NEW INVESTIGATOR AWARDS

Daichi Inoue, MD, PhD – IBRI (Institute of Biomedical Research and Innovation)

$100,000.00 - ***Understanding the role of ZRSR2 mutations in myeloid malignancies***
Over the past few years, genetic analysis of leukemias has identified frequent mutations in a class of genes that encode for proteins participating in a process called "RNA splicing". RNA splicing is the process wherebygenetic information is read from DNA by removing unnecessary portions of genetic code and used to make proteins. Mutations in RNA splicing factors are now known to be the most common type of mutation in patients affected by myelodysplastic syndromes (MDS), and appear to cause abnormal splicing. However, how these mutations cause MDS and leukemia to develop and/or cause cancer to persist in the face of treatment is not well understood. Currently, most efforts to study RNA splicing factor mutations have focused on the effects of the mutations in "major" splicing factors, but this proposal is focusing on the role of the mutations in "minor" splicing factors, especially in ZRSR2. Minor splicing factors are in charge of less than 0.5% of all human genes, but these include a spectrum of essential genes. We therefore hypothesize that understanding of the effects of ZRSR2 mutation will provide novel insights into the cause of MDS and leukemia and illuminate therapeutic opportunities. Here, we propose to investigate the role of ZRSR2 mutations in MDS and leukemia using human RNA splicing data and innovative mouse models containing mutations in ZRSR2 to mimic human disease. We will utilize these models to identify functionally important pathways and illuminate therapeutic opportunities created by ZRSR2 mutations.

Rui Lu, PhD – University of Alabama

$100,000.00 - ***A Novel Stemness Program with Epigenetic Dysregulation in Acute Myeloid Leukemia***
During normal hematopoietic differentiation, a group of genes control self-renewal (i.e. can reproduce themselves) of hematopoietic stem cells, and these so called 'stemness' factors will be turned off to ensure terminal differentiation. However, in leukemia, certain stemness factors fail to be shut down and promote unlimited expansion of immature blood cells in the bone marrow. To develop effective treatment methods that target the aberrant self-renew of leukemic cells, it is important to identify key stemness factors and understand mechanism for their abnormal gene activation in leukemia. DNMT3A mutation occurs in 20-30% of acute myeloid leukemia (AML) cases. In this study, we have identified that DNMT3A mutation facilities activation of a novel stemness factor, which is critical for in AML progression. Completion of this proposal will contribute to a better understanding of the regulation and function of this new stemness factor in in AML, which will serve as the basis for future therapeutic interventions.

Raffaella Di Micco, PhD – Ospedale San Raffaele

$100,000.00 – ***Targeting of Epigenetic Drivers of Immune Evasion in Acute Myeloid Leukemia Relapses After Allogeneic HSCT***
Acute myeloid leukemia is an aggressive blood cancer frequently associated with bad prognosis. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has considerably improved the outcome of AML patients. Still, relapses occur in up to 50% of transplanted patients. Recent studies identified two novel modalities of post-transplantation leukemia immune escape, not explained by genomic alterations that render leukemic blasts invisible to the immune system. These findings support the hypothesis that AML post-transplantation relapses might be explained by alterations in the epigenome, a layer of biological complexity imposed on top of the genetic make-up of cancer cells. The aim of this proposal is to mechanistically dissect the epigenetic regulation of post-transplantation relapses in pair-wise primary human AML samples collected at diagnosis and relapse. Then, we plan to exploit models to functionally test the biological and immune-related effects of a large panel of epigenetic drugs for leukemia eradication. This project will shed light on the mechanisms by which chromatin regulators control AML immune evasion and pave the way for novel therapeutic approaches of personalized medicine.

Christopher Ott, PhD – Massachusetts General Hospital

$100,000.00 - ***Deciphering mechanisms of PAX5 addiction in lymphoma***
Treatment options for B cell lymphomas have greatly expanded over the past decade and now include both immunotherapies and targeted drugs. Many of these treatments have the ability to block signaling pathways that normally function only in normal B cells but are hijacked by lymphoma cells to promote proliferation or survival. These signaling pathways ultimately converge on proteins - transcription factors - that turn on lymphoma gene expression. An example is the essential B cell transcription factor PAX5, which is also required for maintaining lymphoma gene expression patterns. Without PAX5 these cancer cells cannot survive, suggesting that it could be an important factor for potential therapeutic intervention. However, historical perceptions of 'druggability' have led to the dismissal of transcription factors like PAX5 as eligible for earnest therapeutics development. Our goal with this project is to dissect the molecular underpinnings of PAX5 function in malignant B cells with the distinct goal of nominating regions of the protein itself and its associated cofactors that may be amenable for pharmaceutical inhibitor development. To accomplish this we will use sophisticated gene editing techniques and protein complex characterization in order to identify the signaling nodes essential for PAX5 functions in lymphoma.

Steven M. Chan, MD, PhD – Princess Margaret Cancer Centre

$100,000.00 - ***Repurposing Metformin to Prevent Blood Cancers and Cardiovascular Diseases Associated with TET2 Mutation-Driven Clonal Hematopoiesis***
Recent evidence indicate that ARCH is a bona fide pre-malignant state. The annual rate of transformation to hematologic malignancy has been estimated at 1% per year. The risk of transformation in individuals with ARCH is 11 to 12 times higher than those without ARCH. Currently, there are no known effective pharmacologic interventions that can suppress the mutant clone. Our proposed studies, if successful, will nominate metformin as a potential intervention that can be rapidly translated to clinical use. Our group at Princess Margaret Cancer Centre in Toronto and our colleagues in cardiovascular medicine have recently established an “ARCH clinic” to screen patients for the presence of ARCH mutations and monitor them longitudinally in clinic. A similar clinic was also started at Memorial Sloan Kettering Cancer Centre in New York. If successful, we plan to conduct a clinical trial that evaluate the effectiveness and safety of metformin in reducing the risk of hematopoietic malignancy and atherosclerotic cardiovascular diseases in ARCH carriers.

Hamza Celik, PhD – Washington University School of Medicine

$100,000.00 - ***Generation of a faithful patient-derived xenograft model of myelofibrosis for pre-clinical studies***
Myeloproliferative neoplasms (MPNs) are a group of diseases in which the bone marrow generates a detrimental excess of red blood cells, white blood cells, or platelets. Current MPN therapies are ineffective at treating this deadly disease. Moreover, a substantial proportion of MPN patients transform into an aggressive and therapeutically-refractive acute myeloid leukemia (AML). Patients who develop AML have a poor prognosis with an average survival time after transformation of less than five months. Given the poor survival of individuals with MPN or AML, it is important to delineate the genetic mechanisms of these diseases to develop effective therapies. In this study, we developed the first humanized animal model of MPN closely recapitulating the disease characteristics as it is observed in patients. This animal model will act as a reliable platform to study mechanisms of MPN disease biology and for pre-clinical drug screening to accelerate development of more efficacious drugs.

Irum Khan, MD –University of Illinois at Chicago

$100,000.00 – ***Targeting FOXM1 to improve treatment responses in AML***
The development of effective next-generation therapeutics against Acute Myeloid Leukemia (AML) depends on mechanistic understanding of AML biology, especially the *molecular regulators* of AML chemoresistance. Our work will provide a thorough understanding of the regulation and function of FOXM1 in inducing chemoresistance in AML and facilitate the development of specific FOXM1 inhibitors to enhance the efficacy of available AML therapies. The knowledge gained as a result of this work may have a broader application in targeting resistance in other cancers where FOXM1 is upregulated.

Mario A. Blanco, PhD – University of Pennsylvania

$100,000.00 – ***Dual targeting of LSD1 and KAT6A to induce therapeutic differentiation in AML***
20,000 people are diagnosed with acute myeloid leukemia (AML) annually, and the majority will die from the disease. Chemotherapy is often poorly tolerated by the older patients commonly afflicted by AML, and few therapeutic advances have been made in decades. New treatments are desperately needed. An alternative type of AML therapy, called "differentiation therapy" aims to treat patients by changing their rapidly dividing cancer cells into cells that do not divide. Differentiation therapy is the standard treatment for one subtype of AML, and it cures 95% of these patients. However, differentiation therapy has not been developed for other subtypes of AML. Our recent work has identified a combination of drugs that are highly effective in our preliminary experimental models of differentiation therapy. The goal of this project is to test this drug combination in more advanced models of AML to see if they could potentially be entered in clinical trials.

Capucine Van Rechem, PhD – Stanford University

$100,000.00 – ***Identify New Functions for PRMT5 in B-Cell Lymphoma to Unravel Therapeutic Strategies***
Cancer is a leading cause of death world-wide. The principal family of genes altered in cancers are chromatin modifiers. Chromatin modifiers modify the chromatin – the entity responsible for packaging the genome. Modifications of the chromatin regulate how the genome is expressed into proteins – the actors of biological functions. We can here use an analogy from the cooking process. Chromatin modifiers are the spices, chromatin the ingredients. Spices and ingredients are cooked into courses – the proteins, through steps taking place in different parts of the cell. Different spices with the same ingredients will make the course different. The end point is a great diner: an healthy cell. Therefore, chromatin modifiers (spices) regulate key processes necessary for an healthy cell. This is why they are key targets for the development of cancer – if you use wrong or too much/little spices, diner fails. Interestingly, emerging studies show that some of these chromatin modifiers have additional functions away from the chromatin, alteration of which could also be causing cancer. I previously uncovered that one chromatin modifier (spices) not only acts on chromatin (ingredients) but also on protein translation (cooking). These findings opened new opportunities for cancer therapies. Our new preliminary results demonstrate that the most altered chromatin modifiers in cancer influence the cooking too. Our goal, therefore, is to understand new roles for these chromatin modifiers and reveal potential links to cancer. In other words, is their role in cooking and not as spices the reason for the failed diner? This particular project focuses on one chromatin modifier that is expressed too much in blood cancers, specifically B-Cell Lymphomas. Interestingly, inhibitors for this chromatin modifier are being tested in clinical trials. Because of risks linked to the inhibiton of this modifier alone, we want to determine other drugs that could be used in combination therapy. We will be able to define these drugs if we understand the role of this chromatin modifier specifically in B-Cell Lymphoma. This project will ultimately provide new avenues for B-cell lymphoma targeted therapies.

Stephanie O. Berg, DO – Cardinal Bernardin Cancer Center, Loyola University Medical Center

$100,000.00 – ***Germline Mutations Predispose to Familial Myeloproliferative Neoplasms***
Myeloproliferative neoplasms (MPNs) are a group of bone marrow stem cell malignancies that result in increased production of red blood cells, white blood cells or platelets. Most patients develop a sporadic development of MPNs through non-inherited mutations, but familial clusters have been reported passed down in some families affecting several relatives. Clinically the presentation at diagnosis of patients with familial MPNs is similar to patients with sporadic MPNs, and these patients remain at risk for the same complications (thrombosis, bleeding, myelofibrosis, acute leukemia). Our analysis of exome sequence of patients and their first degree relatives with familial MPNs has led to the discovery of three predisposing germline mutations in one family diagnosed with MPNs. We hypothesize that one of these germline mutations, *RBSN* frameshift, represents a novel pathway altering surface receptor trafficking on the bone marrow stem cells leading to MPN pathogenesis in this family. Based on our findings in this proposed study, if confirmed, will further clarify aspects of familial and somatic MPN pathogenesis and may lead to efforts to devise new therapeutic and diagnostic strategies for this disease complex, particularly in affected families.

Michael Milyavsky, PhD – Tel Aviv University

$100,000.00 – ***Harnessing stemness reporter to identify and target critical dependency genes in human Leukemia Stem Cells***
All stem cells can multiply, proliferate and differentiate. Because of these qualities, leukemic stem cells are the most malignant of all leukemic cells. The major reason for the dismal survival rate in blood cancers is the inherent resistance of these leukemic stem cells to cancer treatment. Understanding how leukemic stem cells are regulated has become an important area of cancer research. A lack of tools to specifically isolate leukemic stem cells has precluded the comprehensive study and specific targeting of these stem cells until now. Our team has devised a novel biosensor that can isolate and target leukemic stem cells. By labeling leukemia cells on the basis of their stem character alone, our sensor manages to overcome surface marker-based issues. In this research proposal we will isolate leukemia stem cells from human leukemia sick mice and will characterize their unique vulnerabilities by profiling specific regions in their genome known as superenhancers. Usually, such super-enhancers control expression of the most cellvaluable proteins, thus providing a unique address to identify the Achilles heel of human leukemia stem cells. Then we will pursue experimental targeting of these vulnerability genes to prove that leukemia stem cells cannot survive without them while the normal stem cells will be spared. We believe that our biosensor can provide a prototype for precision oncology efforts to target patient-specific leukemic stem cells to fight this deadly disease.