

NEW INVESTIGATOR AWARDS

Francine Garrett-Bakelman, MD, PhD – University of Virginia

\$100,000.00 – *Determination of age-appropriate risk classification in Acute Myeloid Leukemia*

Acute Myeloid Leukemia (AML) is a blood cancer that affects individuals of all ages. AML is the most common form of acute leukemia in adults with over 15,000 new cases per year in the United States alone. The incidence of the disease increases with age, with the majority of patients over the age of sixty (approximately 4 per 100,000 in individuals younger than 65 and 19 per 100,000 in individuals over the age of 65; SEER Cancer statistics). With aging, treatment options and effectiveness decrease compared to younger individuals, despite advances in the field. To improve upon current treatment options, it is necessary to better understand which patients benefit from current treatments and what are the mechanisms that drive the disease that are unique to patients over the age of sixty. The project proposed will utilize AML samples from patients to identify genetic features that are aberrant in this patient population. The findings will then be used to determine how to best predict which patients benefit from current treatments and what potential mechanisms drive the disease in individuals over the age of sixty. These findings will form the basis for a long-term goal of identifying potential targetable mechanisms of disease that could be used to develop new and more effective treatments for AML patients over the age of sixty.

Austin Brown, PhD – Baylor University

\$100,000.00 - *Pharmacometabolomic Biomarkers of Neuropsychological Outcomes following Pediatric Acute Lymphoblastic Leukemia Therapy*

Due to improved treatments, more than 90% of children diagnosed with acute lymphoblastic leukemia, the most common childhood cancer, are expected to become long-term survivors. As the number of patients who survive beyond their initial diagnosis continues to increase, improving the quality of life for these survivors becomes increasingly important. Unfortunately, many survivors of childhood leukemia suffer from adverse treatment-related side effects, including neurocognitive impairment. Prevention of treatment-related neurocognitive impairment could result in improvements in daily functioning, academic performance, and quality of life for survivors of childhood leukemia. Although neurocognitive impairment is a well-established consequence of modern leukemia chemotherapy, few risk factors have been identified. The lack of established risk factors is a major barrier to improving cognitive outcomes in these patients. Therefore, this study is the first of its kind and seeks to identify biomarkers of neurocognitive impairment in a recently treated, well-characterized population of childhood acute lymphoblastic leukemia patients. Specifically, this study will: 1) evaluate biomarkers of neurocognitive performance using cerebrospinal fluid samples collected from patients during chemotherapy; and 2) combine this information with genetic data to identify genetic markers of susceptibility to adverse neurocognitive performance. In addition to providing vital preliminary data to support future research, this research could uncover important biomarkers to distinguish patients at high risk of experiencing neurocognitive impairment. The results of this study are expected to have a significant positive impact on the long-term quality-of-life of childhood cancer survivors by aiding in identifying high risk patients who may benefit from targeted interventions to preserve neurocognitive performance.

Meelad Dawlaty, PhD – Albert Einstein College of Medicine

\$100,000.00 - *Epigenetic regulation of hematopoietic malignancies by Tet enzymes*

Hematopoietic malignancies account for a significant burden of cancers in our population. Many genes, including those that modify DNA and regulate gene expression, are implicated in maintenance of our hematopoietic system. Tet proteins (Tet1/2/3) are enzymes that modify DNA and allow for proper regulation of gene expression. They are expressed in the hematopoietic stem and progenitor cells to regulate hematopoiesis. Mutations or silencing of Tet1 and Tet2 enzymes are frequently reported in human pre-leukemic and leukemic patients. Consistently, loss of Tet1 and Tet2 in mouse models causally promotes lymphoid and myeloid malignancies, respectively. However, the mechanisms through which these enzymes regulate normal hematopoiesis and contribute to tumor suppression are poorly understood. Tet enzymes have both enzymatic activity (which modifies DNA directly to promote DNA demethylation) as well as non-enzymatic functions (which pertain to regulation of histones and formation of chromatin regulatory complexes). The goal of my research is to define the molecular functions of Tet enzymes in hematopoietic stem cells and hematologic cancers with a main focus on Tet2, which is the commonly mutated Tet family member in myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML). This work will unveil distinct mechanisms of gene regulation by Tet2 in hematopoietic stem cells and open opportunities to target its novel functions for treatment of leukemia.

Wei Du, PhD – West Virginia University

\$100,000.00 – Targeting niche-stem cell interaction for leukemia therapy

Hematopoietic stem cell transplantation (HSCT) is the only curable treatment for certain devastating blood diseases such as leukemia and bone marrow (BM) failure syndromes. However, three major hurdles that have been hampering scientific and clinical advance in the blood cancer HSCT field: 1) ineffective mobilization of patient stem cells; 2) hypersensitivity of recipient patients to pre-conditioning regimens; and 3) inefficient delivery of donor stem cells to the BM of cancer patients. We recently discovered that the activity of a signaling molecule called Cdc42 plays a critical role in the homing and proliferation of donor stem cells in the BM of transplant recipients. Specifically, we found that mouse hematopoietic stem and progenitor cells with low Cdc42 activity exhibited enhanced mobilization out of the BM into peripheral blood and competitive disadvantage in homing into the BM of recipient mice. These findings prompted us to hypothesize that targeting Cdc42 would egress blood cancer stem cells out of BM, therefore open up the BM niches for incoming donor stem cells to home and proliferate. To test this, we propose to use an innovative drug to inhibit Cdc42 activity, aimed at chasing out blood cancer stem cells and allowing donor stem cells to home. Should the proposed strategy be successful, we would establish a new method for blood stem cell harvest and transplantation that may significantly impact on future stem cell therapies for patients with leukemia and other blood cancers. Specifically, targeting Cdc42 would improve both side of the transplant practice - providing a new way to mobilize blood stem cells from donors and improving homing efficiency in recipients without increasing treatment-related toxicity.

R. Katherine Hyde, PhD – University of Nebraska

\$100,000.00 – The Role of *CBFB-MYH11* in the Maintenance of Leukemia Stem Cells

Acute Myeloid Leukemia (AML) is a cancer involving the immature blood cells in the bone marrow. One type of AML involves an abnormality on chromosome 16, which generates a unique fusion gene called *CBFB-MYH11*. Current treatments for *CBFB-MYH11* associated AML include high dose chemotherapy and bone marrow transplantation, both of which are associated with significant toxicity and are not appropriate for all patients. Therefore, there is a great need for the development of new treatments for patients with this subtype of AML. The *CBFB-MYH11* fusion protein is an attractive target for drug development as it is likely expressed in all leukemia cells, but not in normal blood cells. However, the activity of *CBFB-MYH11* in frank leukemia cells is not well understood. This has hampered drug development efforts, and made it difficult to predict whether inhibitors of *CBFB-MYH11* would be able to cure patients. In this study, we will use new mouse models and patient samples to define the role of *CBFB-MYH11* in frank leukemia cells, and to determine whether patients are likely to relapse when treated with *CBFB-MYH11* inhibitors. This work will provide important insights into the development of new treatments for this form of leukemia and contribute to the eventual cure of *CBFB-MYH11* associated AML.

Jing Li, MD, PhD – Shanghai Normal University

\$100,000.00 – The Role of *Sirt2* in the pathogenesis of AML

Drug-resistance and disease relapse are the major problems for current leukemia treatment. Signaling emerged from bone marrow microenvironment (niche) protects leukemic cells from chemotherapy drugs, which is one of the critical mechanisms of drug resistance. Sirt2 is an intracellular enzyme, which regulates cell proliferation, survival and migration by sensing the niche signaling. Sirt2 plays such role by removing acetyl group from its protein substrates such as NF- κ B and Stat3. We found that Sirt2 inactivation promotes leukemia development and drug-resistance, suggesting Sirt2 is a leukemic repressor. Although Sirt2 is highly expressed in leukemic cells, its activity is repressed by bone marrow niche signaling. We predict that activation of Sirt2 by inhibiting such niche signaling might repress AML progression and enhance the treatment effects of chemotherapy. We want to test our hypothesis by using our unique Sirt2 deficient leukemic animal model. The expected results of this study will not only help us to uncover the role of Sirt2 in leukemia pathogenesis but also allow us to develop medications for leukemia treatment.

Sheng Li, PhD – The Jackson Laboratory

\$100,000.00 - Uncovering Hydroxymethylation-mediated 3D Genome Dynamics in AML

Our research will identify the epigenetic “hotspots” that impact the AML 3D genome structure and functions and drive the development of leukemia. Using advanced epigenetic reprogramming techniques, we can then make changes to patient-specific hotspots in patient-derived cell lines. We hope that personalized epigenetics therapies can be used to help reverse the molecular level abnormality and improve AML patients’ clinical outcomes. Our study will also be a good model for other leukemia and lymphoma that are known to have epigenetic disruptions.

Parvathi Ranganathan, PhD – Ohio State University

\$100,000.00 – *Inhibition of PRMT5: a double-edged sword strategy to target acute Graft-versus-Host Disease and relapse/residual disease*

A bone marrow transplant (BMT) is the only known cure for many blood cancer patients. However, this chance for a cure is threatened by a lethal complication called acute Graft-Versus-Host Disease (aGVHD). aGVHD arises when donor T cells recognize the recipient of the BMT as foreign and mount an unchecked, inflammatory response that is ultimately fatal. Research has shown that an enzyme called Protein arginine methyltransferase 5 (PRMT5) is overexpressed in many blood cancers, and we have found that this same enzyme also plays a role in the inflammatory response of T cells. Therefore, this project has two main aims - 1) To fully investigate the function of PRMT5 enzyme in T cells and use this knowledge to 2) Investigate whether inhibiting PRMT5 can prevent aGVHD and target residual cancer at the same time. The efforts of this research will establish the biological rationale upon which to build future clinical trials in aGVHD, and have the potential to improve patient outcomes post-transplant.

Sarah Slavoff, PhD – Yale University

\$100,000.00 - *Discovery and functional evaluation of non-annotated microproteins in leukemia cells*

Leukemia cells express a specialized suite of genes in order to rapidly divide and migrate. It has become clear in recent years that expression of the cancer genome is far more complex than previously appreciated. We have previously developed technologies to demonstrate that regions of the human genome previously thought to be non-coding actually encode short proteins that have been invisible to geneticists – until now. In this proposal, we will apply a newly developed, quantitative version of our technology to identify previously unknown short genes that are expressed in the major classes of leukemia. We will then test whether silencing expression of one of these genes prevents cancer cell proliferation. In summary, we will show that a more complete understanding of genes previously thought to be “non-coding” has the potential to reveal new gene expression signatures, and potential molecular vulnerabilities, in leukemia, and hopefully to lead to new diagnostic tools and therapies in the future.

Britta Will, PhD – Albert Einstein College of Medicine

\$100,000.00 - *Leukemia maintenance through chaperone-mediated autophagy*

Many of our past and current efforts to characterize molecular drivers of leukemia have focused on genetic and epigenetic aberrations. Much less focus has been diverted to the study of mechanisms protecting the quality and function of macromolecules other than DNA. Autophagy (or “self-eating”) comprises several molecular “recycling” pathways which are among the most important intracellular degradation systems cells rely on for safeguarding functional integrity during steady-state and under stress conditions. While we have accumulated substantial knowledge for one autophagy pathway, macroautophagy, which rather unselectively targets proteins for lysosomal degradation, our current understanding of highly selective autophagy pathways has been very limited. With the support of our collaborator Dr. Ana Maria Cuervo, who is one of the leading experts in studying selective autophagy pathways over the last two decades, we will be the first to dissect the role of chaperone-mediated autophagy (CMA), in myeloid malignancy. We will devise a complementary experimental strategy to assess how CMA contributes to sustaining disease-relevant cells in acute myeloid leukemia (AML) using a genetic mouse model as well as primary human patient-derived AML cells. Results from this work will not only generate new insights into the contribution of CMA to leukemia blast and stem cell maintenance, but may also provide a new paradigm for other currently incurable stem cell-derived cancers.