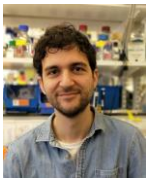


NEW INVESTIGATOR AWARDS



Jeevisha Bajaj, PhD
Rochester University – Rochester, New York
\$100,000.00 – *Role of SLC6A6 in aggressive Myeloid Leukemia*

Although chemotherapy can lead to remission of aggressive myeloid cancers, this is often only a transient solution, with relapse and progression following close behind. The discovery of new pathways that may regulate progression of disease could allow development of new strategies for targeted therapy. The studies we propose here are aimed at determining if signals mediated by the cell surface taurine transporter Slc6a6 are required for the progression of myeloid cancers, and have the potential to identify a new target for intervention in aggressive therapy resistant myeloid leukemias.



Sergi Cuartero, PhD
Josep Carreras Leukaemia Research Institute - Barcelona, Spain
\$97,133.00 – *Identifying novel transcriptional vulnerabilities in MDS with cohesin mutations*

Myelodysplastic syndromes (MDS) are a diverse group of blood malignancies with very poor prognosis, and current treatment options remain very limited. In recent years, several largescale sequencing studies have characterized the mutational spectrum of MDS. Among other genes encoding transcriptional regulators, genes of the cohesin complex have been identified as one of the most frequently mutated protein complexes. Cohesin is a transcriptional regulator that facilitates contacts between distal regulatory elements and gene promoters. Previous findings showing that cohesin is required for the transcriptional response to external stimuli suggest that MDS-specific signaling pathways may cooperate with cohesin mutations to promote a malignant cell state. Using cells with cohesin mutations from MDS patients, we aim to understand the link between impaired differentiation, defective signaling response and altered transcriptional regulation, with the long-term goal of finding new therapeutic options for MDS treatment.



Bridget Marcellino, MD, PhD
Icahn School of Medicine at Mt. Sinai – New York, New York
\$100,000.00 – *Enhancing natural killer cell recognition of leukemic cells*

The prognosis for patients with relapsed/refractory acute myeloid leukemia (AML) is very poor and it is therefore essential to develop new therapeutic options for this malignancy. It is clear that the immune system plays a crucial role in combatting leukemic cells, however, to date no immunotherapeutics have proven successful in the clinic. Natural killer cells are one population of immune cells which have been shown to be important for targeting leukemic cells. Leukemic cells have a mechanism, however, to evade natural killer cells. We are proposing to test a potential therapeutic, the 7C6 antibody, that has the potential to allow for the leukemic cells to be better recognized by natural killer cells. We will test this antibody alone and in combination with drugs that increase the expression of proteins on the surface of leukemia cells which are recognized by NK cells. The studies will be performed on leukemic cells from patients with AML and on mice who have been injected with human leukemic cells. Ultimately, results from this work could serve as preclinical rationale for a clinical trial of this novel therapeutic in AML patients.



Triona Ni Chonghaile, PhD, BSc
Royal College of Surgeons in Ireland – Dublin, Ireland
\$99,500.00 – *Identifying and epigenetically inducing BCL-2 dependence in Multiple Myeloma*

Multiple Myeloma (MM) is a cancer of the antibody-producing cells in our body, called plasma cells. These cells grow uncontrollably in the bone marrow and this leads to a variety of symptoms including tiredness, bone pain and increased infections. Unfortunately, despite major advances in the treatment of MM, it is still incurable. Therefore, new treatments are urgently needed especially for the treatment of drug-resistant disease, which eventually returns. BCL-2 is a survival protein that blocks cell death and increased amount or reliance on BCL-2 is one way in which these cancer cells can adapt to become resistant to treatment. Recently, an inhibitor called ABT-199 was developed; it targets BCL-2 and induces cell death but only in cells that are reliant on BCL-2 for survival. Our aim is to identify MM cell lines and patient samples that are reliant on BCL-2 survival, using a technology called BH3 profiling. We aim to screen a panel of epigenetic drugs (drugs that turn off and on genes in our DNA), to see if they make MM cells more reliant on BCL-2 and more sensitive to ABT199, with a ‘one-two-punch’ treatment approach. Our hope is that this new combination of drugs will work better to ensure a longer response to treatment in MM patients.



Fabiana Perna, MD, PhD
Indiana University – Bloomington, Indiana
\$100,000.00 – *Interrogation of the Leukemia cell Surfaceome for immune-targeting*

Immunotherapy is a promising cancer treatment that uses the immune blood cell system to attack cancer cells. FDA-approved immunotherapies include checkpoint inhibitors that release a natural brake on the immune system so that T cell lymphocytes recognize and attack tumors, and Chimeric Antigen Receptor T cell therapy where T cells from the patient blood are removed and a new gene introduced into those cells enabling them to recognize the surface proteins of cancer cells and attack them after CAR T cells are infused back into the patient’s bloodstream. Patients with Acute Myeloid Leukemia (AML) present a low mutation burden compared to solid tumors. Immune recognition of potential neo-antigens, arising from mutations in coding sequences, is therefore less probable and thus less likely to be responsive to immune checkpoint blockade. CAR T-cell therapy targeting upregulated normal cell-surface proteins represents a potential alternative approach for tumors with low mutation burdens like AML. Developing CAR therapy to AML is challenged by the lack of suitable targets, complex disease heterogeneity, and immunosuppressive microenvironment. In this project, we will investigate how frequently recurring mutations remodel the Leukemia Surfaceome.



Yana Pikman, MD
Dana-Farber Cancer Institute – Boston, Massachusetts
\$100,000.00 – *Novel combination strategy for targeting one-carbon folate metabolism for T-cell Acute Lymphoblastic Leukemia therapy*

Although treatment for acute lymphoblastic leukemia (ALL) has improved over the last decades, ALL remains the second leading cause of pediatric cancer related death. Leukemia that does not respond to standard chemotherapy or returns after treatment is particularly difficult to cure. We thus need novel treatment strategies for curing ALL. We have discovered that T-cell ALL cells are particularly sensitive to inhibition of a metabolic pathway called one-carbon folate pathway, and have worked with a novel inhibitor of this pathway. We have discovered that the combination of this inhibitor, called RZ-2994, with a drug that inhibits how cells sense DNA damage is particularly efficacious in killing T-ALL cells. Given the exciting results of this combination, we will study why this combination is efficacious. Additionally, we will test this combination in mice with leukemia. The combination of these studies will provide the necessary pre-clinical data to inform how this drug combination can be used to treat patients with leukemia.



Giovanni Roti, MD, PhD
University of Parma – Parma, Italy
\$100,000.00 – Targeting NOTCH1 trafficking vulnerabilities in T-Cell Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia is a major cause of illness and death in adults and the most common childhood malignancy. Despite recent advances in treatment, some types of ALL, including T-cell lineage ALL, respond poorly to conventional chemotherapy and require intensive treatment regimens that result in lifelong toxic side-effects. Activating mutations in NOTCH1 have been implicated in more than 60% of adult and pediatric patients with TALL, raising the expectations for a targeted therapy in this disease. However, initial enthusiasm for pan-Notch inhibitors has been moderated by clinical trials showing that broad inhibition of the Notch1 signaling results in treatment-limiting toxicities. Our group showed that inhibition of SERCA, a cell protein that acts as a “gatekeeper” of the Notch1 signaling, affects leukemia growth both in vitro and in vivo, especially in cases with clinically relevant mutations. This proposal advances our understanding of the SERCA and Notch1 signaling and takes to a preclinical phase a new orally available SERCA inhibitor, CAD204520, with excellent drug-like properties.



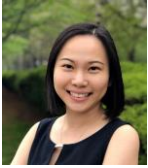
Simone Sidoli, PhD
Albert Einstein College of Medicine – Bronx, New York
\$70,000.00 - Accessible heterochromatin as new target against Acute Myeloid Leukemia development

Acute Myeloid Leukemia (AML) is the most severe of all leukemias. Like many other cancers, AML is characterized by our own cells that begin an uncontrolled proliferation, interfering with the production of normal blood cells. One critical “control panel” of the cell that is always affected during cancer cell proliferation is chromatin. Chromatin is DNA organized in a three-dimensional structure mainly folded around proteins named histones. Gene mutations in AML frequently affect the activity of proteins that are involved in chromatin modifications, readout and accessibility leading to chromatin decondensation and thus uncontrolled gene expression and proliferation. Our work investigates a new perspective to target AML cells, possibly more specific than current treatments targeting chromatin modifying proteins. We aim to identify the proteins that “read” specific chromatin domains, i.e. those domains that are accessible only in aberrantly decondensed chromatin. How will we identify these proteins? We will perform in-vitro experiments using synthetic parts of histones that are modified like a typical aberrantly accessible chromatin domain. In addition, we will survey cells from AML patients with specific mutations in genes/proteins involved in chromatin condensation and we will identify new histone modification patterns unique for aberrantly accessible chromatin. The identification of these domains, and the proteins that bind to these chromatin states, will pave the way to a whole new family of targets to specifically inhibit the growth and proliferation of AML cells.



George Souroullas, PhD
Washington University – St. Louis, Missouri
\$100,000.00 – Understanding the oncogenic mechanisms and chromatin interactions of EZH2 mutations in Lymphoma

Cancer sequencing studies have identified systematic alterations of epigenetic and chromatin-modifying genes in both pediatric and adult/mature B cell malignancies. The epigenome is a layer of chemical marks on the DNA which regulate how genes are expressed. Unlike the DNA, these chemicals marks can be removed. This reversible nature of the epigenome, therefore, has created a remarkable opportunity to develop novel therapeutic strategies, many of which are currently in clinical trials. Despite our best efforts, the genetic and molecular consequences of these genetic alterations are not entirely understood, but they are critical in developing more targeted therapeutic approaches. In this proposal, I aim to understand how mutations in a chromatin-modifying gene, which is mutated in about 15% of all mature B cell lymphomas, drive cancer development. Understanding these mechanisms and the genetic interactions with other mutations will help us better understand which patients will better respond to existing therapies, but also identify new therapeutic approaches.



Liling Wan, PhD

University of Pennsylvania Perelman School of Medicine – Philadelphia, Pennsylvania

\$100,000.00 – Targeting the chromatin reader protein ENL in acute leukemias

Epigenetics refers to the regulation of gene expression mainly through changes in modifications on DNA and histone proteins without changing the underlying DNA sequences. Cancer, in particular leukemia, can result from aberrant function of epigenetic regulators, leading to activating or repressing the wrong genes at the wrong time. Moreover, cancer cells can be highly reliant on certain epigenetic regulators for sustaining their malignant state. Therefore, epigenetic regulators are emerging as attractive therapeutic targets. We previously identified an epigenetic regulator called ENL as a critical requirement for the survival of a wide range of acute leukemias. This work has motivated ongoing efforts to develop inhibitors that targeting the function of ENL. In foreseeing future translational development of ENL targeted therapy, our goal of the proposed study is to investigate precisely how perturbing ENL and its associated pathways elicits anti-leukemic effects, and to identify mechanisms that govern the sensitivity and resistance to ENL inhibition.



Siao-Yi Wang, MD, PhD

Loyola University Cardinal Bernardin Cancer Center – Maywood, Illinois

\$100,000.00 – Engineering CD19-specific chimeric antigen receptor T-cells without inducing cell differentiation

Cellular therapy with chimeric antigen receptor (CAR) T cells have become an exciting form of treatment for B cell malignancies. CARs consist of a region that specifically recognizes a target protein and is linked to the signaling portion of a T cell receptor, which induces T cell reactivity when engaged. CAR T cells engineered to recognize the B cell protein, CD19, have demonstrated remarkable responses to relapsed or refractory B cell leukemia and lymphomas. However, a significant number of patients fail to respond to therapy or progress after initial response. Patients who have disease progression following CAR T cell therapy have a dismal prognosis, highlighting the critical need to improve its efficacy and durability. To engineer CAR T cells, T cells from patients are stimulated to induce cell division, which allows for the introduction of the CAR using a virus containing the genetic code for the receptor. This stimulation causes changes in the characteristics of T cells that make it susceptible to exhaustion and death, which are suboptimal for therapy. We have recently demonstrated that culturing cells in the T cell homeostatic regulating cytokine, IL-7, renders T cells susceptible to gene transfer without prior stimulation. In this project, we will use this strategy to engineer CD19-specific CAR T cells without inducing cell division or differentiation, thereby maintaining maximal therapeutic potential. These studies will provide justification for clinical trials, potentially improving survival for patients with B cell leukemia and lymphomas. In addition, results from this project can be applied to CAR T cells for other blood diseases such as multiple myeloma and myelodysplastic syndromes.



Yibin Yang, PhD

Research Institute of Fox Chase Cancer Center – Philadelphia, Pennsylvania

\$100,000.00 – Investigating and therapeutic targeting of the IL1R1-MyD88 pathway in Anaplastic Large Cell Lymphoma

This study's aim is to investigate the deep mechanisms underlying the inflammatory pathway in anaplastic large cell lymphoma (ALCL) based upon results from a high-throughput CRISPR library screen. Gaining insight into the pathological roles of the inflammatory pathway in ALCL can lead to improved understanding of the molecular circuitry that drives tumor survival and shapes the tumor microenvironment. The therapeutic potential of targeting the identified inflammatory pathway will be tested using a specific kinase inhibitor, which is an approach that can provide novel intervention strategies for targeted therapy in this disease.