NEW INVESTIGATOR AWARDS

S. Onder Alpdogan, M.D. - Thomas Jefferson University

$100,000.00 - *The Strategies to Enhance Graft-Versus-Leukemia Effect of Haploidentical Stem Cell Transplantation*

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for a number of hematological malignancies including leukemia. The use of haploidentical donors broadens the application of HSCT more than other alternative donors, particularly in patients from ethnic/racial groups with high degrees of HLA diversity such as African Americans or in patients with uncommon HLA phenotypes due to mixed racial ancestry. In analyzing the causes of failure of haploidentical transplant, relapse of disease remains the biggest problem. Our approach will be to try to maximize the ability of donor immunity to attack the patient's malignancy, through the use of two donors, which will hopefully make it more difficult for the malignancy to escape the donors' immune systems. We will also explore adoptive therapy and cytokine therapy to enhance anti-leukemia activity of haploidentical stem cell transplantation. We hope with this funding that we will generate new information not only clinically relevant questions, but also about basic stem cell biology and transplantation, which will give us an opportunity to treat the patients with relapsed or recurrent leukemia after standard therapy.

Fotis Asimakopoulos MB, Bchir, Ph.D. – University of Wisconsin

$98,476.00 - *Flexible modeling of novel myeloma mutations in vivo*

Recent progress at discovery of new mutations underlying myeloma development creates new hope for a cure. Despite this essential “roadmap”, the study of each new mutation remains arduous and time-consuming. We have developed an animal model system that can help evaluate the significance of newly-discovered myeloma mutations in a time-efficient fashion. We shall use this novel powerful system to dissect mutations of a growth-promoting gene called BRAF. Inhibitors of BRAF, already in clinical use for other cancers, may represent significant untapped therapeutic opportunity in myeloma. Our system will help evaluate these drugs and guide the design of appropriate clinical trials.

Mohammad Azam, Ph.D. - Cincinnati Children's Hospital

$100,000.00 - *To study the molecular mechanisms of “BCR/ABL addiction” in Chronic myeloid Leukemia*

Chronic myelogenous leukemia (CML) is a slow-growing bone marrow cancer resulting in overproduction of white blood cells. CML is caused by the abnormal phosphorylation of cellular proteins by a deregulated enzyme called as BCRABL tyrosine kinase. Towards this end, a small molecule inhibitor named Imatinib mesylate (GleevecTM) was developed to block the aberrant enzymatic activity of the BCRABL. Discovery of Gleevec and its clinical success was hailed as a major breakthrough in fight against cancer. Indeed, Imatinib treatment not only revolutionized the management of CML but also paved the way for the development of tyrosine kinase inhibitor therapy for various other diseases. Unfortunately, Imatinib treatment is not curative, many patients develop resistance despite continued treatment and some patients simply do not respond to the treatment. A growing body of evidence suggests that a subset of cancer cells dubbed “cancer stem cells“ drive tumor development and are refractory to most treatments. In other words, cancer cells that respond to the drug treatment are critically dependent upon uninterrupted oncogene function addicted to oncogene whereas cancer stem cells are not dependent or addicted to oncogene. Therefore, eradication of these cancer stem cells is probably a critical part of any successful anti-cancer therapy. CML has long served as a paradigm for generating new insights into the cellular origin, pathogenesis and improved approaches to treating many types of human cancer. More recent investigations revealed that the cancer stem cells in CML serve as safe reservoir to develop therapeutic resistance, which emphasizes the need for new agents that effectively and specifically target CML stem cells.

This proposal aimed to study the mechanistic underpinnings of “oncogene addiction” in leukemic cells that will allow us to engineer the similar mechanisms for specifically targeting the CML stem cells in order to produce curative therapies that do not require lifelong treatments. I anticipate that information gained from this study will serve as a paradigm to investigate other disease models and may help in
devising better strategy for developing curative therapeutics

Danielle S. W. Benoit, Ph.D. - University of Rochester

$100,000.00 - ***Targeted Polymeric parthenolide carriers to treat acute myeloid leukemia***

After traditional treatment, 40% of patients with acute myeloid leukemia (AML) suffer recurrence, and the long-term survival rate after recurrence is only 20%. Novel therapies are urgently needed to prevent or treat recurring AML. Parthenolide, a naturally-occuring compound, induces robust AML cell killing and has the potential to reduce recurrence of AML by killing cells resistant to traditional chemotherapeutics and responsible for relapse. However, parthenolide's development as a chemotherapeutic drug has been limited due to low solubility. Therefore, we aim to develop polymer delivery systems to increase parthenolide solubility and enable its use therapeutically. These polymers will be designed to self-assemble into three-dimensional spheres with cores to entrap parthenolide and shells to enhance solubility. To provide specificity to polymer carriers, we will incorporate targeting groups that home directly to AML cells to localize drug release at cells responsible for recurrence of AML. Carriers with different properties including parthenolide loading and release will be evaluated for AML cell killing using established in vitro and in vivo models. The dose and dosing regime will also be modified to achieve the greatest AML cell killing. This approach will provide for more effective treatments for AML, resulting in lower rates of relapse and reduction of overall mortality.

Jennifer S. Carew, Ph.D. - University of Texas

$99,989.00 – ***NEDD8: A Novel Therapeutic Target in Acute Myeloid Leukemia***

Acute myeloid leukemia (AML) is one of the most prevalent forms of adult leukemia and has a dismal prognosis. Novel therapies are urgently needed to improve the survivorship of patients with AML. Identifying specific defects in AML cells will facilitate the development of targeted drugs with fewer side effects. The proteasome acts like a garbage disposal that eliminates unwanted proteins inside of our cells. Timed protein degradation is essential for many cellular processes including cell division and cell death. This process is normally tightly regulated, but often malfunctions in cancer. NEDD8 is a small molecule that helps cells target important proteins to the proteasome for disposal. Inappropriate degradation of these important proteins is problematic since this allows cancer cells to grow in an unrestricted fashion. MLN4924 is a first-in-class small molecule inhibitor of NEDD8 activating enzyme (NAE), which is a critical regulator of the NEDD8 degradation pathway. Our preliminary data demonstrates that MLN4924 has very potent preclinical activity against AML cells and induces disease regression in mice with AML. Our **major goal** is to elucidate the mechanisms by which NAE inhibition leads to AML cell death. We **hypothesize** that inhibition of NAE disrupts cellular redox homeostasis leading to oxidative stress-mediated DNA damage and cell death. The knowledge gained from these studies will enhance our understanding of how the NEDD8 pathway regulates the biology of AML cells, provide critical information regarding the mechanism of action of a desperately needed novel targeted agent, and establish a platform for future clinical trials with MLN4924 in combination with standard AML therapy.

Stephen Oh, M.D., Ph.D. – Washington University

$99,922.00 - ***Functional Characterization of LNK Mutations in Myeloproliferative Neoplasms***

Myeloproliferative neoplasms (MPNs) are blood cancers that originate in the bone marrow and can transform to acute leukemia. The prognosis for such patients is quite poor. These hyperproliferative disorders are commonly associated with genetic mutations that lead to uncontrolled growth of blood cells. One example is a mutation in a gene called *JAK2*. Small molecule inhibitors of JAK2 are currently in clinical trials for MPNs, and early results have been encouraging. However, many MPN patients lack mutations in *JAK2*, and it has therefore been unclear whether these patients will respond to treatment with JAK2 inhibitors. We recently discovered novel mutations in a gene called *LNK* in MPN patients. LNK normally functions as a negative regulator of growth, and loss of LNK function leads to activation of JAK2 and uncontrolled growth, akin to having "faulty brakes". The objective of the studies described in this proposal is to determine how these *LNK* mutations contribute to MPN pathogenesis. This work has direct clinical relevance in that it may help predict which patients will respond to treatment with JAK2 inhibitors, and also potentially provides a novel target for therapeutic intervention.

Narenda Wajapeyee, Ph.D. – Yale University

$100,000.00 - ***Characterization of New Regulators of BCR-ABL+ Leukemia and Their Role in Drug Resistance***

Leukemia is a form of cancer that starts in blood-forming cells and accounts for over 21,000 deaths every year in the U.S.A. Leukemia, like other cancers, arises due to changes in genes. Most chronic myeloid leukemia (CML) and some acute lymphoblastic leukemia (ALL) are caused by a fusion between chromosome 9 and 22. This fusion results in a hybrid chromosome called the Philadelphia Chromosome, which codes for a leukemia causingfusion protein known as BCR-ABL. BCR-ABL participate with many other as-of-yet unidentified cancer-associated changes to cause leukemia. Recently, using a genome-wide shRNA screen we have identified 133 genes that might be involved in leukemias caused by BCR-ABL. shRNAs are hairpin RNAs that are processed by cells into small 21-nucleotide RNAs named siRNAs, which bind and degrade the mRNA of its target gene. The shRNA library that we have employed has allowed us to assess the role of nearly 15,000 human genes for their role in BCR-ABL+ leukemia. In this research proposal, we propose experiments to evaluate the role of these leukemia suppressor genes in the development of BCR-ABL+ leukemia and also to understand why some leukemia fails to respond to treatment or become resistant. The results of our study will provide better understanding of BCR-ABL+ leukemia and likely help us design new methods to prevent, detect and treat BCR-ABL+ leukemia.

Jing H. Wang, Ph.D., M.D. - University of Colorado

$100,000.00 - ***AID induced mutagenesis and genomic stability in lymphocytes and non-lymphocytes***

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.