NEW INVESTIGATOR AWARDS

Claire Edwards, PhD
Vanderbilt University
The Role of Bone Marrow Stromal Cells in the Pathogenesis of Multiple Myeloma

Multiple myeloma is a fatal blood cancer associated with malignant plasma cells which reside and grow within the bone marrow. There is currently no cure for myeloma, and a median survival of only 3 years. It is only by increasing our understanding of the complex mechanisms involved in disease progression that we can identify new therapeutic approaches. There is increasing evidence to suggest that tumor development is not simply due to changes within tumor cells, but that the host microenvironment also plays a critical role. We have shown that specific changes in non-cancer cells (bone marrow stromal cells) found within the bone marrow microenvironment can promote the initial establishment and subsequent disease progression of myeloma in a well-characterized mouse model of multiple myeloma. The proposed studies will identify the specific cellular and molecular mechanisms which these bone marrow stromal cells promote the development of myeloma in vivo, and therefore identify novel therapeutic targets and new approaches for the prevention and treatment of multiple myeloma.

Scott E. Evans, MD
MD Anderson Cancer Center
Mechanisms of stimulated innate resistance to prevent pneumonia in leukemia patients

People with leukemia are extremely susceptible to fatal infections, especially pneumonia. This is made worse when they receive chemotherapy to eliminate their cancerous immune cells. Our laboratory has recently found that we can stimulate the lungs of mice to prevent them from developing pneumonia. Rather than relying on the blood cells to fight the infection, the protection is promoted from the lung cells themselves, making this strategy uniquely suited for use in leukemia patients. We have shown that this phenomenon, called Stimulated Innate Resistance, works against common germs that cause pneumonia among leukemia patients and in the setting of chemotherapy, such as that given to leukemia patients. This grant is focused on learning the mechanisms that underlie the protective phenomenon. We will confirm the cells that are responsible for protection, and then perform experiments to show how they sense the presence of the protective treatment. Then, that information will be used to test new treatments that may work better than the original.

Hans-Guido Wendel, MD
Memorial Sloan- Kettering
MicroRNA functions in follicular lymphomagenesis

Follicular lymphoma (FL) is one of the most common types of Non-Hodgkin's lymphoma and is currently curable only by transplantation and high dose chemotherapy in suitable patients. The Bcl2 protein plays a key, initiating role in FL by blocking the natural turnover of B-lymphocytes. However, excess Bcl2 alone is not enough to transform a lymphocyte into a cancer and additional genetic changes are required. These secondary changes are largely unknown and we will examine the role of microRNAs in FL. MicroRNA genes have been identified very recently as important regulators in cell biology. They are clearly involved in cancers, most notably in chronic lymphocytic leukemia – a disease that is very similar to FL. In fact in CLL the change in microRNAs appears to be very important in explaining this disease and has already led to new ideas for therapies that are currently being tested clinically. We speculate that similarly, microRNAs may be equally important in FL and we have designed a series of genetic and functional experiments to identify exactly which microRNAs are involved in this cancer. We expect our study will produce new insight into the biology of FL and lead to new and improved therapies.

Zaneta Nikolovska-Coleska, PhD
University of Michigan
Discovery of novel DOT1L inhibitors using multiple high throughput screenings

Rearrangements of the mixed lineage leukemia gene MLL, are associated with a variety of acute leukemias. MLL rearrangements are involved in nearly 75% of leukemias in infants and about 5-10% of leukemias in adults. Patients with MLL-rearranged leukemias have a particularly unfavorable prognosis compared to patients with other forms of leukemias. As a result of chromosome translocation, the MLL becomes fused to one of more than 50 proteins resulting in a fusion protein with oncogenic activity. We and others have demonstrated that MLLfusion proteins bind and recruit histone methyltransferase DOT1L, which specifically methylates lysine 79 of histone 3. This DOT1L-mediated methylation is required to maintain increased levels of HOX genes, an event which appears to be pivotal for leukemogenesis. Therefore, strategies to inhibit the enzymatic activity of DOT1L may have a therapeutic potential and represents a rational therapeutic goal. In this study we are proposing discovery and evaluation of DOT1L inhibitors in a series of complementary experiments in order to determine their potency, specificity, mechanism of action and potential for further development as effective targeted therapies for MLL-mediated leukemias.

Hatem Sabaawy, MD, PhD
The Cancer Institute of New Jersey
The Role of ETV6/TEL in Lymphoid Neoplasia

Abnormalities of the short arm of chromosome 12 including deletions and translocations are quite common in various human leukemias and myelodysplasia, but were not investigated in lymphomas. Given the extensive involvement of the E-26 transforming-specific (Ets) transcription factors in normal hematopoiesis and in hematological malignancies, a complete understanding of their critical roles is essential. This proposal is set to investigate the tumor suppressor function of the Ets variant gene 6 (ETV6), also known as TEL (Translocation Ets Leukemia), in lymphoma development. We have generated a novel model of lymphoma development utilizing the zebra fish. Our data demonstrate that modulation of ETV6 functions in zebra fish is involved in the development of lymphoma. Accordingly, we propose the following two aims: (1) To analyze ETV6 expression in lymphoma patients, and correlate this expression to various pathological subtypes and aggressiveness of lymphomas (2) To demonstrate the mechanisms of lymphomagenesis, the selective targets, and pathways involved in lymphoma development in our ETV6 zebra fish lymphoma model. This study provides an analysis for a potential novel tumor suppressor in lymphomas; and will provide a useful biomarker for lymphoma diagnosis and disease progression.

Roger Sciammas, PhD
University of Chicago
Irf4 as a molecular gatekeeper of effector B cell fate and growth

Genetic diseases and laboratory experimentation have taught us that B cells are essential for protection from microbes and cancer. They are the only cell that produces antibody and it is this antibody that is able to recognize the universe of infectious agents. Antibody production is an acquired process, akin to maturation, that is dependent on the turning on and off of key genes. B cell maturation is highly regulated – too much and the possibility of autoimmunity ensues and too little and there is poor protection from infection. Irf4 is a protein that regulates the ability to commence antibody production. Accompanied with antibody production, B cells increase their numbers via cell proliferation. B cell proliferation is highly regulated – too much and the propensity for lymphoma ensues and too little and too few protective antibody producing cells are generated. Interestingly, Irf4 also regulates cell proliferation. The insights gained from the questions raised in this proposal will illuminate how Irf4 controls these two processes and also how these two processes are linked at the molecular level. The implications of this research impacts how we think about vaccination strategies to elicit optimal protective antibody, as well as, how we think of about lymphoma treatment strategies to effectively kill off leukemic cells.

Shobha Vasudevan, PhD
Massachusetts General Hospital
Translation regulation of VEGF by microRNAs in leukemia

The primary goal of this project is to determine the control mechanism of production of VEGF, a highly powerful angiogenic and metastatic factor that correlates with poor survival in leukemias. My previous data and those of other groups' indicate that VEGF is controlled by a complex of proteins and small specificity factors called microRNAs. My previous work identified how these microRNAs can respond to distinct conditions that simulate the tumor environment and control production of a potent tumor and immune system regulator, Tumor Necrosis Factor α (TNFα). Based on these data and the tools developed in these previous studies, I aim to characterize the particular microRNAs that control VEGF in leukemias and elucidate the regulatory changes induced by the tumor environment conditions that cause the microRNAs to abnormally increase VEGF production. Finally, and most importantly, characterization of these specificity factors or microRNAs will permit testing of antisense techniques as potential therapeutic approaches that can control the microRNA and thereby control VEGF expression in leukemias.

Sundaresan Venkatachalam, PhD
University of Tennessee
Chromatin Remodeling Defects and Lymphoma Formation

The DNA of every cell is compactly packaged in structures called chromatin that allows the vast genetic information to be contained within the nucleus. All transactions that relate to DNA including the expression of genes and the duplication of DNA during cell division face this structural barrier. The flexibility of chromatin plays an important role in the control of gene-expression, which is necessary for an organism to develop and function normally. One of the major hallmarks of cancer cells is the loss of cell division control and defects in chromatin dynamics (remodeling) can also lead to uncontrolled growth due to abnormal gene expression. This proposal involves the study of a protein (known as CHD2) that functions in chromatin remodeling and thereby affects the expression of a variety of genes. In order to analyze the role of the chromatin remodeling protein in suppressing cancer, we have developed a mouse model that is defective for this protein. This mouse model displays physiological defects that indicate a role for the CHD2 protein in red blood cell formation, suppression of lymphomas and the regulation of cellular responses to DNA damage. Consistent with our results, our analysis indicates that the human chromosomal region containing human CHD2 is deleted in 15% of the human leukemias and lymphomas. In this proposal we plan to analyze the role of CHD2 in the lymphoma suppression and determine its mechanism of action in regulating DNA damage responses. In the long run, our studies will potentially lead to additional targets that focus on chromatin remodeling for drug development strategies aimed at controlling leukemias and lymphomas. The goal of our research is to understand how the switching activity of MLL works, and to use this information to find new medicines that will fix broken switches in leukemia cells. We will do this by identifying the molecular mechanisms that control how fast MLL works.

Lizhao Wu, PhD
New Jersey Medical School
E2F7 and E2F8 collaborate with Rb to maintain normal hematopoiesis and suppress hematologic malignancies

The myelodysplastic syndromes (MDS) are a series of related disorders characterized by anemia with or without other cytopenias, clonal and inefficient hematopoiesis, and bone marrow failure. Progression to acute myeloblastic leukemia (AML) is common. Enlarged spleen and non bone-marrow derived hematopoiesis (the development of blood cells) are uncommon features of MDS but have been documented to occur in MDS and in MDS/myeloproliferative disorder (MDS/MPD) overlap syndromes. Multiple chromosomal abnormalities have been documented to occur in patients with MDS. Additionally, recent studies have also shown cryptic deletions and gains in about 10% of low risk MDS patients, suggesting that genes not identified as altered by routine cytogenetics may be important in MDS. Therefore, it is likely that alterations in currently unidentified genes contribute to MDS and to the progression from low risk types of MDS to higher grades as well as transformation to AML. We recently established a genetically well-defined animal model in which mice lacking a set of three key proteins, including the retinoblastoma tumor suppressor, develop defects that resemble several symptoms observed in human patients without MDS or MPD. These genetically modified mice are display severe anemia, substantial reduction of lymphocytes, dramatically enlarged spleen, and abnormal red blood cell development in the spleen and liver. Preliminary data also show some sign of possible progression to a leukemic state as the mouse ages. We propose to achieve three specific goals: 1. to determine whether hematopoietic cells lacking the three proteins are tumorigenic, and whether aging mice lacking the three proteins can develop hematologic malignancies; 2. to understand the genetic and molecular mechanisms by which the three proteins collaborate to maintain normal blood cell development and to suppress tumorigenesis; and 3. to determine whether loss of the three proteins in red blood cell progenitors is sufficient to induce the defects in red blood cell development in mice that lack the three proteins. The proposed study will not also allow us to establish an excellent animal model system to study human hematologic cancers, but may also lead us to develop new therapeutic approaches to target specific proteins for to treat patients with MDS, MPD, AML, or red blood cell leukemias.

Zhaohui Wu, MD, PhD
University of Tennessee
TAK1 function in NF-kB signaling by cancer therapeutic agents

The transcription factor NF-κB regulates cellular sensitivities to anticancer drugs, thus it is implicated as an important determinant for cancer resistance. While pharmaceutical industry has begun development of general inhibitors of the NF-κB activation pathways, those that specifically target NF-κB activation by anticancer drugs are not available in part owing to the lack of complete understanding of the mechanisms of NF-κB activation by these agents. In our previous studies, we have discovered an atypical mechanistic pathway mediating NF-κB activation by chemotherapeutic drugs and irradiation. This pathway of NF-κB activation appears to be conserved for different anticancer agents. In this proposal, we focus on determining the mechanistic link involved in several key steps of this NF-κB signaling cascade. We anticipate that deeper understanding of the mechanisms of NF-κB activation by DNA damaging anticancer agents will help develop pathway-selective inhibitors to enhance anticancer efficacy while reducing potential toxicities associated with general NF-κB inhibition. These inhibitors could be applied as potent adjuvant drugs with current chemotherapy to improve the outcome the leukemia and lymphoma treatments.