CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
R1209

Project Title:
Recruitment of First-Time, Tenure-Track Faculty Members

Award Mechanism:
Recruitment of First-Time, Tenure-Track Faculty Members

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

My background and current research reflect my long-term goal of working at the interface of development, metabolism and cancer biology. My goal is to solve challenges in cancer medicine. While at Harvard Medical School, I pursued an interest in genetics and development, and used these techniques to study stem cell biology in the hematopoietic system. During my MD training in the Harvard-MIT Division of Health Sciences and Technology, I spent two years working on a MD honors thesis in hematopoietic stem cell biology in Leonard Zon's group at Children's Hospital of Boston. I established a zebrafish transplant system by generating transgenic fish with hematopoietic stem cells expressing GFP under the control of stem cell promoters. This led to embryonic transplant experiments that aimed to answer questions about the developmental fate of the most primitive blood and endothelial cells. In order to gain insight into the regulatory circuitry of stem cell formation, I performed promoter analysis of the lmo2 gene, a master regulator of hematopoiesis, revealing a role for ETS factors in the transcriptional regulation of blood stem cell formation. In the Zon lab, I gained a deeper appreciation for how disease states co-opt the machinery that is instrumental for normal development (Please see CV references: 6, 8-13).
After an internal medicine residency at UCSF, I pursued clinical training in medical oncology at the Dana-Farber Cancer Institute where I became acutely aware of the lack of options for patients with advanced solid tumors. Scientifically, I became deeply fascinated by the uncanny similarities between tumor development and induced pluripotent stem cell (iPSC) reprogramming. Thus, I returned to Children’s Hospital Boston and joined the lab of George Daley, where the mechanisms and applications of iPSCs were being defined. I envisioned investigating mechanisms shared between cancer cells and iPSCs. I focused on how the Lin28/let-7 pathway, important in pluripotent stem cells, might function in adult physiology and tumorigenesis. The lab had just discovered that the Lin28 RNA-binding proteins suppress let-7 microRNA (miRNA) maturation in ESCs and cancer, which suggested a powerful new mechanism of RNA mediated oncogenesis. While developing mouse models of Lin28 gain and loss-of- function, several genome-wide association studies (GWAS) showed that the human LIN28B locus was significantly associated with human height and puberty timing. I showed that Lin28a hyperfunction in mice led to increased body size, weight, height, and time to puberty, demonstrating a conserved role in developmental timing from worm to mouse to human, work published in Nature Genetics (4).
Upon deeper mechanistic investigation, we found that activation of either Lin28a or LIN28B promoted an insulin-sensitized state that resisted diet-induced diabetes, whereas

loss of Lin28a or let-7 overexpression resulted in insulin resistance and impaired glucose uptake. These phenomena occurred in part through let-7-mediated repression of multiple components of the insulin-PI3K-mTOR pathway, including IGF1R, INSR, and IRS2. mTOR inhibition abrogated these Lin28 phenotypes in mice, indicating strong connections between these pathways. We also found that let-7 targets were enriched for genes identified in human diabetes and fasting glucose GWAS. This work established the Lin28/let- 7 pathway as an unexpected but important regulator of glucose metabolism and growth (1). Given overwhelming evidence for let-7 in tumorigenesis, this work provides a platform for independent investigation on metabolic and RNA-mediated mechanisms of tumor growth.

Commitment to a career in cancer research: My goal is to become a leader in cancer biology, with a focus on disease inspired and clinically relevant research, using creative and versatile mouse models. I am an adult medical oncologist and internist by training, but I have a deep and longstanding interest in a broad range of biological questions. These interests have led me to study disparate topics thematically linked by the use of in vivo developmental systems to study disease. I am firmly committed to leveraging my past experiences, both clinical and scientific, to study cancer biology. Specifically, I want to discover, characterize, and exploit connections between miRNAs, RNA regulatory machinery and cancer. My technical goals are to develop tools that efficiently test these understudied genes and mechanisms in the context of cancer mouse models. Initially, I plan to explore the role of let-7 biology in liver cancer using mouse models that I have established over the last 3 years. I will make every effort to translate basic findings into treatments for advanced liver cancer and other GI malignancies. Support from CPRIT would provide the resources to accomplish these goals, and allow me to more effectively establish a laboratory doing high impact work in cancer. I will continue to practice clinical oncology, a sub-specialization that complements my scientific interests. I will limit my clinical activities to no more than 10% of my time, so that I can devote the effort necessary to accomplish my research goals.