RIZZO MEMORIAL GRANT

Dario Campana, MD, PhD
St. Jude Children's Research Hospital, Memphis, TN
$200,000 – *Detection of Residual Leukemia in Children*
The measurement of minimal residual disease (MRD) at critical intervals during the disease course is a new tool to gauge the effectiveness of therapy in children with acute lymphoblastic leukemia (ALL). We have developed flow cytometric techniques capable of detecting 1 leukemic cell in 10,000 normal cells or greater. In a perspective study of children with ALL, sequential monitoring of MRD by these methods provided highly significant, independent prognostic information.

The greatest remaining obstacle to the use of MRD studies in clinical protocols is the inapplicability of current methods to all patients. In the case of flow cytometry, only approximately 85% of patients currently have leukemia-specific phenotypes at diagnosis. Moreover, the complexity and relative high cost of the current cell marker panels limits the use of this approach to a few specialized centers. Studies proposed under Specific Aim 1 will rely on gene expression profiling of leukemic lymphoblasts and normal lymphoid progenitors to identify new leukemia markers and extend the potential benefits of MRD detection to a larger number of children with ALL. We plan to use DNA microarrays, which allow rapid measurement of the expression of thousands of genes. In preliminary studies, we obtained encouraging results with this new technology. Ultimately, we should identify a few reliable universal markers of leukemia, thus increasing the efficiency of testing and facilitating the establishment of MRD studies in other centers.

In Specific Aim 2 we propose to determine whether levels of MRD in peripheral blood reflect those in the bone marrow. Our preliminary studies of paired blood and marrow samples collected at the end of remission induction therapy suggest that MRD may be present at similar levels in a subset of ALL patients. These studies also suggest that MRD detection in peripheral blood during the early phases of treatment might identify patients with high relapse hazard. We plan to investigate MRD levels in peripheral blood samples at several time points during therapy, and compare the findings with MRD levels in marrow, clinicobiologic features of the disease and treatment outcome.

If successful, the studies proposed here will extend the potential benefits of MRD studies to a larger number of children with ALL, and establish a more efficient and practical approach to remission studies.

Martin Schrappe, MD
Medizinische Hochschule Hannover, Hannover Germany
$200,000 - *Extended Evaluation of Minimal Residual Disease During Randomized Treatment of High Risk Childhood Acute Lymphoblastic Leukemia*
Abstract withheld

NEW INVESTIGATOR AWARDS

Clifford A. Lowell, MD, PhD
University of California, San Francisco, CA
$50,000 – *Mouse Models to Define the Roles of SRC-Family Tyrosine Kinases in Acute Promyelocytic Leukemia*
Acute promyelocytic leukemia (APL) is a unique form of leukemia that results from a specific chromosomal rearrangement that occurs in the malignant cells. This genetic rearrangement results in the formation of a novel hybrid protein molecule, found only in the leukemic cells, that induces their unrelenting growth properties. A model of this disease has been made using transgenic mice which are genetically engineered to produce this same hybrid protein in their blood cells. The mice get a form of APL that closely resembles the human disease and responds to the same therapies used in human patients. A major advantage of mouse models is the ability to breed the disease bearing animal with other mutant mouse strains to determine if mutations in other genes can affect the disease process. We will cross the APL transgenic mouse to an animal that lacks a class of tyrosine kinase proteins normally found in the very blood cells involved in APL. Our laboratory has studied these kinase proteins and has demonstrated that they are responsible for regulating the way normal blood cells sense growth factors and survival signals from their environment. We believe these gene products will have the same function in leukemic cells. Without the kinases, we anticipate that the leukemic process in the transgenic mice will be dramatically altered or even ameliorated. If so, this would demonstrate that therapeutic agents directed at these kinases may offer a new avenue of therapy for this form of leukemia.

Ashok Aiyar, PhD
Northwestern University Medical School, Chicago, IL
$50,000 – *Cellular Proteins that Mediate EBNA-1's Function in EBV Replication*
Epstein-Barr virus (EBV) is a human herpes virus that primarily infects lymphocytes. Upon infection, EBV induces these lymphocytes to proliferate. This proliferation is usually self-limiting, and causes mononucleosis, a mildly debilitating disease. However, a failure to check the proliferation of cells infected by EBV results in malignant conditions. Malignancies that EBV is causally associated with include Burkitt's lymphoma and naso-pharyngeal carcinoma. In addition, EBV is associated with a large number of other leukemias, lymphomas, carcinomas, and other lymphoproliferative diseases, usually in immuno-suppressed individuals. Genes expressed by EBV are required for malignant cells infected by EBV to continue proliferating. EBV is latent within infected malignant cells that are proliferating, i.e., it does not express many viral proteins or produce daughter viral particles, but instead has evolved a mechanism to ensure that its genome is distributed to daughter cells as the infected cells proliferate. This process requires a single region on EBV's genome, called *oriP*, and a single viral protein, EBNA-1 that can bind *oriP*. EBNA-1 is the only EBV protein that is expressed in all malignancies associated with EBV. This is perhaps not surprising considering that EBNA-1 is required for the EBV genome to be distributed into daughter cells. Our work is directed to understanding how EBNA-1 allows EBV's genome to be distributed into daughter cells. It is our hope that understanding this mechanism will facilitate the development of therapeutics that inhibit this process. Such therapeutics will be of tremendous utility to treat individuals who have EBV-associated malignancies. Preventing EBNA-1 from distributing EBV's genome into daughter cells, will rid those cells of EBV, and thereby stop their uncontrolled proliferation.

Weiqun Li, MD
Georgetown University Medical Center, Washington, DC
$50,000 – *Activation of Src Homology 2-containing Inositol 5? Phosphatase (SHIP) in Myeloid Cell Differentiation and B Cell Tumor Development*
This project will promote understanding of the molecular mechanisms of the phospholipid phosphatase, SHIP, in chronic myelogenous leukemia and B cell lymphoma. SHIP aids cells in differentiation, possibly acting as a tumor suppressor. Our objectives are: (1) to determine how SHIP assists in cell differentiation and, (2) to test if and how SHIP suppresses the progression of B cell malignancies. This project may also aid in designing new strategies to treat this disease with differentiation-inducing agents such as SHIP.

Gil Ast, PhD
Tel Aviv University School of Medicine, Ramat Aviv, Tel Aviv, Israel
$48,850 – *Alternative Splicing of Exon 1α in the Human INK4a/ARF Tumor Suppressors Locus*
The INK4a/ARF locus on chromosome 9 is one of the sites mutated most frequently in human cancer. Two genes comprising overlapping reading frames encoding p16INK4a and p19ARF have been discovered at this locus and, remarkably, both play an important role in regulating cell growth, survival, senescence, and both are also potent tumor suppressors. Mutation, deletion, or hypermethylation of INK4a/ARF locus is common in many tumors. For example, gene abnormality is detected in 50% of patients with chronic myeloid leukemia and T cell acute lymphoblastic leukemia.

The p16INK4a is encoded by three closely linked exons (designated 1α, 2 and 3). RNA transcribed from the alternative first exon (1ß), which maps 20 kb upstream in the human genome, is spliced to exon 2, yielding a p19ARF transcript. The translation initiation codon in exon 1ß is not in frame with sequence encoding p16INK4a in exon 2, so that the two mRNAs encode different polypeptides although both mRNAs are transcribed in the same cells. Therefore, we will study the regulatory mechanism by which exon 1α is excluded from p19ARF but included in p16INK4a mRNA. For this purpose, we will generate a mini-gene of genomic p19ARF and determine, both *in vivo* and *in vitro*, which RNA precursor sequences regulate exon 1α exclusion. The long-term objective of this study is to restore normal p19ARF and p16INK4a activity in cancer cells in which the INK4a/ARF locus has been mutated, deleted or hypermethylated.

Ying K. Tam, PhD
Rush Cancer Institute, Chicago, IL
$50,000 – *Molecular Basis for Target Cell Resistance to Natural Killer Cell-Mediated Cytosis*
Natural Killer cells play an important role in defending the body against infection by viruses and bacteria and in providing protection against the development of cancer. Due to their ability to recognize and kill malignant cells, there is great interest in using these cells to treat patients suffering from various forms of cancer. However, although most cancer cells are effectively killed by NK cells, some cancers are naturally resistant to NK killing. In spite of advances made in understanding the mechanisms which control NK killing, it is not clear whether the cancer cells are able to resist the NK cells because of their ability to prevent the NK cells from becoming activated and attacking them or if they are able to avoid killing by resisting or repairing the damage inflicted by activated NK cells. The studies proposed in this project will allow us to begin to understand the basic mechanisms responsible for the resistance of certain cells to NK killing. Furthermore, we will be able to identify the specific proteins directly responsible for cancer cell resistance to the immunological effects of NK cell killing. Identifying the basis for this resistance will provide us with a better understanding of the way in which NK activity is controlled and allow us to use NK cells more effectively as an anticancer treatment.

Avery August, PhD
The Pennsylvania State University, University Park, PA
$45,651 – *Role of P130^{cas} in BCR/ABL Transformation*
Ninety-five percent of all cases of Chronic Myelogenous Leukemia (CML) are caused by a DNA rearrangement resulting in the expression of an enzyme called BCR/ABL that controls cell growth, survival and migration. While drugs that block this enzyme look very promising for the cure of CML, resistance can develop, leading to an inability to control this disease. Other pathways involved in causing CML would be attractive targets in this regard. The protein p130^{cas} appears to be a critical regulator of cell growth, survival and migration, and is modified by phosphates by BCR/ABL. When so modified, this protein assembles a number of other enzymes that regulate signals leading to cell growth, survival and migration. The nature of these enzymes and signals are not well understood. Similarly the role of this protein in the ability of BCR/ABL to cause disease is not understood. The lack of such knowledge poses an important problem, as without such detail, we lack the ability to effectively target this pathway pharmaceutically to block the pathogenesis of CML. The aim of this proposal is to determine the regions of p130^{cas} that regulate BCR/ABL induced cell growth and migration. Upon completion, this project should provide information on novel targets for the therapeutic intervention of CML cell growth and metastasis, as well as a better understanding of general tumor cell growth and metastasis.

Wenqing Xu, PhD
University of Washington, Seattle, WA
$50,000 – ***Structural Studies of Protein Kinase B (PKB/Akt)***
Chemotherapy and gamma irradiation are two major clinical methods to treat leukemia. Chemicals used in chemotherapy are cytotoxins that act primarily by inducing suicide events (so-called "apoptosis") in sensitive target cells. One of the major resistance mechanisms to chemotherapy is the inhibition or prevention of drug-induced apoptosis. In recent years, a protein called PKB has been found to play a central role in apoptosis regulation. The specific inhibitors for PKB may be particularly useful to overcome the resistance of cancer cells to apoptosis during leukemia and cancer chemotherapy. We are analyzing the three dimensional atomic structure of PKB to provide the basis for drug design.

Adam Lerner, MD
Boston Medical Center, Boston, MA
$32,000 – ***The Role of AND-34, a Novel GDP Exchange Factor in the Pathogenesis of Lymphoid Malignancies***
Leukemia cells require signals from their environment in the bone marrow in order to survive and proliferate. In normal and leukemic lymphoid cells, "growth factor" signals are effective only if cells also receive appropriate "adhesion-related" signals. The integration of these two types of signals appears to take place close to the cell surface membrane within a complex of proteins that has been called the "focal adhesion complex." At the center of this complex are the adapter proteins, $p130^{cas}$ and HEF1. We have identified a novel protein, AND-34, which binds $p130^{cas}$ and HEF1 in lymphoid cells. We have also identified a biochemical function for AND-34 that suggests that it will positively regulate (turn on) important signaling pathways in lymphoid cells that regulate both cell proliferation and cell death. We propose to examine what effects AND-34 has on the proliferation and survival of normal and transformed lymphoid cells and to determine how AND-34 exerts such effects.

Martin Sattler, PhD
Dana-Farber Cancer Institute, Boston, MA
$50,000 – ***Novel Lipid Phosphatase Pathway Involved in the Transformation by BCR/ABL***
The BCR/ABL oncogene causes chronic myelogenous leukemia (CML). The exact mechanism of transformation by BCR/ABL is not known and none of the known mechanisms described so far clearly explains the myeloproliferative phenotype of BCR/ABL in CML. We have shown that SHIP (SH2 containing polyinositol-5 phosphatase) protein levels are decreased by BCR/ABL. This is of special interest since the myeloproliferative phenotype in SHIP knock-out mice is similar to that of BCR/ABL transformation in mice. The goal of this project is to investigate the link of SHIP downregulation to transformation by BCR/ABL and therefore elucidate the striking similarities between CML and the SHIP k.o. mice.

POSTDOCTORAL FELLOWSHIP AWARDS

Takashi Nagata, PhD
The Rockerfeller University, New York, NY
$30,000 – *Structure and Function of the t(12;21) Leukemogenic Fusion*
Mutations in proteins which control gene expression are commonly associated with the onset of acute human leukemia. The most frequent mutated protein is AML1, a factor which is essential for normal blood cell development. AML1 forms intimate relationships with several proteins to initiate and regulate development of blood. These proteins include ETS-family proteins which associate with AML1 and enhance its activity. Mutated AML1 fused to the ETS-family protein TEL (TEL-AML1) results in acute leukemia. We propose to investigate the structure and function of TEL-AML1. This study will provide molecular insights into the role of AML1 in leukemogenesis and blood cell development.

Joan David Bettoun, PhD
The Weizmann Institute of Science, Rehovot, Israel
$30,000 – *Deciphering the Role of Transcription Factor AML2 in Hematopoiesis*
Led by Prof. Yoram Groner, our laboratory group previously cloned the human AML2 gene and located it in a region of chromosome 1 known to be involved in cancer. Though the role played by the AML2 gene is as yet undiscovered, several experimental studies suggest that it could play a critical role in white blood cell differentiation and in the development of leukemia. We undertook to explore a function of this gene by specifically disrupting it in an experimental mouse model, using gene "knockout" technology. Our approach involves the functional inactivation of one copy of the AML2 gene in embryonic stem cells. When reimplanted into embryos at a very early stage, these stem cells are capable of contributing to the development of all mouse tissues and organs, therefore generating so-called "chimeric mice." Transplanting these genetically-engineered cells into the reproductive cells (spermatozoa and ovaries) of chimeric mice enables the establishment of a mouse line lacking one copy of the gene in every tissue and organ (heterozygous animals). By cross-breeding, mice lacking both copies of the gene (homozygous animals) can then be generated. Anatomical, physiological and behavioral studies of homozygous animals will then enable us to derive important information on the role played by the AML2 gene, particularly in mice and, in a more general sense, in mammals, including humans. In addition, the data generated by this study should enable us to better understand the role of the AML2 gene in the pathophysiology of a number of leukemias.

Clifford Wang, PhD
University of California, Berkeley, CA
$30,000 – *A High Throughput Screen for Oncogenic Point Mutations*
Identifying the mutations and genes that cause cancer is of paramount importance. It provides a mechanistic understanding of the complex events that lead to the transformation of cells, and helps to identify targets for potential therapeutics. Point mutations are mutations in which individual base changes are made in DNA. They can be caused by external mutagens such as nitrites, cigarette smoke, and oxygen radicals. Currently, there is no systematic method with which to discover cancer causing point mutations in relevant genes. By engineering a virus to carry a gene segment that confers high mutability to cellular DNA, we will introduce point mutations and induce leukemia in mice. Using the inserted virus as a genetic tag, we will locate and identify the tumor inducing genes and point mutations. The sequence of these genes will be analyzed and classified by comparison to the genetic database. We will attempt to obtain a complete listing of mutations leading to leukemia.

Artur Slupianek, PhD
Temple University, Philadelphia, PA
$30,000 – *Investigation of the Downstream Effectors in BCR/ABL → STAT 5 Signaling Pathway*
This project is designed to investigate the molecular mechanisms of leukemias induced by an oncogene named BCR/ABL. BCR/ABL causes chronic meyelogenous leukemia (CML) and a cohort of acute lymphocytic leukemias (ALL). We plan to investigate the role of genes regulating drug resistance in CML cells.

Christel Moog-Lutz, PhD
Hôpital Saint-Antoine, Paris, France
$30,000 – ***Study of Two Novel PML-RARalpha Target Genes, ASB-2 and PRAM-1; Function in Myeloid Development and Oncogenic Dysregulation by PML-RARalpha***
The majority of leukemia cells descends from a small pool of immature bone marrow progenitor cells which have a high capacity to proliferate. In normal progenitor cells, this proliferation stage is temporary to generate a mature progeny while leukemic cells keep proliferation and do not mature. Hence, genes which control the proliferation and maturation of normal progenitor cells are abnormally regulated in leukemic cells. Indeed, leukemia cells harbor chromosomal abnormalities causing the fusion of truncated genes. These fused genes dysregulate the proliferation and maturation in bone marrow cells and finally results in leukemic oncogenicity. Vitamin A derivatives can force proliferation arrest and maturation in human leukemia cells. Our project aims at identifying novel genes which are relevant to the control of maturation of leukemia cells by retinoic acid, a vitamin A derivative and are the target of a specific fusion gene found in 95% of acute promyelocytic leukemia cells. These studies will lead to the identification of potential pharmacological targets for proliferation arrest and maturation in human leukemia.

Martin Teichmann, MD
The Rockerfeller Univerisity, New York, NY
$30,000 – ***Regulation of EBER Gene Transcription in Relation to the Control of EBV-dependent Lymphomas***
Epstein-Barr virus (EBV) infection can result in the loss of normal growth control mechanisms from a certain cell type of the human immune system (B-cells), leading to the development of lymphomas. In doing this, it must inactivate or re-route some cellular functions. The EBV EBER gene products, for example, inactivate a human protein (PKR) that regulates protein production and that acts as a tumor suppressor. I want to hinder the EBER gene products from being produced in B-cells, thereby preventing the inactivation of PKR that in turn should prevent the cells from being cancerous. For achieving this, I will identify the cellular proteins that are required for production (transcription) of the EBER gene products and I will try to identify specific regions within these proteins that are uniquely required for EBER gene transcription and not for transcription of cellular genes. These regions, uniquely required for EBER gene transcription, will be inactivated and the effect of such an inactivation of the growth behavior of B-cells and on the development of B-cell tumors will be analyzed. In the future this knowledge will be used for development of a drug against the genesis of EBV dependent lymphomas.

Mona Ashiya, PhD
Dana-Farber Cancer Institute, Boston, MA
$30,000 – ***Apoptosis Mediated by Mitochondrial Dysfunction***
Programmed cell death is a process whose regulation is crucial for the normal development of an organism, including the immune system. Improper control over this process has been implicated in the development of cancer and leukemia. The *Bcl-2* family of genes encode proteins that can both, positively and negatively, regulate the programmed cell death process. The BID protein is a death-promoting member of the *Bcl-2* gene family and has been demonstrated to be required for irreversible cellular damage in the liver induced by a specific molecule, Fas. Preliminary data indicate that BID carries out its program of cellular destruction at the mitochondria and requires the activity of an additional protein, BAK. However, this destructive program induced by BID may be subverted if liver cells produce the *Bcl-2* protein, a negative regulator of cell death. Determining the molecular mechanism of BID-mediated mitochondrial destruction and determining which molecular step represents a path toward irreversible damage form one focus of this proposal. How and when the *Bcl-2* protein acts to intervene in this pathway from the second focus of this proposal. Achieving a better understanding of this process is an important first step toward uncovering cellular components that may serve as targets for therapeutic intervention in the treatment of leukemia and other diseases where the function of BID type molecules has been implicated.

Timothy Bloss, PhD
University of California, Santa Barbara, CA
$30,000 – *Dissection of the p53 Tumor Suppressor Pathway in Caenorhabditis elegans*
p53 is a protein whose activities suppress tumor development in humans, and is therefore classified as a tumor suppressor. Mutations in p53 that eliminate or severely inhibit p53's activities in the cell are associated with the development of many different types of cancer, including some leukemias and lymphomas. In fact, p53 mutations have been identified in over 50% of all human tumors analyzed, consistent with the idea that disruption of p53 activity in cells is an important step in the genesis of tumors. While p53 has been the focus of a great deal of research, the processes and pathways in the cell used by p53 to suppress tumor formation are not well understood. Our lab has identified a protein (CEP-1) in the model genetic system *Caenorhabditis (C.) elegans* that shares many similarities with the human p53 protein, defining CEP-1 as a homologue of p53. *C. elegans* is a soil worm whose entire genome has been sequenced, and whose development has been characterized such that the fate and function of every cell in the organism has been defined. In the past, *C. elegans* studies have identified and defined many proteins and biological systems in *C. elegans* cells that are nearly identical in human cells (e.g., proteins that carry out programmed cell death). Therefore, *C. elegans* is an excellent model genetic system for the identification and characterization of proteins and pathways that are associated with CEP-1 activity, with the ultimate goal of identifying homologous proteins and pathways that are associated with p53 activity in humans. Through these studies, we hope to gain insights into the processes involved in tumor suppression by p53 in humans. Such insights are essential for the development of cancer diagnostics and treatments that target p53-associated processes defective in tumor cells. These basic insights will provide the foundation for understanding and treating cancers such as leukemia.

Kimberley J. Dej, PhD
Whitehead Institute, Cambridge, MA
$30,000 – *Entering Anaphase: Genes Required for Sister Chromatid Separation*
Fundamental to the development of all organisms is the growth and division of individual cells into two genetically identical daughter cells. To ensure that the two daughter cells are the same, the cells must replicate the chromosomes that carry the genetic information of the entire organism and precisely separate the replicated chromosomes into the two new cells. Mistakes can result in the loss of genetic information including tumor suppressor genes. When whole chromosomes are lost during this cell division cycle, the likelihood of losing these important genes is increasing. In response to the loss of these genes, cells exhibit uncontrolled growth as is seen in leukemia and other cancers in humans. Chromosome separation occurs at a precise point near the end of cell division. The major molecular event associated with this transition is the degradation of target proteins, the anaphase promoting complex; however the exact link between this complex and chromosome separation remains to be elucidated. The numerous divisions that take place in the developing fly embryo serve as an excellent model for the cell division that occur in the human body. A search for mutations that affect these divisions in the fly has revealed a class of loci that exhibit defects characteristic of mutations in chromosome separation. Our studies will focus on the analysis of these mutations and on another protein that is involved in regulating the activity of the anaphase promoting complex. By studying the mechanisms controlling chromosome stability during cell division, we may begin to understand the switch between healthy cell growth and tumorous cell growth.

Koren K. Mann, PhD
Lady Davis Institute for Medical Research, Montreal, Quebec Canada
$30,000 – *The Role of Nuclear Receptor Coregulators in the Development of Retinoid-resistance in Acute Promyelocytic Leukemia*
This proposal deals with understanding how patients with acute promyelocytic leukemia (APL) develop resistance to retinoic acid (RA) treatment. We hypothesize that patients who are resistant to RA may have problems with the machinery involved in turning on and off the genes regulated by RA. Understanding the molecular problems within the cells of resistant patients may facilitate the development of new treatments for those patients who develop RA-resistance.

Zhi-Qiang Ning, PhD
Children's Hospital Medical Center, Cincinnati, OH
$30,000 – *Role of Stat3 Activation in Cytokine Independent Proliferation and Resistance to Apoptosis Mediated by Mutations of c-kit at Codon 816 in AML*
While much success has been achieved in the fight against leukemia, the majority of patients will eventually die of their disease. An improved understanding of how leukemia cells grow and become resistant to treatment remains critical for developing more effective therapies. Normal blood cells are delicately regulated by interaction between factors in their surroundings and specific proteins on their surface cell receptors. Mutations in some receptors can cause uncontrolled growth that leads to leukemia. Investigating the pathways from the receptor mutations to the generation and development of leukemia will enable us to have a better understanding of the disease. We have identified mutations in a receptor named c-kit in leukemia cells and have shown that these mutations confer a growth advantage and resistance to chemotherapy in leukemia cells. We have also demonstrated that mutations of the c-kit receptor specifically activate a molecule inside the cell, Stat3, which is often seen abnormally activated in some forms of cancer, including leukemia. The proposed studies will determine the causal relationship between activated Stat3 and the development and behavior of leukemia induced by c-kit mutations. These studies will provide information critical for the development of potential therapeutic strategies targeted to leukemia and harbor the c-kit mutations and activated Stat3.

Go Totsukawa, PhD
Rutgers University, Piscataway, NJ
$30,000 – *Role of Myosin Phosphatase in Cell Division*
One of the definitive characteristics of cancer cells including leukemia is uncontrolled cell division. This proposal is aimed at understanding the functions of myosin phosphatase in cell division control. Myosin phosphatase regulates phosphorylation of myosin. Because myosin is an essential motor to drive cytoplasmic cell division, and because phosphorylation of myosin controls the activity of the mysosin motor, myosin phosphatase is the key molecule controlling cell division. I have found that myosin phosphatase activity is controlled during cell division. The major aim of this proposal is to elucidate what is the mechanism that controls myosin phosphatase activity during cell division. I will also manipulate the activity of myosin phosphatase during cell division to see whether such manipulation blocks cell division. My studies will help us understand why cancer cells lose cell division control and may help to develop new therapies to treat leukemia.

Tianyan Gao, PhD
University of California at San Diego, La Jolla, CA
$30,000 – *Regulation of Protein Kinase C (PKC) by Phosphoinositide-dependent Protein Kinase-1 (PDK-1)*
Protein Kinase Cs (PKCs) are a family of kinases that play central roles in carcinogenesis. PKC is the primary receptor of tumor-promoting agents, phorbol esters. Aberrant protein kinase C activity in cells leads to leukemia progression and resistance to anticancer drugs. Moreover, many anticancer drugs are designed to target PKC. PKC is regulated by several cellular factors. Recent studies have suggested that PKC function can be regulated by a phosphoinositide-dependent kinase-1 (PDK-1). However, the underlying mechanism of this regulation is not clear. The goal of this proposed study is to understand how PKC is modulated by PDK-1. The protein-protein interaction between PKC and PDK-1, and the functional effects of this interaction will be investigated. The results from this study will help to further elucidate the functional roles of PKC in cancer and leukemia. Ultimately, this study will contribute to the design and development of anticancer drugs targeting PKC.