NEW INVESTIGATOR AWARDS

Ioannis Aifantis, PhD
The University Of Chicago, Chicago, IL
$75,000 - ***Cooperation of Notch and pre-TCR Signaling in the Induction of T Cell Leukemia***
The main focus of our work is to gain an understanding of the mechanisms that govern the development of the immune system. We are using techniques of modern molecular biology and immunology to study the role of proteins-receptors that are expressed on the cell surface, induce the maturation of T lymphocytes that are protecting the organism from infections by destroying pathogen-infected cells and helping the production of antibodies. This project is based on accumulating experimental and clinical observations suggesting that abnormal function of two of these receptors (called Notch and pre-T Cell Receptor) may cause T cell acute leukemia (T-ALL), a common malignant disease afflicting children and adults. We are planning to study the biological interactions of these receptors in the induction of the tumor formation and to identify genes- targets of these receptors responsible for the leukemia phenotype in both mice and humans. These genes can subsequently be targets of gene therapy and pharmacological intervention.

Chang H. Kim, PhD
Purdue University, West Lafayette, IN
$75,000 - ***Redirection of Anti-Lymphoma Effector T Cell Trafficking***
Surveillance by the immune system is important to eliminate tumor cells from our body. But tumor cells, through multiple mutations, acquire the ability to evade this surveillance. Some types of lymphoma cells avoid the attack by immune cells by producing specialized soluble proteins. These lymphoma-derived soluble proteins selectively prevent migration of anti-tumor immune cells to lymphoma sites, while they allow infiltration of several types of immune cells that are favorable for tumor growth. Immune cell migration to tumor sites is mediated through specialized migration pattern of immune cells by changing the expression patterns of these receptors by a gene transfer method so that they can more efficiently migrate to lymphoma sites and kill tumor cells. Our studies proposed in this proposal will provide a new strategy to fight against lymphomas, and have a direct clinical application potential in humans.

Artur Slupianek, PhD
Temple University, Philadelphia, PA
$75,000 - ***Activation of Homologous Recombination Mechanisms by BCR/ABL***
The project is designed to investigate the mechanics of drug resistance in leukemia cells. Our recent studies indicated that RAD51 protein, involved in reparation of DNA lesions caused by radiation or cytostatic drugs, is activated in leukemia cells expressing the oncogenic tyrosine kinase BCR/ABL. Activation of RAD51 is essential for drug resistance. To exert its function RAD51 collaborated with other proteins, which are necessary fro that proper initiation and completion of the repair process. Thus, RAD51 and its partners work together to protect leukemia cells from cytotoxic therapies. I believe that an understating of the mechanisms regulating this process may be useful for the planning of more effective anti-tumor treatment.

Ian P. Whitehead, PhD
UMDNJ, New Jersey Medical School, Newark, NJ
$74,433 - *Investigating a Role for the TSG101 Tumor Suppressor in CML*
Virtually all patients with chronic myelogenous leukemia (CML) have a genetic abnormality called the Philadelphia chromosome. This abnormality produces a dysfunctional protein (Bcr-Abl) that is known to be responsible for CML. Bcr-Abl is a large and complex protein which is known to interact with a number of other proteins in the cell. Determining which of these interactions is relevant to CML is a great challenge to cancer biologists. We have identified a new binding partner for Bcr-Abl, designated TSG101. Interestingly, the TSG101 protein has already been implicated in a number of human cancers, including several leukemias, but has never been examined in the context of CML. We will examine the relationship between the Bcr-Abl and TSG101 contributes to, and is necessary for, disease progression, it would represent a new and exciting target for pharmacological intervention.

Christoph Wuelfing, PhD
University of Texas Southwestern Medical Center at Dallas; Dallas, TX
$75,000 - *Enabling Natural Killer Cells to Lyse Acute Myeloid Leukemia Cells by Interfering with Inhibitory Receptor Function*
The immune system is the part of the human body that recognizes and eliminates pathogens. It has long been hoped that the immune system can be harnessed to also eliminate cancer cells. Two cell types of the immune system have the potential to kill cancer cells, one of which called natural killer cell (NK cell) is the subject of this proposal. In call clinical settings NK cells are rather ineffective in the elimination of leukemia cells. Recently, it has become clear that molecules on the surface of the NK cells, called inhibitory receptors, limit leukemia cell elimination by the NK cells. Here we propose to enhance our understanding of how these receptors function and to develop a first biochemical tool to block their function. Such a release of their inhibitory function will enable NK cells to kill leukemia cells, this potentially contributing to a novel therapeutic approach.

PHYSICIAN-SCIENTIST AWARDS

Roger A. Greenberg, MD, PhD
Dana Farber Cancer Institute, Boston, MA
$90,000 - *BRCA1 and the Repair of Damaged Chromatin*
An almost invariant property of cancer cells is the mutability of their genome (total DNA content). This is particularly true for leukemia. Agents that damage DNA such as ionizing radiation or chemotherapeutic agents greatly predispose to the development of leukemia. Furthermore, individuals that inherit a decreased ability to repair damage to their NDA are also commonly afflicted with leukemia and other cancers. This proposal seeks to uncover the basic mechanisms that human cells employ to maintain integrity of their genome. We hope to gain a greater understanding of the mechanisms cells use to suppress leukemia and other cancers by learning about the role of the important tumor suppressor BRCA1 in DNA repair. The experimental plan outlined in this proposal seeks to address these issues in a systematic manner with broad general applicability to understanding the relationship between genome stability and cancer.

Haytham Khoury, MD
Ontario Cancer Insitute, Toronto, Ontario, Canada
$90,000 - *Noggin and Follistatin Overexpression: Mechanism of Bone Marrow Failure in AML*
AML is a proliferation of abnormal cells in bone marrow leading to reeducation in normal cellular products including red blood cells, platelets and neutrophils. AML patients are more likely to suffer from the consequences of normal cell decreases (shortness of breath, infections and bleeding) rather than the increase of abnormal ones. This reduction in normal cellular production is probably the result of the secretion of inhibitory factors by the leukemic cells themselves. Characterization of these factors is important not only to enhance our understanding of leukemia but also to develop new treatment strategies that improve the outcome of this serious disease.

Benjamin H. Lee, MD, PhD
Brigham & Women's Hospital, Boston, MA
$90,000 - *Murine Models of the Activated Flt3 Receptor Tyrosine Kinase in Acute Leukemia Research*
Tremendous insights into the mechanisms and mutations that underlie human cancers are often uncovered through the careful study of these diseases in well-characterized animal model systems. The molecule Flt3 plays an important role in the development of human leukemia as Flt3 has been found to be the most commonly mutated gene in patients with acute myelogenous leukemia (AML). Through standard genetic engineering techniques, we will be able to generate mice that can express a mutant from Flt3. By studding the effects of this mutated Flt3 protein in a whole animal mouse system, we will be able to better understand both the normal role of this gene and how it contributes to the development of leukemia. Moreover, the development of these mice provides a powerful biological tool that can be used to test the therapeutic efficacy of novel drugs against Flt3-induced leukemia's and they can employed with other mouse model systems to further our understanding of how different classes of mutation can cooperate with one another in the development of acute leukemia.

POSTDOCTORAL FELLOWSHIP AWARDS

Constandache Atanasiu, PhD
The Wistar Institute, Philadelphia, PA
$60,000 - ***NAD-Dependent Regulation of Epstein-Barr Virus Plasmid Maintenance***
Epstein-Barr virus is associated with several human lymphomas. EBNA1 is the only viral protein expressed in many of these tumors and is essential for the survival of the viral DNA in infected tumor cells. We have found that EBNA1 interacts with a cellular enzyme (Tankyrase) that is typically found associated with the ends of human chromosomes (telomeres) and plays a role protecting the cellular genome from deterioration. We propose to investigate the interaction of Tankurase with EBNA1, and to better understand the mechanism of viral survival in latently infected tumor cells. Understanding the mechanism of EBNA1 regulation will help develop strategies against lymphomas produced by EBV.

Piernicola Boccuni, MD
Memorial Sloan-Kettering Cancer Center, New York, NY
$60,000 - ***The function of L (3) MBT in Hematopoietic Cancers***
We have isolated a gene, H-I (3) mbt, which is located on the long arm of chromosome 20 (20q), a region frequently deleted in hematologic malignancies, and we are characterizing its functions, because it is similar to a gene that when lost, causes tumors in the fruit fly. This gene is a member of a family of genes that regulates the overall process of development, and also regulates the growth and differentiation of blood cells. The goal of our research is: I. to define the role of H-l (3) mbt, II. to define its mechanism of action. We will up regulate and down-regulate the expression of H-l (3) mbt in primary human hematopoietic stem cells to learn how it affects the growth and the differentiation ability of these cells, and we will identify the genes whose regulation is under the control of H-l (3) mbt protein. We will look to identify the proteins that interact with H-l(3)mbt protein and that are likely required for the normal function of H-l(3)mbt. We hope that the study of H0l(3)mbt is malignant and normal blood cells will help us understand what mechanisms lead to diseases that are associated with 20q deletions, and will provide information on how blood development is normally regulated.

Mike Boxem, PhD
Dana-Farber Cancer Institute, Boston, MA
$60,000 - ***Functional Studies of the C. Elegans Mitotic Machinery***
The development of cancers, including leukemias, is a multi-step process in which normal cells gradually become deregulated and proliferate unrestricted. It is thought that genetic abnormalities from a large contribution to this process. When a normal cell divides, the genetic material is first duplicated and then segregated into the two daughter cells. Defects in the mechanisms that control these events can lead to genetic abnormalities, and thus may contribute to the development of cancer. To be able to develop better treatments against cancer, it is vital that we understand in great detail the mechanisms that cause a cell to divide, and how they work to maintain genomic stability. My research is aimed at understanding the various functions of the mitotic apparatus, which is responsible for segregating the genetic material into two daughter cells. The approach I am taking is to identify the components of the mitotic apparatus, and determine the interactions between them. Ultimately the goal of these experiments is to better understand how defects in mitosis can lead to cancer development, and to identify key targets for drug therapies.

Ross A. Dickins, PhD
Cold Spring Harbor Laboratory, Cold Spring Harbor, New York
$60,000 - ***Modulation of the p53 Pathway in a Mouse Model of Lymphoma Development and Therapy***
Cancer results from genetic mutations. Likewise, the ability of tumors to survive treatment results from subsequent mutation. The investigation of the relevance of these individual changes in human tumors is, however, problematic. Tumors generally contain large numbers of genetic alterations, and it is exceedingly difficult to determine whether any given change is important for tumor formation, treatment response or is simply an irrelevant byproduct of some other cellular defect. One well-established method to circumvent these problems is to use mouse models for tumor development. In these models, one can investigate the effects of a single genetic alteration on tumor incidence or development. Unfortunately, developing these models is time consuming, and limited: if a protein is essential for mouse development, mice cannot be generated that are deficient for the gene encoding this protein. Two recent technological advances, developed by our lab and others, have significantly enhanced our ability to create meaningful mouse models of tumor formation and progression. The first advance is our ability to put genes into mouse hematopoietic stem cells. Using this technique, we can introduce a gene into white blood cell precursors and determine the effect this gene had on the formation of leukemias and lymphomas. Unlike whole mouse manipulation, this technology allows us to examine many genes in a short period of time. The second advance is the development technique called RNA interference (RNAi), which allows us to inactivate virtually any gene in a cell, including genes that are essential for development. Using these techniques, we now have the tolls to truly ‘model’ leukemias and lymphomas in mouse. In other words, we can start to determine exactly which genetic changes are required to change normal cells into tumor cells. We can also determine how specific changes correlate with disease outcome and treatment response. Work from our lab had already shown that a single genetic change can dramatically change the sensitivity of lymphomas to chemotherapy. This proposal uses these techniques to examine the role of particular genes that we predict will be important modifiers of lymphoma development and therapy.

Niall G. Howlett, PhD
Dana Farber Cancer Institute, Boston, MA
$60,000 - *Elucidation of the Role(s) of the BRCA2 Protein in the FA-BRCA Pathway*
Fanconi Anemia (FA) is a rare hereditary disease characterized by bone marrow failure and juvenile leukemia. Mutation in any one of at least seven genes leads to FA. Six of the known FA proteins interact in a common pathway required for the repair of damaged DNA. We have recently discovered that the seventh FA gene is in fact the known breast and ovarian cancer susceptibility gene BRCA2 protein acts together with the FA proteins in the regulation of the repair of damaged DNA, thus preventing the onset of malignancy. We plan to elucidate how the particular BRCA2 mutations identified leads to impaired DNA repair function and subsequently FA. Finally, it is possible that mutation in any of the seven FA genes may underlie leukemia in the general (non-FA) population. Therefore, we will screen for the integrity of the FA pathway in leukemia cells established from non-FA leukemia patients. A molecular understanding of pathogenesis of FA may lead to greater understanding of bone marrow failure and leukemia susceptibility in the general (non- FA) population, and ultimately lead to the generation of new diagnostic and therapeutic approaches in leukemia.

Jiann-Kae Luo, PhD
The Scripps Research Institute, La Jolla, CA
$60,000 - *Molecular Mechanism for the Inhibition of Chronic Myeloid Leukemia by the ISG15 Protein Modification Pathway*
Chronic myeloid leukemia (CML) accounts for 15-20% of all cases of leukemia, with a peak incidence among individuals aged between 40 and 50 years. Treatment of CML with the protein interferon-α (IFN-α) has proved to be very effective in improving the long-term survival rates of patients. IFN-α plays an important role in organisms by mediating a host of cellular defense responses, including antiviral and anti-tumor functions. It is thought that IFN-α performs these functions by "switching on" various genes involved in inhibiting cell growth and proliferation. One of the genes activated by IFN-α produces a protein known as ISG15. ISG15 is usually found at very low levels within the cell. However, upon stimulation by IFN-α, cells show much higher levels of ISG15, as well as higher levels of other proteins attached to ISG15. Our lab has shown strong evidence that this attachment of ISG15 to other proteins, or ISGylation, is vital to the ability of the cell to respond to interferon treatment. Cells with defective ISGylation are resistant to IFN-α treatment, whereas cells with enhanced ISGylation are extremely sensitive to the effects of IFN-α. We have also found that one of the targets for ISGylation is the protein Erk1/2, a key protein in the cellular pathways controlling cell growth. As mentioned above, one of the effects of IFN-α is to inhibit cell growth. Since this effect requires functional ISGylation in the cell, and since Erk1/2 is found to be ISGylated, we hypothesize that the ISGylation of Erk1/2 plays a vital role in the biological mechanism of IFN-α action. Thus we have undertaken to investigate the mechanism of ISGylation and the effects of ISGylation on Erk1/2 function and metabolism. Results from these studies will yield new insight into designing novel strategies for enhancing the efficacy of IFN-α, as well as identifying potential drug targets in Erk1/2 and other ISGylated proteins.

Tomas Stopka, MD, PhD
Albert Einstein College of Medicine, Bronx, New York
$60,000 - *Role of Chromatin Remodeling Gene SNF2h in Leukemia and Normal Development*
Leukemia results from genetic changes of normal progenitor blood cells and propagates as a clone with growth advantage and blocked in its ability to become a mature blood cell. We recently obtained evidence that chromatic remodeling gene SNF2h is associated with highly proliferative, undifferentiated leukemia cells and that it is down regulated SNF2h expression upon their differentiation *in vitro* or *in vivo* treatment-related depland in leukemia patients in remission while undergoing treatment. To investigate the role of SNF2h in health and disease, we have prepared several biological models including SNF2h knockout animals and SNF2h-overexpressing leukemia cell lines. I propose to use these models and determine the role of SNF2h in development of pluripotent embryonic stem cells and in leukemic proliferation and differentiation.