of this horrible disease, there lacks a practical means of connecting genotype (static snapshots of molecular profiles) with phenotype (spatial and temporal understanding of the disease evolution). In preliminary analysis of the TCGA patients, we performed gene set enrichment analysis (GSEA) to seek gene expression patterns that predictively correlate with our patient-specific kinetic rate estimates inferred from MRIs of those same patients. Additionally, traversing the scales between an experimental model and the human reality is rife with challenges. In collaboration with the Canoll Lab at Columbia University, we have already used mathematical modeling to quantitatively bridges between cellular level insights provided by Dr. Canoll's experimental glioma model and human gliomas. For instance, it has been observed in his experimental model that normal progenitor cells in the rodent brain can be recruited to contribute dramatically to the overall tumor mass (with as as much as 80% of the tumor consisting of non-tumorigenic recruited progenitor cells). We have already developed mechanistic mathematical models for recruitment of progenitor cells to the tumor mass that reveals that this mechanism may lead to tumors that appear to be less invasive histologically. Thus, understanding of cell-level biology can provide insight into the overall tumor dynamics through mathematical modeling.

1. A. Trister, B. Bot, A. Hawkins-Daarud, K. Fontes, C. Bridge, J. K. Rockhill, M. Mrugala, R. Rockne, E. Huang, **K. R. Swanson**. A novel patient-specific model of glioma growth kinetics elucidates underlying biology as measured by gene expression microarray. Markers in Cancer, October 11-13, 2012 (Hollywood, FL)
Awarded 2012 Conquer Cancer Foundation of ASCO Merit Award
2. M. Szeto, G. Chakraborty, J. Hadley, R. Rockne, M. Muzi, E. C. Alvord Jr, K. A. Krohn, A. M. Spence, **K. R. Swanson**. Quantitative metrics of net proliferation and invasion link biological aggressiveness assessed by MRI with hypoxia assessed by FMISO-PET in glioblastomas. *Can Res*, 69(10):4502-9, 2009 PMID: 19366800
3. S. Massey, M. Assanah, K. Lopez, P. Canoll, **K. R. Swanson**. Progenitor cell recruitment drives aggressive glioma growth: mathematical and experimental modeling. *Journal of the Royal Society Interface*, 9(73):1757-66, Aug 2012 PMID: 22319102
4. A. Baldock, K. Yagle, D. Born, S. Ahn, A. Trister, M. Neal, S. Johnston, C. Bridge, D. Basanta, J. Scott, H. Malone, A. Sonabend, P. Canoll, M. Mrugala, J. Rockhill, R. Rockne, **K. R. Swanson.** Invasion and Proliferation Kinetics in Enhancing Gliomas Predict IDH1 Mutation Status, *Neuro-Oncol,* 2014;16(6):779-86. PMID: 24832620

V. New models for brain metastasis Cancer metastasis (mets) is the second leading cause of death in the United States and the leading cause of cancer-related deaths, despite innovations in surgery, chemotherapy and radiotherapy. Median overall survivals as short as one month have been reported for patients with untreated symptomatic mets. Lung, breast, and melanoma cancers represent the highest incidence of brain mets and demonstrate differential angiogenic tumor biology, hence raising the treatment potential for anti-angiogenics in select brain mets cases. Brain mets represent a heterogeneous group of tumors that ignores tumor intrinsic biological differences and has resulted in minimal treatment advances. We aim to quantify these previously unstudied biological differences across brain mets. We have proposed a novel mechanistic mathematical model that provides a nexus between tumor angiogenic biology and differential spatial growth profiles seen on patient-specific MRI. We hypothesize that a model of differential angiogenic mechanisms will precisely predict differential localization and spatial growth tendencies, hence providing a basis for differential response to anti-angiogenic therapy in brain mets.

1. P. R. Jackson, F. Grady, M. Lester, E. Kokkinos, A. Rosenberg, R. C. Rockne, C. Bridge, M. Marymont, J. Chandler, **K. R. Swanson**, and P Kumthekar. A paradigm shift in determining brain metastasis treatment: does number really matter? in Society for Neuro-Oncology Annual Meeting; 2014; Miami, FL, USA. BM–14.
2. T. R. Smith, R. R. Lall, R. R. Lall, I. J. Abecassis, O. M. Arnaout, M. H. Marymont, K. R. Swanson, and J. P. Chandler, "Survival after surgery and stereotactic radiosurgery for patients with multiple intracranial metastases: results of a single-center retrospective study.," *J. Neurosurg*., 121(4), 839–45, 2014. PMID: 24857242
Complete List of Published Work: http://mathematicalneurooncology.org/?page_id=51

D. Research Support

Ongoing

NCI R01 CA 16437 (MPI: Kinahan, Swanson) 09/21/2011-07/31/2016

Patient-Specific Predictive Modeling that Integrates Advanced Cancer Imaging. The primary goal of this to award is to prospectively generate longitudinal advanced imaging data to be used as a validation and test set for a mathematical model for angiogenesis and response to therapy in brain tumors.

NCI R01 CA164371-03S1 (MPI: Kinahan, Swanson) 08/01/2013-07/31/2016

Patient-Specific Predictive Modeling that Integrates Advanced Cancer Imaging. This is an administrative supplement to support the post-doctoral fellowship of Pamela Jackson, PhD

James D. McDonnell Foundation Collaborative Activity Award (PI: Swanson) 09/01/2014-08/31/2017

ENDURES: ENvironmental Dynamics Underlying Responsive Extreme Survivors of GBM. The major goals of this multi-institutional investigation are to understand and predict extreme survivorship in patients with glioblastoma through the integration of mathematical modeling, clinical imaging, histology and molecular features across this unique patient cohort.

NIH T32 Neuroscience of Human Cognition (Co-mentors: Swanson, Wang) 09/01/2014-08/31/2016

Neural Capacity as Predictors of Cognition in Extreme Survivors of Glioblastoma. This T32 funding supports C. Paula de los Angeles as she completes the PhD component of her MD/PhD program. Her research is focused on integrating patient-specific mathematical model of tumor growth kinetics with computational neuroanatomical measures of patient brains.

NCI U54 R01 CA 193489 (PD: Gatenby; Project 2 MPI: Swanson, Silva, Gatenby) 09/23/2015-08/31/2020

Cancer As a Complex Adaptive System. Project 2 Title: *Clinical Translation of the Unifying Principles of Tumor Growth: Evolution and Ecology.* We focus on developing computational models that use first principles and available clinical data to: 1. understand the patient-specific dynamics that govern response and resistance and 2. develop computational models that predict the outcomes of different therapies in individual patients.

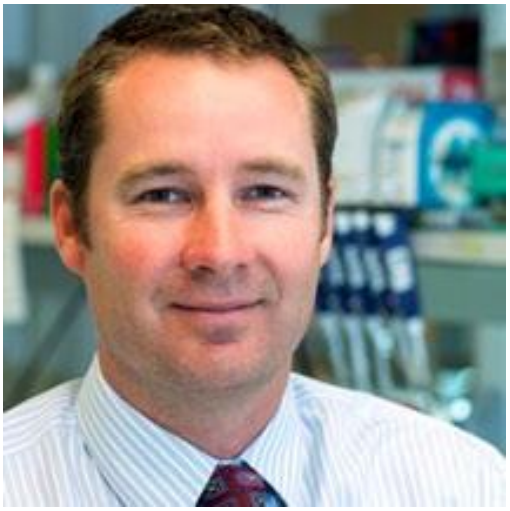
Past

NINDS R01 NS060752 (PI: Swanson) 08/05/2009-07/31/2015

Novel Tools for Evaluation and Prediction of Radiotherapy Response in Individual Patients. The major goals of this investigation are to apply mathematical modeling techniques to assess and predict response to radiation therapy in human glioma patients in vivo using routinely available MRIs.

NCI U54 CA143970 PSOC (PD: Gatenby; Project 3 PI: Swanson) 09/30/2009-08/31/2015

The Physical Microenvironment in Cancer Biology and Therapy Project 3 Title: *Clinical Imaging and the Tumor Physical Microenvironment*. The major goals of this project are to develop mathematical models for the physical tumor microenvironment that can be assessed through clinical imaging.



OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contr butors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Cameron John Turtle

eRA COMMONS USER NAME (credential, e.g., agency login): CTURTLE

POSITION TITLE: Associate Member, Fred Hutchinson Cancer Research Center (FHCRC)
Assistant Professor, University of Washington (UW)

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Sydney, Australia	MBBS	01/1993	Medicine
Royal Australasian College of Physicians		01/2001	Hematology/oncology
Royal College of Pathologists of Australasia		01/2001	Hematopathology
University of Queensland, Australia	PhD	05/2005	Immunology
Postdoctoral Fellow, FHCRC, Seattle, WA, USA		05/2008	Immunology

A. Personal Statement

I trained in Australia in hematology/oncology and hematopathology, completed dual Fellowships of the Royal Australasian College of Physicians and the Royal College of Pathologists of Australasia, and serve as an attending physician on the Hematopoietic Stem Cell Transplant (HCT) Service and the Immunotherapy Service at FHCRC, Seattle Cancer Care Alliance (SCCA), and the UW Medical Center.

My laboratory in the Clinical Research Division at FHCRC is focused on understanding the characteristics of distinct subsets of human $CD8^+$ T cells, their potential utility for tumor immunotherapy, and their role in immune reconstitution after HCT. We have extensive expertise in the isolation, culture, genetic modification and propagation of conventional and non-conventional T cells, and we are highly proficient in the phenotypic, transcriptional, and functional analysis of rare human T cell subsets in healthy individuals and patients with hematologic malignancies. I am PI/co-PI of three investigator-initiated clinical trials of CD19-targeted chimeric antigen receptor (CAR)-modified T cell therapy for patients with B cell malignancies, for which my lab oversees CAR-T cell manufacturing, monitoring, and all research studies. Our experience and funding places us in an exceptionally good position to study novel approaches to manufacturing adoptive T cell therapies.

B. Positions and Honors

Positions and Employment

1993 Intern at Royal North Shore Hospital, Sydney
1994 Resident at Royal North Shore Hospital, Sydney

1995 - 1996	Basic physician trainee (medicine) at Royal North Shore Hospital, Sydney
1997 - 2000	Fellow in hematology/oncology/hematopathology at Royal North Shore Hospital, Sydney
2000	Fellow in hematology/oncology/hematopathology at Royal Prince Alfred Hospital, Sydney
2001 - 2004	PhD scholar, The University of Queensland, Mater Medical Research Institute, Brisbane.
2004	Attending Physician in Hemato-oncology, Mater Adult Hospital, Brisbane
2004 - 2005	Attending Physician in Hemato-oncology, Westmead Hospital, Sydney, Australia
2005 - 2008	Postdoctoral Research Fellow, Fred Hutchinson Cancer Research Center, Seattle, WA
2008 - 2010	Research Associate, Fred Hutchinson Cancer Research Center, Seattle, WA
2008 - 2012	Acting Instructor, University of Washington, Seattle, WA
2010 - 2011	Associate in Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA
2011 -	Assistant Member, Fred Hutchinson Cancer Research Center, Seattle, WA
2012 -	Assistant Professor, University of Washington, Seattle, WA

Honors

1992	Walter and Elisa Sharp Prize for Surgery and Clinical Surgery
1992	Ku-ring-gai District Medical Association Prize for Surgery
2001	Multiple Myeloma Research Foundation Research Fellow Award
2001	The Mater Tzu-Chi Scholarship
2003	The Sister Regis Mary Dunne Medal for Science (Mater Medical Research Institute)
2016	Fialkow Award, The University of Washington School of Medicine

Professional Memberships
American Society of Hematology
American Society of Gene and Cell Therapy (ASGCT)

Committee Memberships
National:
1. ASGCT New Investigator Committee
2. ASGCT Immune Responses to Gene and Cell Therapy Committee
3. Clinical and Translational Cancer Research Panel, Cancer Prevention and Research Institute of Texas (CPRIT)

Institutional:
1. FHCRC Therapeutic Products Program Steering Committee - Chair
2. SCCA Institutional Biosafety Committee
3. FHCRC BMT Safe Medical Practice Committee
4. SCCA Immunotherapy Clinic Operations Oversight Committee
5. FHCRC Immune Monitoring Shared Resource Advisory Committee
6. FHCRC Flow Cytometry Shared Resource Advisory Committee
7. FHCRC Radiation Safety Committee
8. FHCRC Immunotherapy Working Group

Data Safety Monitoring Boards (DSMB):
1. “Dose-Intensive Chemotherapy in Combination with Chemoprotected Autologous Stem Cells for Patients with Malignant Gliomas”
2. “Engineered Neuroblastoma Cellular Immunotherapy (ENCIT)-01: A Phase 1 Feasibility and Safety Study of Cellular Immunotherapy for Recurrent/Refractory Neuroblastoma using Autologous T cells Lentivirally Transduced to Express CD171-specific Chimeric Antigen Receptors”

C. Contribution to Science

1. Therapeutic T cell priming

I developed a unique blood DC (BDC) isolation platform using immunoselection with the CMRF-56 antibody. The clinical CMRF-56+ immunoselection platform enabled isolation of BDC from MM patients that could be used to prime CD4+ and CD8+ T cell responses to tumor antigens. I was aware of the difficulty in controlling the signals provided in vivo by APC to T cells; therefore, I turned my attention to developing approaches that employed in vitro priming of T-cells using artificial antigen presenting cells (AAPC) as a strategy to generate optimally effective T cells for adoptive immunotherapy.

- **Turtle CJ**, Hart DN. Dendritic cells in tumor immunology and immunotherapy. *Curr Drug Targets*. 2004; 5(1):17-39.
- *Radford KJ, ***Turtle CJ**, Kassianos AJ et al. Immunoselection of functional CMRF-56+ blood dendritic cells from multiple myeloma patients for immunotherapy. J Immunother. 2005; 28(4):322-331.
- *Radford KJ, ***Turtle CJ**, Kassianos AJ, Hart DN. CD11c+ blood dendritic cells induce antigen-specific cytotoxic T lymphocytes with similar efficiency compared to monocyte-derived dendritic cells despite higher levels of MHC class I expression. J Immunother. 2006; 29(6):596-605.
- **Turtle CJ**, Riddell SR. Artificial antigen-presenting cells for use in adoptive immunotherapy. *Cancer J*. 2010; 16(4):374-381.

***equal first author

2. Regulation of homeostasis and TCR signaling in MAIT cells

MAIT cells are abundant, innate-like CD8+ T cells that express semi-invariant TCRs that enable their activation by microbe-derived ligands presented by the nonclassic MHC-like molecule MR1. On encounter with gastrointestinal commensal microbiota during bacterial colonization in neonates, MAIT cells briskly proliferate and accumulate in the first few months of life. However, in adults MAIT cells are quiescent, depite the presence of the GI microbiota. We were able to reconcile this apparent paradox, by uncovering a novel acquired mechanism of TCR signaling that is present in MAIT cells in adult blood, but not in umbilical cord blood (UCB).

- **Turtle CJ**, Delrow J, et al. Innate signals overcome acquired TCR signaling pathway regulation and govern the fate of human CD161(hi) CD8alpha(+) semi-invariant T cells. *Blood*. 2011; 118(10):2752-2762.
- Bhattacharyya A, Fredricks D, Srinivasan S, Morgan MT, Boeckh M, Pergam SA, Budiarto TM, Riddell SR, **Turtle CJ**. Factors Influencing Reconstitution of Mucosal-Associated Invariant T Cells Following Allogeneic Hematopoietic Stem Cell Transplantation. *Blood*. Abstract. ASH Annual Meeting. 2014; 124(21):3918.
- **Turtle CJ**, Swanson HM, Fujii N, Estey EH, Riddell SR. A distinct subset of self-renewing human memory CD8+ T cells survives cytotoxic chemotherapy. *Immunity*. 2009; 31(5):834-844.

3. Engineering of T cell subsets for adoptive immunotherapy

The extraordinary sensitivity and specificity of T cells for their cognate antigen make them a highly attractive cancer therapeutic. Technologies that enable genetic modification of T cells have been refined and are being used to redirect the specificity of T cells to tumor antigens. An important issue is how the diverse phenotypic and functional heterogeneity in T cells that could potentially be genetically modified can be capitalized upon to enhance the efficacy, safety and reproducibility of cancer immunotherapy. We found that the potency of CD19 CAR-T cells is maximized by manufacturing them from distinct T cell subsets and formulating them in a defined T cell subset composition.

Two CAR-T cell engineering approaches were established:

1) Treatment of patients who had previously received allogeneic HCT. To enable safe delivery of CD19 CAR-T cell therapy to allogeneic HCT recipients without a high risk of causing acute graft versus host disease (GVHD), we developed a clinical platform to manufacture CAR-T cells that had limited potential for alloreactivity by engineering virus-specific T cells isolated from the HCT donor to express the CD19 CAR.

2) Treatment of patients who had never undergone allogeneic HCT. For non-transplant recipients we developed a clinical platform to engineer CD4+ and CD8+ central memory-derived CAR-T cells from the patient. Both of these platforms were tested in clinical trials.

- **Turtle CJ**, Riddell SR. Genetically retargeting CD8+ lymphocyte subsets for cancer immunotherapy. *Curr Opin Immunol*. 2011; 23(2):299-305.
- Bleakley M*, **Turtle CJ***, Riddell SR. Augmentation of anti-tumor immunity by adoptive T cell transfer after allogeneic hematopoietic stem cell transplantation. *Expert Rev Hematol*. 2012; 5(4):409-425.
- **Turtle CJ**. Chimeric antigen receptor modified T cell therapy for B cell malignancies. *Int J Hematol.* 2014; 99(2):132-140.
- Riddell SR, Sommermeyer D, Berger C, Liu LS, Balakrishnan A, Salter A, Hudecek M, Maloney DG, **Turtle CJ**. Adoptive therapy with chimeric antigen receptor-modified T cells of defined subset composition. *Cancer J.* 2014; 20(2):141-4.

4. Clinical trials of CD19 CAR-T cell therapy

I am Principal Investigator (PI) and IND sponsor of the first clinical trial (NCT01865617) in which HCT recipients with $CD19^+$ B cell malignancies received allogeneic donor bi-specific CAR-T cells (specific for CD19

and a viral peptide) manufactured from a defined composition of CD8+ central memory T cells. I am co-PI of a second trial in which patients receive autologous CD8+ and CD4+ T cells engineered to express a CD19 CAR, and a third trial in which this therapy is combined with an anti-PDL1 antibody. We have now treated over 110 patients with B cell malignancies.

- Gardner, R., Wu, D., Cherian, S., Fang, M., Hanafi, L., Finney, O., Smithers, H., Jensen, M.C., Riddell, S.R., Maloney, D.G., and **Turtle, C.J.** Acquisition of a CD19 negative myeloid phenotype allows immune escape of *MLL*-rearranged B-ALL from CD19 CAR-T cell therapy. 2016. *Blood*. 127(20):2406-10.
- **Turtle, C.J.**, Hanafi, L.A., Berger, C., Gooley, T.A., Cherian, S., Hudecek, M., Sommermeyer, D., Melville, K., Pender, B., Budiarto, T.M., Robinson, E., Steevens, N.N., Chaney, C., Soma, L., Chen, X., Yeung, C., Wood, B., Li, D., Cao, J., Heimfeld, S., Jensen, M.C., Riddell, S.R., Maloney, D.G. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. 2016. 126(6):2123-38.

I have 38 peer-reviewed publications.

D. Research Support

Ongoing Research Support

R01 (1 R01 HL132350-01A1) Project grant 4/1/2016 – 3/31/2021
NIH/NHLBI
The colonic microbiota and immunity after allogeneic hematopoietic stem cell transplantation.
Role: PI
$1,865,724

Bezos Foundation 7/1/2015 - 6/30/2017
Bezos Family Immunotherapy Initiative
Dissecting the heterogeneity of adoptively transferred T cells by single cell RNA sequencing.
Role: PI
$150,000

Clinical trial (FHCRC 2639) research funding 2014 – 2016
Juno Therapeutics
Defined composition $CD4^+$ and $CD8^+$ CD19-specific CAR-T cells for B cell malignancies.
PI: Turtle, Maloney, Riddell
$2,780,500

Clinical trial (FHCRC 9457) research funding
Juno Therapeutics and Medimmune
Combination therapy of MEDI4736 (anti-PDL1 mAb) and CD19-specific CAR-T cells.
PI: Turtle
Budget: In negotiation. Approximately $10 million.

Damon Runyon Cancer Research Foundation 7/1/13-6/30/16
Damon Runyon Clinical Investigator Award
The impact of the colonic microbiota on $CD161^{hi}$ cells and clinical outcomes after allogeneic hematopoietic stem cell transplantation.
Role: PI
$450,000

Completed Research Support

K99 1K99CA154608-01A1 8/2011 - 5/2013
NIH
Pathway to Independence Award
Quiescent Tc17 programmed CD8 T cells and their role in graft versus host disease
Role: PI

R00 – 4R00CA154608-03 6/2013 - 5/2016
NIH
Pathway to Independence Award

Quiescent Tc17 programmed CD8 T cells and their role in graft versus host disease.
Role: PI

American Recovery and Reinvestment Act (RC1 AI086683-02) 9/2009 – 9/2011
NIH
Analysis of a Novel Subset of Human $CD8^+$ Memory Cells with Stem Cell Qualities
PI: Riddell; AI: Turtle
$1,000,000

Pending Research Support
None.

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: **Eliezer Van Allen, MD**

eRA COMMONS USER NAME (credential, e.g., agency login): EMVANALLEN

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Stanford University, Stanford, CA	B.S.	06/2003	Symbolic Systems
UCLA School of Medicine, Los Angeles, CA	M.D.	06/2007	Medicine Internal
UCSF, San Francisco, CA	Residency	06/2010	Medicine Medical
Dana-Farber Cancer Institute, Boston, MA	Fellowship	07/2010	Oncology

A. Personal Statement

I am currently an Assistant Professor of Medicine at Harvard Medical School and a medical oncologist at Dana-Farber/Partners Cancer Care. My research focuses on computational cancer genomics, the application of new technologies such as massively parallel sequencing to personalized cancer medicine, and resistance to existing and emerging therapeutics across cancer types, with a specific clinical focus on prostate cancer. As both a computational biologist and medical oncologist, I have specific expertise in clinical computational oncology and the development of algorithms to analyze and interpret genomic data for clinically focused questions. These include algorithms to identify mechanisms of selective response to prostate cancer hormonal therapies (Robinson, Van Allen, et al *Cell* 2015), targeted therapies (Van Allen, et al Cancer Discovery 2016), chemotherapies (Van Allen, et al *Cancer Discovery* 2014), and immunotherapies (Van Allen, et al, *Science* 2015). Furthermore, I have created an analytical platform for the clinically oriented analysis and interpretation of massively parallel sequencing data from prospectively acquired patient tumors (Van Allen, et al *Nature Medicine* 2014). I am also implementing computational approaches to characterize tumor genetic alterations from clinical samples at the time of initial treatment and once there is evidence of treatment resistance across tumor types, with a focus on second generation androgen deprivation therapies in prostate cancer. Overall, this research will make important contributions to the field of precision cancer medicine and resistance to cancer therapeutics via expertise and study in translational and clinical bioinformatics.

B. Positions and Honors

Positions and Employment

2007 – 2010 Internship and Residency in Internal Medicine, UCSF, San Francisco, CA
2008 – 2010 Laboratory of Dr. Elad Ziv, UCSF, San Francisco, CA. Thesis: "*SMAD2* and biologically associated genes in the Latina breast cancer population: a case-control genome study"
2010 – 2013 Fellowship in Medical Oncology, Dana Farber/Partners Cancer Care, Boston, MA

2011 – 2014 Laboratory of Dr. Levi Garraway, Dana-Farber Cancer Institute, Boston, MA
2013 – 2015 Instructor in Medicine, Harvard Medical School
2016 – Assistant Professor of Medicine, Harvard Medical School
2016 – Associate Member, Broad Institute of MIT and Harvard

Other Experience and Professional Memberships

2008 – 2010 Member, PRIME (Program in Residency Investigation Methods and Epidemiology)
2010 – Member, Massachusetts Medical Society
2010 – Member, American Society of Clinical Oncology
2011 – Member, American Association for Cancer Research
2011 – 2012 Clinical Investigator Seminar at Dana-Farber Cancer Institute
2012 CEC Molecular and Translational Oncology Workshop
2012 – Clinical Sequencing Exploratory Research Working Groups
2013 AACR Molecular Biology in Clinical Oncology Workshop

Honors

2003 Phi Beta Kappa, Stanford University
2006 Alpha Omega Alpha Honor Medical Society, UCLA
2007 Award of Excellence of the Department of Medicine Clinical Faculty Association, UCLA
2009 Graduation Clinical Teaching Award, UCSF
2010 Reza Gandjei Humanism in Medicine Award, UCSF
2012 New England Journal of Medicine Gold Scholar
2012 Conquer Cancer Foundation Merit Award
2012 NIH Loan Repayment Program (NHGRI)
2013 Conquer Cancer Foundation Merit Award
2013 AACR-Millennium Prostate Cancer Fellowship (Awarded)
2013 ASCO Young Investigator
2013 Prostate Cancer Foundation Young Investigator
2015 Clinical Investigator Award (Damon Runyon Foundation
2015 Medical Oncology Discovery Award (Dana-Farber Cancer Institute)
2016 Phillip Sharp Collaboration Award (Stand Up 2 Cancer)

C. Contribution to Science

I am a major contributing author on all papers cited below. Source of citation information when available through 2014: Google Scholar.
Link to all of my publications:
http://www.ncbi.nlm.nih.gov/sites/myncbi/eliezer.van_allen.1/bibliography/46727732/public/?sort=date&direction=ascending

1. Establishing clinical computational oncology. When I began my postdoctoral fellowship, large scale cancer genomic profiling was predominantly being performed in retrospective research-oriented settings. The ability to translate these complex and large data sets for clinical use at the individual patient level was typically not considered feasible, and there were very few medical oncologists directly performing bioinformatics and computational genomic research. My goal was to blend my unique background in clinical oncology and computer science with my computational genomics research interests, so I created, developed and applied the first clinical cancer genomics algorithm (Van Allen, et al *Nature Medicine* 2014, PMCID: 4048335, 83 citations). Not only did this algorithm result in genomics-driven clinical trial enrollment for multiple patients in the pilot setting (who often received clinical benefit from these actions), the algorithm I developed has since been applied broadly to inform the clinical relevance of cancer genomics data among over 3,000 tumor exomes (Yuan, Van Allen et al, *Nature Biotech* 2014, PMCID: 4102885,47 citations) and is now being used as the primary cancer genomics interpretation method for multiple clinical trials (e.g., NHGRI-funded U01 effort in metastatic lung and colon adenocarcinoma). Broadly, this approach has empowered me to establish clinical computational oncology as an academic discipline, whereby bioinformatics methodology are being directed specifically for clinical use at the point of care and are publically available online. I have been fortunate to guide the formation of this field at the regional, national, and international level through leadership in multiple venues. I have since expanded these algorithm development efforts to include increasingly complex data types while focusing on high need clinical settings (e.g., metastatic prostate cancer, refractory pediatric oncology).

2. Discovering genomic mediators of clinical response to targeted therapies, chemotherapies, and immunotherapies. The ability to comprehensively profile clinically acquired patient samples before treatment and after resistance was greatly limited due to lack of adequate biopsies, since it was unclear whether such data would yield clinically relevant insights. In order to demonstrate the potential of this approach, I led scientific efforts to

genomically profile and computational interrogate pre-treatment and resistance tumor biopsies in multiple clinical contexts to determine mechanisms of response and resistance to targeted therapies. These include RAF (Van Allen, et al *Cancer Discovery* 2013, PMCID: 3947264, 195 citations) and RAF/MEK (Wagle, Van Allen et al, *Cancer Discovery* 2013, PMCID: 3947296, 130 citations) in BRAF-mutant metastatic melanoma or BRAF-mutant colorectal cancer, mTOR inhibitors in anaplastic thyroid cancer (Wagle, et al, *New England Journal Med* 2014, PMCID: 4564868, 48 citations), and EGFR inhibitors in head and neck squamous cell carcinoma. To effectively integrate this scientific approach with my clinical practice in prostate cancer I have focused these efforts towards the study of acquired resistance to second generation androgen deprivation therapies in prostate cancer, where I lead a multi-institutional effort through a Stand Up 2 Cancer Dream Team project.

While these efforts have greatly accelerated prospective biopsy acquisition and translational cancer genomics discovery in the targeted therapy arena, there has since been far less activity focused on applying these precision cancer medicine techniques to study response mediators to conventional chemotherapy has been incompletely characterized. To establish the foundation for these studies, I led a team to discovery the relationship between complete response to cisplatin-based neoadjuvant chemotherapy and mutations in *ERCC2*, a nucleotide excision repair gene (Van Allen et al *Cancer Discovery* 2014, PMCID: 4238969, 49 citations). Finally, as with conventional chemotherapies, the ability to identify genomic mechanisms of response to emerging immunotherapies may enable enhanced patient stratification for these agents. I led the largest study of genomic correlates of response to CTLA4 immune checkpoint blockade in metastatic melanoma, identifying how mutational load, neoantigen load, and immune microenvironmental features correlate with response (Van Allen, et al, *Science*. 2015, PMID: 26359337, 21 citations). Expansion of this effort across immunotherapies and tumor types, with an emphasis in exceptional responders to immunotherapies in prostate cancer, is ongoing.

3. Integrating clinical cancer genomics with *in vitro* modeling. In order to most effectively understand the molecular characterization of patient tumor samples, I felt that developing approaches to integrate these data with emerging preclinical models was critical to understanding the basis behind the findings described in each setting. Towards that end, I led efforts to dissect shRNA and/or kinome screening studies in multiple contexts, including RAF inhibitor resistance in BRAF-mutant melanoma (Whittaker et al, *Cancer Discovery* 2013, PMCID: 3606893, 80 citations), hormone independence in ER-positive breast cancer (Bhola et al *Cancer Research* 2015), and mTOR pathway vulnerabilities in osteosarcoma (Perry et al PNAS 2014, PMCID: 4280630, 11 citations). I have since expanded these efforts within my clinical area of excellence (genitourinary malignancies) to discover new mediators of resistance to androgen deprivation therapies (Robinson, Van Allen, et. al. *Cell* 2015, PMCID: 4484602, 84 citations; Hsieh, et al, *Cancer Res* 2015, PMCID: 4433564, 2 citations), as well as extending my laboratory's capabilities to understand cisplatin sensitivity through *in vitro* modeling in collaboration with the Center for DNA Damage and Repair. The ability to blend computational and clinical oncology with preclinical experimental studies is a critical focus of my laboratory, and I plan to leverage these skills for the project described in this proposal.

4. Examining complex system relationships between the inherited genome, somatic genome, and environment. To maximize the scope of precision cancer medicine, I determined that efforts focused on discovery of novel germline alterations that may impact the somatic cancer genome was critical to stratifying patients from diagnostic and therapeutic perspectives. Thus, I led efforts to discover the high frequency of patients with advanced prostate cancer who harbor pathogenic DNA repair germline alterations in genes like BRCA2 and ATM, among other genes (Robinson, Van Allen et. al. *Cell* 2015, PMCID: 4484602, 84 citations). Using an exceptional responder paradigm, we identified a patient who had a complete and durable response to an investigational PD-L1 inhibitor and discovered germline and somatic alterations in *JAK3* present in the patient's monocytes and tumor cells cooperating to induce PD-L1 (Van Allen, et al *Cancer Immunol Res*. 2015, PMCID: 4527885, 3 citations). These efforts have now expanded to multiple cancer types and algorithm development to investigate the relationship between somatic and germline genetics in cancer. Furthermore, I have expanded these efforts to determine how the environment and treatment exposures may impact the inherited genome, which has relevance for cancer survivorship and informs the intersection of that field with genomics. For example, my lab identified the absence of genetic effect of chemotherapy exposure in children of testicular cancer survivors (Kryukov, et al. *Clin Cancer Res* 2015, PMID: 26631610, NIHMS742541 [in process]), which to our knowledge is the first such effort exploring the intersection of the genome and exposome directly in patients.

D. Research Support

Current

Young Investigator Award (Van Allen) 07/01/13-06/30/16
Prostate Cancer Foundation
Dissecting Clinical Response and Resistance to Abiraterone Acetate
This proposal is divided into the following two specific aims: 1) To develop computational algorithms that evaluate existing and emerging hypotheses of clinical resistance to abiraterone acetate; 2) To determine the biological and

clinical significance of genomic resistance effectors by computational integration with in vitro and in vivo models.
Role: PI

Post-doctoral Fellowship (Van Allen) 07/01/13-06/30/16 American Cancer Society
Dissecting clinical resistance to PI3 kinase inhibitors
This proposal is divided into the following two specific aims: (1) To generate comprehensive genomic data from tumors treated with PI3K inhibitors and corresponding data in contextually relevant cell lines; (2) To test leading hypotheses of PI3K inhibitor resistance by creating and applying novel computational algorithms.
Role: PI

1K08CA188615-01 09/10/2014 – 08/31/2019
NIH/NCI
Resistance to Emerging Androgen Deprivation Therapies in Prostate Cancer
This proposal is divided into three specific aims: 1) To develop computational algorithms that characterize genomic resistance mechanisms to emerging androgen deprivation therapies. 2) To determine the biological and clinical significance of preclinical resistance mechanisms using integrative computational biology. 3) To establish inferential and heuristic models that may define subsequent therapeutic avenues based on distinct resistance mechanisms.
Role: PI

Clinical Investigator Award 07/01/2015 – 06/30/2018 Damon Runyon Foundation
Dissecting response to convention and emerging DNA damage and repair therapies
The main scientific goal of this project is to dissect genomic mechanisms underlying response to conventional cytotoxic chemotherapies across tumor types, functionally characterize known mutations in key DNA repair genes for clinical utility, and prospectively genotype patients to enroll on a DNA repair-oriented therapy.
Role: PI

Translational Science Award 07/01/2015 – 06/30/2017
AACR-KureIt
Response predictors to PD-1/PD-L1 inhibitors in renal cell carcinoma
The specific goals of this proposal are to develop computational algorithms that characterize genomic mechanisms of response to PD-1/PD-L1 inhibition in metastatic renal cell carcinoma through genomic and metabolomics approaches.
Role: PI

Prostate Cancer Foundation (Taplin) 12/24/14 – 12/23/16
2014 Movember-PCF Global Treatment Sciences (GTSN) Challenge Award for Metastatic Prostate Cancer
Eradicating Lethal Micrometastic prostate cancer through high intensity short course AR suppression
The primary objective of this proposal is to evaluate the frequency of achieving a pCR or MRD (defined as residual tumor in RP specimen measuring ≤ 5 mm) at RP following therapy with ARM 1 compared to ARM 2. Role: Junior Investigator

MO Internal Award 07/1/15 – 06/30/16
Clinical informatics implementation of guideline-driven genomics for precision cancer medicine
Specific Aims: Aim 1: To develop informatics algorithms that create guideline-driven cancer genomic reports. Aim 2: To conduct a randomized survey study to determine whether exposure to the evidence-based interactive genomic reports, as compared to static reports, improves physicians' genomic understanding and evidence-based decision making.
Role: PI

Movember Foundation-PCF Challenge Award 7/31/15 – 7/30/17
Prostate Cancer Foundation
Exploiting DNA Repair Vulnerabilities as a Precision Oncology Target in Metastatic Prostate Cancer
Specific Aims: Aim 1. Determine the frequency of heritable (germ-line) genomic aberrations encoding DNA damage/repair proteins in men with metastatic CRPC. Aim 2. Conduct a Phase 2 clinical trial to ascertain response rates to FDA-approved genotoxic therapeutics in patients with germ-line or somatic alterations in DNA repair pathways. Aim 3. Develop minimally invasive biomarkers capable of distinguishing patients for therapeutics targeting DNA repair pathways.
Role:Sub PI

BMS 8/13/15 – 5/12/16
RCC Nivo Next-Gen": Using next generation sequencing to explore oncogenomic and gene expression patterns in nivolumab treated patients with advanced renal cell carcinoma
Specific Aims: Aim 1: To correlate clinical effects of nivolumab therapy with A) tumor mutational load, B) predicted

and expressed neoantigens, and C) RNAseq based expression signatures, including inflammatory and antigen presentation pathway activation. Aim 2: To correlate clinical effects of nivolumab with checkpoint inducers through integrative exome and transcriptome analysis of somatic/germline, pre-treatment tumor (FFPE, DNA/RNA ideal) and any resistant tumors if pre/post treatment biopsies are available.
Role: PI

Completed

Young Investigator Award 7/1/13 – 12/31/14
ASCO
Dissecting clinical resistance to PI3K inhibitors in PIK3CA or PTEN-mutant cancers
This proposal is divided into two specific aims: (1) To generate comprehensive genomic data from tumors treated with PI3K inhibitors and corresponding data in contextually relevant cell lines. (2) To test leading hypotheses of PI3K inhibitor resistance by creating and applying novel computational algorithms.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contr butors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: **VanBrocklin, Henry F.**

eRA COMMONS USER NAME (credential, e.g., agency login): hfvanb

POSITION TITLE: Professor of Radiology and Biomedical Imaging, Director of Radiopharmaceutical Research

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Rensselaer Polytechnic Institute, Troy, NY	B.S.	06/1984	Chemistry
Rensselaer Polytechnic Institute, Troy, NY	M.S.	06/1986	Nuclear Chemistry
Washington University, St. Louis, MO	Ph.D.	09/1990	Radiopharmaceutical Chemistry

A. Personal Statement

Dr. VanBrocklin has over 30 years experience with the preparation and application of radiopharmaceuticals. He has developed several imaging agents targeting cell surface proteins (receptors, enzymes and transporters) including receptor-based imaging agents for hormone receptors, growth factor receptors, neuroreceptors and recently prostate specific membrane antigen. He has developed imaging agents for cardiac blood flow and metabolism. These imaging agents have included a broad range of molecular motifs from small molecules, antibodies, antibody fragments (Fabs, scFv, diabodies…), aptamers, to proteins and peptides. These molecules have been labeled with a variety of isotopes for PET and SPECT imaging. As part of the development of these imaging agents he has been engaged in the evaluation and validation of the tracer mechanism of localization and retention at the target site. He has prepared several in vitro and in vivo model systems and interpreted the data collected from these systems to determine the utility of the probes. He has successfully translated many of these tracers into humans. He has helped to write and secure several INDs for first-in-human tracer studies.

B. Positions and Honors

Positions and Employment

1990-1992	DOE Alexander Hollaender Distinguished Postdoctoral Fellow, University of Illinois
1992-2005	Staff Scientist, Group Leader, Radiopharmaceutical Chemistry, Department of Functional Imaging, LBNL
1992-2005	Assistant Adjunct Professor of Radiology, University of California San Francisco
2005-	Professor of Radiology and Biomedical Imaging, University of California San Francisco
2005-	Joint Faculty Scientist, Department of Functional Imaging, LBNL
2009-2012	Visiting Professor, Huazhong University of Science and Technology, Wuhan China

Other Experience and Professional Memberships

2003-2007	NIH Diagnostic Radiology Study Section Charter Member
2009-2013	NIH CMIP Study Section Charter Member
2011-present	Editor-in-Chief – "Molecular Imaging"
2012	NAS panel "Assuring a Future US-based Nuclear Chemistry Expertise"
2015-2017	President – Society of Radiopharmaceutical Sciences

Honors

DOE Alexander Hollaender Distinguished Postdoctoral Fellowship: 1990-92
Lawrence Berkeley National Laboratory Outstanding Performance Award: 1993, 1997, 1998, 2000
SNM President's Distinguished Service Award 2006, 2010

C. Contribution to Science

1. Throughout my career I have developed radiochemical methods and applied those methods for labeling radiotracers with a variety of isotopes, including ^{18}F, ^{11}C, $^{122, 123, 124, 125, 131}$I, ^{64}Cu, ^{68}Ga, ^{89}Zr, for applications in oncologic, cardiac and neurologic imaging. The referenced publications, among others in my full CV, demonstrate my creative chemistry contributions to new radiosynthetic methods for the preparation of new tracers. Many of the tracers were subsequently evaluated and applied to further imaging applications. I provided key insight into the synthetic chemistry, performed the radiochemistry personally, or directly mentored student or postdoctoral fellow who conducted the radiochemistry research.
   a. Hope TA, Aggarwal R, Simko JP, **VanBrocklin HF**, Ryan CJ. Somatostatin Imaging of Neuroendocrine-Differentiated Prostate Cancer. *Clin Nucl Med*. 40(6):540-1. 2015 doi: 10.1097/RLU.0000000000000776. PubMed PMID: 25783510
   b. Hope, TA; Pampaloni, MH; Nakakura, E; **VanBrocklin, HF**; Slater, J; Jivan, S; Aparici, CM; Judy Yee, J; Bergsland, E. Simultaneous 68Ga-DOTA-TOC PET/MRI with gadoxetate disodium in patients with neuroendocrine tumor. *Abdom Imaging,* Aug;40(6):1432-40. 2015 doi: 10.1007/s00261-015-0409-9. PubMed PMID: 25820755
   c. James, S; Ahmed, SK; Murphy, ST; Braden, MR; Belabassi, Y; **VanBrocklin, HF**; Thompson, CM; Gerdes, JM. A Novel Fluorine-18 β-Fluoroethoxy Organophosphate Positron Emission Tomography Imaging Tracer for Central Nervous System Acetylcholinesterase. *ACS Chem. Neurosci.*, 5:519-524, 2014. PMCID: PMC4102964
   d. Li L, Che L, Wang C, Blecha JE, Li X, **VanBrocklin HF**, Calvisi DF, Puchowicz M, Chen X, Seo Y. [11C]acetate PET Imaging is not Always Associated with Increased Lipogenesis in Hepatocellular Carcinoma in Mice. *Molecular Imaging and Biology*, in Press 13 Nov 2015. DOI 10.1007/s11307-015-0915-8

2. Our laboratory in collaboration with Dr. Cliff Berkman (WSU) is developing a new series of fluorine-18 labeled prostate cancer imaging agents targeting PSMA, a cell transmembrane protein that is upregulated in prostate cancer cells and is associated with high grade, androgen independent and metastatic tumors. The molecule has a phosphoramidate backbone within the peptidomimetic structure. It binds with pseudo-irreversibility to the PSMA with high affinity. High uptake and retention with >200 tumor to background ratio was exhibited in tumors overexpressing PSMA. Two of the molecules are being progressed to first-in-man studies. Cliff and I have been co-PIs on this effort since the late 2000's. We have worked together to

develop the tracer with suitable imaging characteristics. I have contributed intellectually to the radiochemistry and translation to human aspects of this project.

a. Lapi, SE; Wahnishe, H; Pham, D; Wu, LY; Nedrow-Byers, JR; Liu, T; Vejdani, K; **VanBrocklin, HF**; Berkman, CE; Jones, EF. Assessment of a [^{18}F]-labeled phosphoramidate peptidomimetic as a new PSMA targeted imaging agent for prostate cancer. *J. Nucl. Med.* 50:2042-2048, 2009. PMCID: PMC2751863
b. Ganguly, T; Dannoon, S; Geruntho, JG; Hopkins, MR; Murphy, S; Cahaya, H; Blecha, JE Jivan, S; Barinka C; Drake, CR; Jones, EF; **VanBrocklin, HF**; Berkman, CE. A high affinity [^{18}F]labeled phosphoramidate peptidomimetic PSMA-targeted inhibitor for PET imaging of prostate cancer. *Nucl. Med .Biol.*, 42:708-787, 2015. doi: 10.1016/j.nucmedbio.2015.06.003. PMCID: PMC4624265
c. Ley, CR; Beattie, NR; Dannoon, S; Regan, M; **VanBrocklin, H**; Berkman, CE. Synthesis and Evaluation of Constrained Phosphoramidate Inhibitors of Prostate-Specific Membrane Antigen. *Bio. Med. Chem. Lett.*, 25(12): 2536-39, 2015. PMID: 25956413
d. CE Berkman, **HF VanBrocklin** "Peptidomimetic inhibitors as PSMA imaging agents." Provisional application PCT/US2011/060088 filed November 12, 2010. Application filed WO/2012/064914 filed 11/10/2012.

3. Rotenone is a neutral lipophilic natural product that binds to complex I of the electron transport chain. While investigating radiolabeled rotenone as an imaging agent for the loss of complex I related to Parkinson's Disease, I discovered that the tracer had very rapid and high uptake in cardiac tissue. I investigated rotenone as a potential cardiac flow tracer. In collaboration with Robert Marshall, labeled rotenone was evaluated in an isolated perfused rabbit heart versus current clinical cardiac blood flow tracers. Labeled rotenone was found to have improved uptake versus flow characteristics. I chose the rotenone class of compounds for radiolabeling studies. I prepared the precursors and radiolabeled the rotenone analogs. I performed the initial rat studies and collaborated with Drs. Marshall and Glover to perform head-to-head studies in in vitro and ex vivo models to assess the flow characteristics of the fluorine-18 and iodine labeled rotenone analogs.
   a. Marshall, RC; Powers-Risius, P; Reutter, BW; Taylor, SE; **VanBrocklin, HF**; Huesman, RH; Budinger, TF. Kinetic Analysis of [^{125}I]Iodorotenone as a Deposited Myocardial Flow Tracer: Comparison to [^{99m}Tc]Sestamibi. *J. Nucl. Med.* **42**:272-281, 2001.
   b. **VanBrocklin, HF**; Enas, JD; Hanrahan, SM; O'Neil, JP. Mitochondrial Electron Transport Chain (ETC) Radioprobes. Preparation and Evaluation of 7'(E)-[^{125}I]Iodorotenone and 7'(E)-[^{125}I]Iodorotenol. *Nucl. Med. Biol.* 34:109-16, 2007. PMCID: PMC1852529.
   c. Broisat, A; Ruiz, M; Goodman, NC; Hanrahan, SM; Reutter, BW; Brennan,KM; Janabi,M; Schaefer, S; Watson, DD; Beller, GA; **VanBrocklin, HF**; Glover, DK. Myocardial Uptake of 7´-(Z)-[^{123}I]Iodorotenone During Vasodilator Stress in Dogs with Critical Coronary Stenoses. *Circ Cardiovasc Imaging* 4:685-692, 2011. PMCID: PMC3587960
   d. **HF VanBrocklin**, JP O'Neil "Rotenone analogs: Method of preparation and use" Int'l Patent Appl. PCT/US2007/069178 filed May 17, 2007. US Patent Application 12/273,509 filed November 18, 2008. Published May 28,2009 US-2009-0136424-A1. Patent Issued October 8, 2013 US-8,551,448.

4. Proteases are cell surface enzymes that are responsible for increased proteolytic activity in tumors, are targets for therapeutic intervention and may be biomarkers for therapeutic efficacy. With UCSF collaborator Charles Craik (Chem. Biology), antibody-based (e.g. IgG, Fab fragments, scFvs) imaging agents have been developed for upregulated matriptase and uPAR that are associated with multiple types of cancer, especially breast and prostate. Tracer development and specific uptake of the tracers in xenografts and disseminated preclinical models have been reported. Two important findings were discovered – i) imaging matriptase requires protease concentrations to be greater than the endogenous inhibitor HAI1 and ii) binding of the U33 antibody to uPA initiates a unique mechanism of binding and internalization of the tracer into uPA receptor rich cells. Also a uPAR antibody labeled with ^{177}Lu demonstrated radiotherapeutic efficacy in prostate cancer tumor xenograft models. These agents monitor protease changes throughout the life cycle of the tumor and following therapeutic intervention. Intellectual input was provided by me for the design of the labeled agents and preparation of the evaluation protocols. Along with Charles Craik, I mentored the postdoctoral fellow, Aaron LeBeau, who conducted the bulk of the studies.
   a. LeBeau, AM; Murphy, ST; Hann, BC; Warren, RS; Delos Santos, R; Kurhanewicz, J; **VanBrocklin, HF**; Craik, CS. Imaging Cancer-Associated Proteolytic Activity with Human Antibodies. *PNAS*, 110:93-98, 2013. PMCID: PMC3538269

b. LeBeau, AM; Duriseti, S; Murphy, ST; Pepin, F; Gray, JW; **VanBrocklin,' HF**; Craik, CS. Targeting uPAR with antagonistic human recombinent antibodies in aggressive breast cancer. *Cancer Research*, 73:2070-208, 2013. PMCID: PMC3618559
c. LeBeau, AM; King, ML Murphy, LL; Duriseti, S; Murphy, ST; Craik, CS and **VanBrocklin, HF**. Imaging The Urokinase Plasminongen Activator Receptor In Drug-Resistant Breast Cancer. *Theranostics,* 4(3): 280-289, 2014. PMCID: PMC3915090
d. LeBeau, AM; Sevillano, N; Markham, K; Winter, MB; Murphy, ST; Hostetter, DR West, J; Lowman, H; Craik, CS; **VanBrocklin, HF**. Imaging Active Urokinase Plasminogen Activator In Castration-Resistant Prostate Cancer With An Internalizing Antagonistic Human Antibody. *Cancer Res.*, 75(7):1225-1235, 2015. PMCID: PMC4383704

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/henry.vanbrocklin.1/bibliography/47187611/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

1U01FD005517-01 (Elizanov/ VanBrocklin) 09/15/15 - 08/31/18
FDA
Mitigation of quality and compliance risks in radiopharmaceutical production by implementation of an automated release testing technology
The goal of this project is to develop and validate automated tests for radiopharmaceutical quality control.
Role: MPI

W81XWH-14-1-0603 (VanBrocklin) 09/22/14 – 09/21/16
DoD
Development of a PET prostate specific membrane antigen imaging agent: Preclinical translation for future clinical application.
The goal of this project is to collect the necessary data to bring two PSMA radiotracers through the IND process in anticipation of future first in human studies.
Role: PI

U01 NS083454 (MPI Thompson, Gerdes U Montana; VanBrocklin UCSF) 07/01/15 – 06/30/20
NIH CounterACT
In Vivo Dispositions of Positron Radiolabeled OrganoPhosphonate Chemical Agents
The goal of this project is to develop radiolabeled analogs of known organophosphate chemical agents and evaluate their distribution in rodents.
Role: MPI

R21AI114283 (MPI Hamilton-Nilsen, M.,VanBrocklin, H.) 07/15/14 – 06/30/17
NIH
In Vivo reporters of gene expression
The goal of this proposal is to develop radiotracers that bind to aptamers that are genetically expressed in cells.
Role: MPI

R44 CA192451-01 (Langton-Webster CTT; VanBrocklin UCSF) 03/15/15 – 03/14/17
NIH/ CTT
Initial Clinical Evaluation of Prostate Cancer PET Diagnostic Agent
The goal of this research is to perform the first in man studies with a new fluorine-18 labeled PSMA imaging agent.
Role: Subcontract PI

HHSN2612013000663C (Yaghoubi, S.) UCSF Sub (VanBrocklin, H.) 09/20/13 – 06/30/16
NIH/ Cellsight Technologies
Monitoring Anticancer Immune Response Non-invasively with [^{18}F]F-AraG PET Imaging
The goal of this project is to conduct the first-in-human studies with F-AraG.
Role: Subcontract PI

R01 CA166766 (Wilson) 04/01/12 – 03/31/17
NIH/NCI
Ascorbate-based biomarkers for predicting radiation response in prostate cancer
The principal motivation of the proposed project is the development of non-invasive methods to predict, and characterize the response of prostate cancer to radiation therapy using new redox-sensitive molecular imaging techniques.
Role: Co-I

R01 CA154561 (Seo) 04/01/11 – 03/31/17
NIH/NCI
Pretherapy ^{124}I-MIBG Dosimetry for Planning ^{131}I-MIBG Neuroblastoma Therapy
The goal of this project is to develop a pretherapy dosimetry tool for ^{131}I-MIBG radionuclide treatment of neuroblastoma using ^{124}I-MIBG PET/CT imaging.
Role: Co-Investigator

R21 CA185689 (PI: Craik) 01/01/25-12/31/16
NIH/NCI
Non-invasive Differentiation of Benign Lesions from Aggressive Pancreatic Cancer
A proof-of-principle study to target single or multiple cathepsins with a non-invasive protease activated imaging technology is proposed to test their accumulation in a mouse model of pancreatic cancer. Data from this study will prove critical for the translation of this technology into the clinic by defining key proteases associated with disease progression.

Completed Research Support

W81XWH-12-1-0440 (Craik) 09/01/12 – 08/31/15
DoD
Novel Imaging Biomarkers for Aggressive Prostate Cancer
The goal of this project is to develop imaging agents that target TMPRSS2, a protease over-expressed in prostate cancer and related to tumor aggressiveness.
Role: Co-I

R21 CA171766 (MPI VanBrocklin/Kurhanewicz) 08/01/12 – 07/31/15
NIH
PET and MR-Compatible Bioreactor for Cross-Platform Biomarker Development
The goal of this research is to optimize a 5mm MR-compatible PET 3D cell/tissue culture bioreactor and test it by using a combination of hyperpolarized (HP) 13C MR and PET probes.
Role: PI

R01 CA140617 (Berkman, C.) UCSF Sub (VanBrocklin, H.) 04/05/10 – 01/31/15
National Cancer Institute
Probe Optimization for Prostate Cancer Detection
The goal of this proposal is to devlop new small molecule PSMA based imaging agents for prostate cancer.
Role: UCSF Co-I

DOE DE-SC002061 (Sutcliffe, J UC DAVIS) Subcontract PI 09/01/09 – 08/31/14
CARE - California Alliance for Radiotracer Education
This purpose of this proposal was to train new radiochemists.

R21 NS072079 (MPI:Thompson, C.; Gerdes, J.; VanBrocklin, H.) 10/01/10 – 08/31/13
NIH CounterACT
In vivo pharmacokinetic and pharmacodynamic dispositions of positron radiolabeled organophosphate chemical threats
The goal of this proposal is to label organophosphate compounds with a radioactive isotope and to follow the distribution of the compounds in small animals using PET imaging.

Role: PI

SBIR (Kelly, iTi Health) 02/01/12 – 06/30/13
NIH
Developing a plectin-1 targeted imaging agent for the detection of Pancreatic Cancer
The goal of the project is to evaluate a gallium-68 labeled probe for pancreatic cancer imaging.
Role: Subcontract PI

OMB No. 0925-0001/0002 (Rev. 08/12 Approved Through 8/31/2015)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES**.

NAME: Wu, Lani F

eRA COMMONS USER NAME (credential, e.g., agency login): LANIWU

POSITION TITLE: Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
National Taiwan University	B.A.	06/85	Mathematics
University of California, San Diego	M.A.	06/87	Mathematics
University of California, San Diego	Ph.D.	06/90	Mathematics

A. Personal Statement

Over the past decade, my laboratory has pioneered multiple approaches for quantifying and interpreting cancer heterogeneity in normal and diseased tissues. Traditionally, this phenotypic heterogeneity, whether arising from microenvironment, epigenetic or genetic sources, has been viewed as an impediment to understanding and treating cancer. I have worked to develop the ability to identify biological and clinical information hidden within patterns of heterogeneity. My research program is focused on: Identifying principles underlying how cells and tissue make robust spatial patterns; understanding heterogeneity arising from drug resistance; and accelerating the path of early cancer drug discovery through phenotypic profiling.

My lab has a strong mentoring component at the undergraduate, graduate, and post-doctoral levels. The current composition of my lab is 4 graduate students (3 in iPQB), and 6 post-docs. I have graduated 5 graduate students with doctoral degrees. Two of my graduate students have been recognized with national awards (National Science Foundation Graduate Research Fellowship). The research projects of my more junior graduate students are well integrated with the projects of my post-doctoral fellows and staff scientists to allow the more experienced lab members to share their knowledge. Training grants have provided crucial support for my current students, allowing them to excel in their scientific endeavors, and I look forward to continuing to mentor and train my graduate students to become independent scientists capable of identifying good problems and tackling them with the best approaches.

Beyond my own lab, I take an active role in helping to train the next generation of young scientists. I am very active in the UCSF graduate programs, teaching an intensive bootcamp to incoming graduate students and a minicourse on systems biology, guest lecturing in numerous other graduate classes and retreats, and meeting after hours to talk about science or the process of doing science. I am an active participant in both national and international programs aimed at teaching/mentoring the next generation of young scientists, from high school to junior faculty levels. These activities include founding and directing a course on quantitative image analysis for the past five years at MBL and a summer school for mathematical biology graduate students in MSRI at UC Berkeley, as well as teaching at numerous international workshops.

a) Ramirez M, Rajaram S, Steininger RJ III, Osipchuk D, Roth MA, Morinishi LS, Evans L, Ji W, Hsu C-H, Thurley K, Wie S, Zhou A, Koduru PR, Posner BA, Wu LF*, Altschuler SJ*, Diverse drug-resistance mechanisms can emerge from drug-tolerant cancer persister cells, Nature Communications, 2016 to appear.
b) Kang J, Hsu CH, Wu Q, Liu S, Coster AD, Posner BA, Altschuler SJ*, Wu LF*.; Improving drug discovery with high-content phenotypic screens by systematic selection of reporter cell lines. Nature Biotechnology. 2015. PMCID in process.
c) Ku C-J, Wang Y, Weiner OD, Altschuler SJ*, Wu LF*, Evolving cross-talk in neutrophil polarity network. Cell 2012 May 25; 149(5):1073-1083. PMCID: PMC3614011.
d) Thorne CA, Wichaidit C, Coster AD, Posner BA, Wu LF*, Altschuler SJ*. GSK-3 modulates cellular responses to a broad spectrum of kinase inhibitors. Nat Chem Biol. 2014 Nov 17. PMCID: PMC4270937.

(* = co-senior author)

B. Positions and Honors

Positions and Employment

1990-1991	Instructor, Mathematics Department, **Princeton University**, Princeton, NJ.
1991-1992	Research Associate, **Australian National University**, Centre for Mathematics and its Applications, Canberra, Australia.
1992-1994	Instructor, Mathematics Department, **Princeton University**, Princeton, New Jersey.
1994-2000	Senior Researcher, **Microsoft Corporation**, Redmond, WA.
2000-2001	Senior Researcher, Informatics, **Rosetta Inpharmatics**, Kirkland, WA.
2001-2005	Fellow, Bauer Center for Genomics Research, **Harvard University**, Cambridge, MA.
2005-2009	Assistant Professor, **U.T. Southwestern Medical Center**, Dallas, TX.
2009-2014	Associate Professor, **U.T. Southwestern Medical Center**, Dallas, TX.
2014-	Professor, **University of California at San Francisco**, San Francisco, CA.

Other Experience and Professional Memberships

Scientific Advisory Panels

2011-2015	Scientific Advisory Board, European Systems Microscopy Network of Excellence
2012	Editorial board, Developmental Cell

Conferences/Classes

2008	Organizer, Institute for Mathematics Annual Program Year Workshop, Organization of Biological Networks, Minneapolis, MN
2008	Poster review committee for Workshop on Bio-Image Informatics: Biological Imaging, Computer Vision, and Data Mining, Santa Barbara, CA
2008-2014	UTSW graduate student admission committee
2010	Organizing Committee, Bioimage Informatics, Carnegie Mellon University, Pittsburgh, PA
2010	Program committee, ISMB, Bioimaging session, Boston, MA
2011-2016	Co-director & instructor, MBL CIAN course (10 day class), Woods Hole, MA
2011	Organizer, American Society of Cell Biology (ASCB) Minisymposium on Using Large Data Sets as Tools to Understand Cell Biology, Denver, CO
2015-2016	Co-director & instructor, Tetrad graduate student programming bootcamp (1 week), UCSF, CA
2015	Co-director & instructor, Mathematical Topics in Systems Biology (2 week class), Mathematical Sciences Research Center, UC Berkeley, CA
2015	Session chair and keynote speaker, The Society for Biomolecular Imaging and Informatics, Boston, MA
2016	Co-director & instructor, Systems biology mini-course (3 weeks), UCSF, CA

Grant Reviews

2009	NIH, Challenge Grants (RFA-OD-09-003) Stage I Review Committee
2009	NIH, Technology Centers for Networks and Pathways (TCNP)
2011	NIH, MABS Study Session Ad Hoc
2015	NIH, NIH Director's New Innovator Award Program Review Committee

Other

1985	Research Assistant, Mathematics, Academia Sinica, Taipei, Taiwan
1997	Visiting Researcher, Mathematical Sciences Research Institute, Berkeley, CA
1998-	Awarded 7 U.S. Patents
2003	Yeast Genetics Course, Cold Spring Harbor, NY
2003	Microscopy Course, Woods Hole, MA

Honors

2005	UTSW endowed scholar: Cecil H. and Ida Green Scholar in Biomedical Computational Science

C. Contribution to Science

1. Spatial patterning. A major research focus in my lab has been to understand how biological networks give rise to robust spatial patterns. We made significant contributions by decomposing complex signaling systems into distinct "modules", which allowed us to study how they operate separately and together. In budding yeast, we dissected how cytoskeleton-dependent and -independent feedback mechanisms work separately to establish CDC42 polarization during the G1/S transition. Our work: revealed that the precision of spatial patterning is tuned by off-rate, not the strength of positive feedback (a); and identified a fundamentally new polarity mechanism by which cells can break symmetry (or "polarize") through the use of positive feedback alone, which challenges a paradigm established 60 years ago by Alan Turing (b). In chemotaxing primary human neutrophils, we developed approaches to understand how three, spatially distinct signaling modules work together to maintain directional persistence while flexibly sensing minute environmental changes. Our work revealed that: the paths of signaling transduction that regulate the activity or polarity of these modules are reversed (c); and the core motif that is required to maintain the consistency of the back polarity regardless of changes in the front activity (d).

a) Marco E, Wedlich-Soldner R, Li R, Altschuler SJ*, Wu LF*. Endocytosis optimizes the dynamic localization of membrane proteins that regulate cortical polarity. Cell 2007 Apr 20;129(2):411-22. PMCID: PMC2000346.
b) Altschuler SJ*, Angenent SB, Wang Y, Wu LF*. On the spontaneous emergence of polarity. Nature 2008 Aug 14, 454:886-890. PMCID: PMC2562338.
c) Ku C-J, Wang Y, Weiner OD, Altschuler SJ*, Wu LF*, Evolving cross-talk in neutrophil polarity network. Cell 2012 May 25; 149(5):1073-1083. PMCID: PMC3614011.
d) Wang Y, Ku C-J, Zhang ER, Artyukhin AB, Weiner OD, Wu LF*, Altschuler SJ*, Identifying network motifs that buffer front-to-back signaling in polarized neutrophils, Cell Reports 2013 May 6. pii: S0955-0674(13)00067-7. doi: 10.1016/j.ceb.2013.04.004. PMCID: PMC3674638.

2. Cellular heterogeneity. Cell-to-cell differences have been widely observed in essentially every biological system. However, it is not clear which components of this heterogeneity contain information and which simply reflect noise. These observations raise profound questions about how living systems can give rise to reliable behaviors as well as present impediments to treating disease. We have developed analytical methodologies to quantify, compare, and model patterns of cellular signaling heterogeneity observed in microscopy (a-b). This has allowed us to demonstrate that patterns of heterogeneity can serve as a robust readout of cellular populations, and that the complexity of heterogeneity can have a practical, finite limit (a). Importantly, we have shown that functional heterogeneity can be identified to predict mechanism of drug action (a), paths of cellular differentiation (c), and the sensitivity of cellular populations to drugs (d).

a) Slack MD, Martinez ED, Wu LF, Altschuler SJ*. Characterizing heterogeneous cellular responses to perturbations. Proceedings of the National Academy of Sciences USA, 2008 December 9; vol. 105, no. 49, 19305–19310. PMCID: PMC2614757.
b) Loo LH, Lin HJ, Steininger RJ, Wang YQ, Wu LF*, Altschuler SJ*, On an Approach for Extensibly Profiling the Molecular States of Cellular Subpopulations. Nature Methods 2009, vol. 6, 759-765. PMCID: PMC2779244.
c) Loo LH, Lin HJ, Singh, DK, Lyons, KM, Altschuler SJ*, Wu LF*, On Heterogeneity in the physiological states and pharmacological responses of differentiating 3T3-L1 preadipocytes. Journal of Cell Biology 2009 Nov 2;187(3):375-84. PMCID: PMC2779244.
d) Singh DK, Ku C-J, Wichaidit C, Steininger RJ, Wu LF*, Altschuler SJ*, Patterns of basal signaling heterogeneity can distinguish cellular populations with different drug sensitivities. Molecular Systems Biology 2010 May 11;6:369. PMCID: PMC2890326.

3. Cytological profiling . Recent advances in high-content fluorescence microscopy have accelerated progress in many areas of cell biology. Approaches from computer vision are essential for analyzing image data sets that are too large to examine by human eye. Over the last decade, our lab pioneered machine-learning approaches for extracting informative signatures of cellular perturbations and identifying stereotyped subpopulations. Our work helped to start the field of high throughput cytological profiling and set standards in both academics and industry (a-b). We released to the research community a software tool, called "PhenoRipper," that vastly simplified and accelerated the process for cell biological laboratories to make use of automated phenotypic profiling (c), as well as tools, "Simucell," to facilitate development and comparison of new tools (d).

a) Perlman ZE, Slack MD, Feng Y, Mitchison TJ, Wu LF*, Altschuler SJ*. Multi-dimensional drug profiling by automated microscopy. Science 2004 Nov 12;306(5699):1194-8. PMID: 15539606.
b) Loo LH, Wu LF, Altschuler SJ. Image-based multivariate profiling of drug responses from single cells. Nature Methods 2007 May;4(5):445-53. PMID: 17401369.
c) Rajaram S, Pavie B, Wu LF*, Altschuler SJ*, PhenoRipper: an approach for rapid analysis and exploration of high content microscopy images. Nature Methods 2012 July Vol. 9, No. 7: 635-637. PMCID: PMC3842428.
d) Rajaram S, Pavie B, Altschuler SJ*, Wu LF*, Simulcell: a flexible framework for creating synthetic microscopy images. Nature Methods 2012 July Vol. 9, No. 7: 634-635. PMCID: PMC3842437.

4. Theoretical mathematics. My work in mathematics focused on developing approaches to use nonlinear partial differential equations to solve problems in differential geometry and topology. In particular, I showed that the Ricci flow, recently used to solve the 100 year-old Poincare conjecture, converged to soliton solutions (ones that move by simple symmetries) on singular surfaces called "orbifolds" (a). Just as there are canonical metrics for well-known surfaces, such as the round metric on spheres or the flat metric on tori, my solutions provided the first metric for orbifolds. Interestingly, I was able to make the surprising connection that this abstract, geometric equation was equivalent in two dimensions to equations for how fluids percolate through porous media (b). By changing the equation from the Ricci to the Mean Curvature Flow, I was also able to show how surfaces defined a wetting angle in capillaries converge also to soliton solutions that move simply by a constant translational speed (c). Finally, I demonstrated that high-dimensional fields of hyperplane could be evolved in such a way as to make them everywhere non-integrable (d).

a) Wu, L.F. The Ricci Flow on 2-orbifolds with positive curvature. Journal of Differential Geometry. 1991; 33:575-596.
b) Wu, L.F. A new result for the porous medium equation derived from the Ricci flow. Bulletin of American Mathematical Society. 1993; 28 (1):90-94.
c) Altschuler, S.J., Wu, L.F. Convergence to translating solitons for a class of quasilinear parabolic boundary problems. Math. Annalen. 1993; 295:761-765.
d) Altschuler, S.J., Wu, L.F. On deforming confoliations. Journal of Differential Geometry. 2000; 54(1):75-97.

List of Published Biological Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/lani.wu.1/bibliography/40592509/public/?sort=date&direction=ascending.

Bob Riter

Biography

Bob is the Executive Director of the Cancer Resource Center of the Finger Lakes, an organization that partners closely with Cayuga Medical Center in serving the needs of individuals and families in our community touched by cancer.

In addition, Bob writes a regular column about living with cancer for the *Ithaca Journal*. Those columns have been compiled in a book titled, *When Your Life is Touched by Cancer: Practical Advice and Insights for Patients, Professionals, and Those Who Care*.

Bob's involvement with cancer support and education began in 1996 when he was diagnosed with breast cancer. Bob decided to be public about his diagnosis and has been involved with cancer advocacy and education ever since.

He's particularly interested in connecting cancer researchers with individuals personally affected by cancer. The Cancer Resource Center and Cornell University have developed a unique model of collaboration that specifically connects doctoral students engaged in cancer research with members of the local cancer community.

A native of Huntington, WV, Bob received his undergraduate degree from Oberlin College and a master's degree in health services administration from the University of Michigan.

Bob Riter

Contact:

Ithaca, NY 14850
607-277-0960 (office)

Work Experience

2010 – present
Executive Director, Cancer Resource Center of the Finger Lakes. Overall responsibility for the Cancer Resource Center, a locally-based cancer support organization serving individuals affected by cancer who live in and around Ithaca, NY.

2000 – 2010
Associate Director, Cancer Resource Center of the Finger Lakes, Ithaca, NY. (Organization was first known as the Ithaca Breast Cancer Alliance). Duties included grant writing and implementation, community education, communications (newsletters, website), client services, staff supervision, and human resource management.

1994-2000
Assistant Professor, Department of Health Services Administration, School of Health Sciences and Human Performance, Ithaca College, Ithaca, NY. Taught numerous courses and advised students in health care management and gerontology.

1985-1988
Administrator of Therapeutic Operations, Heritage Village, Columbus, Ohio. Administratively responsible for the patient care services of Heritage House, the Columbus Home for the Jewish Aged.

1980-1985
Administrator, Peterson Hospital, Division of the Ohio Valley Medical Center, Inc., Wheeling, West Virginia. Served as chief operating officer of a 176 bed hospital-based long-term care facility.

1980-1981
Assistant Administrator, Peterson Hospital, Division of Ohio Valley Medical Center, Wheeling, WV.

Education

1978-1980:
School of Public Health, University of Michigan, Ann Arbor, Michigan. Master's in Health Services Administration, Program in Hospital Administration.

1974-1978:
Oberlin College, Oberlin, Ohio. Bachelor of Arts in Sociology.

Selected Publications

Riter, Bob (2014). *When Your Life is Touched by Cancer: Practical Advice and Insights for Patients, Professionals and Those Who Care*. Hunter House.

Riter, Bob (2012 – present). Columnist/blogger for *Oncolink*. (Penn Medicine)

Riter, Bob (2011). *The Elephant in the Room: Practical Advice When the Diagnosis is Cancer*. iUniverse.

Riter, Bob (2010). *Cancer and Community*. CR Magazine.

Riter, Bob (2006 – present). *Cancer Connections.* A regular column in the *Ithaca Journal*. Columns can be read at online at http://www.crcfl.net/index.php/cancer-info/bobs-columns/

Riter, Bob (1997) "I Have Breast Cancer." *Newsweek*. Vol. CXXX, No 2, July 14, 1997.

Cancer Advocacy & Related Service

Project LEAD graduate (2001)

Department of Defense Breast Cancer Research Program Reviewer (2000, 2015)

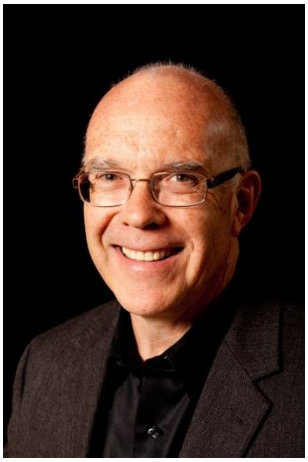
Susan G. Komen Breast Cancer Research Reviewer (2001)

San Antonio Breast Cancer Symposium, San Antonio, TX. December 13, 2006. Panelist in case presentations.

Member, New York State Health Research Science Board (2008-2014)

Member, IRB, Cayuga Medical Center, 2015 – present

2007 awardee in the "health professional" category of the New York State Innovation in Breast Cancer Research and Education Program.



C. Glenn Begley, M.B., B.S., Ph.D., F.R.A.C.P., F.R.C.P.A., F.R.C.Path., F.A.H.M.S.

Dr. Begley is Chief Scientific Officer for Akriveia Therapeutics. He consults for a number of biotechnology companies, serves on the Board of Directors of the UK-based Oxford BioTherapeutics, and on the Scientific Advisory Board for the Cancer Science Institute of Singapore.

From 2002-2012, he was Vice-President and Global Head of Hematology/Oncology Research at Amgen, responsible for building, directing and integrating the research program at Amgen's 5 research sites. During this time he became interested in the issue of research integrity and scientific reproducibility.

Before joining Amgen he had over 20 years of clinical experience in medical oncology and hematology. His personal research has focused on regulation of hematopoietic cells and translational clinical trials. His early studies first described human G-CSF, and in later clinical studies, he first demonstrated that G-CSF-"mobilized" blood stem cells hastened hematopoietic recovery compared with bone marrow transplantation. This finding revolutionized the approach to clinical hematopoietic cell transplantation.

He is Board Certified in Australia as a Medical Oncologist and Hematologist and has a PhD in cellular and molecular biology. He has received numerous honors and awards, including being elected as the first Foreign Fellow to the American Society of Clinical Investigation in 2000, and to the Association of American Physicians in 2008.

CURRICULUM VITAE

NAME: BEGLEY, C. Glenn

DATE OF BIRTH: 7th November, 1955

CURRENT POSITIONS:

Chief Scientific Officer and Senior Vice-President Research & Development, TetraLogic Pharmaceutical Corporation, Malvern PA

Non-Executive Director, Oxford BioTherapeutics, UK

Scientific Advisor, including
Cancer Science Institute, National University of Singapore;
Acerta, San Carlos, CA;
Cellastra, San Francisco, CA;
Selvita, Krakow, Poland;
Bionomics, Adelaide, Australia;
BioCryst, Durham, NC;
Bullet Biotechnology, Redwood City, CA;
Pierre-Fabre, Toulouse, France;
Threshold Pharmaceuticals, San Francisco, CA;
Rigel Pharmaceutics, South San Francisco, CA.

SUMMARY:

Currently Dr Begley is Chief Scientific Officer and Senior Vice-President at TetraLogic Pharmaceuticals Corporation, an early stage biotech company based in Malvern, PA. TetraLogic is developing novel therapies for oncology and infectious disease.

He also serves as a Non-Executive Director and Scientific/Clinical Advisor for several biotech and pharmaceutical companies, including Acerta in which AstraZeneca acquired a 55% stake for $4billion in December 2015.

From 2002 to 2012, Dr Begley was Vice-President and Global Head of Hematology and Oncology Research, Amgen Inc. He joined Amgen in 2002, and was responsible for building the Hematology and Oncology research program, and for the strategy, coordination and integration of the research effort at Amgen sites in Thousand Oaks CA, San Francisco CA, Seattle WA, Burnaby BC, and Cambridge MA. His scientific responsibilities included Amgen marketed products (Neupogen, Neulasta, Kepivance, Stemgen, Aranesp, Nplate, Xgeva) which involved preparation and presentations for multiple FDA face-to-face meetings, multiple FDA Drug

Advisory Committee meetings, and interactions with medical and scientific opinion leaders and patient advocate groups. In addition over 25 clinical-stage molecules emerged from his group including fully human monoclonal antibodies, small molecules, protein ligands and antibody-drug conjugates. A key element of this effort involved the development of biomarkers and clinical strategy for early phase trials. He was the key advocate for in-licensing of the bi-specific T-cell engager (BiTE) molecule blinatumomab, the oncolytic virus talimogene laherparepvec (T-Vec), and carfilzomib. He was also a member of the decision-making body that spanned all Amgen's therapeutic areas.

Before joining Amgen, he had over 20 years of clinical experience in medical oncology and hematology. His personal research focused on regulation of hematopoietic cells and translational clinical trials.

His early research studies first described human G-CSF, and in later clinical studies he first demonstrated that G-CSF-"mobilized" blood stem cells hastened hematopoietic recovery compared with bone marrow transplantation (so called "stem cell transplantation"). This finding revolutionized the approach to hematopoietic cell transplantation.

He performed a number of key studies that defined the function of the hematopoietic growth factors, their receptors, and the regulation of hematopoietic stem cells. He was the first to molecularly clone the transcription factor SCL (also known as Tcl5 or Tal-1), and demonstrated its critical role in leukemia and normal hematopoiesis. He also performed the earliest clinical studies with thrombopoietin.

Recently Dr Begley has focused attention on the need to improve the quality of scientific research. His pivotal publications highlighted the need for robust, reproducible research. This has catalyzed an ongoing, broad-based discussion within the scientific community and the lay press. He has numerous invitations to present his work including at the President's Science Council, National Academies Meetings, National Institute of Standards and Technology, and biotech/pharmaceutical companies.

He has published over 200 papers. These have been highly cited (total citations 17,696; h-index 68; i10 index 171; source Google Scholar, January 2016).

He graduated in from the University of Melbourne with M.B., B.S. degrees (MD-equivalent) in 1978, and trained primarily in Melbourne, Australia, at the Walter and Eliza Hall Institute of Medical Research and at the Royal Melbourne Hospital. He is Board Certified in Australia as a Medical Oncologist and Hematologist (F.R.A.C.P.), is a Fellow of the Royal College of Pathologists, United Kingdom, and received an honorary Fellowship from the College of Pathologists, Australia. He has a Ph.D. in cellular and molecular biology from the University of Melbourne. He has received numerous honors and awards, including being elected as the first Foreign Fellow to the American Society of Clinical Investigation in 2000, and to the prestigious Association of American Physicians in 2008. In 2014 he was an inaugural inductee into the "Hall of Fame" at his alma mater, the Royal Melbourne Hospital, and elected to the Australian Academy of Health and Medical Sciences.

UNIVERSITY TRAINING:

1973	Matriculated, University of Melbourne.
1976	A.Mus.A (Pianoforte), University of Melbourne.
1978	M.B., B.S., University of Melbourne.
	Honours in: Chemistry Biology Medical Studies Anatomy Biochemistry Microbiology and Epidemiology Pharmacology Physiology Medicine (including Jamieson Prize in Clinical Medicine)
1986	Ph.D., University of Melbourne
1986	Fellow, Royal Australasian College of Physicians
1997	Fellow, Royal College of Pathologists (U.K.)
2002	Honorary Fellow, Royal College of Pathologists of Australasia
2014	Fellow, Australian Academy of Health and Medical Sciences

POSITIONS HELD:

1979	Intern, Royal Melbourne Hospital
1980	Medical Officer, Royal Melbourne Hospital
1981	Registrar, General Medicine, Royal Melbourne Hospital
1982	Registrar, Clinical Research Unit, Royal Melbourne Hospital
1983- 1985	Lyndal Skea Research Fellow, Cancer Research Unit, Walter and Eliza Hall Institute of Medical Research
1983- 1985	Oncology Fellow, Royal Melbourne Hospital
1984- 1985	National Health and Medical Research Council Postgraduate Scholar
1986	Registrar, Haemato-Oncology Unit, Royal Melbourne Hospital
1986	Research Associate, Cancer Research Unit, Walter and Eliza Hall Institute of Medical Research
1987	Winthrop Travelling Fellow, Royal Australasian College of Physicians
1987- 1989	Neil Hamilton Fairley Fellow, National Health and Medical Research Council
1987- 1989	Visiting Research Fellow, Metabolism Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, U.S.A.
1989-1994	Developmental Haematologist, Royal Melbourne Hospital
1989- 2000	Fraser Fellow, The Anti-Cancer Council of Victoria and Head, Human Leukemia Laboratory, Cancer Research Unit, The Walter and Eliza Hall Institute of Medical Research and Medical Oncologist, Royal Melbourne Hospital
1990-1995	Occupational Health and Safety Committee, The Walter and Eliza Hall Institute of Medical Research
1990- 2000	Institutional Biosafety Committee, Royal Melbourne Hospital
1990- 2000	Death Audit Committee, Royal Melbourne Hospital

1990- 2000	Institutional Biosafety Committee, Ludwig Institute for Cancer Research
1990- 2000	Clinical Instructor, University of Melbourne Medical School
1991-1996	Organizing Committee, Lorne Cancer Conference
1994-2000	Founding Member, and Member of Executive Committee, the Centre for Developmental Cancer Therapeutics
1994- 2000	Director, Bone Marrow Research Laboratories, Royal Melbourne Hospital
1994- 2002	National Health and Medical Research Council Assignors' Panel
1994- 2002	National Health and Medical Research Council Regional Grants Committee
1994-1996	Professorial Associate, Department of Medicine, University of Melbourne
1995-1998	Senior Associate, Department of Medical Biology, University of Melbourne
1995- 2000	Founding Member, KConFaB, the Kathleen Cunningham Consortium for Familial Breast Cancer
1995- 2000	Genetic Advisory Committee, Anti-Cancer Council of Victoria
1995- 1997	Chairman, Clinical Genetics Advisory Committee, Royal Melbourne Hospital
1996-1999	Elected Councilor, Board of Trustees, International Society of Experimental Hematology
1996-1999	Cancer Research Advisory Committee, University of Sydney
1997	Committee Member, External Review Panel, Royal Adelaide Hospital/Institute of Medical and Veterinary Science Campus
1997	Committee Member, External Review of Leukaemia Research Fund Centre for Cell and Molecular Biology, London
1997- 2000	Professorial Associate, title of Professor, Department of Medicine, University of Melbourne
1998- 2000	Senior Principal Research Fellow, The Walter and Eliza Hall Institute of Medical Research

1998- 2000	Chairman, Director's Clinical Advisory Committee, The Walter and Eliza Hall Institute of Medical Research
1999	Committee Member, External Review Panel, NSW Cancer Council Research Fellow
1999- 2002	Member Discipline Panel, National Health and Medical Research Council, Australia
2000- 2002	Executive Director, The Western Australian Institute for Medical Research and Professor, Faculty of Medicine, University of Western Australia
1999- 2002	Scientific Advisory Committee, Queensland Institute for Medical Research
2000- 2002	Scientific Advisory Committee, Cooperative Research Centre for Gene Discovery
2000	External Scientific Expert, Australian National University
2000- 2002	Honorary Haematologist, PathCentre, Western Australia
2001- 2002	Member, Program Grants Committee, National Health and Medical Research Council, Australia
2002- 2004	Senior Director and Head, Hematology Research, Amgen Inc., CA
2004- 2012	Vice President and Global Head, Oncology and Hematology Research, Amgen Inc., CA
2004- 2006	Member, Scientific Advisory Committee of ViaCell Inc.
2005- 2008	Member, Hematopoietic Growth Factors Scientific Sub-Committee of the American Society of Hematology
2005- 2007	Chairman, Amgen Inc., Neutralizing Antibody Task Force
2005- 2007	Chairman, Amgen Inc. Global Scientific Advisory Board for Pure Red Cell Aplasia
2005- 2012	Member, Queensland-North America Biotechnology Advisory Council
2006	Member, University of Queensland's Research Quality Assessment for the Centre for Immunology and Cancer Research

2006- 2008	Chairman, Amgen Inc. Expanded Access & Compassionate Use Task Force
2009-	Member, Scientific Advisory Board, Cancer Science Institute of Singapore
2009- 2012	Member, Program Committee, Accelerating AntiCancer Agent Development and Validation Workshop
2009- 2012	Executive Sponsor, Amgen Inc. Gay and Lesbian Society (ANGLE)
2010- 2012	Member, Steering Committee, Amgen Inc. Women's Interactive Network
2010- 2012	Executive Sponsor, Amgen Inc. Committee for Laboratory Animal Care and Use
2011- 2012	Member, Amgen Inc. Committee for Use of Clinical Samples for Research Purposes
2012-	Non-Executive Director, Oxford BioTherapeutics, Oxford, UK
2012-	Senior Vice-President of R&D and Chief Scientific Officer, TetraLogic Pharmaceuticals, Malvern PA
2012- 2014	Scientific Advisory Board, CytomX
2012-	Scientific Advisory Board, Cellastra
2012-	Scientific Advisory Board, BioCryst
2012-	Consultant, Selvita
2012- 2013	Consultant, BioTechnology Value Fund
2012- 2013	Consultant, Aquilo Capital Management
2012- 2014	Scientific Advisory Board, Pieris
2013- 2014	Non-Executive Director, and Chairman of Scientific Advisory Board, Cyterix
2013- 2015	Scientific Advisory Board, Acerta
2013- 2014	Scientific Advisory Board, Reproducibility Initiative
2013-	Scientific Advisory Council, Global Biological Standards Institute

2014-	Scientific Advisory Board, Bionomics
2015-	Scientific Advisory Board, Pierre Fabre
2015- 2016	Scientific Advisory Board, Threshold Pharmaceuticals
2015-	Scientific Advisor, Rigel Pharmaceutics
2015-	Commercialization Committee, Centenary Institute, Sydney, Australia

HONOURS AND AWARDS

1978	Jamieson Prize in Clinical Medicine
1984- 1985	Postgraduate Scholar, National Health and Medical Research Council, Australia
1987- 1989	Neil Hamilton Fairley Fellow, National Health and Medical Research Council, Australia
1990	Albert Baikie Memorial Medal, Haematology Society of Australia
1991	Visiting Professor, Leukemia Foundation of Queensland
1991	Burnet Prize, The Walter and Eliza Hall Institute of Medical Research
1993	Member, Royal College of Pathologists (U.K.)
1995	Principal Research Fellow, National Health and Medical Research Council, Australia
1996	The Australian Society for Medical Research, Amgen Research Award
1996	Eric Susman Prize, The Royal Australasian College of Physicians
1997	Fellow, Royal College of Pathologists (U.K.)
1997	Council Member, The Anti-Cancer Council of Victoria
1997	Professorial Associate, title of Professor, University of Melbourne
1998	Visiting Fellow Commoner, Trinity College, University of Cambridge (U.K.)
1998	Senior Principal Research Fellow, National Health and Medical Research Council, Australia
1998	Fellow, International Union Against Cancer (UICC)
2000	Elected the first Foreign Fellow, the American Society for Clinical Investigation
2002	Fellow, Royal College of Pathologists of Australasia
2008	Elected, Association of American Physicians

2014	Inaugural Inductee into the Royal Melbourne Hospital's Research "Hall of Fame"
2014	Elected Fellow Australian Academy of Health and Medical Sciences

PROFESSIONAL ACTIVITIES

Memberships:

Australian Haematology Society

Fellow, Royal Australasian College of Physicians

American Association of Immunologists

International Society of Experimental Hematology

Medical Oncology Group of Australia

Fellow, Royal College of Pathologists (U.K.)

Clinical Oncology Society of Australia

American Association for Cancer Research

American Society of Hematology

American Society for Clinical Investigation

Fellow, Royal College of Pathologists of Australasia

Fellow, Australian Academy of Health and Medical Sciences

Editorial Boards:

International Journal of Biochemistry and Cell Biology (1996-2001)

Cytokines, Cellular and Molecular Therapy (1996-1998)

Blood (1998-2002)

International Journal of Hematology (1999-2001)

Experimental Hematology (1997-2000)

The Hematology Journal (2000-2002)

INVITED LECTURES

February 1989	Keystone Symposium, CO, USA: Hematopoiesis
September 1990	Sapporo, Japan: Myelodysplastic Syndromes and Cytokines
August 1990	Sydney, Australia: Westmead Hospital Medical Grand Rounds
September 1990	Christchurch, NZ: Presidential Symposium, Haematology Society of Australia
February 1991	Lorne, Australia: Lorne Cancer Conference
May 1991	Brisbane, Australia: Leukaemia Awareness Week
September 1991	Kobe, Japan: Progress in G-CSF Research
January 1992	Keystone Symposium, CO, USA: Hematopoiesis
April 1992	Kuala Lumpur, Malaysia: Clinical Applications of Hemopoietic Growth Factors
February 1993	Lorne, Australia: Lorne Cancer Conference
March 1993	Perth, Australia: State Cancer Conference
April 1993	Melbourne, Australia: Seminar, Baker Medical Research Institute
May 1993	Melbourne, Australia: Seminar, Department of Medicine, Austin Hospital
June 1993	Sydney, Australia: Prince of Wales Hospital Medical Grand Rounds
October 1993	Melbourne, Australia: Monash Medical Centre, Symposium in honour of Professor A. Clarke
November 1993	Adelaide, Australia: Plenary Lecture, Australian Society of Medical Research
December 1993	Sydney, Australia: Australian Society of Immunology
December 1993	Brisbane, Australia: Association of Regulatory and Clinical Scientists
February 1994	Melbourne, Australia: Lecturer, UICC Cancer Training Course
March 1994	Melbourne, Australia: Seminar, Murdoch Institute

March 1994	Melbourne, Australia: Symposium, Neurosciences Towards 2000
May 1994	Melbourne, Australia: Transfusion Medicine in Obstetrics and Neonatology
July 1994	Brisbane, Australia: Keynote Speaker: Medical Research Week
September 1994	Dublin, Ireland: The Metcalf Forum
November 1994	Adelaide, Australia: The Hanson Meeting
November 1994	Perth, Australia: Keynote Speaker, Royal Perth Hospital Annual General Meeting
March 1995	Tokyo, Japan: Clinical Application of Cytokines
April 1995	Adelaide, Australia: Symposium, Haematology Society of Australia
May 1995	Sydney, Australia: Seminar, Children's Medical Research Institute
June 1995	Melbourne, Australia: The Australian and New Zealand Intensive Care Society
June 1995	Sydney, Australia: St George Hospital: Brenda Jackson Memorial Lecture
June 1995	Melbourne, Australia: Seminar, Institute of Reproduction and Development
July 1995	Alice Springs, Australia: Australian and New Zealand Breast Cancer Trials Group
August 1995	Düsseldorf, Germany: Presidential Symposium, International Society of Experimental Hematology
September, 1995	Marysville, Australia: First Australia-Japan Workshop on Cancer Research
December 1995	Bethesda, MD: Hematopoiesis Symposium, Howard Hughes Medical Institute Conference
December 1995	Buffalo, N.Y.: Roswell Park Cancer Institute Staff Conference, Roswell Park Cancer Institute Medical Grand Rounds
February 1996	Lorne, Australia: Lorne Cancer Conference

May 1996	Philadelphia, USA: American Society of Clinical Oncology
May 1996	Bethesda, MD: Seminar, National Institutes of Health
June 1996	Tokyo, Japan: Clinical Application of Cytokines
August 1996	Singapore: International Society of Hematology
October 1996	Düsseldorf, Germany: Presidential Symposium, Congress of the German and Austrian Societies of Hematology and Oncology
October 1996	Melbourne, Australia: 21st Australian and New Zealand Scientific Meeting on Intensive Care
November 1996	Brisbane, Australia: Plenary Lecture, Clinical Oncology Society of Australia.
November 1996	Marysville, Australia: Plenary Lecture, Society of Hospital Pharmacists of Australia, Victorian Branch Conference
December 1996	Orlando, Florida: Educational Session, Annual Meeting, American Society of Hematology
May 1997	Sydney, Australia: Symposium, Haematology Society of Australia
May 1997	Sydney, Australia: Annual Inflammation Symposium
June 1997	Florence, Italy: Congress of the International Society on Thrombosis and Haemostasis
July 1997	Vienna, Austria: First UICC Cancer Management Meeting
August 1997	Melbourne, Australia: Seminar, Murdoch Institute
August 1997	Sydney, Australia: Seminar, Westmead Hospital
September 1997	Perth, Australia: Symposium, Haematology Society of Australia
October 1997	Singapore: Joint Scientific Meeting, RCPA/AMS/SSP/MSP
October 1997	Melbourne, Australia: Seminar, Box Hill Hospital
November 1997	Cambridge, U.K.: Seminar, MRC
November 1997	Melbourne, Australia: Seminar, Thalassaemia Society of Australia

January 1998	Keystone Symposium, Lake Tahoe, USA: Thrombopoiesis
April, 1998	Sydney, Australia: Symposium, The Garvan Institute of Medical Research
May, 1998	Berlin, Germany: 7th International Hematology Conference
July, 1998	Amsterdam, The Netherlands: Education Session, International Society of Hematology and European Haematology Association Combined Haematology Congress
July, 1998	Cambridge, U.K.: Symposium, East Anglia Haematology Society
August, 1998	Buffalo, N.Y.: Seminar, Roswell Park Cancer Institute
August, 1998	Vancouver, Canada: Session Chairman and Speaker, International Society of Experimental Hematology Meeting
September, 1998	London, U.K.: Seminar, Randall Institute, Kings College
September, 1998	Paris, France: Seminar, Institut Gustave Roussy
September, 1998	Birmingham, U.K.: Seminar, University of Birmingham
September, 1998	London, U.K.: Seminar, University College Hospital
September, 1998	London, U.K.: Wellcome Molecular Haemopoiesis Meeting
November, 1998	Melbourne: Symposium, Victorian Breast Cancer Initiative
April, 1999	Brighton, U.K.: The British Journal of Haematology Lecture, British Haematology Society Meeting
June, 1999	Monte Carlo, Monaco: Session Chairman and Speaker, The International Society of Experimental Hematology
October, 1999	Tasmania, Australia: Session Chairman and Speaker, The Haematology Society of Australia.
December, 1999	New Orleans, USA: Annual Meeting, The American Society of Hematology

March, 2000	Sydney; Australia: Royal College of Pathologists, Haematology Update Training Course
March, 2000	Melbourne, Australia: Seminar, The Walter and Eliza Hall Institute of Medical Research
May,2000	Indianapolis, USA: Seminar, the Wells Center for Cancer Research
May, 2000	Baltimore, USA: Annual Meeting, The American Society for Clinical Investigation
June, 2000	Tokyo, Japan: Seminar, 15th ICFP Hamamatsu 2000
June, 2000	Birmingham, U.K.: Education Session, European Haematology Association Annual Meeting
October, 2000	Kobe, Japan: Oxford-Kobe Meeting, Gp130 Cytokines in Health and Disease
November, 2000	Adelaide, Australia: The Hanson Symposium
June, 2001	Perth, Australia: Seminar, PathCentre
July, 2001	Perth, Australia: Seminar, Bone and Cartilage Research Group
October, 2001	Sydney, Australia: Childhood Cancer Conference
October, 2001	Brisbane, Australia: Session Chairman and Speaker, The Haematology Society of Australia.
June, 2002	Pasadena, CA: International Conference on Stem Cell Biology, Immunology and Gene Therapy.
September, 2003	Cambridge, MD, USA: International Society for Cellular Therapy.
October, 2003	Cairns, Australia: International Society for Cytokine Research.
May, 2004	Seminar, Cold Spring Harbor Laboratories
October, 2004	Melbourne, Australia: Don Metcalf Symposium
November, 2004	Adelaide, Australia: The Hanson Symposium
February, 2005	Lorne, Australia: 17th Lorne Cancer Conference
July, 2005	Aspen, CO, USA: Aspen Cancer Conference

November, 2005	Queensland, Australia: Queensland Institute for Medical Research Diamond Symposium
April, 2006	Washington, DC: Symposium, American Association for Cancer Research
September, 2006	Minneapolis, MN: International Society of Experimental Hematology
December, 2006	Melbourne, Australia: Australian Health and Medical Research Congress
December, 2006	Melbourne, Australia; Seminar, The Walter and Eliza Hall Institute of Medical Research
February 2007	Boston, MA, USA: Dana Farber/Massachusetts General Hospital
November 2007	Los Angeles, CA, USA: American Physician-Scientists Association
December 2007	Washington, D.C.: National Cancer Institute Workshop
April 2008	Santa Barbara, CA, USA: University of California Santa Barbara
August 2008	Chicago, IL, USA: Evanston Hospital
August 2008	Chicago, IL, USA: Northwestern University
August 2008	New York, NY, USA: Memorial Sloan Kettering Cancer Center
August 2008	Bronx, NY, USA: Albert Einstein College of Medicine
September 2008	Paris, France: First INCa – LEEM Recherche Symposium
October 2008	Melbourne, Australia: AusBiotech
February 2009	Philadelphia, PA, USA: Global Technology Community Conference
March 2009	Melbourne, Australia: Donald Metcalf Lecture
May 2009	Camarillo, CA, USA: California State University, Channel Islands
June 2009	Seattle, WA, USA: Fred Hutchinson/University of Washington
October 2009	Melbourne, Australia: AusBiotech

October 2009	New York, NY, USA: French Physicians Symposium
December 2009	Princeton, NJ, USA: Princeton University
May 2010	Los Angeles, CA, USA: University of California, Los Angeles
June 2010	Bethesda, MD, USA: Accelerating Anticancer Agent Development and Validation Workshop (Session Chair and Case Study Discussion)
July 2010	Montreal, Canada: IRIC/Université de Montréal
September 2010	Melbourne, Australia: International Society of Experimental Hematology
November 2010	Princeton, NJ, USA: Princeton University
March 2011	Thousand Oaks, CA, USA: TEDx Conejo
April 2011	Yale, CT, USA: Global Health and the Arts; Cancer
August 2011	Miami, FL, USA: National Breast Cancer Coalition, Era of Hope
September 2011	Princeton, NJ, USA: Princeton University
February 2012	Los Angeles, CA, USA: City of Hope Inaugural Symposium, International Translational Regenerative Medicine Center
March 2012	Chicago, IL, USA: American Association for Cancer Research
April 2012	Boston, MA, USA: Health Research Alliance
May 2012	Arlington, VA, USA: National Breast Cancer Coalition
May 2012	Washington DC, USA: Accelerating Anticancer Agent Development and Validation Workshop
August 2012	San Diego, CA, USA: Sanford-Burnham Medical Research Institute Symposium
October 2012	Carlsbad, CA, USA: Prostate Cancer Foundation Annual Meeting
November 2012	Princeton NJ, USA: Princeton University
December 2012	Tokyo, Japan: 17th Japanese Foundation for Cancer Research-International Symposium on Cancer Chemotherapy (JFCR-ISCC)

December 2012	San Francisco, CA, USA: American Society for Cell Biology
February 2013	San Francisco, CA, USA: Molecular Medicine Tri-Conference
May 2013	Sydney, Australia: Lowy Cancer Conference
June 2013	Chicago, IL, USA: American Society of Clinical Oncology
August 2013	Burlingame, CA, USA: Igenica Biotherapeutics Inc.
December 2013	Washington, DC, USA: National Press Club, launch of Global Biological Standards Institute
December 2013	Princeton NJ, USA: Princeton University
January 2014	Washington DC, USA: President's Science Council
February 2014	Lorne, Australia: Lorne Cancer Conference
April 2014	Claremont, CA, USA: Keck Graduate Institute of Applied Sciences
April 2014	San Diego, CA, USA: American Association of Cancer Research
May 2014	Muncie, IN, USA: Midwest Biopharmaceuticals Statistics Workshop
May 2014	New York, NY, USA: New York BIO Conference
June 2014	Washington, DC, USA: National Academies Meeting on Animal Research
October 2014	Santa Barbra, CA, USA: University California Santa Barbara Chancellor's Breakfast
November 2014	Princeton NJ, USA: Princeton University
February 2015	London, UK: NC3Rs Conference
March 2015	Washington DC, USA: National Institute of Standards and Technology
March 2015	Sydney, Australia: Cure Cancer, Researchers Symposium
May 2015	Washington DC, USA: National Breast Cancer Coalition Annual Advocate Meeting

July 2015	Melbourne, Australia: the Walter and Eliza Hall Institute of Medical Research Centenary
July 2015	Melbourne, Australia: University of Melbourne
August 2015	South San Francisco, CA: Amgen Inc.
September 2015	San Francisco CA, USA: Rigel Pharmaceuticals
October 2015	Washington DC, USA: National Academy of Microbiology Colloquium
October 2015	South San Francisco, CA: Pfizer Inc.
February 2016	Costa Rica: Association of Medical School Pharmacology Chairs (AMSPC) annual meeting
February 2016	Singapore: Cancer Sciences Institute
March 2016	Palo Alto, CA: Stanford University, Meta-Research Innovation Center
March 2016	New Orleans, LA: Society of Toxicology annual meeting

PUBLICATIONS *(total citations 17,696; h-index 68; i10-index 171, source Google Scholar, January 2016).*

1. BEGLEY CG, Roberts-Thomson I. Spontaneous improvement in pancreatic function in chronic pancreatitis. Digestive Diseases and Sciences 1985; 30:1117-1120. *(21 citations)*

2. Doyle T, Tress B, BEGLEY CG. Embolic control of massive haematobilia after liver biopsy. Australas. Radiol. 1985; 29:35-38. *(3 citations)*

3. BEGLEY CG, Lopez AF, Vadas MA, Metcalf D. The clonal proliferation in vitro of enriched populations of human promyelocytes and myelocytes. Blood 1985; 65:951-958. *(18 citations)*

4. Lopez AF, BEGLEY CG, Andrews P, Butterworth A, Vadas MA. Identification of a human granulocyte functional antigen (GFA-2) involved in antibody-dependent cell mediated cytotoxicity and phagocytosis. J. Immunol. 1985; 134:3969-3977. *(26 citations)*

5. Metcalf D, BEGLEY CG, Nicola NA. The proliferative effects of human GM-CSF-α and β and murine G-CSF in microwell cultures of fractionated human marrow cells. Leuk. Res. 1985; 9:521-527. *(11 citations)*

6. Nicola NA, BEGLEY CG, Metcalf D. Identification of the human analogue of a regulator that induces differentiation in murine leukaemic cells. Nature 1985; 314:625-628. *(228 citations)*

7. Burns GF, Triglia T, Werkmeister JA, BEGLEY CG, Boyd AW. TLiSA1, a human T lineage-specific activation antigen involved in the differentiation of cytotoxic T lymphocytes and anomalous killer cells from their precursors. J. Exp. Med. 1985; 161:1063-1078. *(99 citations)*

8. Metcalf D, Nicola NA, BEGLEY CG. The colony-stimulating factors and myeloid leukemia. In: Gale RP, Golde DW, eds. Leukemia: UCLA Symposium on Molecular and Cellular Biology. New York: Alan R. Liss, 1985; 28:267-276. *(5 citations)*

9. BEGLEY CG, Mackay IR, Bhathal PS. Another immune-mediated disease associated with hairy cell leukemia: Chronic active hepatitis. Acta Haemat. 1985; 73:104-105. *(8 citations)*

10. BEGLEY CG, Metcalf D, Lopez AF, Nicola NA. Fractionated populations of normal human marrow cells respond to both human colony stimulating factors with granulocyte-macrophage activity. Exp. Hematol. 1985; 13:956-962. *(18 citations)*

11. Burns GF, BEGLEY CG, Mackay IR, Triglia T, Werkmeister JA. Supernatural killers. Immunol. Today 1985; 6:370-373. (*18 citations)*

12. Metcalf D, BEGLEY CG, Johnson GR, Nicola NA, Vadas MA, Lopez AF, Williamson DJ, Wong GG, Clark SC, Wang EA. Biological properties in vitro of a recombinant human granulocyte-macrophage colony stimulating factor. Blood 1986; 67:37-45. *(427 citations)*

13. Lopez AF, BEGLEY CG, Williamson DJ, Warren DJ, Vadas MA, Sanderson CJ. Murine eosinophil differentiation factor: An eosinophil-specific colony-stimulating factor with activity on human cells. J. Exp. Med. 1986; 163:1085-1099. *(141 citations)*

14. BEGLEY CG, Lopez AF, Nicola NA, Warren DJ, Vadas MA, Sanderson CJ, Metcalf D. Purified colony-stimulating factors enhance the survival in vitro of mature human neutrophils and eosinophils in a lineage-specific manner: A rapid sensitive microassay for colony-stimulating factors. Blood 1986; 68:162-166. *(272 citations)*

15. Metcalf D, BEGLEY CG, Johnson GR, Nicola NA, Lopez AF, Williamson DJ. Effects of purified bacterially-synthesized murine Multi-CSF (IL-3) on hemopoiesis in normal adult mice. Blood 1986; 68:46-57. *(290 citations)*

16. Burns GF, Cosgrove L, Triglia T, Lopez AF, Werkmeister JA, BEGLEY CG, Haddad AP, d'Apice AFJ, Vadas MA, Cawley JC. The IIb-IIIa glycoprotein complex which mediates platelet aggregation is directly implicated in leukocyte adhesion. Cell 1986; 45:269-280. *(79 citations)*

17. Lopez AF, Williamson DJ, Gamble JR, BEGLEY CG, Harlan JM, Klebanoff JS, Waltersdorph A, Wong G, Clark SC, Vadas MA. A recombinant human granulocyte-macrophage colony-stimulating factor stimulates in vitro mature human neutrophil and eosinophil function, surface receptor expression and survival. J. Clin. Invest. 1986; 78:1220-1228. *(703 citations)*

18. McLean CA, BEGLEY CG, Harris RA. Diflunisal-induced neutropenia. Aust. N.Z. J. Med. 1986; 16:811-812.

19. Metcalf D, BEGLEY CG, Johnson GR. Hemopoietic effects of purified bacterially synthesized Multi-CSF in normal and marrow-transplanted mice. Immunobiol. 1986; 172:158-167. *(15 citations)*

20. Metcalf D, BEGLEY CG, Williamson DJ, Nice EC, DeLamarter JF, Merrod JJ, Thatcher D, Schmidz A. Hemopoietic responses in mice injected with purified recombinant murine GM-CSF. Exp. Hematol. 1987; 15:1-9. *(289 citations)*

21. BEGLEY CG, Metcalf D, Nicola NA. Primary human myeloid leukemia cells: Comparative responsiveness to proliferative stimulation by GM-CSF or G-CSF and membrane expression of CSF receptors. Leukemia 1987; 1:1-8. *(109 citations)*

22. BEGLEY CG, Metcalf D, Nicola NA. Purified colony stimulating factors (G-CSF and GM-CSF) induce differentiation in human HL60 leukemic cells with suppression of clonogenicity. Int. J. Cancer 1987; 39:99-105. *(137 citations)*

23. Burgess AW, BEGLEY CG, Johnson GR, Lopez AF, Williamson DJ, Merrod JJ, Simpson RJ, Delamarter JF. Purification and properties of bacterially synthesized human granulocyte-macrophage colony stimulating factor. Blood 1987; 69:43-51. *(222 citations)*

24. Colman PG, BEGLEY CG, Tait BD, Roberts-Thomson IC, Harrison LC. Evidence against an immunogenetic basis for diabetes in chronic pancreatitis. Aust.&N.Z. J. Med. 1987; 17:392-395. *(1 citation)*

25. Metcalf D, BEGLEY CG, Johnson GR, Nicola NA. Quantitative responsiveness of hemopoietic populations in mice to injected recombinant Multi-CSF (IL-3). Exp. Hematol. 1987; 15:288-295. *(75 citations)*

26. Williamson DJ, BEGLEY CG. Colony-stimulating factors. B.J. Hosp. Med. 1987; 38:281.

27. Williamson DJ, BEGLEY CG. Colony-stimulating factors in the pathogenesis and treatment of disease. Postgrad. Med. J. 1987; 63:1061-1068. *(1 citation)*

28. BEGLEY CG, Tait B, Crapper R, Briggs PG, Brodie GN, Mackay IR. Familial hairy cell leukemia. Leuk.Res. 1987; 11:1027-1029. *(17 citations)*

29. Johnson GR, BEGLEY CG, Matthews RN. Transfusion-dependent β-thalassemia: In vitro characterization of peripheral blood multipotential and committed progenitor cells. Exp. Hematol. 1987; 15:394-405. *(8 citations)*

30. Williamson DJ, BEGLEY CG, Vadas MA, Metcalf D. The detection and initial characterization of colony-stimulating factors in synovial fluid. Clin. Exp. Immunol. 1988; 72:67-73. *(55 citations)*

31. BEGLEY, CG, Metcalf D, Nicola N. Binding characteristics and proliferative action of purified granulocyte colony-stimulating factor (G-CSF) on normal and leukemic human promyelocytes. Exp. Hematol. 1988; 16:71-79. *(71 citations)*

32. BEGLEY, CG, Nicola NA, Metcalf D. Proliferation of normal human promyelocytes and myelocytes following pulse stimulation by purified GM-CSF and G-CSF. Blood 1988; 71:640-645. *(56 citations)*

33. Kannourakis G, Johnson GR, BEGLEY CG, Werkmeister JA, Burns GF. Enhancement of in vitro β-Thalassemic and normal hemopoiesis by a non-cytotoxic monoclonal antibody 9.1C3: Evidence for negative regulation of hemopoiesis by monocytes and NK cells. Blood 1988; 72:1124-1133. *(9 citations)*

34. Kannourakis G, BEGLEY, CG, Johnson GR, Werkmeister JA, Burns GF. Evidence for interactions between monocytes and natural killer cells in the regulation of in vitro hemopoiesis. J. Immunol. 1988; 140:2489-2494. *(13 citations)*

35. Boyd AW, Ellis AW, Kannourakis G, BEGLEY CG, Mackay IR, Burns GF. Activated killer cell lymphoma: an erythrophagocytic syndrome simulating histiocytic medullary reticulocytosis. Pathology 1988; 20:265-270. *(10 citations)*

36. BEGLEY CG, Metcalf D. Culture and analysis of human progenitor cells. In: Chanarin I, ed. Laboratory Haematology: an account of laboratory techniques, 1989; 253-256.

37. BEGLEY CG, Aplan PD, Davey MP, Nakahara K, Tchorz K, Kurtzberg J, Hershfield MS, Haynes BF, Cohen DI, Waldmann TA, Kirsch IR. Chromosomal translocation in a human leukemic stem-cell line disrupts the T-cell antigen receptor δ-chain diversity region and results in a previously unreported fusion transcript. Proc. Natl. Acad. Sci. USA. 1989; 86:2031-2035. *(244 citations)*

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39. Rosenberg YJ, Nurse F, BEGLEY CG. IL-2 receptor expression in autoimmune MRL-*lpr/lpr* mice: the expanded L3T4$^-$, Lyt2$^-$ population does not express p75 and cannot generate functional high affinity IL-2 receptors. J. Immunol. 1989; 143:2216-2222. *(8 citations)*

40. Green JE, BEGLEY CG, Wagner DK, Waldmann TA, Jay G. Trans-activation of Granulocyte-Macrophage Colony-Stimulating Factor and the Interleukin-2 receptor in transgenic mice carrying the Human T-lymphotropic Virus Type 1 tax gene. Mol. Cell. Biol. 1989; 9:4731-4737. *(71 citations)*

41. BEGLEY CG, Aplan PD, Haynes BF, Waldmann TA, Kirsch IR. The gene, SCL, is expressed during early hematopoiesis and encodes a differentiation-related DNA-binding motif. Proc. Natl. Acad. Sci. USA 1989; 86:10128-10132. *(376 citations)*

42. Ruhl S, BEGLEY CG, Bickel M, Pluznik DH. Interleukin-2 receptors on monocytes and their relation to the process of monocytic cell differentiation. In: Gorin NC, Donay L, ed. Experimental Hematology Today, Springer Verlag, New York, 1989; pp33-37. *(6 citations)*

43. BEGLEY CG, Burton JD, Tsudo M, Brownstein BH, Golomb HM, Ambrus JL, Waldmann TA. Human B lymphocytes express the p75 component of the interleukin-2 receptor. Leuk. Res. 1990; 14:263-271. *(28 citations)*

44. Felix CA, Poplack DG, Reaman GH, Steinberg SM, Cole DE, Taylor BJ, BEGLEY CG, Kirsch IR. Characterization of immunoglobulin and T-cell receptor gene patterns in B-cell precursor acute lymphoblastic leukemia of childhood. J. Clin. Oncology 1990; 8:431-442. *(85 citations)*

45. BEGLEY CG, Aplan PD, Waldmann TA, Kirsch IR. A novel gene, SCL, identified by a chromosomal translocation in a human stem-cell leukemia. In: Golde D, Clark S, ed. Hematopoiesis: UCLA Symposia on Molecular and Cellular Biology, New Series, Vol. 120. New York: Alan R Liss, 1990; pp197-206. *(1 citation)*

46. Aplan PD, BEGLEY CG, Bertness V, Nussmeier MA, Ezquerra A, Coligan J, Kirsch IR. The SCL gene is formed from a transcriptionally complex locus. Mol.Cell.Biol. 1990; 10:6426-6435. *(108 citations)*

47. Visvader J, BEGLEY CG, Adams JM. Differential expression of the LYL, SCL and E2A helix-loop-helix genes within the hemopoietic system. Oncogene. 1991; 6:187-194. *(158 citations)*

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49. BEGLEY CG, Green AR, Visvader J, Gough NM. Molecular analysis of the SCL and GM-CSF Receptor genes in leukemia. In: Miyazake T, Takaku F, Uchino H, ed. Myelodysplastic Syndrome and Cytokines. Amsterdam: Elsevier, 1991; pp29-38.

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51. Parker NJ, BEGLEY CG, Fox RM. Human M1 subunit of ribonucleotide reductase: cDNA sequence and expression in stimulated lymphocytes. Nucleic Acids Research. 1991; 19:3741. *(22 citations)*

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54. Cicuttini FM, BEGLEY CG, Boyd AW. The effect of recombinant stem cell factor (SCF) on purified CD34-positive human umbilical cord blood progenitor cells. Growth Factors. 1992; 6:31-39. *(18 citations)*

55. Elwood N, BEGLEY CG. Chromosomal Translocations in lymphoid tumours. Todays Life Science. 1991; 3:16-23. *(1 citation)*

56. Sheridan WP, BEGLEY CG, Juttner CA, Szer J, To LB, Maher D, McGrath KM, Morstyn G, Fox RM. Effect of peripheral-blood progenitor cells mobilised by filgrastim (G-CSF) on platelet recovery after high-dose chemotherapy. Lancet, 1992; 339:640-644.
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210. Bradley CK, Takano EA, Hall MA, Gothert JR, Harvey AR, BEGLEY CG, van Eekelen JA. The essential haematopoietic transcription factor Scl is also critical for neuronal development. Eur J Neurosci. 2006;23:1677-89. *(28 citations)*

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215. Gothert JR, Brake RL, Smeets M, Duhrsen U, BEGLEY CG, Izon DJ. NOTCH1 pathway activation is an early hallmark of SCL T-leukemogenesis. Blood. 2007; 110: 3753-62. *(18 citations)*

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2. BEGLEY CG, Basser R, Mansfield R, Maher D, To B, Juttner C, Fox R, Cebon J, Grigg A, Szer J, McGrath K, Thompson B, Sheridan W, Menchaca D, Collins J, Russell I, Green M Randomized prospective study demonstrating a prolonged effect of SCF with G-CSF (filgrastim) on PBPC in untreated patients: Early results Blood. 84(10 SUPPL. 1). 1994. 25A. Meeting. *(13 citations)*

3. Basser R, Rasko J, Clarke K, Green M, Cebon J, Grigg A, Berndt M, Zalcberg J, Marty J, Menchaca D, Tomita D, Fox R, BEGLEY CG Pegylated megakaryocyte growth and development factor (PEG-rHuMGDF) enhances the mobilization of peripheral blood progenitor cells (PBPC) by chemotherapy and filgrastim Blood. 88(10 SUPPL. 1 PART 1-2). 1996. 641A. Meeting. *(4 citations)*

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5. Rasko JEJ, Basser R, O'Malley CJ, Mansfield R, Boyd J, Grigg A, McGrath K, Marty J, Sheridan W, Hussein S, Berndt MC, BEGLEY CG. In vitro studies from a phase I randomized, blinded trial of pegylated megakaryocyte growth and development factor (PEG-rHuMGDF) Blood. 86(10 SUPPL. 1). 1995. 497A. Meeting. *(5 citations)*

6. Basser R, BEGLEY CG, Maher D, To B, Juttner C, Fox R, Cebon J, Grigg A, Szer J. The use of peripheral blood progenitor cells (PBPC) mobilized by stem cell factor (SCF) and filgrastim (G-CSF) to support multiple cycles of high-dose chemotherapy in untreated women with poor prognosis breast cancer British Journal of Haematology. 87(SUPPL. 1). 1994. 91. Meeting. *(3 citations)*

7. Basser R, BEGLEY CG, Mansfield R, To B, Juttner C, Maher D, Fox R, Cebon J, Szer J, Grigg A, Clark K, Marty J, Menchaca D, Thompson B, Russell I, Collins J, Green M Mobilization of PBPC by priming with stem cell factor (SCF) before filgrastim compared to concurrent administration Blood. 86(10 SUPPL. 1). 1995. 687A. Meeting. *(10 citations)*

8. To LB, Basser RL, Olver I, BEGLEY CG, Gill PG, Malycha P, Ward G, Collins J, Russell I, Fox RM, Sheridan WP, Green MD, Szer J, Juttner CA Multiple cycles of sub-maximal high-dose therapy and peripheral blood rescue for poor prognosis breast carcinoma Bone Marrow Transplantation. 14(SUPPL. 1). 1994. S29-S30. Meeting. *(1 citation)*

9. Briddell R, Stoney G, Sutherland W, Argento J, Kern B, BEGLEY G, Molineux G An in vitro investigation of the mode of clearance of erythropoietin by human bone marrow cells. Experimental Hematology (New York). 31(7 Supplement 1). July 2003. 214. Meeting. *(1 citation)*

10. Basser R, To B, Green M, Szer J, Bayly J, Duggan G, BEGLEY G, Dyson P, Fox R. Rapid hematopoietic reconstitution following 3 cycles of high dose chemotherapy with filgrastim (G-CSF)-mobilized peripheral blood progenitor cells (PBPC) and filgrastim in patients with high risk breast cancer Blood. 82(10 SUPPL. 1). 1993. 233A. Meeting. *(1 citation)*

11. Hartley C, McElroy T, Molineux G, BEGLEY CG. The novel thrombopoietic agent AMG 531 is effective in pre-clinical models of chemo/radiotherapy induced thrombocytopenia. Cancer Research (9 SUPPL.) 2005. 286-287. *(12 citations)*

PATENTS

1. Kirsch IR and BEGLEY CG
   SCL gene and a hematopoietic growth and differentiation factor encoded thereby.
   USA Patent Application No. 07/437,819 filed November 17, 1989.
   USA Patent Application 5,132,212, July 21, 1992

2. Kirsch IR and BEGLEY CG
   SCL: a hematopoietic growth and differentiation factor
   USA Patent Application No. 07/826,470 filed January 27, 1992
   USA Patent Application 5,214,133, May 25, 1993

3. Douglas AM, BEGLEY CG
   Cytokines and their use in treatment and/or prophylaxis of breast cancer
   PN6242 filed October 27, 1995
   International PCT Application PCT/AU96/00676 filed October 25, 1996

European Patent Application No. 96934201.3 filed October 25, 1996
USA Patent Application No. 09/051939 filed October 16, 1998
USA Patent Application 20020106347 filed March 5, 2001

4. Robb LG, Nandurkar HH, BEGLEY CG
Method of modulating fertility in animals by IL-11
PO4393 filed December 24, 1996
International PCT Application PCT/AU97/00880 filed December 24, 1997
European Patent Application No. 97948654.5 filed December 24, 1997
USA Patent Application No. 09/331,569 filed August 27, 1999.
USA Patent Application 6,669,934, December 30, 2003

5. Robb L, BEGLEY CG, Harvey RP
Isolated nucleic acid encoding murine musculin
International PCT Application PCT/AU99/00623 filed July 30, 1999
USA Patent Application No. 09/744,778 filed January 26, 2001.
USA Patent Application 6,884,617, April 26, 2005
USA Patent Application 20050118681, June 2, 2005

6. Deisher T, Wang, X, BEGLEY CG
Using G-CSF mobilized c-Kit + cells in the production of embryoid body-like cell clusters for tissue repair and in the treatment of cardiac myopathy
USA Patent Application No. 10/985,835 filed November 10, 2004.
USA Patent Application 20050186182, August 25, 2005

7. Pellegrini M, Ebert GKP, BEGLEY CG
Method of treating intracellular infection.
International Patent Application Number PCT/AU2014/050092,
Publication number WO2014205516

8. BEGLEY CG, Chunduru S, McKinley M, Minderman H, Mitsuuchi Y, Wend D.
Method of treatment.
International Patent Application Number PCT/US2014/48841.
Publication number WO2015017520

9. Rothbaum W, BEGLEY CG
Treatment of skeletal-related disorders.
USA Patent Application Number 61767645, filed February 21, 2013
USA Patent Application Number 14/186902, filed February 21, 2014
USA Patent Application 20140357636, December 4, 2014

10. BEGLEY CG, Benetatos C, Chunduru S.
Combination therapy comprising administration of a Smac mimetic and GM-CSF.
USA Patent Application Number 61678360 filed August 1, 2012.
International Patent Application Number PCT/US2013/53126 filed January 30, 2015
Publication number WO2014022612
USA Patent Application 20150190470, July 9, 2015

10. BEGLEY CG, Russell L.
Combination therapy.
International Patent Application Number PCT/GB2015/053533

11. BEGLEY CG, Benetatos C, Mitsuuchi Y.
Coadministration of a Smac mimetic and a PD-1 antagonist
International Patent Application Number US62/242041

Biosketch for

RENZO CANETTA, M.D.

CAREER

During his early years at the Istituto Nazionale Tumori in Milan, Italy (1974-1980), Dr. Canetta's focus was on clinical trials in lymphomas and gastrointestinal tumors, among others. Since joining Bristol-Myers Squibb (BMS) in 1980, Dr. Canetta has held numerous roles of increasing responsibility and leadership, including head of clinical cancer research; head of development, life cycle management; vice president, oncology global clinical research; and, finally, as vice president, global R&D oncology policy. His experience can be summarized with the introduction of 18 new BMS drugs to the general medical use (two outside of oncology) and the approval of over 50 regulatory dossiers for additional indications/formulations, including some outside of oncology. Dr. Canetta retired from BMS on August 14, 2015.

EDUCATION

Universita' degli Studi, Milan, Italy. Graduate, Medicine and Surgery (M.D.), 1976.

Istituto Nazionale Tumori, Milan, Italy. State Certification, Clinical Oncology, 1977.

Universita' degli Studi, Milan, Italy. Board Certification, Clinical and Laboratory Hematology, 1979.

AREA OF EXPERTISE

Cancer patient care, diagnosis and experimental treatment of hematologic malignancies and solid tumors, methodology of clinical trials, new drug development, and regulatory policy.

CURRICULUM VITAE

RENZO MAURO REMO CANETTA, M.D.

Address:

Madison, Connecticut 06443
USA

Personal Data:

Born:	May 3, 1951 in Milan, Italy
Nationality:	Italian
Resident status:	U.S. Permanent Resident
Family status:	Married, five children

Education:

Secondary level:	Liceo-Ginnasio "Giuseppe Parini," Milan, Italy Certificate in Classical Disciplines	July 13, 1970
University:	Universita' degli Studi, Milan, Italy Graduate in Medicine and Surgery (M.D.)	October 13, 1976
	Universita' degli Studi, Milan, Italy State License for Practice in Medicine and Surgery	November 1, 1976
Post-graduate:	Istituto Nazionale Tumori, Milan, Italy State Certification in Clinical Oncology	September 15, 1977
	Universita' degli Studi, Milan, Italy Board Certification in Clinical and Laboratory Hematology	July 11, 1979

TRAINING AND APPOINTMENTS

- from November 1, 1974 to October 13, 1976 — Intern student, clinical oncology, Istituto Nazionale Tumori, Milan, Italy.
- from October 15, 1976 to January 31, 1977 — Attending physician, clinical oncology, Istituto Nazionale Tumori, Milan, Italy.
- from November 30, 1976 to June 15, 1979 — Member, chemotherapist, GSTG (Gruppo di Studio Tumori Gastroenterici), Milan, Italy.
- from March 1, 1977 to August 31, 1977 — Postgraduate trainee, clinical oncology, Istituto Nazionale Tumori, Milan, Italy.
- from September 1, 1977 to September 30, 1979 — Research fellow, clinical oncology, Istituto Nazionale Tumori, Milan, Italy.
- from December 28, 1976 to July 11, 1979 — Postgraduate trainee, clinical and laboratory hematology, Universita' degli Studi, Milan, Italy.
- from October 1, 1979 to December 31, 1979 — Attending physician, clinical oncology, Istituto Nazionale Tumori, Milan, Italy.
- from February 7, 1980 to March 31, 1982 — Associate director, clinical anticancer research, Bristol-Myers Company, International Division, New York, USA.
- from April 1, 1982 to April 28, 1986 — Director, overseas clinical oncology, Bristol-Myers Company, Pharmaceutical Research and Development Division, New York, USA.
- from February 1, 1983 to December 31, 2003 — Adjunct assistant professor of medicine, New York University, School of Medicine, New York, USA.
- from April 28, 1986 to October 4, 1989 — Director, clinical cancer research, Bristol-Myers Company, Pharmaceutical Research and Development Division, Wallingford, USA.
- from May 7, 1987 to November 27, 1991 — Research affiliate, Department of Internal Medicine, Yale University School of Medicine, New Haven, USA.
- from October 5, 1989 to November 26, 1991 — Director, clinical cancer research, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, USA.
- from November 27, 1991 to September 9, 2001 — Vice President, clinical cancer research, Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, USA.
- from September 10, 2001 to October 27, 2003 — Vice President, life cycle management, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton and Wallingford, USA.
- from September 1, 2002 to May 4, 2004 — Vice President, clinical design & evaluation oncology Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, USA.
- from May 5, 2004 to January 5, 2014 — Vice President, oncology global clinical research Bristol-Myers Squibb Pharmaceutical Research Institute*, Wallingford, USA. *Renamed in 2007 as Research and Development Division.
- from January 6, 2014 to August 14, 2015 — Vice President, global R&D oncology policy Bristol-Myers Squibb, Research & Development, Wallingford, USA.

SOCIETIES MEMBERSHIP

- January 1, 1977 — Member of Associazione Italiana di Oncologia Medica (AIOM) (Italian association of medical oncology).
- January 28, 1977 — Member of Ordine dei Medici della Provincia di Milano (Milan medical list).
- May 27, 1980 — Member of American Society of Clinical Oncology (ASCO).
- December 13, 1983 — Member of European Society of Medical Oncology (ESMO).
- May 3, 1990 — Member of American Association for Cancer Research (AACR).

EDITORIAL WORK

- Reviewer for several oncology journals.
  (*Journal of Clinical Oncology, Annals of Oncology, Journal of the National Cancer Institute, Cancer Chemotherapy and Pharmacology).*
- Member of the Editorial Board for:
  Geriatric and Medical Intelligence (since 1994)
  Molecular Cancer Therapeutics (2001-2012)
  CR (Collaborations-Results) (2006-2010)
  La Rivista Di Onco-Immunoterapia (since 2014)

AWARDS

- **The Chemotherapy Foundation XXXI Award**
  October 16, 1999
  New York, NY, USA

- **Bristol-Myers Squibb Oncology-Immunology Division**
  Commitment to the Mission Award
  February 2, 2000
  Orlando, FL, USA

- **Craig D. Tifford Foundation**
  Orchid of Life Award
  November 8, 2007
  New York, NY, USA

- **Bristol-Myers Squibb**
  James B.D. Palmer Award for Excellence in Drug Development
  November 15, 2007
  Wallingford, CT, USA

- **Bristol-Myers Squibb**
  January 29, 2014
  CEO Inspirational Integrity Award
  Princeton, NJ, USA

SPECIAL ACTIVITIES

- **Bristol-Myers Squibb Company and Foundation (1992 - 2006)**
  Unrestricted Cancer Grant
  Selection Committee Member
- **American Association for Cancer Research (1999 - 2000)**
  Clinical Cancer Research
  Committee Member
- **National Breast Cancer Coalition (2000)**
  Summit on Breast Cancer Research
  Invited Participant
- **US National Cancer Institute (2001)**
  Gynecologic Cancers Progress Review Group
  Member and Co-signatory
- **Institute of Medicine of the National Academies (2001 - 2005)**
  Committee on Shortening the Time Line for New Cancer Treatments
  Consultant and Presenter
- **American Society of Clinical Oncology/Food and Drug Administration (2003)**
  Lung Cancer Endpoints Workshop
  Member and Invited Presenter
- **American Association for Cancer Research (2003)**
  Think Tank: Lessons Learned - Translational Issues for Targeted Drug Development
  Organizing Committee Member and Session Chairman
- **Biotherapy Development Association (2004)**
  Strategies for early clinical development of molecular targeted therapy of cancer
  Scientific Steering Committee Member and Session Co-chair
- **Duke University, AACR, ASCO, NCI, FDA (2004 - 2011)**
  Accelerating Anticancer Agent Development and Validation - Workshop
  Co-Founder, Program Committee Member, Faculty Member and Session Chairman
- **American Society of Clinical Oncology (2006 - 2009)**
  Clinical Trials Committee Member
- **American Association for Cancer Research (2007 - 2009)**
  Clinical Research and Experimental Therapeutics Committee
  Richard and Hinda Rosenthal Memorial Award and Joseph H. Burchenal Award
  Selection Committee Member
- **American Association for Cancer Research (2009 - 2011)**
  AACR-Women in Cancer Research Charlotte Friend Memorial Lectureship
  Selection Committee Member
- **Institute of Medicine of the National Academies (2008 - 2009)**
  Committee on Cancer Clinical Trials and the NCI Cooperative Groups
  Consultant and Presenter
- **Institute of Medicine of the National Academies (2009)**
  Meeting on Transforming Clinical Research in the U.S
  Moderator and Breakout Session Chair and Reporter.
- **American Association for Cancer Research (2010 - 2011)**
  AACR Minorities in Cancer Research - Jane Cooke Wright Lectureship
  Selection Committee Member
- **Institute of Medicine of the National Academies (2011 - 2014)**
  National Cancer Policy Forum
  Member

SPECIAL ACTIVITIES (Continued)

- **Bristol-Myers Squibb (2011)**
  SciX (Science of Clinical Innovation and Excellence)
  Workshop on Patient Advocacy: We Are All Patients
  Princeton, NJ, USA, June 22, 2011
  Executive Sponsor and Panel Moderator
- **Institute of Medicine of the National Academies (2011)**
  Workshop on Combination of Investigational Cancer Therapies
  Planning Committee Member, Moderator and Session Chair
- **American Association for Cancer Research (2012 - present)**
  Science Policy and Government Affairs Committee Member
  Regulatory Science and Policy Subcommittee Member
- **United Kingdom House of Lords**
  Parliamentary Office of Science and Technology (Chair: Lord Robert Winston)
  Shifting Paradigms in Cancer Treatment (Presentation)
  London, U.K., December 3, 2013
- **American Association for Cancer Research (2014 - present)**
  Clinical Trials Committee Member
- **Duke University, AACR, ASCO, NCI, FDA (2014 - present)**
  Accelerating Anticancer Agent Development and Validation Workshop
  Program Committee Member
- **American Association for Cancer Research (2014-2015)**
  2015 Annual Meeting Scientific Program Co-Chair
- **Italian Ministry of Health (Beatrice Lorenzin)**
  BMS Leadership in Immuno-Oncology: a transformational opportunity for cancer patients (Presentation)
  Anagni, Italy, February 12, 2015
- **Cancer Drug Development Forum (formerly Biotherapy Development Association) (2014 - present)**
  2015 Alpine Meeting Co-Chairman and Session Chairman

AREAS OF INTEREST AND ACHIEVEMENTS

A. From the beginning of my academic career, I was interested in cancer patient care, in the diagnosis and experimental treatment of hematologic malignancies and solid tumors, in the methodology of clinical trials, and in new drug development, the latter two aspects in both oncology and in other therapeutic areas. During my early years of work at the Istituto Nazionale Tumori in Milan, Italy (1974-1980), I focused on clinical trials in lymphomas and gastrointestinal tumors, among others.

B. As a member of the clinical cancer research organization at Bristol-Myers Squibb (1980-1991), I contributed to the development and to the successful introduction of the following anticancer drugs:

- VePesid (etoposide, US, 1983, testicular tumors, and Japan, 1987, various indications)
- Briplatin (cisplatin, Japan, 1984, various indications)
- Amsakrin (AMSA, EU, 1987, acute myeloid leukemia)
- Ifex (ifosfamide, US, 1988, germ cell tumors)
- Mesnex (mesna, US, 1988, uroprotection)

In addition, I contributed to the introduction of an antiviral drug:

- Videx (didanosine, US, 1991, secondary treatment of the HIV infection)

During that period I had the primary responsibility for the development and introduction of:

- Paraplatin (carboplatin, EU, 1985, and US, 1989, ovarian cancer; Japan, 1990, various indications)

Among other supplemental registrational dossiers approved during that period, I participated to the regulatory approval process for VePesid (etoposide, US, 1986, small cell lung cancer i.v. and oral formulations), Briplatin (cisplatin, Japan, 1986, non-small cell lung and head and neck cancers; 1998, cervix and esophageal cancers; 1990, gastric cancer), and Paraplatin (carboplatin, US, 1991, first-line ovarian cancer).

C. As the head of the clinical cancer research department at Bristol-Myers Squibb (1991-2001), I was in charge of the activities leading to the successful introduction of the following drugs:

- Taxol (paclitaxel, US, 1992; EU, 1993; and Japan, 1997, ovarian cancer)
- Hydrea (hydroxyurea, Japan, 1992, chronic myeloid leukemia)
- Vumon (teniposide, US, 1992, acute pediatric lymphatic leukemia)
- Etopofos (etoposide phosphate, US, 1996 and EU, 1997, small-cell lung cancer)
- Uftoral (UFT, EU, 2000, colorectal cancer)

Among other supplemental registrations approved during that period: Taxol (paclitaxel, US, 1994, ovarian cancer, second-line, short infusion and breast cancer; 1996 semi-synthetic process; 1997 Kaposi's sarcoma; 1998, ovarian cancer, first-line, long infusion; 1999, non-small cell lung cancer, adjuvant breast cancer and plant cell fermentation process; 2000, ovarian cancer, first-line, short infusion; Japan, 1999, non-small cell lung and breast cancers; 2001 gastric cancer; EU, 1994, breast cancer second line, 1996, ovarian cancer first-line, 1999, non-small lung; 1996, semi-synthetic process; 1999, plant cell fermentation process), VePesid (etoposide, Japan, 1994, oral formulation; 2000, cervix cancer); Paraplatin (carboplatin, Japan, 2000, non-small cell lung cancer), Blenoxane (bleomycin, US, 1995, intrapleural administration), Briplatin (cisplatin, Japan, 1999, small cell lung cancer and neuroblastoma); and Megace (megestrol acetate, EU, cancer-related cachexia).

AREAS OF INTEREST AND ACHIEVEMENTS (Continued)

D. During my tenure as the head of development for life cycle management (2001-2003), I was involved in the successful approval of the following supplemental indications (oncology products not listed):

- Videx EC (didanosine extended release, US, 2002)
- Sustiva 600 mg (efavirenz, US and EU, 2002)
- Plavix secondary prevention (clopidogrel, US and EU, 2002)
- Avapro diabetic nephropathy (irbesartan, US and EU, 2002)
- Tequin skin infections (gatifloxacin, US, 2002)
- Glucovance/Avandia (metformin/glyburide/rosiglitazone, US, 2002)
- Metformin/Glipizide (US, 2002)
- Zerit XR (stavudine extended release, US and EU, 2002)
- Serzone (nefazodone pediatric, US, 2002)
- Pravachol (pravastatin pediatric, US, 2002)
- Monopril (fosinopril pediatric, US, 2002)
- Glucophage 750 mg XR (metformin extended release, US, 2003)
- Pravigard (pravastatin plus aspirin, US, 2003)
- Glucovance (metformin and glyburide, pediatric, US, 2003)
- Avapro/Avalide RMT (irbesartan, irbesartan + chlorothiazide, reduced mass tablet, US, 2003)

E. Finally, after resuming the leadership of the clinical oncology research group (2002-2014), I contributed to the first approvals of

- Erbitux (cetuximab) for the treatment of metastatic colorectal cancer in the US (2004) and in Japan (2008);
- Sprycel (dasatinib), worldwide, for the treatment of Chronic Myeloid Leukemia (CML) and Philadelphia^{+} Acute Lymphocytic Leukemia (ALL), (US, 2006; EU, 2007; and Japan, 2009);
- Ixempra (ixabepilone) in the US for the treatment of metastatic breast cancer (2007);
- Yervoy (ipilimumab) in the US and EU (second-line) for the treatment of metastatic melanoma (2011);

and, in addition, to the approvals for

- the supplemental indication for Taxol (paclitaxel) in Japan for the plant cell fermentation process (2003), for endometrial cancer (2005), for metastatic breast cancer (weekly schedule) (2007), for esophageal cancer (2007-2012)*; for metastatic head and neck cancer (2008-2012)*; for angiosarcoma (2012)*; for cervical cancer (2012)*; and for ovarian cancer (weekly schedule) (2012)*:
- the supplemental indication for VePesid (etoposide) in Japan for ovarian cancer (2012)*;
- the supplemental indication for Briplatin (cisplatin) in Japan for the treatment of liver cancer (2004) , for breast cancer (2011), for angiosarcoma, biliary tract cancer, cervical cancer and ovarian cancer (weekly schedule) (2012)*;

- the supplemental application for Paraplatin (carboplatin) aqueous solution (2003) and multi-use aqueous solution formulation in the US (2004), as well as to the completion of the pediatric research program for Paraplatin in the US (2004);
- the Erbitux (cetuximab) approval for the treatment of locoregional head and neck cancer (2005), of third-line colorectal cancer (2007), of metastatic head and neck cancer (2011), of first-line colorectal cancer accompanied by a diagnostic companion test (2012) in the US, and of head and neck cancer in Japan (2012);
- the dose-optimization of Sprycel (dasatinib) for the second-line treatment of CML and Ph+ ALL in the European Union and in the US (2007), the introduction of new dosage form, 100 mg tablet (2008), as well as the approval for the first-line treatment of CML in the US and EU (2010) and Japan (2011);
- the completion of the pediatric research program for Ixempra in the US (2010); and
- the supplemental application for Yervoy (ipilimumab) in the EU for the first-line treatment of metastatic melanoma (2013).

**Special PMDA-MHLW program for additional indications in Japan*

During this period of time, I was asked to contribute to the program of approval for

- Baraclude (entecavir) in the US, for the treatment of hepatitis B (2005)

F. Altogether, my experience can be summarized with the introduction of 17 new Bristol-Myers Squibb chemical entities (including 2 outside of oncology) and with the approval of more than 50 additional, independent regulatory dossiers for additional indications/formulations (15 outside of oncology).

G. In January 2014 I moved to the Global Regulatory Science & Biometrics division of Bristol-Myers Squibb, with the title of Vice President, Global R&D Oncology Policy. These responsibilities encompassed the relationship with government, government agencies in regulatory and health care functions, and the advocacy community at large.

At the end of 2014 the U.S. regulatory review of the 18th new drug I had worked on, Opdivo (nivolumab), for the treatment of metastatic melanoma was completed and followed in 2015 by the U.S. regulatory approval of the supplemental indication of non-small cell (squamous) lung cancer. In mid-2015 the U.S. regulatory submission for Empliciti (elotuzumab) for the treatment of multiple myeloma was initiated.

H. On August 14, 2015, I retired from Bristol-Myers Squibb.

PUBLICATIONS

Co-author of one book, more than 100 articles and book chapters, and more than 200 abstracts and presentations at scientific congresses.

List of publications available upon request.

Terence G. Porter, Ph.D.
Vice President, Search and Evaluation, Takeda Pharmaceuticals International

Terry Porter heads Takeda's Search and Evaluation (S&E) team within the recently formed Center for External Innovation. In this role, Terry leads the team responsible for identifying and evaluating in-licensing opportunities across a number of Takeda's core therapeutic areas.

Terry has over 25 years experience in the pharmaceutical and biotechnology industry. Before joining Takeda in 2011, he was a Managing Director at Aqua Partners for two years, which provided strategic advisory services to life science companies and investors across multiple therapeutic areas including Oncology. In addition, he had a long and successful career at GlaxoSmithKline (GSK), first as a research investigator, then as an integral member of GSK's global business development group where he held various leadership positions including heading Oncology Licensing at GSK for over 6 years driving several multi-national deals during this time. Starting out in Biotech at Seragen Inc in Boston Terry was part of the core team that developed ONTAK an approved therapy for cutaneous T-cell lymphoma.

Terry holds a BSc (Hons) in Biochemistry and a Ph.D. in Chemistry from the University of Manchester, UK.

TERENCE (Terry) PORTER, Ph.D.

. Chicago, IL 60614 ●

Summary: Over 25 years experience in pharmaceutical and biotechnology industry with broad knowledge of technical and commercial aspects of successful drug R&D, product and technology licensing. Experience across all aspects of business development (BD) activities including compound and technology assessment, licensing and M&A. Proactive, entrepreneurial-minded individual with proven ability to drive BD opportunities to successful completion. Experienced team leader and creative problem solver. BD and R&D experience covers various therapeutic modalities across multiple therapeutic areas as well as cutting edge science and technology platforms. Via extensive deal interactions with US, European and International companies have built a solid network across the industry.

PROFESSIONAL EXPERIENCE

TAKEDA PHARMACEUTICALS (Deerfield, IL) **(2011 – present)**

VP Search & Evaluation, Center for External Innovation *(Apr 2015 – present)*

- Lead a team in Takeda's Center for External Innovation (CEI) responsible for identifying and evaluating business development opportunities across Takeda's core therapeutic areas including Gastroenterology, CNS, Specialty CV and Regenerative Medicine.
- The CEI is a recently formed dynamic organization built to recognize the essential network of innovative partnerships required to sustain a successful modern R&D organization becoming the one-stop shop for R&D business development.
- ➢ Selected deals include: **Altos Therapeutics -** exclusive option to acquire following ongoing Phase 1 studies of ATC-1906 for the treatment of gastroparesis; **Theravance -** exclusive rights to TD8954, a selective 5HT4 receptor agonist in Phase II trials for GI motility disorders; ***Cour Pharma*** **-** exclusive option to acquire a global license to TIMP-gliadin for celiac disease; ***Gencia*** **-** global research collaboration and licensing agreement to develop a series of Mitochondrial Agonists of the Glucocorticoid Receptor (MAGR); ***Enterome*** **-** collaboration and option agreement to develop new therapeutics directed at microbiome targets in GI disorders; ***Center for Cell Research & Application (CiRA)*** **-** one of the largest collaborations (>$200M over 10 yrs) between academia and pharma to fully exploit iPS cell technology applied to drug discovery and regenerative medicine.

VP Search & Evaluation, Global Business Development *(Dec 2011 – Mar 2015)*

- Headed the Search and Evaluation (S&E) team within Global Business Development responsible for identifying and evaluating in-licensing opportunities across a variety of therapeutic areas including Cardiovascular-Metabolic, CNS, Inflammation-Respiratory and General Medicine.
- Core member of Business Development & Licensing Committee (BDLC) the key governance body for internal decision-making for R&D through commercial global and regional BD opportunities.
- ➢ Selected deals include: ***Macrogenics*** **-** option-based collaboration around MGD010 product candidate for the treatment of auto-immune disorders; ***Natrogen*** **-** option collaboration around Natura-alpha for ulcerative colitis, Phase II; ***Trianni*** **-** license to transgenic mouse

technology for human antibody discovery; ***Resolve*** **-** option to acquire collaboration on RSLV-132 and RSLV-133 for SLE; ***Tri-Institutional Therapeutics Discovery Institute (Tri-I TDI)*** **-** ground-breaking major collaborative academic research alliance with 3 premier New York Research Institutes.

AQUA PARTNERS (Los Altos Hills, CA) **(2009 – 2011)**

Managing Director

- Principal member of this established Strategic Bus/Corp Dev Advisory group that provides senior level experience to develop and implement value-enhancing strategies for healthcare clients. Create, identify, support and enhance premium investment and partnership opportunities. Buy-side experience helping client companies access partnerships and capital investment.

GLAXOSMITHKLINE PHARMACEUTICALS (King of Prussia, PA) **(2000 – 2009)**

Vice President, External Science & Technology, Worldwide Business Development *(2006–2009)*

- Led the External Science & Technology (EST) group to successfully deliver upon global external science and technology goals including identification, evaluation and negotiation of access to key scientific and enabling/platform technology opportunities.
- Core member of Business Development Executive Committee (BDEC). Core member of the Technology Investment Board (TIB), GSK's most senior R&D scientific review and governance committee for technology and compounds up to clinical proof-of-concept. Chair of the "pre-TIB" review of all business development related opportunities going to TIB.

➢ Selected deals included: ***Domantis Acquisition*** **-** largest GSK technology M&A at the time ~$450MM; ***Praecis Acquisition*** **-** Encoded Library chemistry discovery platform; led due diligence and supported M&A deal team; ***Harvard Stem Cell Institute*** **-** Broad-based $25 million dollar 5-year collaboration covering multiple therapeutic areas (Oncology, CV, CNS).

Senior Director, Head of Technology Licensing, Worldwide Business Development *(2003-2006)*

- Head of Commercial Technology Licensing a group of 5 professionals responsible for licensing technologies and establishing alliances in support of Drug Discovery through Clinical Development. Responsible for identification and evaluation of platform technology or target-related opportunities, deal valuation, negotiation and transaction completion.
- Chair of the Biopharmaceuticals In-Licensing Strategy (BILS) team responsible for key decisions on external compound and technology licensing opportunities for the Biopharm Center for Excellence in Drug Discovery (CEDD).

➢ Selected deals included: **Morphotek** **-** novel platform for improved cell line production; **Evogenix** **-** Novel platform for antibody optimization.

Senior Director, Scientific Licensing, Worldwide Business Development *(2000–2003)*

- Head of Oncology Licensing, responsible for worldwide in-licensing of cancer therapeutics and cancer supportive care products. Core member of the Therapeutic Area Strategy Team (TAST) and CEDD matrix teams. Chaired licensing strategy forum identifying licensing opportunities. Led multidisciplinary Due Diligence teams.

➢ Selected deals included: ***Cytokinetics*****:** Major Research alliance to discover, develop and commercialize novel small-molecule therapeutics targeting cancer and other diseases; ***Inex*****:** Research alliance to create a novel liposomal formulation of topotecan.

SMITHKLINE BEECHAM PHARMACEUTICALS (King of Prussia, PA) **(1988-2000)**

Director, Scientific Licensing, Worldwide Business Development *(1998-2000)*

- Responsible for worldwide in-licensing of cancer and cancer supportive care therapeutics. Core member of the Inflammation, Tissue, Repair and Oncology (ITR-O) Therapeutic Area.
- ➢ Selected deals included: **Taiho Pharmaceutical Co:** alliance to develop TAS-106 (SB 596168), a novel anti-metabolite in Phase I; **Hayashibara Pharmaceutical Co**. - alliance to develop IL-18, a novel cytokine with therapeutic potential in cancer and infectious disease.

Assoc Director, Scientific Licensing, Worldwide Business Development *(1996-1998)*

- Generalist responsible for worldwide opportunities across several therapeutic areas, including traditional small molecule and biotechnology-based agents.
- ➢ **Laboratoires Fournier** – Alliance to develop a novel antithrombotic agent in Phase I.

Assistant Director, Protein Biochemistry, Biopharmaceutical R&D *(1991–1996)*

- Led a research group that provided protein biochemistry support to multidisciplinary Drug Discovery matrix teams. Development Project Team participation and Program Team leadership roles with emphasis on monoclonal antibody-based therapeutics. Co-directed from inception a program evaluating a humanized monoclonal antibody for the treatment and prevention of Respiratory Syncytial Virus (RSV) with the lead clinical candidate reaching Phase III pivotal trials.
- ➢ Inventor on core patent for mepolizumab (anti-IL5 MAb; Nucala®) recently approved in Europe and US for severe refractory eosinophilic asthma in adult patients.

Senior Investigator - Protein Biochemistry, Biopharmaceutical R&D *(1988–1991)*

- Development Project Team and Discovery Program Team roles in the research and development of recombinant sub-unit malaria vaccine candidates that included Mosquirix™ the world's first malaria vaccine.

SERAGEN INC. (Hopkinton, MA) **(1986-1988)**

- Senior Scientist, Manager of Process Development (1987-1988) .
- Staff Scientist, Department of Biochemistry (1986-1987)
- ➢ Successfully developed initial purification process for ONTAK now an approved therapy for cutaneous T-cell lymphoma.

EDUCATION

Albany Medical College & New York State Department of Health (Albany, New York)
NIH postdoctoral fellow and Research Affiliate in laboratory of Dr. David Martin.
University of Manchester (Manchester, UK) - Ph.D. in Chemistry
Thesis Advisors: Colin Wynn & David Garner
University of Manchester (Manchester, UK) - BSc (Hons) in Biochemistry

Awards:

- Multiple Impact awards relating to successful completion of a variety of business development deals including a GSK Gold Award for the Domantis Acquisition; GSK Silver Award for contribution to the discovery of mepolizumab (anti-IL5 MAb; Nucala®) for severe refractory eosinophilic asthma; recipient of SmithKline Beecham Vice President's Impact Award for leadership of RSV Program.

Publications : List (34 total) available on request.

she has continued to work part time in active clinical practice, and is currently an attending physician in the Hematology/Oncology clinic at the Veteran's Administration Medical Center in Durham, NC.

Sandra Silberman, M.D., Ph.D.

Dr. Silberman is a Hematologist/Oncologist who earned her B.A., Sc.M. and Ph.D. from the Johns Hopkins University School of Arts and Sciences, School of Public Health and School of Medicine, respectively, in Baltimore, MD. She received her M.D. from Cornell University Medical College in New York City, and then completed both a clinical fellowship in Hematology/Oncology as well as a research fellowship in tumor immunology at the Brigham & Women's Hospital and the Dana Farber Cancer Institute in Boston, MA. She continued to do basic research in Boston after being granted a Clinical Investigator Award from the National Institutes of Health and was an Instructor in Medicine at Harvard Medical School. She subsequently served as an attending physician at Yale University Hospital in New Haven, CT.

Her career in clinical development began at Pfizer, Inc., where she oversaw the first clinical trials of Tarceva™. She left Pfizer after having the opportunity to lead the global development of Gleevec™ at Novartis, resulting in the submission of a New Drug Application (NDA) and then several supplemental NDAs. Dr. Silberman then became the first Vice President and Global Therapeutic Area Head in Oncology at Eisai, a role in which she advanced five original, proprietary compounds into Phases I through III, gaining the first oncology approval for Eisai, with an NDA for Halavan™. She then served as a senior advisor to a number of biopharmaceutical companies, including Bristol-Myers Squibb, AstraZeneca, Imclone, Roche, and numerous biotech companies as an independent industry consultant, initiating and leading numerous INDs and NDAs. She has also been a consultant for several non-profit organizations, including the Chordoma Foundation and ABC^2. She joined Quintiles (Durham, NC) as the Vice President of Oncology and Global Head of Translational Medicine in the newly formed Innovation division, overseeing how changes in clinical drug development using novel technologies could lead to better and more effective trial designs as well as new partnerships with the pharmaceutical and biotechnology industries. She is currently the managing partner in a consulting company providing guidance for biotechnology and pharmaceutical companies in the advancement of new and pioneering cancer therapies through translational research, clinical trial designs, as well as later development programs. Throughout her career in industry

SANDRA L. SILBERMAN, MD PhD

Durham, NC 27713

PROFILE

SLS ONCOLOGY, LLC **JANUARY 2000 — PRESENT**
INDEPENDENT CONSULTANT TO THE PHARMACEUTICAL / BIOTECH INDUSTRY
CLIENTS: ROCHE, T-CELL SCIENCES, IMCLONE, NOVARTIS, RPS, BMS, AZ, GPC-BIOTECH, ALFACELL, ARCHER BIOSCIENCES, CORTICE BIOSCIENCES, MDS PHARMA, VIAMET PHARMACEUTICALS, HEAT BIOLOGICS, GUARDANT PHARMACEUTICALS, AVILLION LLP, JW PHARMA, INC.; ROIVANT ONCOLOGY; CIELO THERAPEUTICS (CO-FOUNDER);

VETERANS AFFAIRS MEDICAL CENTER (VAMC) DURHAM, NC **NOVEMBER 2011 – PRESENT**
ATTENDING PHYSICIAN

QUINTILES TRANSNATIONAL **DECEMBER 2009 – FEBRUARY 2013**
VICE PRESIDENT, GLOBAL HEAD OF TRANSLATIONAL MEDICINE
4850 Emperor Blvd
Durham, NC 27705

ARCHER BIOSCIENCES, INC. (FORMERLY TAPESTRY) **APRIL 2008 – APRIL 2009**
PRESIDENT AND CHIEF MEDICAL OFFICER
50 West 57th Street 15th Floor
New York, NY 10019

TAPESTRY PHARMACEUTICALS, INC. **MARCH 2007 – APRIL 2008**
CHIEF MEDICAL OFFICER
103 Eisenhower Parkway
Roseland, NJ 07068

EISAI MEDICAL RESEARCH **MAY 2004 – SEPTEMBER 2006**
EISAI GLOBAL CLINICAL DEVELOPMENT
VICE PRESIDENT
GLOBAL THERAPEUTIC AREA HEAD, ONCOLOGY
55 Challenger Road, Ridgefield Park, NJ 07660

NOVARTIS CLINICAL RESEARCH **SEPTEMBER 2000 – MAY 2004**
NOVARTIS PHARMACEUTICALS
SENIOR CLINICAL RESEARCH PHYSICIAN/SENIOR DIRECTOR/EXECUTIVE DIRECTOR
CLINICAL PROJECT LEADER
1 Health Plaza, East Hanover, NJ 07369

PFIZER CENTRAL RESEARCH **MARCH 1992 – JANUARY 2000**
SENIOR ASSOCIATE DIRECTOR, EXPERIMENTAL MEDICINE
PFIZER, INCORPORATED
Eastern Point Road, Groton, CT 06340

EDUCATION

MD Cornell University, New York, NY, Sept 1981 – June 1985

PhD The Johns Hopkins University, School of Medicine, Department of Microbiology, Baltimore, MD, Sept 1976 – June 1980; degree 1981

ScM The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD, September 1974 – August 1976, degree 1976

BA The Johns Hopkins University, Division of Arts and Sciences, Baltimore, MD, September 1971 – August 1974, degree 1975

POSTGRADUATE TRAINING/APPOINTMENTS

(all dates reflect July through June of the respective years)

Instructor in Medicine, Harvard Medical School, Division of Hematology/Oncology, Brigham and Women's Hospital, 1991 - 1992

Research Fellow, Harvard Medical School, Department of Pediatric Oncology, Dana Farber Cancer Institute, 1989 - 1991

Clinical Fellow, Harvard Medical School, Division of Hematology, Brigham and Women's Hospital, 1988 - 1991

Instructor in Medicine, Harvard Medical School, Dana Farber Cancer Institute, 1991-1992

Resident, Internal Medicine, Bellevue Hospital/New York University Medical Center, 1986 - 1988

Intern, Internal Medicine, Bellevue Hospital/New York University Medical Center, 1985 - 1986

Postdoctoral Fellow, The Johns Hopkins Hospital, Department of Oncology, July 1980 – June 1981

AWARDS/SCHOLARSHIPS/GRANTS

President's Award – Eisai 2005
President's Award – Novartis 2002
Excellence Award - Early Candidate Management Team, Pfizer Central Research, 1996
Clinician Investigator Award, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1991
Summer Fellow, New York Arthritis Foundation, 1983
Summer Fellow, New York Lung Association, 1982
Postdoctoral Fellow, American Cancer Society, 1980 – 1981

MEMBERSHIPS/BOARDS

Scientific Advisory Boards:
- Heat Biologics
- Oncolin Therapeutics, Inc.
- N-of-One
- Teen Cancer America
- Guardant Health

American Board of Internal Medicine, Board Certified, Internal Medicine
American Board of Internal Medicine, Board Certified, Hematology
American Board of Internal Medicine, Board Eligible, Oncology
Memberships:

- American Medical Association
- American College of Physicians
- American Board of Internal Medicine
- Massachusetts Medical Society

American Association for the Advancement of Science
American Society of Clinical Oncology
American Association for Cancer Research
American Society of Hematology
American Medical Women's Association
Vice President, Cornell Chapter, 1981 - 1982
National Student Representative, 1982 - 1983
American Medical Student's Association, 1981 - 1985
Permanent Commission on the Status of Women, 1986 - 2000
Appointed Representative, Congressional District 2
Women's Health Advisor, Connecticut State Chapter

HOSPITAL APPOINTMENTS/PRIVILEGES

Attending Staff Physician, Department of Hematology/Oncology, Veterans Administration Medical Center, Durham, NC 2011 - Present

Attending Staff Physician, Department of Medicine, Hematology/Oncology, Lawrence and Memorial Hospital, New London, CT March 1997 – August 2000

Attending Staff, Internal Medicine, Yale-New Haven Hospital, New Haven, CT 1992 - 1994

Associate in Medicine, Beth Israel Hospital, Boston, MA 1989 - 1992

Associate in Medicine, Dana Farber Cancer Institute, Boston, MA 1989 - 1992

Associate in Medicine, Brigham and Women's Hospital, Boston, MA 1988 - 1992

Teaching Assistant in Medicine, New York University Medical Center/Bellevue Hospital, New York, NY 1986 - 1988

LICENSES/REGISTRATION

NJ Medical License (Expires 6/30/17)

Federal DEA Registration (Expires 2/29/17)

NC Medical License (Pending 3/2016)

PERSONAL/CAREER GROWTH AND DEVELOPMENT

- Harvard Manage Mentor
- Strengthening Communication Workshop – Rogen International, Ltd
  - Presenting to Persuade
  - Communication Skills
  - Facilitation Skills
- Leading at the Front Line- Development Manager Program (CDR International, LLC)
- Positive Power and Influence Workshop
- Effective Meetings Workshop
- Time Mastery Workshop
- Member of WIN (Women's Issues Network), Pfizer Central Research, Quintiles Transnational
- Pharmaceutical Manufacturers Association – PERI Courses
  - Clinical Monitoring Skills
  - Regulatory Agency Skills
- Center for Creative Leadership – Executive Course (Colorado Springs, CO)
- Representative and Advisor, Connecticut Permanent Commission on the Status of Women
- Advisor, Outreach Project on Prostate Cancer, American Cancer Society, Connecticut Chapter
- Panelist and Discussant, Women's Health Fair, Hartford Courant
- Leadership Strategies: Mercer Delta Consulting

PUBLICATIONS

Zhu J, Davis C, Silberman S, Spector N. Hormonal Therapy in the Treatment of Male Breast Cancer: A Case Report. 2015 Crit Rev Oncol Hematol. 2016 Feb;98:358-63. doi: 10.1016/j.critrevonc.2015.11.013. Epub 2015 Nov 26

Goldlust S, Nabors L, Duic P, Conrad C, Silberman S, Farmer G. A Phase 1/2 Trial of Bevacizumab Plus TPI 287, a Novel, Brain Penetrable Anti-Microtubule Agent, in Patients with Recurrent Glioblastoma 2015 *In Press*

Fitzgerald DP, Emerson DL, Qian Y, Anwar T, Liewehr DJ, Steinberg SM, Silberman S, Palmieri D, Steeg PS. TPI -287, a new taxane family member, reduces the brain metastatic colonization of breast cancer cells. Mol Cancer Ther. 2012 Sep;11(9):1959-67

Johnson BE, Fischer T, Fischer B, Dunlop D, Rischin D, Silberman S, Kowalski MO, Sayles D, Dimitrijevic S, Fletcher C, Hornick J, Salgia R, Le Chevalier T. Phase II study of imatinib in patients with small cell lung cancer. Clin Cancer Res. 2003 Dec 1;9(16 Pt 1):5880-7

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