NEW INVESTIGATOR AWARDS

Hui Feng, M.D., Ph.D. – Boston University

$100,000.00 - ***Dissecting The Regulatory Role Of Dlst In Myc-Driven Leukemogenesis***

MYC is a cancer-causing gene whose enhanced activity contributes to most human cancers including blood cancers. Growing evidence indicates that targeting the altered metabolism in MYC-dependent cancer cells could lead to effective new strategies for cancer treatment. Our previous research on T-cell acute lymphoblastic leukemia (T-ALL) identified a specific gene encoding dihydrolipoamide S-succinyltransferase (DLST), whose inactivation represents a promising approach to killing MYC-dependent cancer cells. In this proposed study, we will characterize how DLST inactivation disrupts metabolism in MYC-driven leukemia cells while sparing normal cells. This research will generate important information that will inform the development of DLST inhibitors as a future metabolism-based therapy.

Qing Li, M.D., Ph.D. – University of Michigan

$100,000.00 - ***Cell extrinsic signaling in oncogenic Nras-induced pre-leukemic stem cell transformation***

One of the challenges of the treatments of human leukemias is the frequent relapses, which is attributed to the persistence of pre-leukemic cells. These pre-leukemic stem cells are not leukemic yet but they set the stage to initiate the process of leukemia development. These cells often escape chemotherapy and re-initiate a new leukemia development while patients are in remission. A cure of leukemia depends on the eradication of these pre-leukemic stem cells (pre-LSC). These pre-LSCs arise from normal blood stem cells and mutations of leukemia genes in these cells allow them to hijack normal stem cell growth and survival programs. However, the mechanisms of how this occurs in pre-LSCs are largely unknown. We have recently developed experimental system to dissect these abnormal programs in pre-LSCs. In particular, we will study the interaction between the pre-leukemic cells with the bone marrow microenvironment to identify novel approaches to eliminate pre-leukemic cells.

Daniel Lucas, Ph.D. – University of Michigan

$100,000.00 - ***Regulation of quiescence in normal and malignant stem cells by the gut microbiota***

All the cells in the blood are produced by a specific stem cell inside the marrow of the bone. These are called hematopoietic stem cells (HSC). To be able to maintain blood production through life HSC are capable of self renewal. This means that when they divide at least one of the daughter cells is also an HSC. To ensure self renewal most HSC are in a state of quiescence where they divide very rarely.

In blood cancers HSC are lost due to the chemotherapy treatment and displacement by leukemia cells. This might lead to insufficient blood cell production, anemia and bone marrow failure and death. Previous work has shown that increasing the quiescence of HSC protects them from chemotherapy and increases their function. We have found that manipulation of the microbial flora found in the intestine of mice induces HSC quiescence. In Aim 1 of this proposal we will investigate whether this can be utilized to increase HSC self-renewal or their function (their ability to generate new blood cells). Leukemic stem cells are a very rare population of cancer cells that are responsible for maintaining and propagating the leukemia. They share many of the characteristics of HSC including quiescence. In Aim 2 we will test whether gut microbes can induce quiescence in normal HSC but not in leukemic stem cells and whether gut microbes can be utilized to protect HSC from leukemia cells. This is critical to be able to manipulate gut microbes to protect HSC but not leukemic stem cells during blood cancer. If successful the studies outlined here will open the door for clinical studies aimed at manipulating the gut microbiota during leukemia.

Michael J. Nemeth, Ph.D. – Roswell Park Cancer Institute

$100,000.00 – ***Regulation of therapeutic response in AML by myeloid-derived suppressor cells***
Acute myeloid leukemia (AML) is a devastating blood cancer that affects nearly 11,000 people each year in the United States. It is three times more common in people over the age of 65 than in younger people. Sadly, and despite extensive research into this disease, the overall five-year survival for patients with AML remains around 25%. One of the causes for this lies in the capacity of leukemia cells to survive chemotherapy. This is partly due to the presence of non-leukemia cells in the bone marrow that form an environment that supports the growth and survival of leukemia cells. We propose to study one specific type of cell in the leukemia environment called myeloid-derived suppressor cells (MDSCs). As their name implies, these cells suppress the effectiveness of our immune system as well as chemotherapy agents to eliminate leukemia cells. In this proposal, we will determine how these cells contribute to survival of leukemia cells during chemotherapy and also how leukemia cells cause these cells to expand in the first place. These cells are not just found in AML but in other blood cancers as well. Thus, by identifying processes by which the cellular environment protects leukemia cells, we will gain a potential approach for broadly improving treatment of patients with blood cancers that can complement and enhance current chemotherapy regimens.

Reshmi Parameswaran, MS, Ph.D. – Case Western Reserve University

$100,000.00 - ***Targeting B cell activating factor receptor (BAFF-R) as a novel therapeutic strategy for drug resistant Acute Lymphoblastic Leukemia (ALL)***
Acute Lymphoblastic Leukemia (ALL) is a type of cancer caused by accumulation of white blood cells in the body. In the United States, about 3000 new cases of ALL are identified every year, mostly children aged 2-8 years. A key issue in the treatment of ALL is the development of resistance to chemotherapeutic drugs. This drug resistance is mediated, in part, by the factors produced by various cells in the bone marrow microenvironment (environment in which cells exist). B cell activating factor (BAFF) is one such protein produced in the bone marrow. Our preliminary data shows that BAFF and its receptor are found on the surface of ALL cells and not on its normal counterparts. Addition of BAFF protected ALL cells from chemotherapy-induced cell death. Hence, we hypothesize that BAFF might mediate drug resistance in ALL cells. We propose to study the mechanism of BAFF signaling in ALL cells and design novel therapeutic methods targeting BAFF and BAFF-R to specifically kill ALL cells, without affecting normal cells.

Paul A. Spagnuolo, Ph.D. – University of Waterloo

$99,400.00 – ***Inhibition of fatty acid oxidation in selective leukemia cell death*** DLBCL
Acute myeloid leukemia (AML) is a blood cancer associated with poor patient outcome. For example, older patients (> 60 years) have a 2-year survival probability of less than 10%. Poor patient outcome is mainly because of the suboptimal quality of current drugs. Indeed, these do not kill leukemia stem cells, the cells responsible for disease onset and patient relapse. Thus, there is a need for improved drug treatments in these patients. My lab has determined that avocatin B can kill leukemia and leukemia stem cells without killing normal cells through a unique pathway of inhibiting the ability of these cells to use fat. This is important because leukemia cells need fat to survive. Normal cells do not need fat to survive. The goal of this proposal is to detail how avocatin B selectively induces death through this unique pathway. This research will be important to understand how leukemia cells growth and could lead to improved outcomes for AML patients who are currently faced with poor outcomes.

Ran Taube, Ph.D. – Ben-Gurion University

$100,000.00 – ***Targeting the transcription elongation machinery for treating MLL***

Mixed Lineage Leukemia (MLL) is a type of cancer, which appears in cells of the blood, and is generally characterized with poor prognosis. Conventional therapy is ineffective, emphasizing the need for new treatments. MLL is characterized with genetic changes that lead to expression of novel fusion protein activators with oncogenesis potential. These disrupt the expression of genes that play a key role in development and maintenance of progenitor blood cells, thus may promote MLL malignancy. Our research aims to understand the molecular mechanisms that control the function of the transcription elongation machinery, positioning its proteins as targets for the development of drugs that will suppress the progression of MLL. We will focus on two important gene expression regulators termed Super Elongation Complex (SEC) and Positive Transcription Elongation Factor b (P-TEFb). Both gene activators act synergistically and enhance the activity of RNA Polymerase II and promote gene expression. Our preliminary results show that inhibition of the transcription activity of these two complexes or modulation of their expression disrupts growth and survival of leukemic cells. This proposal will establish the role of SEC and P-TEFb in the control of genes that are involved in development of hematopoietic stem cells, and will examine the efficacy of small molecules inhibitors that specifically inhibit their activity. It will elucidate the cross talk between gene expression, epigenetic regulators that combine and promote malignancy. Given the importance of gene expression in promoting MLL leukemia, we envision the knowledge gained from this study will have a wide impact on both the molecular mechanisms that drive MLL and on developing new therapeutic strategies to treat this disease.

Eda Yildirim, Ph.D. – Duke University

$100,000.00 - ***Xist long noncoding RNA mediated gene expression and epigenetic stability in hematologic malignancies***

In mammals unequal number of X chromosomes in XX females and XY males is balanced by a dosage compensation mechanism called X chromosome inactivation (XCI). Initiation of this process depends on expression of the Xist RNA, which induces shutting off of gene activity on one of the two X chromosomes in female cells. The inactive state of this X chromosome is tightly controlled and maintained during cell divisions throughout the organismal life of the female. Interestingly, loss of Xist expression and elevated number of X chromosomes have long been associated with various cancers including blood cancers. These findings suggest a role for dysregulated X-chromosome dosage in cancer. Yet, causality has not been established. By deleting the Xist gene in the blood compartment of mice, we have discovered that Xist is also essential for maintaining the right dose of X chromosome and its loss leads to female-specific blood cancers in the form of mixed myeloproliferative neoplasm/myelodysplastic syndrome (MPN/MDS) and chronic myelomonocytic leukemia (CMML). Importantly, our findings show that deletion of Xist causes increase in expression of X-chromosome linked genes, progressive loss of blood-forming stem cells and inefficient production of blood cells. Here, we propose to build on these results and investigate how disregulation in the maintenance of X-chromosome dose leads to MPN/MDS.

Jing Yang, Ph.D. – University of Texas

$100,000.00 - ***Targeting Bone Marrow Adipocytes for Chemotherapy Resistance in Myeloma***

Our overall goal is to develop a novel strategy to prevent chemotherapy resistance in patients with multiple myeloma. We found that bone marrow adipocytes interact with myeloma cells and that this interaction contributes to chemotherapy resistance by promoting adipokine chemerin secretion from adipocytes. Our hypothesis is that adipocyte-secreted chemerin inhibits myeloma cell apoptosis, and counteracting adipocytes' protection can enhance antimyeloma activity of chemotherapeutic agents. The successful completion of the proposed work will inform the development of new strategies to combat relapsed or refractory myeloma, thereby improving the care of myeloma patients.