NEW INVESTIGATOR AWARDS

Rosa Bernardi, Ph.D. - San Raffaele Scientific Institute

$95,000.00 - ***Study of the synergism between HIF inhibition and retinoids for leukemia treatment***

The aim of our research project is to understand whether a class of therapeutic agents that are currently used to treat patients with a specific type of acute myeloid leukemia can be exploited for treating other acute myeloid leukemia (AML) patients who at the moment have less therapeutic options and worse prognosis. These agents are known as "differentiation therapy" because they promote elimination of leukemic cells by triggering their differentiation into myeloid cells that have a shorter half-life and exhaust soon after treatment. Based on preliminary data that we have obtained in the laboratory, we hypothesize that treatment with differentiation therapy may activate molecular pathways that oppose differentiation and leukemia exhaustion. Therefore, targeting these molecules along with the differentiation agents may induce a better response in AML patients by licencing differentiation and synergizing in eliminating leukemia cells. We will test our hypothesis by using a number of experimental approaches that include *in vitro* and *in vivo* studies with cell lines, cells derived from AML patients, and mouse models of acute myeloid leukemia. With our studies, we will be able to understand in a short time whether pharmacological agents that are already used in the clinic for treating patients with different tumors or different pathological conditions can be used together with differentiation therapy also in the treatment of AML patients.

William L. Blalock, Ph.D. – National Research Council

$50,000.00 - ***In-Depth Analysis of Nuclear Signaling Involving the Innate Immune/Stress Response Kinase, PKR***

Acute leukemias arise from the selection of a few early progenitor cells in the bone marrow, which have gained resistance to the normal cellular controls limiting growth and survival. In many bone marrow failure disorders, such as myelodysplastic syndromes (MDS), there exists a selective pressure on the bone marrow progenitors exacerbated by the presence of mediators of inflammation that can induce both cell death, as well as cell survival and proliferation, depending on the context. The project proposed seeks to define in detail the role of an inflammatory regulator of the immune system, implicated in both cell killing and survival/growth, whose activity and sub-cellular localization to the nucleus in bone marrow progenitor and acute leukemia derived cells has been correlated with MDS progression to acute myelogenous leukemia (AML) and the survival and proliferation of acute leukemia derived cells. The information gained from these studies has the potential to lead, in quick succession, to the development of new diagnostic technologies and therapies for many blood related disorders.

Samuel G. Katz, M.D., Ph.D. – Yale University

$100,000.00 – ***Genetic and environmental contributions to Mantle Cell Lymphoma pathogenesis***

Mantle cell lymphoma (MCL) is a deadly form of B cell lymphoma that is believed to arise from hyperactivity of a growth-promoting protein called cyclin D1. Recent work suggests that elimination of a cell death-promoting protein named BIM may also be required for the development of MCL. By generating a new mouse model that has excess cyclin D1 but no BIM, I will explore the impact of BIM loss in causing MCL. Whereas it was once thought that MCL would arise only from naïve Mantle Zone B cells, recent results now suggests that MCL B cells have been exposed to antigen. I will use our novel mouse model of MCL to directly test the ability of antigen to promote malignant progression in B cells stimulated to grow by increased cyclin D1 and unable to die due to loss of BIM. Using my expertise as a pathologist, I will also test our theory directly in human MCL samples. I will apply a battery of new approaches, drawing from the fields of immunology, biology, and clinical translational medicine, to advance a new understanding of how an antigenic stimulus, an apoptotic blockade and a proliferative advantage cooperate in the development of MCL. This in turn will lead to new strategies that reactivate apoptosis to overcome MCL's resistance to modern anticancer treatments.

Andrew G. Muntean, Ph.D. – University of Michigan

$100,000.00 - ***A functional analysis of the PAFc epigenetic regulator complex in AML***

The functions of cells are controlled through the expression of genes encoded by the DNA in a cell. The expression of different subsets of genes leads to the functional specification of a cell but can also lead to transformation from a normal cell into a transformed cancer cell with unlimited proliferative capacity. The control of these gene expression programs is linked to chemical changes to DNA structures, called epigenetic modifications. Proteins called epigenetic regulators mediate these chemical changes. Recent work has revealed mutations in these epigenetic regulators are recurrently found in several forms of cancer, including leukemia, and play a crucial role in driving cancer through the deregulated expression of gene programs that promote survival and proliferation. Our long-term goal is to understand the proteins and mechanisms regulating these epigenetic modifications mediating the transformation of a normal cell into a cancerous cell. Our work focuses on a central epigenetic regulator, termed the PAFc, which has known roles in pancreatic, breast and endocrine tumors as well as leukemia. The PAFc functions as a platform to recruit other epigenetic regulators with enzymatic activity to specific locations on DNA leading to gene expression changes. Importantly, we have shown the PAFc interacts directly with proteins known to drive leukemia progression and that this interaction is essential for leukemia cell survival. This proposal aims to understand the gene expression program controlled by the PAFc and how this contributes to leukemia progression. Using next generation gene expression analysis tools and several gene manipulation techniques, we will reveal the molecular mechanisms and critical gene targets of the PAFc that contribute to leukemia. In addition, we aim to reveal the leukemic subtypes dependent on the PAFc for survival. Thus, this proposal will elucidate not only the biological impact of a crucial epigenetic regulator complex, but also the general importance of this protein complex in leukemia. Given the importance of the PAFc in various cancers, we envision the knowledge gained from this proposal will have wide ranging impact on many cancer types.

Sean M. Post, Ph.D. – MD Anderson Cancer Center

$100,000.00 – ***Understanding aberrant hnRNP K expression in myeloid homeostasis and AML***

AML is a devastating disease with dismal outcomes that are related to its aggressive nature. Furthermore, it is an extremely difficult disease to treat due to the numerous genetic alterations that occur during disease progression. These two factors have contributed to our inability to develop new treatment options for patients with AML. Thus, there is a great need to identify and understand the molecular consequences of these genetic alterations so that we can develop individually tailored treatment strategies. We have identified hnRNP K as a protein aberrantly expressed in AML. Furthermore, the *hnRNP K* gene is located on a chromosome that is frequently deleted in patients with AML. hnRNP K is a protein implicated in regulating numerous critical pathways that govern cell growth and cell death. Therefore, garnering a better mechanistic understanding of how abnormal hnRNP K expression disrupts these cell growth and death pathways will assist us in designing these personal treatment strategies. Data generated from these studies will assist us in the laboratory by determining how hnRNP K regulates tumorigenesis and in the clinic by evaluating whether hnRNP K can serve as a prognostic biomarker and possibly a therapeutic target.

Antonio Postigo, M.D., Ph.D. – University of Barcelona

$100,000.00 - ***Regulation of stemness and differentiation in normal and malignant hematopoietic cells by the ZEB***

B-lymphocytes are cells that circulate in the blood to defend our bodies against infections. They are formed inside our bones in what is known as bone marrow. The formation of new lymphocytes and their correct maturation requires the timely expression of a set of proteins. In leukemias and other hematologic malignancies, the expression of some of these proteins is altered, absent or, in other cases, two different proteins fuse to form a new protein with cancer-promoting properties. We are working on two proteins, ZEB1 and ZEB2, which are known to regulate some important proteins in B-lymphocytes. Mice without ZEB1 protein have very low numbers of some types of lymphocytes. Preliminary results in our laboratory indicate that the expression of ZEB1 and ZEB2 is altered in lymphomas and leukemias and we are trying to understand how ZEB1 and ZEB2 participate in the maturation of lymphocytes, the set of proteins that they regulate in this process and how they contribute to the malignant transformation of B-lymphocytes to generate lymphomas.

Chozha Vendan Rathinam, Ph.D. – Columbia University Medical Center

$100,000.00 – ***Role of A20 in the restriction of myeloid leukemia***

Myeloid Leukemia is a very common, but not well understood, disease of the blood system. The proposed research aims to unravel the biology behind the transformation events mediated by the ubiquitin editing enzyme A20. Knowledge obtained from the proposed experiments will provide directions for therapeutics that may aid the treatment of patients with *TNFAIP3* mutations.

Lan Wang, Ph.D. – University of Miami

$100,000.00 - ***Targeting the abnormal transcription regulators in leukemia***

Blood cells are generated by a group of immature cells in the bone marrow called hematopoietic stem cells (HSCs). These HSCs are proposed to be the cell of origin in childhood leukemia and we are studying how their behavior goes awry when the cells become transformed into childhood leukemia. However, leukemia stem cells (LSCs) show loss of normal growth control mechanisms, leading to abnormal cell division, survival, and expansion. The development of childhood leukemia is commonly associated with aberrant transcriptional regulation, where genes are inappropriately turned on or off. In most cases, correcting these abnormalities may block the development or progression of leukemia in patients. Our recent work showed that a specific gene, Id1, is required for maintaining HSC self-renewal. As a key regulator of blood cell production, Id1 could serve as a target for attacking LSCs, because eliminating the ability of Id1 to maintain the immaturity of LSCs should lead to their death. Here we propose to study the relevance of Id1 in turning normal blood cells into LSCs using mouse models of childhood leukemia. We plan to study the effect of Id1 on LSCs by eliminating its presence using genetics means or a technique called RNA interference. We also will test the effects of inhibitors of Id1 function on the formation of LSCs and the progression to childhood leukemia. Our prediction is that blocking Id1 will inhibit the development of LSCs. The information generated by this study can be useful for developing targeted therapeutics for childhood leukemia.

Junping Xin, M.D., Ph.D. – Loyola University Medical Center

$100,000.00 - ***Induced switch of Stat3 isoforms for better AML treatment***

The fate of a cell is controlled by many factors that pass the signal from the surface of the cell to its nucleus. One of such factors is Stat3, which is an important factor supporting tumor cell growth in over 70% of human cancers, including leukemia. Therefore, we are interested in targeting Stat3 in order to treat leukemia. Stat3 has two molecular forms: a fully-functional form and a non-functioning form. The latter form can block the effects of fully-functional form. However, it is unknown what factor controls the levels of the two forms of Stat3 in cells. We recently found that a protein called tumor necrosis factor-α (TNF) controls the balance between the active and inactive forms of Stat3. The primary function of TNF is to induce the cell to undergo necrosis, but leukemic cells have acquired an ability to escape this cell death by converting the death signal to a growth signal, probably through regulating the levels of the two forms of Stat3. When the TNF signal is blocked, leukemic cell cells start to express the defective Stat3 form, their growth slows, and they begin to take on the appearance of more mature cells. The studies proposed for the current project are intended to aid understand of how the TNF signal, Stat3 and cell fate are interconnected. The knowledge obtained from this study will allow to us to develop new strategies to better treat leukemia, especially for cases which are currently refractory to treatment regimens.

Fengtian Xue, Ph.D. – University of Maryland

$100,000.00 – ***Small molecule BCL6 inhibitors for diffuse large B-cell lymphoma (DLBCL)***

DLBCL are life-threatening cancers that arise from germinal center B-cells and are the most common form of non-Hodgkin's lymphomas. The goal of this proposal is to develop novel therapeutics for the treatment of DLBCL by targeting the protein-protein interactions between the BCL6 BTB domain and its corepressors, and ultimately to provide one of the first or possibly the first example where small molecules have been shown to be effective against an oncogenic transcription factor. Our hypothesis is that the BTB lateral groove of BCL6 has specific features that are amenable to rational design of novel inhibitors. The approach applies computer-aided design strategies targeting novel binding pockets in the lateral groove of BCL6 to develop potent inhibitors of BCL6-corepressor interactions. Also, the proposed studies will culminate in the first clinically tractable inhibitor of a novel therapeutic target, BCL6, for which there are currently no therapeutic agents available. The proposed research also has the potential to treat other important human cancer such as FLs and various forms of leukemia, and teach us how the inhibition of BCL6 and subsequent gene repression affects blood cancer.