Leukemia Research Foundation

2016 – 2017 Scientific Research Grant Recipients

NEW INVESTIGATOR AWARDS

Leonardo Salmena, PhD – University of Toronto

$100,000.00 - *Studying the regulation of stemness in normal and leukemic progenitor cells by INPP4B*
Dr. Salmena's research group has identified *INPP4B* as a biomarker to identify leukemia patients that are likely to fail therapy. Subsequently, they have discovered that INPP4B is important for maintaining the 'health' of the leukemia stem cells (LSC) that drive aggressive disease and relapse in leukemia. The Salmena group will study how INPP4B controls LSC and use this knowledge to conceive new therapies to treat leukemia.

Bruno Paiva, PharmD, PhD – University of Navarra

$100,000.00 - *Next-generation flow and sequencing to establish the pathogenesis and chemoresistant reservoirs of multiple myeloma*
Despite recent therapeutic advances, blood cancers remain largely incurable mostly because of minimal residual disease chemoresistant cells and/or more immature cancer stem cells. Here, we propose an innovative approach based on next-generation cell sorting and DNA sequencing to characterize both reservoirs of eradicate chemoresistant subclones.

Panagiotis Ntziachristos, PhD – Northwestern University

$99,204.00 - *Therapeutic targeting of the oncogenic methylation-ubiquitination crosstalk in acute lymphoblastic leukemia*
Treatment of childhood acute lymphoblastic leukemia (ALL) using chemoradiation has a 75% cure rate, but it is difficult to manage treatment-associated adverse events and secondary malignancies. Furthermore, in relapsed/refractory patients, the overall prognosis remains dismal. Direct inhibition of the key proteins promoting cancer (the "oncogenes") has not been successful in ALL. We propose that certain molecular oncogene-supporting mechanisms might be specific to a diseased and not to a healthy state. We characterize one of these mechanisms and use combinations of small molecule for clinical trials for high-risk disease.

Hrishikesh Mehta, PhD – Virginia Commonwealth University

$100,000.00 - *Stress responses in leukemogenesis*
As the life expectancy improves due to better medical facilities and treatment options, incidence of age related diseases such as myelodysplastic syndromes (MDS) also increase, which can transform to leukemia. To understand the process of how normal blood cells become dysfunctional and then leukemic, is critical in development of preventive and curative therapies that would target the disease at an early pre-leukemic stage. A pediatric bone marrow disorder develops MDS and then leukemia, and may thus mimics the events that lead to adult MDS and leukemia. Mutations in certain genes have been identified during the progression of the disease to leukemia. Further I have identified two fundamental stress responses associated with the mutations; one resulting from misfolding of proteins and the other due to excessive production of oxidants. I propose to identify the mechanism underlying the stress responses associated with the pediatric mutations and how interaction of these stress promote leukemia. I propose key molecular targets will be identified that represent viable targets for drug development.

Alessandro Gardini, PhD – The Wistar Institute

$100,000.00 - *Enhancer RNAs in leukemogenesis: a new class of cancer markers and therapeutic targets*
My project investigates the role of DNA regulatory elements called 'enhancers' during the onset of Acute Myeloid Leukemia (AML). Enhancer elements encode a special category of molecules termed 'enhancer RNAs' that are important regulators of cell differentiation and cell growth. I investigate how enhancers are hijacked during leukemogenesis to drive uncontrolled cell expansion and block normal differentiation. My goal is to identify small molecules that halt activation of enhancers and restore physiological conditions in leukemic cells, setting the stage for innovative pharmacological approaches in AML.

Jaehyuk Choi, MD, PhD – Northwestern University

$100,000.00 - *Identification of the Drivers of Disease Progression in Cutaneous T Cell Lymphoma*

Cutaneous T cell lymphoma is a non-Hodgkin lymphoma of the skin-homing CD4+ T cell. In early stage disease, the tumor cells are restricted to thin patches of the skin. However, as the disease progresses, the cells proliferate locally, which leads to the development of thick tumors. Eventually the cells escape the skin and metastasize to the blood, the lymph nodes, and at times the visceral organs. There is no cure for CTCL, and the median survival for patients with advanced disease is 4 years. Given the step-wise evolution in disease, we hypothesize that there are genetic drivers of cancer progression in CTCL. To elucidate these mechanisms, we propose to utilize the valuable resources we have at Northwestern: our large and growing biobank of CTCL samples and our robust genomic analysis pipelines. We will perform whole genome or targeted sequencing of large cohorts of CTCLs of varying stage. We will then use our functionally validated bioinformatics pipelines to identify clinically actionable drivers of tumor progression and validate their clinical utility as prognostic biomarkers. Because of the intractable nature of advanced CTCL, these studies will be critical for the identification of patients at high-risk for disease progression and novel therapeutic strategies to halt this process.

Zhiqiang Qin, MD, PhD – Louisiana State University

$100,000.00 – *Targeting spingolipid metabolism in AIDS-related lymphomas*

Primary effusion lymphoma (PEL) constitutes a variant of non-Hodgkin's lymphoma (NHL) whose incidence is highly increased in the context of HIV infection. Kaposi's sarcoma-associated herpesvirus (KSHV) is the causative agent of PEL. Even under conventional chemotherapy and effective anti-HIV therapy, PEL is a rapidly progressive malignancy carrying a very poor prognosis. This necessitates development of novel therapeutic strategies for this cancer. Sphingolipid metabolism has important role of regulating solid tumor cell fate, however, its role in KSHV+ PEL remains largely unknown. Understanding how sphingolipid metabolism and related molecules is closely related to PEL cell survival and pathogenesis, and assessing the effects of targeting sphingolipid on PEL growth and tumor progression, will provide a scientific basis for developing novel strategies for improving clinical outcomes for these AIDS-related lymphomas.

Yan Liu, PhD – Indiana University

$100,000.00 – *Targeting PRL2 phosphatase in acute myeloid leukemias*

Acute myeloid leukemia (AML) is a devastating illness with over 20,000 new diagnoses and 10,000 patients die from AML each year in the United States. Despite improvements in treatment outcomes, a considerable number of individuals relapse or do not response to conventional chemotherapy. Clearly, new treatments are urgentlyneeded to improve leukemia treatment. We found that an enzyme called PRL2 is elevated in human AML cells, and inhibiting PRL2 activity with a small molecule inhibitor kills these cancer cells. We speculate that PRL2 is a new target in AML treatment. We will determine the effect of PRL2 inhibitors on human AML cells and understand how elevated PRL2 activity leads to leukemia. The long-term goal of this project is to develop a novel therapeutic approach to treat patients with AML.

David Dominguez-Sola, MD, PhD – Icahn School of Medicine at Mt. Sinai

$100,000.00 – *Context dependency in MYC-driven B-cell lymphomas*

Some human B cell lymphomas, as is the case of Burkitt lymphoma and a fraction of Diffuse Large B cell lymphomas, carry alterations in the MYC gene. Presence of these genetic alterations leads to the onset of aggressive lymphomas, which require treatment with very intensive and toxic chemotherapeutic regimes, and are often associated to rather poor clinical outcomes. Many research efforts have been dedicated to understand how MYC gene alterations associate to these aggressive features, and it is believed that targeting the activity of this gene can significantly improve patient outcome or provide a means for a cure. An important strategy to do this is the generation of animal models that closely reproduce these human lymphomas, where to learn more about their biology, natural history, and find and test alternative treatments that could significantly improve or surpass current strategies. This project aims to generate and characterize a new model for these specific types of aggressive lymphomas. Different from previous imprecise models of these cancers, it provides a faithful replica of the detailed circumstances underlying their origin. Validation of this model can help

fulfill all these expectations, and impact how we understand and manage these diseases.

Christopher Oakes, PhD – The Ohio State University

$100,000.00 – ***The Role of Early Growth Response (EGR) in Establishing a Malignant Epigenetic Program in CLL***

Recent large scale research efforts have identified numerous gene mutations in leukemia. As many are associated with poor clinical responses and patient survival, a current challenge is to understand how these mutations alter the biological behavior of normal cells transforming them into tumor cells and promoting their growth. Another type of change that can affect genes (without requiring a mutation) is alterations to the structure and modifications surrounding DNA, termed 'epigenetic' changes. Like mutations, epigenetic changes have been broadly observed in leukemia and are known to change the biology of cells. Despite the importance and universality of epigenetic alterations, how they are established and their relationship to mutations are not well understood. We have recently uncovered that in chronic lymphocytic leukemia (CLL) patients with aggressive disease, a significant proportion of epigenetic alterations across the genome associate with regions that are known to interact with a gene family called early growth response (EGR). We also found that mutations in the EGR2 gene are associated with a bleak prognosis in CLL patients. Our further preliminary data suggest that these mutations specifically alter the way EGR2 interacts with DNA, redirecting it to different places in the genome and possibly creating novel epigenetic changes with disease-relevant consequences. We hypothesize that the EGR pathway is an important regulator of the epigenetic landscape in CLL cells and that elucidation of its direct effects will uncover key mechanisms of aggressive disease and novel avenues for therapeutic intervention. In this proposal, we plan to investigate leukemic cells in which we have experimentally introduced EGR2 mutations to uncover the mechanism of how these mutations create aggressive disease. Specifically, we propose to use a variety of state-of-the-art techniques based on next-generation sequencing technology to determine how and why the mutant proteins introduce epigenetic changes and alter the behavior of cells. As we have further evidence that EGR plays a role in resistance the novel therapeutic, ibrutinib, we secondly plan to determine the role of EGR-dependent epigenetic changes in acquired treatment resistance. In summary, this project represents a unique and powerful strategy to uncover how aberrant epigenetic changes occur and promote the development of aggressive leukemia and therapy resistance.

Xinyang Zhao, PhD – The University of Alabama at Birmingham

$100,000.00 – ***Targeting PRMT1 in acute megakaryocytic leukemia***

Finding drug targeting specific gene is urgent for acute megakaryocytic leukemia (AMKL), which still relies on chemotherapy as a first line of defense. However, AMKL is a fatal disease that are often not responsive to chemotherapy. We found that protein arginine methyltransferases 1 (PRMT1) is constitutively expressed in acute megakaryocytic leukemia, and inhibition of PRMT1 stimulates leukemia cells to re-enter differentiation. Thus, inhibition of PRMT1 activity is a pro-differentiation therapy for leukemia. In addition, we found that inhibition of PRMT1 activity sensitizes chemotherapy for leukemia cells. In this proposal we will systematically investigate the role of PRMT1 in leukemogenesis at molecular and organism levels, and the efficacies of using PRMT1 inhibitors in mouse models. Given that higher expression of PRMT1 is correlated with shorter survival time in acute myeloid leukemia patients, our findings will have broader impact on leukemia therapy, which may lead to using PRMT1 inhibitors for clinical trials.

Feng Yue, PhD – Penn State University

$100,000.00 – ***Identification of Regulatory Variants in Childhood Acute Lymphoblast Leukemia***

We have generated a list of genetic variations in childhood acute lymphoblastic leukemia (ALL) patients by targeted re-sequencing and plan to identify the subset of SNPs that are located in distal regulatory elements in normal human lymphoblastic and a variety of ALL cell lines. We will explore how the genetic variants might contribute to leukemogenisis by testing how they can influence transcription factor binding, affect enhancer activity, and further induce aberrant expression for their target genes. Finally, we will investigate whether genetic deletion of selected enhancers will induce leukemia phenotype using mouse model.