NEW INVESTIGATOR AWARDS

Inaugural Hy Wolff Memorial Grant
Zhe Yang, PhD – Wayne State University

$100,000.00 - *Structural insights into deregulated epigenetic mechanisms and DNA demethylation in myeloid leukaemogenesis*

The exciting new discovery of frequent mutation of a novel epigenetic regulator (Tet2) in a wide range of myeloid disorders, including acute myeloid leukemia, myelodysplastic syndromes, myeloproliferative disorders, chronic myelomonocytic leukemia, and systemic mastocytosis, highlights the clinical significance of this myeloid relevant protein with potential applications to disease diagnosis, treatment and prognosis. However, the pathological consequences of its mutations are unclear, and little is known about the role it plays in disease progression, evolution, and leukemic transformation. The long-term goal of the proposed work is to provide structural basis for the epigenetic events that regulate normal hematopoiesis and malignant myeloid transformation, as a necessary prerequisite of discovering factors that could fine-tune hematopoietic differentiation program or induce leukemia apoptosis. In this project, we will investigate the structure and function of Tet2, and test the hypothesis that the different myeloid mutations in Tet2 exert their pathogenic effects through different mechanisms. Given the enormous importance of Tet2 in mammalian epigenetics and myeloid disease, we believe that the successful completion of this project will lead to important insights into the structure and function of this myeloid relevant DNA dioxygenase, and will potentially open avenues to novel therapeutic strategies to ameliorate a variety of myeloid disorders such as acute myeloid leukemia, myelodysplastic syndromes, and chronic myelomonocytic leukemia.

Inaugural Jacob Zelenietz Memorial Grant
Chih-Chi Andrew Hu, PhD – H. Lee Moffitt Cancer Center

$100,000.00 - *Antigen stimulation in malignant progression of chronic lymphocytic leukemia*

Chronic lymphocytic leukemia (CLL) represents ~30% of adult leukemia. CLL is still an incurable malignancy that arises from aberrant growth of a B cell, whose normal function is to recognize protein antigen via its B cell receptor and produce antibodies to protect our body from infections. Although the occurrence of CLL is often attributed to stimulation by protein antigen, the role of antigen stimulation in the pathogenesis of CLL is still unclear. The IRE-1/XBP-1 pathway of the unfolded protein response (UPR) can be evoked by exposure to antigen and it provides critical survival mechanisms for cancer. However, such a critical pathway has never been investigated in the pathogenesis of CLL. In this proposal, we aim to understand whether exposure to protein antigen can promote malignant progression of CLL in mice via activation of the IRE-1/XBP-1 pathway. To achieve our goals, we have produced a novel antigen-specific CLL mouse model to allow our investigation of antigen-induced malignant progression of CLL in vivo. We have also produced a new CLL mouse model in which the function of the IRE-1/XBP-1 pathway is deleted. This mouse model should allow us to study in detail how the lack of the IRE-1/XBP-1 pathway can contribute to block or slow down malignant progression of CLL in mice. Besides, we have produced novel inhibitors that target the IRE-1/XBP-1 pathway. We will test whether these inhibitors can kill CLL cells in mice. Our studies may contribute to new therapeutic strategies for CLL.

16th Annual David Sachs Memorial Grant
Ryan Wilcox, MD, PhD - University of Michigan

$100,000.00 - ***GATA-3 as a Master Regulator of the Tumor Microenvironment in Peripheral T-cell Lymphomas***

DNA is the carrier of genetic information, which is packed as a structure termed chromosome in a cell. A human cell has 23 pairs of chromosomes. Internal or external damage can cause breakages of chromosomes, incorrect juxtaposition of different piece of chromosomes leads to chromosomal translocation. Leukemia and lymphoma are often associated with cancer type-specific chromosomal translocations. However, many aspects of the mechanisms underlying their generation and specificity still need to be elucidated. Activation induced deaminase (AID) can cause mutations in DNA in B lymphocytes during normal immune responses. There are numerous reports that show aberrantly expressed and/or alternatively spliced AID in human leukemia and lymphoma samples. These studies suggest AID may play an important role in the pathogenesis of leukemia and lymphoma. However, it is unclear how or under what conditions AID becomes deregulated. In addition, the mechanism by which deregulated AID induces chromosomal translocation or mutations during the disease process is less well understood. Our proposed project will attempt to elucidate the molecular mechanism that directs where AID targets in the genome and how deregulated AID promotes chromosomal translocations.

Inaugural ITxM Blood Science Foundation Research Grant
Maria E. Figueroa, MD - University of Michigan

$100,000.00 - ***The contribution of epigenetic gene silencing to leukemogenesis***

Acute leukemia is a form of cancer that affects the blood-forming cells from the bone marrow. This disease is extremely heterogeneous, consisting of many different subtypes. A variety of genetic abnormalities have been described that are associated with the different subtypes of leukemia. In our previous work we identified a set of genes that are abnormal in almost every acute leukemia subtype, irrespective of what other genetic abnormalities are present. The fact that the genes we identified are affected in almost all leukemia patients leads us to believe that they play a central role in contributing to the malignant transformation of bone marrow cells into leukemia cells. In this study we will investigate how this group of genes we identified cooperates with other genetic abnormalities to cause the development of acute leukemias. Identifying genes that affect the vast majority of patients and that play a central role in causing the disease is crucial in helping us recognize potential new targets for the development of novel therapies that can be used in the treatment of acute leukemias.

7th Annual George Richard Memorial Grant
Gang Huang, PhD - Cincinnati Children's Hospital

$100,000.00 - ***Molecular Mechanism of MLL-PTD Oncoprotein Transformation***

Studies have demonstrated that distinct mutations can cause similar cancers via their effects on key components of a regulation network. The key regulators for blood cell development are transcription factors and chromatin modifiers, which are often targeted by mutations or chromosomal translocations in human leukemia. Both the Mixed-Lineage Leukemia (MLL) protein, which methylates lysine 4 of histone H3 tails and is associated with transcriptional activation, and RUNX1, a DNA-binding transcription factor, are required for the establishment of definitive hematopoiesis in mice and act as tumor suppressors in leukemia. Previously, we found that RUNX1 regulates another transcription factor, PU.1, through the upstream regulatory region of the PU.1 gene, and that the epigenetic changes that occur in the PU.1 regulatory region correlate with PU.1 expression changes. Our proposal is to use mouse models that we developed to elucidate the role of MLL in helping open the chromatin structure at the PU.1 locus so RUNX1 can activate it, while as MLL-PTD downregulate RUNX1 and PU.1 and causes long term blood stem cells defects. We propose a novel concept of interplay between genetic and epigenetic regulators (RUNX1 and MLL), critical downstream transcriptional factors (PU.1) and self-renewal and anti-apoptosis genes (MCL-1, BCL-XL) underlying MDS and AML. The proposed research will increase our understanding of pathways amenable to therapeutic intervention, as well as to inform risk for current therapies.

Floyd A. Schlossberg Honorary Research Grant
Brian McNaughton, PhD – Colorado State University

$100,000.00 - *Overcoming Resistance to Chemotherapeutic Intervention in Leukemia and Lymphoma*
Many leukemias and lymphomas are resistant to chemotherapy treatment. This resistance makes these cancers particularly difficult to treat. We have recently identified potential drugs that overcome this resistance to chemotherapy treatment. During the course of this research we will optimize the potency and efficacy of these drugs, and take significant steps toward the development of next-generation treatments for leukemias and lymphomas that make it possible to combat and treat these diseases using existing chemotherapeutic reagents.

16th Annual Charles A. Sachs Memorial Grant
Gheath Al-Atrash, DO, PhD – The University of Texas MD Anderson Cancer Center

$100,000.00 – *Cathepsin G Is A Novel Myeloid Target*
The prognosis of patients with acute myeloid leukemia (AML) and aggressive chronic myeloid leukemia (CML) remains dismal, highlighting the need to identify novel strategies to manage this group of diseases. Although hematopoietic stem cell transplantation (HSCT) is the main immunotherapeutic modality for patients with AML and CML, because of its significant toxicity, HSCT is reserved for patients with aggressive or relapsed disease. In recent years, several protein antigens have been identified and targeted by immunotherapies (i.e. antibodies and vaccines) in leukemia with some success, but to date such therapies remain primarily investigational. One of the critical components for developing effective cancer immunotherapies is to identify targets that are distinctly expressed by the malignant cells, which can be specifically attacked to achieve cancer elimination with minimal off-target toxicity. Because of the diversity in antigen expression by leukemia, and since leukemia cells can change the expression of proteins on their cell surface to escape recognition by the immune system, targeting a single antigen is insufficient to completely eradicate the malignant clone(s). It is therefore critical that novel antigens be identified that can be targeted in leukemia. Cathepsin G (CG), an enzyme confined to granules in distinct populations of normal white blood cells, is abnormally expressed by leukemia cells. This makes CG an ideal target for immunotherapy. The following proposal aims to further characterize and define CG as a novel target for myeloid leukemia immunotherapy. We have confirmed the abnormal expression of CG in myeloid leukemia and showed that targeting CG1, a small 9 amino acid peptide derived from CG, eliminates myeloid leukemia in vitro. In this proposal, we will test anti-CG1 therapy in leukemia animal models to provide a foundation to build upon, as we further develop CG1-targeting therapies in clinical trials. Furthermore, since CG appears to be a promising leukemia target, we plan to characterize the potential role of targeting 4 small proteins derived from CG, in addition to CG1, that may also prove to be effective targets for leukemia immunotherapy. Together, this research will set the stage for the application of CGtargeting therapies to patients with myeloid leukemia.

14th Annual Ann Sherman Memorial Grant
Michael Kharas, PhD – Memorial Sloan-Kettering Cancer Center Cancer Center

$100,000.00 – *The role of MSI2 in the progression from Myelodysplastic syndrome into Acute Myeloid Leukemia*
Myelodysplastic syndrome (MDS) is characterized by a dramatic decrease of the number of cells in the blood. This is caused by a failure of the stem cells in the bone marrow to manufacture all the different cell types found in the blood. In elderly populations, these stem cells can accrue genetic changes that lead to dysfunction arising from mutant cells. Many of the elderly patients are difficult to treat due to their inability to tolerate bone marrow transplants. Moreover, many patients later progress to leukemia that is rapid and leads to poor survival. Our laboratory has found a novel factor that is found in the stem cells in the blood, but greatly increased in patients that progress from MDS to leukemia. We will use powerful mouse tools to test how this factor can force MDS cells toward leukemia and study how removal of this factor can change the course of the disease in mice. We believe that this factor may be a critical regulator in patients with a worse clinical prognosis. By testing this factor, we will develop a new model for this disease and identify a novel therapeutic target for both MDS and leukemia that may lead to inhibitors and treatments for this devastating set of diseases.