NEW INVESTIGATOR AWARDS

Kenneth A. Frauwirth, PhD
University of Maryland
$77,304.00 - ***Regulation of T Cell and Lymphoma Function by Amino Acid Metabolism***
The ability of the immune system to fight infections, and potentially tumors, depends on the rapid activation of resting cells, especially lymphocytes. When stimulated, these cells undergo dramatic growth and division, and acquire new abilities, giving them the numbers and tools needed to protect the body. One cost of these processes is a high demand for resources, as lymphocytes need building blocks to grow and divide, and energy to power everything. This is particularly true of amino acids, which serve as both building blocks and energy sources for lymphocytes. Controlling access to amino acids may be one way the body regulates immune responses, preventing unwanted responses and conserving resources when nutrients are limited. We propose that leukemias and lymphomas have likely escaped from normal regulation of amino acid metabolism, allowing them uncontrolled growth. Our research is aimed at understanding the regulation of amino acid use by T lymphocytes, and how these cells sense and respond to amino acid limitation. We are particularly interested in comparing amino acid metabolism in normal and leukemic cells, with a goal of finding novel potential targets for leukemia and lymphoma therapy. We also hope to identify key amino acids that may enhance immune system function during, and recovery after, anti-cancer treatments.

Andrei L. Gartel, PhD
University of Illinois at Chicago
$100,000.00 – ***Targeting Pathways in Human Leukemia***
Human leukemia (HL) is a complex and life-threatening disease. Much progress has been made in understanding the biology of HL. This has been translated into new therapies, but long-term prognosis of adult leukemia patients is still very bleak. For this reason development of innovative strategies against HL is essential. We recently identified a small molecule, named ARC, which in low concentrations induces potent cell death in HL cells, but not in normal human cells. He goal of this proposal is to investigate the mechanisms of ARC-induced cell death in HL cells and to determine whether ARC can inhibit tumorigenesis in a mouse xenograft model of HL. If ARC prevents and/or inhibit HL tumor growth in mice it will suggest that ARC may have a potential as an anticancer drug against HL. In addition the data from this grant will help us to predict whether particular types of HL will be sensitive or resistant to ARC treatment. Completion of our proposal will enable us to determine if ARC is suitable for further clinical development.

Hisashi Harada, PhD
Virginia Commonwealth University
$100,000.00 - ***Promotion of Glucocorticoids-induced apoptosis by MEK inhibitors in ALL***
Glucocorticoids (GC) are one of the most effective therapies for leukemia and myeloma. Although the effects of GC on lymphocytes have been scrutinized for many years, the molecular mechanisms of sensitivity and resistance are not entirely clear. We and others have previously shown that BIM, a pro-death molecule, is up-regulated by Dexamethasone (Dex) treatment in acute lymphoblastic leukemia (ALL) cells and plays an essential role in Dex-induced cell death. Furthermore, BIM is modified and inactivated by ERK, a protein critical for cell survival. The main concept is that we have a novel and potentially effective way to increase GC activity against ALL cells, which may reflect the fact that a) GC up-regulate BIM; and b) pharmacologic ERK inhibitors further potentiate BIM activation. In this proposal, we will establish the mechanistic evidence how ERK-BIM pathway involves the synergistic interaction of Dex and ERK inhibitors. Information derived from this proposal will provide a rational foundation for future attempts to improve the activity of glucocorticoids such as dexamethasone with clinically relevant pharmacologic ERK inhibitors in the treatment of ALL and possibly other hematologic malignancies.

Lori Hazelhurst, PhD
H. Lee Moffitt Cancer Center & Research Institute
$100,000.00 - ***Role of topoisomerase II beta in repair of DNA damage induced by alkylating agents***
Alkylating agents are considered the first class of chemotherapeutic drugs used to treat cancer and were derived from sulfur mustard gas, a compound initially developed for warfare use. Alkylating agents continue to show marked anti-tumor activity and these agents continue to be used routinely for the treatment of lymphoma and multiple myeloma. Like most anti-cancer agents the overall success of alkylating agents is limited by the emergence of drug resistance. Thus understanding mechanisms of resistance continues to be an important avenue for increasing the efficacy of currently used cytoxics. We recently showed that reducing topoisomerase IIβ levels increases the sensitivity of tumor cells to melphalan induced cell death. Furthermore increased sensitivity to cell death correlated we with the inhibition of the repair of melphalan-induced interstrand DNA crosslinks. Together these data indicate that topoisomerase IIβ functions in a DNA repair pathway(s). However, currently it is unclear (A) which DNA repair pathway(s) topoisomerase IIβ facilitates and (B) what signals activate the repair function of topoisomerase IIβ. In this proposal we will directly test whether (A) topoisomerase IIβ is required for efficient functioning of the fanconia anemia/BRCA pathway and (B) whether the DNA damage sensor ATR activates the repair functions associated with topoisomerase IIβ. Overall these studies will provide insight into targets that inhibit DNA repair functions with the therapeutic goal of enhancing the efficacy of alkylating agents in resistant disease.

Katrin Karbstein, PhD
University of Michigan
$100,000.00 - ***Regulation of Ribosome Assembly via Phosphorylation of the Essential GTPase Bms1***
Cancer cells are distinguished by a rapid rate of cell division and growth. This growth requires the cells to be able to produce everything they need in large quantities. One key component of all growing cells are ribosomes. Ribosomes are the cellular factories responsible for making proteins, thereby enabling cells to work and expand. Because of this key requirement for ribosomes, their synthesis is tightly regulated and a required for cell division. Interrupting the cell's ability to produce new ribosomes represents therefore a potentially powerful new target for drug therapy of malignant cell growth. Indeed, research in the late sixties has shown that blood cells that do not grow do not produce ribosomes, while rapidly growing cells efficiently produce ribosomes. Despite the obvious importance of this pathway and its promise as a target for drugs that treat cancers including leukemia, it has not yet been exploited for drug purposes. The reason for this is that it is poorly understood and its regulation remains uncharacterized. The work in this proposal will address these issues and determine how an essential component in the ribosome assembly machinery is regulated. This work will start shedding light on the workings of the ribosome assembly machinery and help uncover drug targets in this pathway.

Piers D. Nash, PhD
University of Chicago
$100,000.00 - ***CXCR4 stability and trafficking is controlled by the deubiquitylating enzyme USP8***
White blood cells respond to chemical attractants that direct their movement throughout the body to sites where they can develop and then on to sites where they fight infection. These chemical attractants, or chemokines, work by binding to specific receptors on the surface of white blood cells. Perhaps the most important of these chemical attractants is the chemokine SDF-1 and its cognate receptor, CXCR4. The SDF-1/CXCR4 system is critical for many functions, including stem cell homing to key sites in the body and the correct development of immune cells and blood cells. Not surprisingly, CXCR4 is also central player in the development of a variety of leukemias, including B-cell chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL) and acute myelogenous leukemia (AML), as well as nonhematopoietic malignancies such as breast and lung cancer. We have recently identified the protein product of the USP-8 gene as a central regulator of CXCR4 protein levels in the cell. USP8 functions to control the stability of CXCR4 protein by determining how much CXCR4 is removed from the cell surface and degraded inside the cell. In doing so, USP8 is a significant determinant of CXCR4 levels in the cell. CXCR4 is often elevated in leukemia and is a poor prognostic indicator in a number of cancers. USP8 is a highly specific proteinase, and is therefore a potentially drugable target. While drug development is not part of this proposal, we are already working with one biotechnology company to develop and test USP8 inhibitors. As CXCR4 levels are important for stem cells to home to their correct niches within the body, manipulating CXCR4 levels with USP8 drugs or

gene therapy may also have application in stem cell therapy. For this proposal, we are seeking to understand exactly how it is that USP8 controls CXCR4 levels, and what the effect of this manipulation is on the migration ability of acute lymphoblastic leukaemia (ALL) cells. The studies proposed are a combination of biochemistry and cell biology examining the pathways by which CXCR4 protein degradation is achieved and how USP8 acts within these.

Michael R. Verneris, MD
University of Minnesota
$100,000.00 - ***Two pathways of NK Cell Differentiation: Generation of Alloreative NK Cells***
Bone marrow transplantation (BMT) is a curative form of treatment for leukemia that is refractory to chemotherapy. BMT works through: 1) higher doses of chemotherapy and 2) an immune-based recognition of the leukemia cells. One of the cells which has been shown to be important for the recognition of leukemia after BMT are natural killer cells (NK cells). NK cells recover quickly after BMT and these cells kill leukemia cells without prior activation. Current studies suggest that only some NK cells are capable of killing leukemia cells. Understanding how NK cells recover after BMT is critical to developing strageties to prevent leukemi reaplse. In this proposal we will investigate a newly identified NK cell developmental pathway. Our preliminary studies suggest that this pathway generates NK cells with the ability to kill leukemia cells. These studies will help us develop strageties to prevent leukemia relapse after BMT (by giving drugs that favoring this type of NK cell development). As well, the knowledge gained from these studies may allow us to generate NK cells in the laboratory that could be given back to patients to either prevent or treat relapse.

Qun Tian Wang, PhD
University of Illinois at Chicago
$100,000.00 - ***The chromatin remodeling ATPase Smarcal in blood cell development and acute leukemia***
Genomic DNA in mammalian cells is packaged into chromatin. The higher order structure of chromatin can be modified, or remodeled, to allow genes in specific regions to be expressed or turned off. Defects in chromatin remodeling may underlie many diseases, including leukemia and lymphoma. We have recently discovered a role for the chromatin remodeling protein Smarca1 in the proper expression of a number of genes that are normally expressed in blood cells, including two transcription factors that have been implicated in acute leukemia. We will use two types of Smarca1 mutant models to investigate the function of Smarca1 in blood cell development. We will also use Smarca1 knock-down leukemia cell lines to examine the role of Smarca1 in tumor cell survival, proliferation, and gene expression.

Michael C. Yu, PhD
The State University of New York
$100,000.00 - ***The Role of PRMT6 in the Maintenance of Genome Stability***
Cells face constant bombardment by mutagens that affect the integrity of the cellular genome. Failure of a cell to properly protect or repair its genome results in increased genome instability, a hallmark feature for leukemia and lymphoma. An increase in genome instability translates into a higher probability for cells to generate a mutation that disrupts processes crucial for the control of cell division. To circumvent these challenges, cells are equipped with machineries that help to maintain the integrity of its genome by repairing DNA lesions. Understanding how these cellular machineries are regulated, therefore, will help us gain insights into possible drug targets that will control their biological functions. Recently, biomedical researches have found a novel link between an enzyme called PRMT6 and the regulation of DNA repair. To better understand how PRMT6 helps to preserve genome integrity, we propose to determine which proteins are associated with PRMT6 in lymphohematopoietic progenitors. This will help us to identify the biological roles of PRMT6 either as a regulator or as a substrate. Second, we wanted to comprehensively map the interactions between PRMT6 and the genome in the context of lymphohematopoietic progenitors. This information will lead us to elucidate specific genomic events, such as specific gene expression programs, modulated by PRMT6.