The Teddy Kim Foundation
and the Leukemia Research Foundation
A Partnership in pursuit of a cure for Acute Myeloid Leukemia

The Leukemia Research Foundation (LRF) applauds the outstanding efforts of the Teddy Kim Foundation (TKF) and all of its supporters in helping to fund research and raise awareness about Acute Myeloid Leukemia (AML).

Teddy was clearly loved and respected by his family and many friends. His passing was a tremendous loss for all. You chose to mobilize and pay tribute by creating a lasting memorial through the TKF so that, in the future, others don't have to experience the heartache you have all endured.

To that end, the TKF embraced the mission of the LRF which is *dedicated to conquering all blood cancers by funding research into their causes and cures and enriching the quality of life of those touched by these diseases.*

During the past several years, the TKF has donated the proceeds from a series of fundraising events to the LRF to support gifted researchers and their projects advancing progress toward an ultimate cure for AML.

Recent Progress in AML research

Progress in treating acute myeloid leukemia (AML), one of the most pressing challenges in the blood cancers, is advancing. Lifesaving breakthroughs – from precision medicine to immunotherapies – have emerged from researching cancer cells in the blood, which are easier to access and study than those in solid tumors. Many scientists, clinicians and clinical trial participants have developed and improved current standards of care over time. It takes about eight years to develop a successful new drug.

After a 40-year drought in the approval of new therapies for this lethal disease a number of FDA approvals for AML have been introduced since 2017:

- *Glasdegib (Daurismo®),* which targets a cell signaling pathway called Hedgehog, which is critical for the development of immature cells into cells with more specialized functions.
- *Enasidenib (Idhifa)*, which inhibits the activity of mutant forms of a protein called IDH2
- *Venetoclax (Venclexta)*, which inhibits the activity of a protein called BCL-2
- Gemtuzumab ozogamicin (Mylotarg), which targets a protein on leukemia cells called CD33 and delivers a toxin to the cells
- *Midostaurin (Rydapt)*, which inhibits the activity of a protein called FLT3
- *Gilteritinib (Xospata)*, which inhibits the activity of mutant forms of FLT3

What's more, these approvals show that we are headed in the right direction with a precision medicine approach to conquering this difficult cancer. Looking ahead, we expect this dizzying rate of progress to continue for AML patients.

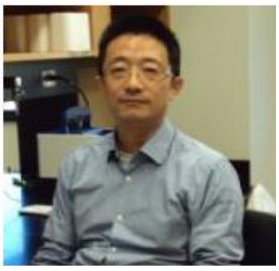
- **Looking at newer targeted therapies.** One promising drug, called pevonedistat, targets a protein called NAE that is involved in cell division and is being studied in clinical trials.
- **Studying ways to target AML cells indirectly.** An ongoing clinical trial is adding the drug uproleselan to chemotherapy. Uproleselan targets a protein called E-selectin on non-cancerous cells that helps protect cancer cells from being killed by chemotherapy.
- **Exploring other drugs that may have use in AML.** These include HDAC inhibitors and related treatments that alter how genes are switched on and off. Many of these drugs are also being studied for the treatment of myelodysplastic syndromes (MDS), which can eventually progress to AML.

Researchers Funded in part by the Teddy Kim Foundation

2017

Dr. Xinyang Zhao, PhD at the University of Alabama

Project Title: *Targeting PRMT1 in Acute Megakaryocytic Leukemia (AMKL)*



Overall, Dr. Zhao's research has been published more than five dozen times and received more than 2,900 citations. Following his funding from the LRF/TKF he became a of the LRF's Medical Advisory Board.

Finding new treatment for AML by targeting protein arginine methyltransferase 1(PRMT1) was the goal of this LRF funded grant. Dr. Zhao tested an array of PRMT1 inhibitors in this project. One PRMT1 inhibitor was found to be very potent and cures acute myeloid leukemia in a mouse leukemia model. Other proposals to further this research have been submitted. At the mechanism side, Dr. Zhao discovered new mechanism for leukemia development. An enzyme, which dephosphorylates proteins such as oncogenic kinases p38, was discovered as a downstream target for PRMT1. The new mechanism can be used to elucidate how targeting PRMT1 works in leukemia treatment.

The most significant finding is that *the small molecule inhibitor PRMT1 MS023 is a very promising drug for treating acute myeloid leukemia.* Testing the drug using patient derived xenograft models is next. In the meantime, Dr. Zhao also has a panel of PRMT1 inhibitors, developed in collaboration with Dr. Yujun Zheng at University of Georgia, waiting for further investigation. As more PRMT1 inhibitors are being tested in various types of solid tumors, Dr. Zhao hopes to be the first group to publish the efficacies of inhibiting PRMT1 for AML treatment in the near future.

2018

Dr. Jing Li, Assistant Professor, Department of Biology, Shanghai Normal University

Project Title: *The role of Sirt2 in the pathogenesis of acute myeloid leukemia (AML)*

The role of Sirt2 in AML is largely unknown. Drug-resistance and disease relapse are the major problems for current leukemia treatment. Signaling emerged from bone marrow protects leukemic cells from chemotherapy drugs, which is one of the critical mechanisms of drug resistance.

Aim 1. Determine the role of S368 residue phosphorylation of Sirt2 on its deacetylase activity and leukemia repressive function *in vivo.*
The experiments designed for Aim 1 of this project were successfully completed. In this part, we've made progresses as below:

1. Generated Sirt2^{S658A} and Sirt2^{S658E} AML cells.
2. *Completed the leukemogenic ability study of the transduced AML cells.* Results showed that mice receive Sirt2^{S658A} AML cells required longer latency for leukemia development compare to mice received other types of AML cells.
3. *The drug-sensitivity test of the transduced AML cells were studied.* We observed the Sirt2^{S658A} AML cells were more sensitive to chemotherapy than other types of AML cells.

Aim 2. Determine whether Sirt2 regulates leukemogenic capacity and chemotherapy response of AML cells through deacetylating Ac-NF-κBK310 and Ac-Stat3K685 *in vivo*. In this part, the Sirt2$^{-/-}$ Stat3^{K685R} AML cells and the Sirt2$^{-/-}$NF-kB^{K310R}Stat3^{K685R} AML cells were already generated by Crispr-cas9 mediated genome editing technique. Work continues to study the leukemogenic ability of the gene edited AML cells.

2019

Shunji Egusa, PhD, Assistant Professor, Department of Physics and Optical Science the University of North Carolina – Charlotte.

Project Title: *Au nano-linker: Turning standard AML drugs into lineage-targeted therapeutics*

Traditional cancer treatments that destroy normal cells along with the cancer cells can result in substantial toxicities to the patients. Destruction of normal cells is especially problematic when treating myeloid cancers (*e.g.*, acute myeloid leukemia, AML), where normal hematopoietic stem cells are needed to reverse low blood counts that can lead to morbidity and death. A solution is to deliver drugs selectively to cancer cells and thereby spare normal ones.

However, existing technologies have limitations. We examined a novel nanochemistry, Au nanolinker, exploiting ligand-exchange chemistry to release a drug payload selectively at redox-stressed cancer cells. The Goals were to establish proof of versatility, stability and effectiveness of this nanochemistry. The results will be used to justify concrete advancement toward investigational new drug (IND)-enabling studies and clinical applications.

Accomplishments

- The drug linking condition for Au nano-linkers was fine-tuned, starting from our prior publication. The newly established synthesis is far more versatile, allowing for linking of amine-containing as well as nonamine- containing drugs without chemical aleration.
- Myeloid-targeting molecule was successfully linked to Au nano-linker, simultaneously with abundant and unmodified drug molecules.
- Myeloid-targeted drug delivery and intracellular drug release was preliminarily demonstrated *in vitro* using several leukemia cell lines.

2020

Dr. Mario Andres Blanco, PhD, Assistant Professor, Department of Biomedical Sciences, University of Pennsylvania

Project Title: *Dual targeting of LSD1 and KAT6A to induce therapeutic differentiation in AML*

Given the COVID crisis, Dr. Blanco and its impact on various medical institutions, Dr. Blanco and other researchers were granted a no cost extension to complete their projects. However, September is Blood Cancer Awareness Month and Dr. Blanco will be interviewed LIVE on the LRF's Facebook page on Friday, September 11 at 7:00 pm (eastern) and provide an update on his progress with this project.

"While it certainly has been a unique time, things are actually progressing very well with the project funded by the LRF grant. This grant has been tremendously helpful to my laboratory, and with the support we're now in the process of submitting a manuscript reporting our findings."

Acute Myeloid Leukemia (AML) is the most deadly blood cancer, causing more than 10,000 deaths in the US annually. Patients are treated with chemotherapeutic regiments, but many relapse and have few therapeutic options. An alternative type of AML therapy, called "differentiation therapy" aims to treat patients by changing their rapidly dividing cancer cells into cells that do not divide. Differentiation therapy is the standard treatment for one subtype of AML, and it cures 95% of these patients. However, differentiation therapy has not been developed for other subtypes of AML. Our recent work has identified a combination of drugs that are highly effective in our preliminary experimental models of differentiation therapy.

The overall goal of this study is to test the efficacy of a promising new differentiation therapy regiment for non-APL AML in mouse models and to understand the molecular mechanisms by which this drug combination induces differentiation. The basis of the grant is using a chromatin-focused CRISPR/Cas9 sgRNA screen to identify epigenetic regulators of the differentiation block in acute myeloid leukemia cells.