NEW INVESTIGATOR AWARDS

Michael Cosgrove, PhD
Syracuse University
$100,000.00 - ***Molecular mechanisms for the assembly and regulation of the MLL-core complex***
Mutations in the Mixed Lineage Leukemia (MLL) protein are present in a number of infants and adults with acute lymphoblastic or myelogenous leukemia. These mutations either increase or decrease MLL's function, which contributes to the transformation of normal cells into leukemia cells. For mutations that increase MLL's function, it is expected that new medicines that reduce MLL's activity will help convert the
leukemia cell back to a normal cell. However, these new medicines have been difficult to find due to a lack of understanding of how MLL works. One of MLL's functions is to act as a molecular switch that turns on and off genes at the right time in our cells. It does this by adding a small chemical group, called a methyl group, to another protein called a histone. When this switch works too fast or to slow it is believed that leukemia
develops. The goal of our research is to understand how the switching activity of MLL works, and to use this information to find new medicines that will fix broken switches in leukemia cells. We will do this by identifying the molecular mechanisms that control how fast MLL works.

Niall G. Howlett, PhD
University of Rhode Island
$99,505.00 - ***Regulation of the Mono-Ubiquitination of the Fanconi Anemia D2 Protein***
Fanconi anemia (FA) is a rare pediatric genetic disease characterized by bone marrow failure and pronounced susceptibility to leukemia. Defects in any one of thirteen different genes gives rise to FA. The protein products of these genes act cooperatively in a pathway, the FA pathway, to repair damaged DNA and to maintain chromosome stability. A failure to accurately repair damaged DNA can lead to the generation of
a transformed or 'cancerous' cell. Indeed, extremely unstable (i.e. broken, amplified, or rearranged) chromosomes are a hallmark of cancer cells. In order to carry out its function in DNA repair, the FA pathway needs to be activated or 'switched-on' under certain conditions. The FA pathway is activated *via* the transfer of a single ubiquitin molecule to the FANCD2 protein. Ubiquitin is a 76 amino acid protein that is critical for the regulation of many important cellular functions, including DNA repair. An inability to ubiquitinate FANCD2 results in a failure to activate the pathway and consequently can lead to the onset of chromosome instability. Therefore, the regulation of the ubiquitination of FANCD2 is of major importance in cancer prevention. Using a bioinformatics strategy, we have recently uncovered three new domains of the FANCD2 aminoacid sequence that may be critical for the regulation of its ubiquitination. We will change the amino acids of these domains and introduce modified FANCD2 into an FA patient cell line that lacks FANCD2. We will then be able to determine the importance of these amino acids for the ubiquitination of FANCD2 and for the activation of the FA pathway. Thus, we hope to uncover and characterize novel modes of regulation of this important pathway. A greater understanding of the regulation of the activation of the FA pathway may lead to improved diagnostic and therapeutic approaches to FA, as well as a greater understanding of leukemia susceptibility in the FA and non-FA populations.

Adam Lacy-Hulbert, PhD
Massachusetts General Hospital
$94,900.00 - ***Role of Alpha(v) Integrins in B Cell Leukemia***
White blood cells turnover constantly and new cells are generated daily in the bone marrow and other parts of the body. The growth and development of these cells is tightly controlled by many factors. Leukemia and lymphoma occur when blood cells escape from this tight control and grow uncontrollably. It is therefore important to understand how development of white blood cells is normally controlled and which of these signals are lost when cancerous cells develop. We are interested in a family of molecules that are found on the surface of developing white blood cells, the vitronectin receptors (also known as alpha-v integrins). These receptors allow blood cells to sense signals that control their growth and movement around the body and there is evidence that these signals may also be used by cancerous blood cells. In this grant we aim to find out how these molecules control white blood cell growth using mice in which these receptors have been mutated. We will also see whether cancerous white blood cells use these receptors and test whether blocking these receptors will stop cancer cell growth. These experiments will be important in furthering our understanding of white blood cell development and identifying potential new targets for tumor therapy.

Alexander Minella, MD
Northwestern University
$100,000.00 - ***Deregulated cyclin E in the pathogenesis of hematologic cancers***

Increased levels of the cell division cycle regulatory protein, cyclin E, are often found in human cancers, including in acute lymphoid and myeloid leukemias. In a significant portion of human cancers, especially in acute lymphoblastic leukemias, a protein complex (called the SCFFbw7) that controls the normal degradation of cyclin E and other potentially oncogenic proteins is mutated. In a cyclin E gene knockin mouse model that was developed to study the consequences of impaired Fbw7-controlled cyclin E protein degradation, I found that animals consistently developed anemia and abnormally appearing red blood cells, as well as increased cell proliferation and dysplasia in their spleens and bone marrows. Many of these findings are similar to those present in patients with some subtypes of the preleukemic, myelodysplastic syndromes. Surprisingly, in the cyclin E knockin mice, all the abnormal findings were restricted to the cells that give rise to mature red blood cells, and furthermore, the mice did not go on to develop leukemias. We hypothesize this is because red blood cell progenitors are especially sensitive to the effects of cyclin E deregulation and that an important tumor suppressor protein, p53, is able to inhibit the deleterious consequences of cyclin E overexpression in other hematopoietic cell types. The overall goals of this project are to determine how increased cyclin E promotes abnormal red cell development and dysplasia and to define the key physiologic barriers against cyclin Eassociated hematologic cancers. With a precise understanding of how deregulated cell cycle controls promote hematologic malignancies, further work to identify new potential therapies for these cancers will be facilitated.

Satoshi Nagata, PhD
Sanford Research Center University of South Dakota
$100,000.00 – ***Intracellular Signaling from Fc receptor- like proteins expressed in chronic lymphocytic leukemia: possible interaction with ZAP-70***
Progression of chronic lymphocyte leukemia (CLL) is likely induced through several chain reactions that take place in leukemia cells. Cell surface proteins initiate the reaction cascades upon stimulation by external factors. The exact mechanisms for disease progression is not yet known, but a special site, called ITAM, found in many cell surface proteins is considered to be crucial for initiating the chain reactions. Also, an accessory molecule, called ZAP-70, that boosts the chain reactions is detected in nearly all aggressive CLLs. Recently, Fc receptor-like (FCRL) proteins containing ITAMs were discovered from human genome research. Our work showed that FCRL proteins are found at high levels on malignant cells of CLL. In this study, we will analyze the chain reactions initiated from FCRL proteins and study their relationships with ZAP-70. We expect that the results of this study will help to elucidate the process of CLL progression, leading to development of effective therapy for CLL.

Ulrich Steidl, MD, PhD
Albert Einstein College of Medicine
$100,000.00 - ***Transcriptional Regulation of Leukemia Stem Cells in PU.1 Knockdown-Induced Acute Myeloid Leukemia***
Acute myeloid leukemia (AML) is a malignant disease that originates from a single transformed cell which has progressively acquired critical genetic changes that disrupt key growth-regulatory pathways. Despite the established use and optimization of regimens applying chemotherapy and the development of multiple new agents that are effective at reducing the tumor burden in patients with leukemia, relapse continues to be the most common cause of death in AML. Newer experimental evidence demonstrates that AML arises from a small population of leukemia stem cells (LSC). Similar to normal blood stem cells, LSC do not proliferate at a high rate but are rather quiescent and thus, conventional cytotoxic therapies are not effective against LSC in the majority of cases. However, therapeutic eradication of the LSC within the total leukemia cells will be essential for a cure of disease. Therefore, an improved understanding of the molecular pathways that suppress the formation and maintenance of LSC is required for the development of therapies that target LSC rather than the bulk leukemic cells (blasts). Recent findings from our own group and others demonstrate a critical role of PU.1 and Junb -- two proteins important for regulation of gene transcription -- in the genesis and function of LSC in AML, and that PU.1 and Junb are already deregulated in immature blood stem cells. However, their exact mechanism of action in the development of LSC is largely unknown. Therefore, the objectives of this research project are 1) to investigate the mechanisms of how PU.1 and Junb lead to formation and maintenance of LSC, and 2) to identify novel target genes of PU.1 in stem cells that are important for LSC generation and function. To identify implicated pathways PU.1-deficient blood stem cells were isolated by means of a specialized technology, multi-parameter highspeed fluorescence-activated cell sorting, and then subjected to gene expression analysis. Newly identified candidate target genes of PU.1 in LSC will be biochemically and functionally tested for their importance in LSC function. These studies will contribute to a better understanding of the master regulator PU.1 and its target genes in leukemogenesis, and provide the basis for the development of targeted, LSC-directed therapies that might ultimately lead to a cure of AML.

Jianguo Tao, MD, PhD
Moffitt Cancer Center
$98,077.00 - ***Biologically-targeted Therapy for Mantle Cell Lymphoma: focus on stromal cell-derived BAFF***
Mounting evidence now suggests that dynamic interactions, between the cancer cells and its local and systemic microenvironment, play a critical role in tumor development and that all of the clinical properties of a tumor, including response to therapy, depend heavily on the tumor stroma. This study will contribute to understanding the influence of the microenvironment on lymphoma cell survival and drug resistance and identifying new molecular target for future therapies of lymphoma and other blood related tumors. The knowledge to be gained will allow us to improve therapy of lymphoma.

Jiwang Zhang, MD, PhD
Cardinal Bernardin Cancer Center at Loyola University Medical Center
$100,000.00 - ***The role of C-MYC in the pathogenesis of leukemia initiation, progression and relapse***
Leukemia initiates from a mutant blood stem cell or progenitor (leukemia initiation cell, LIC) that accumulates additional mutations thus gaining growth advantage. The LIC then serves as a seed (leukemia stem cell, LSC) for leukemia development. After leukemia develops, LSCs are relatively quiescent, resistant to chemotherapy treatment, and have self-renewal capacity (can produce themselves). LSCs are also responsible for the leukemia relapse after chemotherapy induced complete remission. It is vital for the development of new leukemia therapies to gain a better understanding of the roles of specific molecules on leukemia initiation, progression and relapse. *C-MYC,* a common target of most leukemic oncogenes, has been proposed to be an appealing target for developing novel anti-leukemia therapy. We have found that *C-MYC* is required for *Notch1* induced-leukemia initiation, but dispensable for leukemia progression. We hypothesize that *C-MYC* is not necessary for LSC survival and self-renewal, but essential for the accumulation of additional mutations in LICs as well as LSC differentiation and proliferation. Therefore, we propose to study the role of *C-MYC* in leukemia initiation and relapse. Inhibition of *C-MYC* may not able to cure leukemia, but can significantly delay the leukemia relapse after chemotherapy induced remission. Our results will provide essential insights into the molecular details of leukemia initiation, progression and relapse and help in the development of new strategies for leukemia therapy.