NEW INVESTIGATOR AWARDS

2nd Annual ITxM Blood Science Foundation Research Grant
Z. Basar Bilgicer, PhD – University of Notre Dame

$99,932.00 - *Designer Nanoparticles to Treat Multiple Myeloma and Its Microenvironment*

Multiple myeloma (MM) is caused by the proliferation of plasma cells (a specific type of blood cells) in the bone marrow (BM). MM is still incurable due to development of drug resistance, at least in part, caused by the survival advantages provided by the BM microenvironment. Adhesion of MM cells to the BM via VLA-4 (a unique protein on MM cell surface) results in drug resistance. As a result, the MM cells in the BM environment are much less sensitive to therapeutics such as doxorubicin (Dox) and bortezomib (Bort). Hence, VLA-4 is an attractive target, both for selective targeting of MM cells, and for inhibition of drug resistance. Nanotechnology has been recognized as a paradigm-changing opportunity in cancer diagnosis and therapy. Nanopharmaceuticals are drug containing tiny particles designed to make drugs more effective and less toxic. An important premise of nanomedicine is the enhanced drug accumulation in tumor tissue due to the "leaky" blood vessels seen around the tumors. Until recently, it was believed that leaky blood vessels were not present in blood cancers, which resulted in underutilization of nanotechonology in treating blood cancers. Recent studies, however, have established that leaky blood vessels indeed play a major role in various blood cancers, providing a strong rationale to apply nanotechnology in managing these diseases. Dox and Bort are both FDA approved therapeutics in MM, albeit with severe toxic side effects prohibiting their use in the broader patient population. The overall objective of this proposed project is to apply nanotechnology to blood cancers, specifically to MM, and engineer VLA-4 targeted nanoparticles with Dox and Bort payloads with four major benefits: 1) enhanced drug accumulation into tumor, 2) enhanced tumor killing, 3) decreased toxic side effects, and 4) overcoming drug resistance. The VLA-4 targeting in our design serves the dual function of selective targeting of MM cells and inhibiting their adhesion to the BM stroma to overcome drug resistance. The nanoparticular delivery of Dox and Bort increases their efficacy and decreases their toxic side effects. In our preliminary experiments, we have successfully synthesized and characterized nanoparticles with Dox and Bort payload. Importantly, the engineered nanoparticles significantly enhanced drug accumulation in MM tumors, showed increased tumor killing and much reduced toxic-side effects. From a technological standpoint, this study establishes a novel strategy to synthesize targeted nanoparticles that yields nanoparticles with high purity and without batch-to-batch variation, which provides a significant advantage in bench to bedside translational research. In the long term, the engineered nanoparticles will show superior efficacy and decreased side effects than the standard care treatments of Dox and Bort for improved patient outcome. Importantly, this platform can readily be expanded to target and selectively deliver Dox and Bort in a nanoparticle-based platform with improved efficacy and decreased systemic toxicity to improve patient outcome in other blood cancers including lymphomas and leukemias.

17th Annual David Sachs Memorial Grant
Ido Bachelet, PhD – Bar Ilan University

$98,960.00 - *Targeted leukemia therapy by logic-guided DNA nanorobots*

Cancer drugs are toxic, not because the molecules themselves are toxic – this is exactly what they should be. Rather, they are toxic because we cannot control them properly inside the body. The ideal of controlling molecules can be perceived by thinking of a robot linked to a molecule. However, this is impossible since ten orders of magnitude separate the ordinary robot from the molecule. In this project we propose a unique solution: to build the robot itself from molecules, thereby bridging the interface gap. Our "nanorobots" are designed and fabricated by folding DNA molecules into complex 3D objects with logic gates and moving parts, using a technique known as "DNA origami". These nanorobots can be loaded with drugs, programmed to seek target leukemia cells and switch the drug from "off" to "on" when such a target cell is found. Once the cell dies the nanorobot switches the drug back to "off" until the next cell is encountered. We already demonstrated very promising results in multiple types of leukemia, with drug-loaded nanorobots killing the cancer cells while leaving healthy bystander cells completely unharmed. Here we are aiming at demonstrating efficacy of the nanorobots in an animal model of leukemia, highlighting the nanorobots as a next-generation platform for safe and effective therapy of cancer.

Suzanne Dreebin Wilensky Memorial Grant
Ann Mullally, MD – Harvard University, Brigham and Women's Hospital

$100,000.00 - ***Determining the impact of TET2 loss-of-function mutations on hematopoietic stem cell clonal dynamics and on susceptibility to hypomethylating agents in myeloid malignancies***

The earliest cells within the bone marrow are called hematopoietic stem cells (HSC). These can be considered "parent" cells since they give rise to all of the blood cells in the body, which can therefore be thought of as "daughter" cells. Bone marrow cancers such as leukemia arise in these HSC parent cells. Leukemia occurs because a parent cell develops an abnormality called a "mutation" which causes the cell to make too many copies of it self. In this way, these abnormal parent cells take over the bone marrow and since all of the daughter cells come from them, soon there is no normal blood remaining in the body. All of the current treatments that we use in leukemia are good at killing abnormal daughter cells but poor at killing the abnormal parent cells. If we think of leukemia cells as weeds and chemotherapy as weed killer, then our current chemotherapy does a good job at killing the weed but a poor job at killing the root of the weed, so there is always the possibility that the weed (i.e. the leukemia) will grow back. My project is focused on understanding how a mutation that we know commonly occurs in HSC parent cells affects the growth of these cells and if the use of a specific treatment that is currently available can decrease the growth of the abnormal parent HSC cells as well as the daughter cells. If this is the case, this would allow us to develop smarter ways of treating leukemia that would involve using a combination of drugs that we would pick based on the particular mutations that are present in an individual patient with leukemia and would have the possibility of killing not just the abnormal daughter cells but also the abnormal parent cells from which they came.

Inaugural Genentech Research Grant
Adam Mead, MA, BM, Bch, MRCP, MRCPath, PhD - University of Oxford

$100,000.00 - ***Exploring Stem Cell Heterogeneity in the Myeloproliferative Disorders***

The myeloproliferative neoplasms (MPNs) are a group of pre-leukemic blood cancers encompassing a wide variety of disorders with different clinical presentations and prognosis. Damage to a gene called JAK2 is known to be present in many different subtypes of MPN. However, the mechanism by which identical damage to the JAK2 gene contributes to heterogeneous clinical presentations in patients with MPNs remains unclear. This is important as some patients with MPN experience a more aggressive disease course with transformation to more aggressive forms of blood cancer over time. Therefore, gaining insight into the factors predicting a more aggressive disease course is important in order to better select these patients for different treatment. The herein described studies are will explore two possible explanations for the varied disease presentation and progression seen in patients carrying a damaged JAK2 gene in heir blood cells. The first possibility to be explored is that the JAK2 mutation is damaged in different types of stem cells and it is the initial damage to these stem cells which is critical for determining subsequent disease phenotype. The second possibility that will be explored is that damage to other genes influences the disease phenotype in patients with JAK2 damaged MPNs. Once the influence of these different factors is determined we will use state of the art cellular and molecular techniques to gain novel insights into the biology of "cancer stem cells" which propagate MPNs and how they might be better eradicated in patients.

Inaugural Tellabs Foundation Research Grant
Johannes Zakrzewski, MD – Memorial Sloan Kettering Cancer Center

$99,536.00 – ***A novel therapy for graft versus host disease without compromising tumor immunity***

Bone marrow transplantation (BMT) represents the most potent immunotherapy of cancer, promising cure for patients with high-risk leukemias and lymphomas. However, a major challenge in fulfilling such a promise lies in the limited ability to modulate immune reactions during BMT in order to avoid unfavorable graft-versus-host disease (GVHD) without inducing broad suppression of the immune system, compromising both antimicrobial and anti-tumor immunity. The goal of the proposed research program is to elucidate mechanisms involved in GVHD and anti-tumor activity and develop rational approaches for effective amelioration of GVHD while preserving anti-tumor immunity. Importantly, we already identified a group of small molecule compounds with highly promising properties and potential for clinical trial and drug development. The outcome of this research is expected to decrease the toxicity of BMT while increasing cure rates.

8th Annual George Richard Memorial Grant
Sebastien Malinge, PhD – INSERM U985, Institut Gustave Roussy

$100,000.00 - ***Predisposing role of Trisomy 21 in Down syndrome associated acute lymphoid leukemia***

Children with Down syndrome (trisomy 21) face a 20-fold increased risk to develop acute leukemia affecting B-cell lymphocytes (DS-ALL) compared to the general population. Whereas the other additional genetic events implicated in DS-ALL are well characterize, the molecular consequences of the trisomy 21 as an initial event of this disease is not well understood. In this project, we propose to use trisomic animal models to reproduce the human disorder in order to understand how trisomy 21 predisposes and promotes leukemia. We already obtained preliminary results showing that several genes that are present on the chromosome 21 may be responsible for those mechanisms. Among them, *Dyrk1a* has already been implicated in leukemia predisposition in Down syndrome patients and therefore represent a promising candidate. We are now seeking to understand how trisomy 21 or trisomy of *Dyrk1a* alone affects normal and pathological hematopoietic compartment. Since trisomy 21 is a recurrent event in acute lymphoid leukemia in general, not only associated with Down syndrome, we believe that our work may provide new targets for therapeutic strategies.

17th Annual Charles A. Sachs Memorial Grant
Andrew Holland, PhD – Johns Hopkins University School of Medicine

$100,000.00 – ***Investigating the contribution of centrosome amplification in hematological malignancies***

Leukemia and lymphoma are caused by the unregulated cell division of blood and bone marrow cells. When a cell divides it must ensure that each daughter cell inherits one copy of each chromosome. If the segregation of chromosomes into the daughter cells is not equal, a cell will gain or lose chromosomes. Centrosomes are structures within cells that play an important role in controlling the accuracy of chromosome partitioning during division. Centrosome copy number is normally maintained at one or two per cell; however, in leukemia and lymphoma, diseased cells frequently contain too many centrosomes, which leads to abnormal cell divisions that result in the unequal distribution of chromosomes into daughter cells. An incorrect chromosome content can cause cells to behave abnormally and is widely believed to contribute to the development of cancer. However, whether extra centrosomes directly contribute to the development of leukemia and lymphoma remains untested. In this proposal, we aim to understand how cells normally maintain a tight control of centrosome copy number and establish the role that supernumerary centrosomes play in the development of blood-borne cancer.
To achieve our goals we have produced a novel mouse model in which extra centrosomes can be created in specific cell types in the animal. This model will allow us to study in detail how centrosome amplification contributes to the development of leukemia and lymphoma. Our work may contribute to the development of centrosome-related diagnostics and will provide a platform for testing new treatments that target and destroy cancer cells possessing too many centrosomes.

15th Annual Ann Sherman Memorial Grant
Katia Basso, PhD – Columbia University

$100,000.00 – ***The miRNA-mediated program of BCL6 in germinal center B cells***

Lymphoma, as all tumors, is a genetic disease meaning that is driven by alterations of the genetic material in a normal cell leading to the acquisition of novel characteristics. These genetic changes may result in the production of molecules with aberrant activity and/or expression. The study of the molecules that are targeted by genetic alterations during tumorigenesis leads to the identification of critical players of the normal cell function and provides the basis to design tailored cancer therapies. BCL6 is a critical molecule that is deregulated in B cell lymphomas. BCL6 functions as a transcription factor that means it can regulate the expression of a very large number of other genes. The tumor cells de-regulate BCL6 in order to hijack its ability to control the expression of genes. This study aims to identify the complete set of genes controlled by BCL6, including a novel set of regulatory molecules named microRNAs. The full comprehension of the transcriptional network of BCL6 is essential to understand its normal functions, to identify the portion of the BCL6 network that needs to be hijacked by the tumor cells, and to determine new therapeutic targets.