

NEW INVESTIGATOR AWARDS

Daniel Herranz Benito, PhD – Rutgers Cancer Institute

\$100,000.00 - *Dissecting the role of PKM2 in NOTCH1-induced T-ALL*

T-ALL is an aggressive cancer of the blood that affects both children and adults. The cure rates in the recent years have increased due to novel advances in treatments, however, 20-50% of the patients eventually relapse, and in these relapsed cases the therapeutic options are scarce, leading to high mortality rates in these patients. Therefore, we need to discover new therapeutic targets that could be promising for the treatment of this disease. The main cause of T-ALL are activating mutations in a gene called NOTCH1. Related to this, my preliminary findings suggest that inhibition of NOTCH1 has drastic metabolic consequences in leukemic cells, and identified a particular metabolic enzyme (PKM2), as a potentially attractive therapeutic target. Thus, in this proposal I seek to dissect the role of PKM2 in TALL, and to address the therapeutic effects of inhibiting PKM2 using advanced mouse models of leukemia and human T-ALL cells, as well as state-of-the-art molecular biology techniques. Therefore, the results from this innovative proposal might lead to novel therapeutic strategies in T-ALL patients.

Kishore Challagundla, PhD – University of Nebraska Medical Center

\$100,000.00 - *Exosomal miRNAs and PD-L1 in AML Therapy Resistance*

Cancer is a lack of regulation in the cells of the body, and begins with uncontrolled cell growth, usually in one organ or location. Cancer is said to have metastasized when cancer cells spread to another organ or organs. There are many kinds of cancer. Acute myeloid leukemia (AML) is a type of cancers that start in cells that would normally develop into different types of blood cells. AML can progress quickly if not treated, and would be fatal in a few months. There are about 21,380 new cases and 10,590 deaths every year in the United States. People with AML often show a failure to respond to chemotherapy because their cancer cells develop resistance to chemotherapy drugs. However, we recently discovered exosomes, which are vesicles or envelopes involved in inter-cellular communication between AML cells and bone marrow mesenchymal cells (the surrounding cells of the tumor). These exosomes can deliver a cargo of small RNA molecules (microRNA) that are not changed into the kinds of proteins that can affect tumor growth or the tumor microenvironment. High expression of miRNA-155 and PD-L1 protein is associated with developing resistance in AML. However, the role of tumor microenvironment and exosomal communication in PD-L1 stabilization is unclear. The purpose of this proposal is to identify the mechanisms involved in drug resistance, and to develop new approaches for tumor cells to accept chemotherapy in relapsed AML. In this application, we propose to investigate the role of exosomes in the development of drug resistance and how AML and surrounding cells become drug-resistant, in AML. Upon successful completion, this work will provide important insights into drug resistance. The study has significant implications for the most efficient design of treatment after relapse, potentially sparing patients unnecessary rounds of chemotherapy, and ultimately increasing survival of children with this high-risk cancer.

Shunji Egusa, PhD – The University of North Carolina

\$100,000.00 - *Au nano-linker: Turning standard AML drugs into lineage-targeted therapeutics*

Two basic and related problems that face cancer patients are that treatments can be very difficult, even brutal, yet the pay-offs in terms of benefits can be uncertain. This is because toxic treatments destroy many normal cells while often permitting the most aggressive cancer cells to survive. A straightforward solution is to selectively deliver cancer drugs to cancer cells and not normal cells. Unfortunately, existing technologies to do this, for example, direct joining of drugs to antibodies, have significant limitations and the impact of the existing technologies on patient health has not been as great as hoped. Here, we use a new, versatile nanotechnology approach as a way to link a myriad of cancer drugs to leukemia-targeting molecules, to readily and simply address the problem of selectively delivering cancer drugs to cancerous cells. This nanotechnology, **Au nano-linker**, uses extremely small (“nano”-scale) gold (Au) as intermediaries with unique chemical properties to which drugs and leukemia-targeting molecules are simultaneously linked by simple but different chemistries. In essence, this approach can turn off-the-shelf drugs into advanced disease-targeted drugs, allowing the drugs to be selectively released in leukemic cells while sparing normal cells/tissues to reduce overall toxicity/side-effects, and to improve effectiveness of treatment.

Jin Seon Im, MD, PhD – The University of Texas MD Anderson Cancer Center

\$100,000.00 – *Third Party Gene-Modified iNK T cells to Prevent GVHD and Relapse after Transplantation*

Allogeneic stem cell transplantation (ASCT) can cure several blood cancer including acute leukemia, where patients receive donor immune cells after the high dose chemotherapy. While Graft-versus-Host Disease (GVHD) is very serious complication of ASCT and caused by hyperactive donor immune cells attacking recipients' body, the relapse of blood cancer often caused by insufficient donor immune activity is the major reason for the treatment failure. Therefore, the innovative strategy is urgently needed to decrease occurrences of GVHD and relapse of blood cancer. The invariant Natural Killer (iNK) T cells are the unique T cells that may help regulating the activity of donor immune cells to prevent GVHD in ASCT and may have activity against blood cancer. Therefore, additional iNK T cells can be given to patients to prevent GVHD and relapse of blood cancer in ASCT. Previously, we developed an efficient way to grow iNK T cells outside body and demonstrated that these iNK T cells can prevent GVHD in mice with ASCT. In proposed works, we plan to enhance anti-tumor activity of iNK T cells by putting "chimeric antigen receptors (CAR)" that will allow iNK T cells to attack leukemia cells so that CAR-iNK T cells can not only prevent GVHD but also prevent relapse of blood cancer in ASCT. We believe this CAR-iNK T cells are an innovative approach to improve the success of ASCT.

Matthew Mei, MD – City of Hope National Medical Center

\$100,000.00 - *Overcoming Resistance to Chemotherapeutic Intervention in Leukemia and Lymphoma*

Chronic myelomonocytic leukemia (CMML) is a blood cancer primarily affecting older adults. The overall prognosis (disease outlook) is poor, and the only known cure is allogeneic stem cell transplant. However, the potential for harm including chronic disability and death with transplant is high, and other patients will have their disease recur despite having gone through a transplant. At present, our ability to predict outcomes for patients with CMML after transplant is limited. More recent research has shown that nearly all CMML patients carry specific mutations that differ from person to person. These mutations affect the overall disease outcome in patients who do not undergo transplant. We wish to see if these mutations also influence the outcome of patients who go through transplant. This knowledge would help to choose appropriate patients who would have a higher likelihood of benefiting from a transplant, as well to guide innovative future therapies which can improve transplant outcomes.

Esther A. Obeng, MD, PhD – St. Jude Children's Research Hospital

\$100,000.00 - *Uncovering how SF3B1 and TET2 mutations cooperate to develop aggressive MDS*

Myelodysplastic syndromes (MDS) are a group of blood cell disorders characterized by low blood counts, and risk of progression to secondary acute myeloid leukemia (AML); an aggressive subtype of AML that is inherently resistant to conventional chemotherapy. The incidence of MDS is as common as primary AML at 3 to 4 cases per 100,000 population per year. The median age of diagnosis is 68 years of age and MDS incidence is expected to increase as life expectancy increases. Presently, bone marrow transplantation (BMT) is the only curative therapy available for MDS. However, it is a treatment option for fewer than 5% of MDS patients due to its significant morbidity and mortality. Effective targeted therapies for MDS that can be tolerated by older patients are urgently needed. The splicing factor, *SF3B1*, and the DNA methylation regulator, *TET2*, are the two most commonly mutated genes in MDS. It is common for patients with MDS to have mutations in both genes at the time of diagnosis. These mutations are thought to occur early in MDS development, thus determining the genes and pathways that are critical for the development of MDS in *SF3B1* and *TET2* mutant cells presents an important opportunity for early intervention, and possibly even prevention, of a disease that is near-universally fatal. The project proposed will use DNA and RNA sequencing to identify the key genes and pathways that are aberrantly expressed in double mutant cells compared to single mutant cells. Candidate genes will be validated in genetic mouse models and MDS patient samples. These findings will form the basis for my long term goal of developing novel agents for the treatment of MDS.

Chintan Parekh, MD – Children's Hospital Los Angeles

\$100,000.00 – *Molecular characterization of minimal residual disease cells in pediatric ALL*

Leukemia is one of the most common childhood cancers. With current tests, it is difficult to identify early on during treatment which children truly have leukemias resistant to standard treatment and thus need more intensive treatment. We are trying to develop new tests that use advanced DNA sequencing techniques for the more accurate early identification of children who need more intensive treatment. The results from this research could also help identify the DNA errors that make leukemia cells resistant to treatment, an important step toward the development of new anti-leukemia treatments that target these errors.

Paulina Podszywalow-Bartnicka, PhD – Nencki Institution of Experimental Biology

\$100,000.00 – *Synthetic lethality in leukemia - effect of PARP1 inhibitors in bone marrow niche*

Leukemia is a type of cancer that originates from the cells which create our defense-immune system. They reside in the bone marrow, but during cancer progression the cells get into the blood stream. Nowadays, there are various therapeutics which target leukemia cells and kill them, but they are very effective towards the cells circulating in the blood. Unfortunately, cancer cells residing in the bone marrow are protected from medicines by the unique environment. There is an urgent need to develop some new strategies to eliminate such cells. Our previous research indicates that the novel personalized therapeutic strategy, based on the phenomenon called ‘synthetic lethality’, might eliminate from the bone marrow leukemia cells, including those resistant to therapy. Synthetic lethality can lead to cell death by blocking one of two compulsory factors in cells in which the second factor is already deactivated. We found that a drug, which is in the final phase of clinical tests for treatment of breast cancer, also effectively induces death of leukemia cells. However, it is important to verify effectiveness of such therapeutics in the human bone marrow, where these cells are protected. Thus, the aim of this project is to create small human bones with human bone marrow, called ‘ossicles’, underneath the mice skin and then transplant human leukemia cells into them. This would allow us to test response of leukemia cells to the treatment and monitor the process. It would be one of the first attempts to use such model to verify potential of anti-leukemia treatment based on synthetic lethality. Completion of this project would on one hand support development of personalized therapy for leukemia treatment and on the other hand would advance introduction of human bone marrow based model into early step of verification of putative medicines.

Brittany Knick Ragon, MD – The University of Texas MD Anderson Cancer Center

\$100,000.00 – *Identification of molecular and genetic determinants of response to hypomethylation agents in AML*

Acute myeloid leukemia (AML) is a cancer of the blood and bone marrow. It grows quickly and is rapidly fatal without urgent treatment. AML is usually treated with very strong chemotherapy, which has very severe side effects. Hypomethylating agents (HMAs) are now available as an alternative treatment option for patients, particularly older ones, who cannot tolerate such intensive chemotherapy. The HMAs have much milder side effects but are still effective against AML in many patients. However, there is not a good way to predict whether HMAs will work for a given patient. This research proposal explores different factors that might affect whether HMAs will work for an individual patient’s leukemia, so that we can better use these agents to treat AML patients and also ultimately develop better therapies for AML.

Russel J. H. Ryan, MD – University of Michigan

\$100,000.00 - *Identifying Unique /myc Enhancer Dependencies in B-Lymphoblastic Leukemia*

The MYC gene is essential for the growth of many aggressive blood cancers (leukemias and lymphomas). Unfortunately, drugs that directly block MYC have been challenging to develop. We are using a new approach to study the complex series of ‘switches’ in the human genome, called enhancers, that are needed to turn on MYC in leukemias and lymphomas, but not in normal tissues. By defining the mechanisms needed to activate these switches, we hope to develop MYC-blocking therapies that will kill leukemia and lymphoma cells in patients, while minimizing toxic side-effects.

Cristina Scielzo, PhD – IRCCS

\$100,000.00 – *Decipher the dynamic expression of targetable signalling pathways in CLL tissues by exploiting new 3D models*

Blood cancer cells develop and accumulate in specialized tissue such as bone marrow and lymph nodes. Here leukemic cells dialogue with the surrounding cells present in these tissues (namely: microenvironment) to drive a tumor-supportive environment. A paradigmatic example is Chronic Lymphocytic Leukemia (CLL), the most common leukemia in the western world, accounting for about one quarter of all new cases of leukemia with an incidence of 2 - 6 new cases/year/100.000 inhabitants. **CLL remains incurable despite significant advances in therapies over the last decade.** Unfortunately, current treatments appear to eradicate leukemic cells less efficiently in the tissues than in peripheral blood, suggesting that what occurs in the the tissue context needs to be further elucidated. Our previous studies on CLL have demonstrated that the expression and activation of Hematopoietic Cell-Specific Lyn Substrate 1 (HS1) protein has a key role in the cytoskeletal activity of the cells by mediating the dialogue with the microenvironment. We showed that interfering, *in vitro* and *in vivo*, with HS1 activity or expression led to an increased homing of CLL cells in the bone marrow tissue. Recently, we identified **a new HS1/CXCR4/PIM1 axis** whose expression and activation is dynamically regulated in CLL lymphoid tissues *vs* peripheral blood. With this proposal we AIM at identifying new signalling pathways that are exploited by leukemic cells to develop, progress and become resistant to therapies, by using new 3D models coupled with dynamic growth in bioreactors. **We believe that our INNOVATIVE models, once optimized, will become a benefit to study the dynamics and biology of many haematological cancers.**

Yue Wei, PhD – The University of Texas MD Anderson Cancer Center

\$67,468.00 – *Characterize the pathological role and therapeutic potential of histone demethylase KDM6B in MDS*

Myelodysplastic syndromes (MDS) are a group of disorders in which bone marrow overproduces immature red blood cells (hematopoietic stem/progenitor cells, or HSPCs), frequently presenting clinically as anemia, fatigue, and bone marrow failure. MDS are associated with aging and often progresses to acute myeloid leukemia (AML). Currently, treatment options for MDS are limited due to the complex pathological features of the disease, and prognosis remains unacceptably poor. As the population ages, the need for development of new treatments against MDS is increasingly urgent.