The Bejar Laboratory Newsletter

Spring 2019

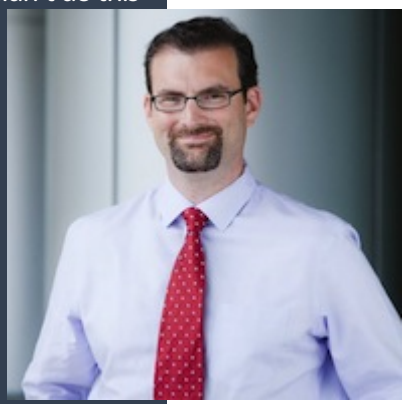
Dear Friends,

As we navigate through the new year, our team has been hard at work to make a difference in MDS Research.

We want to take a moment to share our progress and to express our thanks as many of you have supported our work through financial donations, contributions to our sample bank, and as participants in our clinical trials.

Through countless hours of study, our research has improved our understanding of blood disorders like MDS. We have traced from its genetic origins and developed approaches to individualized patient care. It is with this knowledge that we are able to make the breakthroughs necessary to turn research into clinical solutions. In this newsletter we would like to share several of those stories and successes with you.

2019 is looking to be a year full of exciting progress with many success stories in the lab. We couldn't do this without you. Your support is helping to make finding cures a reality for more patients every day.



We sincerely thank you.

Rafael Bejar, MD, PhD

This Issue:

Metformin and Preventing Secondary Blood Cancers

Clonal hematopoiesis describes a common pre-cancerous condition where blood stem cells gain one or more mutations in cancer-associated genes. This allows them to grow and expand abnormally at the expense of their normal counterparts.

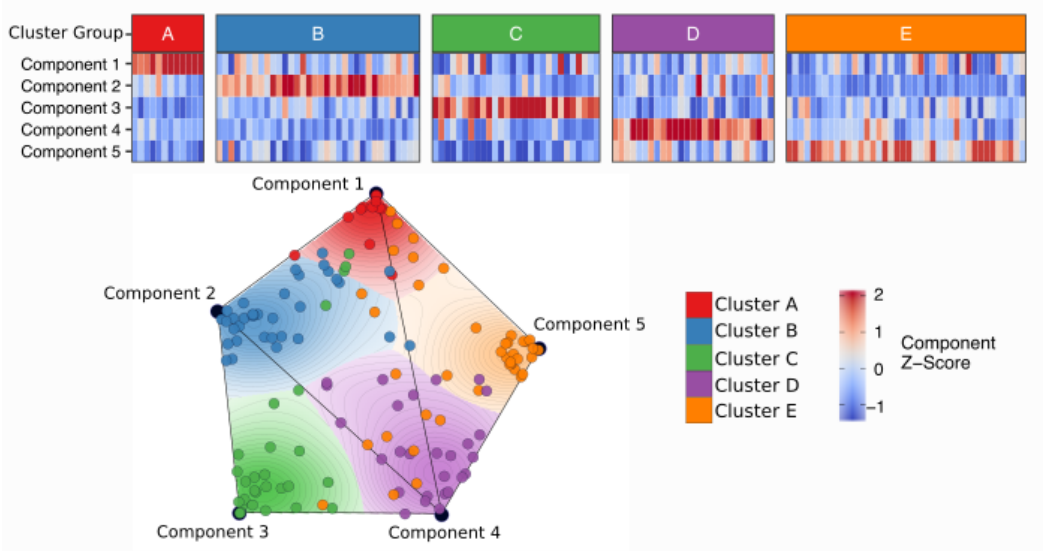
Chemotherapy triggers DNA damage and inflammation within the bone marrow microenvironment prompting certain blood stem cells with adverse mutations to expand even further, significantly increasing the risk for developing very aggressive blood cancers for which current treatments are ineffective and survival is measured in months.

There is a critical need for improved predictive and preventative measures for secondary blood cancers in patients who are otherwise cured from their primary cancer.

Metformin is a widely-used diabetes drug that blocks several Inflammatory pathways and could have profound effects on the bone marrow microenvironment to reduce the risk of secondary blood cancers in individuals treated with particularly high risk chemo-therapeutic agents.

We will study how treatment with metformin affects clonal hematopoiesis and disease outcomes in women who received chemotherapy after surgery for breast cancer.

Exploring how inflammation after chemotherapy exposure affects mutant blood stem cells leading to predisposition for secondary blood cancers will impact how we screen and follow clonal hematopoiesis in the foreseeable future and integrate preventative efforts long term for breast cancer and other solid tumors.



This figure depicts 5 patient clusters that can be discerned by examining methylation patterns in bone marrow DNA. Each cluster is enriched for different genetic mutations and is associated with differences in clinical outcomes

Changing How We Classify MDS

Somatic mutations have been a key element in understanding the underlying drivers of disease and can help in predicting prognosis. We are currently researching how patient DNA methylation patterns can enhance our knowledge of MDS disease biology and improve prognostication.

Through a descriptive study on epigenetic regulation in MDS, our lab used DNA from bone marrow mononuclear cell specimens obtained from over 140 patients. These samples were sequenced and DNA methylation was measured at ~140,000 targeted regulatory regions across the genome. Patients that shared similar DNA methylation patterns were then grouped together, identifying 5 distinct subtypes of MDS.

Each of the five subtypes identified surprisingly had distinct mutation profiles with several groups displaying enrichment of mutations associated with an adverse prognosis. The subgroups we identified displayed differences in survival that were not fully explained by other known clinical measures or the presence of prognostic gene mutations which indicates that DNA methylation patterns may provide a novel method to refine prognostication in MDS.

The importance of this is underscored when identifying treatment options for patients as even patients with diverse genetic mutations can have similar DNA methylation states which we showed were related to pathogenic mechanisms and clinical outcomes.

DNA methylation, not currently used by prognostic models, can be added to help identify clinically relevant subtypes and improve patient outcomes.

We will continue to study the biological differences between subgroups in order to get a better understanding of the role of DNA methylation in MDS and how that can be applied to better treatment options.

Persimmune Study

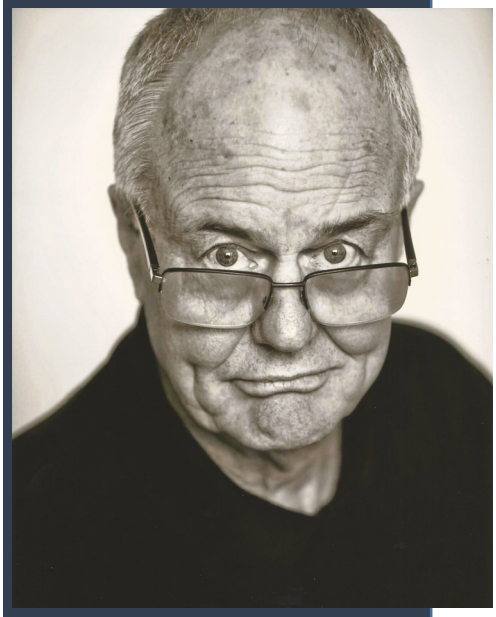
Developed collaboratively by the Bejar Laboratory and PersImmune, Inc., located in Sorrento Valley, CA, we activated a phase I immunotherapy clinical trial in 2018 that is assessing the safety of an adoptive T cell therapy for patients with relapsed or refractory MDS.

This approach uses a patient's own immune cells (T cells) to kill cancer cells bearing the protein products of the patient's specific MDS mutations. These mutant proteins are uniquely expressed by malignant cells and not by normal ones, which minimizes off-target toxicity or side effects to the patient

DC Trip

Soo Park, A fellow in the lab recently returned from a trip to Washington DC with the American Association of Cancer Research. While there she spoke with other researchers and members of congress sharing their experiences as cancer researchers.

She also spoke about the importance of continued bipartisan support for biomedical research through increasing the budget for the National Institute of Health.



Our research is supported by a generous Memorial Fellowship established in honor of Dr. Vernon 'Skip' Maino.

Skip was a pioneering R&D leader in monoclonal antibody technology and flow cytometry with over 90 peer reviewed publications to his credit.

After obtaining graduate degrees from the University of California San Diego and the University of Rochester, he had a prosperous career spanning five decades that included becoming the Scientific Director of R&D at Becton Dickinson.

He continually sought and led the development of basic research into commercial products that have been widely accepted by both the academic and clinical research communities.

New Research

Dr. Tanaka was recently awarded a KL2 Mentored Career Development Award by the UCSD Altman Clinical and Translational Research Institute, providing protected research time with Dr. Bejar's mentorship.

The aim of her study is to carefully describe immune cell populations and function in MDS and how they are altered by standard treatment with approved drugs called azacitidine (Vidaza) and decitabine (Dacogen). These drugs can prolong life and delay progression to leukemia but show benefit in less than 50% of patients. Since we do not have a good understanding of how these drugs work at the cellular and molecular level, we do not have good means of predicting which patients are likely to respond and which are more likely to suffer side-effects for months without improvement. Better ways of predicting how patients will respond to HMAs and clearer insight into how they work are sorely needed.

Our goal is to find features of the immune system in MDS that help us predict which patients will benefit from treatment through genomics (study of DNA and RNA), immune profiling and tests of immune function. In the short term, we expect to find markers that predict which patients will benefit from standard therapy and which should avoid the toxicity of this treatment and explore other options. In the longer term, we hope to identify immune mechanisms that might be targeted with other therapies to improve the likelihood that a patient will benefit from treatment.

MDS Sample Bank for Research

To create a collection of MDS patient samples, we have partnered with Genoptix, a diagnostic company that reviews blood and bone marrow from patients suspected of having MDS and other blood disorders. When the pathologists as Genoptix complete their evaluation of a patient sample, a report of their findings is returned to the patient's physician and the remaining patient sample is discarded. We proposed to collect these discarded samples from patients diagnosed with MDS, strip them of all potentially identifying information, and use them to create a large bank of samples for use in research. To this end, we have negotiated an agreement with Genoptix detailing how samples will be acquired and the anonymity of patients protected

We have collected over 1100 samples from over 500 patients diagnosed as having MDS. Their associated diagnostic information has been entered into a secure, searchable database and combined with samples collected at our MDS Center of Excellence at the UC San Diego Moores Cancer Center. All samples and their associated data are now available for use in research. This is an invaluable resource for researchers studying how genetic changes and other DNA modifications are linked to clinical features of MDS. We hope that his will lead to improvements in how we diagnose these disorders, how we predict whether the disease will progress, and ultimately, how we treat patients more effectively.

Bejar Laboratory Staff:

Rafael Bejar, MD, PhD
Principal Investigator

Tim Luger
Lab Manager/ Research Associate

Tiffany Tanaka, MD
Hematology/ Oncology Attending Physician

Brian Reilly
Graduate Student

Soo Park, MD
Hematology/ Oncology Fellow

Laura Williamson
Undergraduate Researcher

Designed by: Brandon Ilie
Lab Volunteer

Dr. Soo Park (bottom left) in D.C. with AACR

Brian Reilly Presenting at The American Society of Hematology Annual Meeting

Upcoming Events:

March 22-23: Great Debates and Updates in Hematologic Malignancies meeting
Marina Del Rey, CA

March 30: AA MDS International Foundation 2019 Patient and Family Conference
Albuquerque, NM

April 5-6: Great Debates and Updates in Hematologic Malignancies meeting
New York City, NY

April 11-12: Acute Leukemia Forum: Advances in Myelodysplasia
Newport Beach, CA

May 8-11: The 15th International Symposium on Myelodysplastic Syndromes
København, Denmark

September 20-21: Canadian Conference on Myelodysplastic Syndromes and AML
Vancouver, British Columbia

Patient Resources & More information on MDS & other MPNs can be found at:

The Bejar Laboratory UC San Diego

35 YEARS AA·MDS INTERNATIONAL FOUNDATION

mds foundation the myelodysplastic syndromes foundation, inc.

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers