

MPN RESEARCH FOUNDATION

CHANGE YOUR PROGNOSIS UPDATE



VOLUME XX, NO. 2 SUMMER 2021

PERIODIC NEWSLETTER FOR THE MYELOPROLIFERATIVE NEOPLASMS COMMUNITY

SPECIAL SCIENCE EDITION

TWO DECADES OF GROWTH AND INNOVATION

By Barbara Van Husen



MPN Research Foundation
Annual Roundtable Meeting

When Bob Rosen was diagnosed with polycythemia vera (PV) in 1996, he asked his doctor whether there were established treatments, and who was doing the best research into new therapies or a potential cure. What he learned was discouraging. Although PV was recognized as one of three classic MPNs, there was not a lot of active research into MPNs. Bob resolved to tackle this issue, and with three other like-minded patients he formed the MPN Research Foundation (MPNRF) in 2000.

At first the Foundation's funding strategy was simple: get any credible researcher to do any credible work related to MPNs. In 2000, the Foundation's first grant went to Dr. Josef Prchal, one of several researchers searching for the gene(s) responsible for MPNs. Over the next several years, the Foundation worked independently as well as jointly with the Leukemia & Lymphoma Society (LLS) to identify, review, and fund several additional projects, to fill gaps in early stage research.

A GREAT LEAP FORWARD FOR MPD/MPN SCIENCE

A profound opportunity to advance MPN science came in 2005. The identification of the JAK2V617F mutation by multiple researchers made the possibility of a targeted drug that could affect and potentially control MPN disease (similar to what Gleevec had done for CML) within reach. With the help of our scientific advisors, MPNRF began the MPD Research Alliance, a four-year effort to fund preclinical testing that might lead to new drugs based on JAK inhibition. We are proud that our researchers (Drs. Gilliland, Hoffman and Tefferi) were able to lay the groundwork that ultimately led to multiple drug approvals.

By 2008, it became clear that academic and industry research was well underway in this area, leading MPNRF to look for other areas of unmet needs. From 2008 through 2011, we focused on full genome sequencing and on bringing new academic researchers to study MPNs. Many of our new researcher awards went to scientists who are now leaders in the field, and our genome grants included a project that identified the Calreticulin (CALR) mutation as it related to MPNs (more details on Page 2). This finding was a key puzzle piece that solidified the understanding of the genomic background of MPNs.

THE MPN ROUNDTABLE TAKES ITS PLACE IN OUR FUNDING STRATEGY

In 2012, through an initial partnership with LLS, the Foundation began the program that continues to drive our research funding to this day. We held our inaugural MPN Roundtable, a two-day meeting that brought industry and academic researchers together to discuss the state of MPN science and to identify unmet need that would drive our funding program in the upcoming year. Patients and Foundation representatives also participated, making this meeting especially meaningful to participating scientists, many of whom rarely heard from the patients directly served by their work.

Today, annual Roundtable discussions set focus areas for our signature research grant program, The MPN Challenge. The focus changes from year to year based on scientific advances, new opportunities and ideas coming to the forefront. Over the past decade, MPN science has expanded dramatically, and the Foundation continues to be a catalyst for new research ideas and directions.

REVISING AND EXPANDING OUR STRATEGY BASED ON ADVANCES IN SCIENCE

In 2016 the Foundation mounted an effort to refocus our research strategy. We developed

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THE MISSION OF THE MPN RESEARCH FOUNDATION IS TO STIMULATE ORIGINAL RESEARCH IN PURSUIT OF NEW TREATMENTS — AND EVENTUALLY A CURE — FOR MYELOPROLIFERATIVE NEOPLASMS (MPNs).

WWW.MPNRESEARCHFOUNDATION.ORG

EARLY FUNDING ON CALR MUTATION UNCOVERS NOVEL THERAPY APPROACH

By Brandon Goetzman

"FOUNDATION FUNDED CALR RESEARCH LEADS TO CLINICAL TRIAL OF VACCINE"

One of the most exciting MPN discoveries in the last decade was the 2013 discovery of the Calreticulin (CALR) mutation, which accounts for disease in 73% of JAK2-negative MPN patients. MPNRF is proud to have been a part of the funding efforts focused on this key discovery announced by Dr. Robert Kralovics' research team in Austria, one of the two teams that discovered the mutation. The discovery of the CALR mutation led to a better understanding of why a large subset of patients with essential thrombocythemia (ET) and myelofibrosis (MF) have the disease.

After this monumental discovery, MPNRF made several subsequent investments into CALR-specific research with the hope that a deeper exploration of the mutation will lead to therapies that can target CALR. One area of particular focus is immunotherapy, which has recently produced innovative therapies in blood cancers outside of the MPN space. Shortly after the discovery of the CALR mutation, several researchers hypothesized that by selectively targeting mutant CALR with immunotherapies, they could avoid

harm to normal (wildtype) calreticulin found throughout the body.

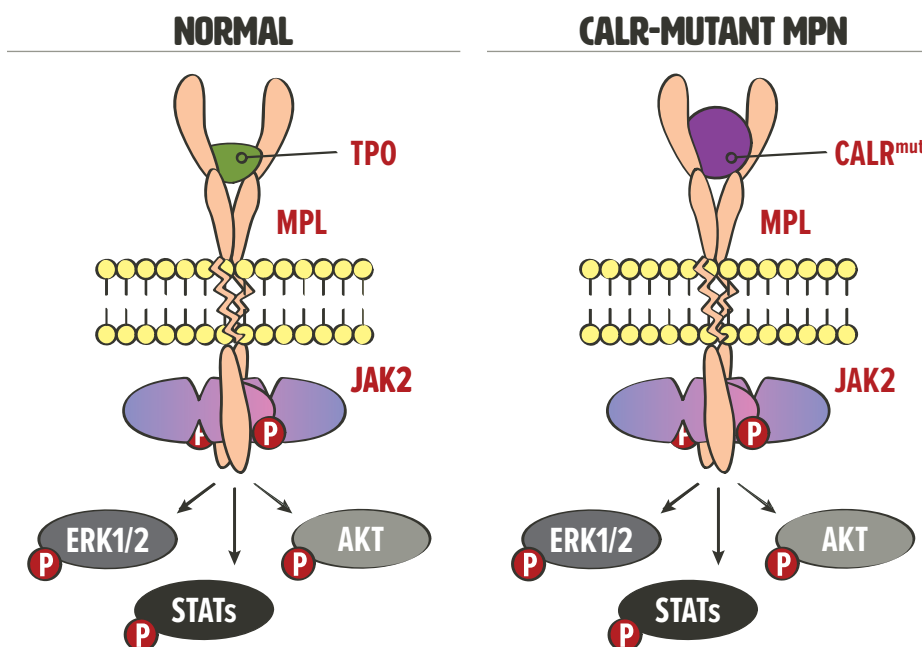
In 2015, MPNRF funded a two-year MPN Challenge Grant to a team of researchers, Dr. Camelia Iancu-Ruben and Dr. Nina Bhardwaj, at Mount Sinai Hospital in New York City to explore whether mutant CALR could be targeted by immunotherapies. The preliminary findings from the MPN Challenge Grant research affirmed that mutant CALR is immunogenic and potentially may be targeted with certain immunotherapies, including a to-be-developed peptide therapy vaccine and checkpoint inhibitors already approved for other forms of cancer. In this context vaccines are used as treatments and potentially curative therapies.

The Mount Sinai research team was able to leverage the early research results for additional grant funding to develop a novel peptide vaccine and test it in animal models with the goal of translating the vaccine into a Phase 1 clinical trial. After several years of preclinical research, the research team at Mount Sinai has announced the development

of a cancer vaccine targeting mutant CALR. The Mount Sinai version of the CALR vaccine is expected to be materially different than the CALR vaccine developed and tested in Europe, which showed limited efficacy.

After late unexpected delays due to the COVID-19 pandemic, Mount Sinai will be opening a Phase 1 trial of the therapy vaccine in 2021 for certain CALR positive ET and MF patients. Dr. Iancu-Rubin, principal investigator of the CALR peptide vaccine research said: "By funding the initial laboratory work, MPNRF made possible the first vaccine-based clinical trial in MPN in the United States. With its patient-oriented vision, the Foundation understood and anticipated the potential impact such work will have when translated to the clinic. MPNRF support underscores the importance of preclinical research in paving the way to better, innovative cures in MPN."

Patients and caregivers can find out more information about the CALR vaccine trial on clinicaltrials.gov when the trial formally launches later this year. ■



Volunteers diagnosed with Myelofibrosis or Essential Thrombocythemia who have a documented CALR gene mutation are needed to participate in a research study from home. If you qualify, you can contribute to the development of new treatments and earn \$100 for your time. Visit our website www.mpnresearchfoundation.org/news/calr_research/ to learn more.

THE CALR MUTATION CAN ACTIVATE JAK2 IN A MANNER THAT CAN LEAD TO ET AND MF.



MPN Board

a working hypothesis that we reviewed with our patients, academic researchers, and biopharma partners. The result was an overarching strategy that has directed efforts in recent years. Key components of that strategy are:

- + **A major focus on progression.** Patients were very clear in their responses to our surveys regarding key research objectives. The ability to slow or stop disease progression was the top priority for these patients. The Foundation's current **Progression Initiative** began with this in mind.
- + **The collection of patient-reported outcomes in the first MPN Patient Registry.** For many years, the Foundation had been investigating technical options for collecting and maintaining patient data, ultimately launching **myMPN to collect patient-reported data**. Research results from myMPN have been presented at American Society of Hematology (ASH) and other hematological meetings. Collecting patient data continues to be a major focus of our research activity.
- + **A multi-institutional collaboration to understand interferon and its potential as an MPN treatment.** For years interferon alpha was recognized as one of the few drugs that appeared to have a strong ability to mitigate MPN symptoms.

Interferon in a variety of forms, in real world usage and clinical trials has shown high rates of symptom, hematologic and molecular responses in some MPN patients. However, there was not a clear consensus on how Interferon achieved these results, why *some* patients and *not others* achieved these results, and why the results were not long lasting for some patients. The Foundation began a multi-year, collaborative project called **the Interferon Initiative** to address these issues with outcomes to be shared in communities.

- + While the Progression and Interferon Initiatives were underway, **The MPN Challenge Grant Program** continued to address ongoing research and emerging ideas in the expanding MPN field.

OUR WORK CONTINUES

MPN Research Foundation has always believed that that our best strategy for advancing MPN science is to fund research based on the evolving understanding of these diseases and the rapid evolution of technologies and approaches in MPN research. Our research approach continues to be governed by the following guidelines:

- + **Be flexible.** Seek high risk/high reward ideas that can dramatically impact the development of treatments.
- + **Identify unmet need.** Look for the missing pieces. Academia and industry will follow up on ideas that have developed data and traction.
- + **Fund new and innovative research.** Be additive, not duplicative, to other funding efforts. Make the most of patient-raised dollars to impact patient lives.

- + **Actively support the broadening field of MPN researchers.** As new academic researchers and biopharmaceutical companies enter the field, the combined impact of their efforts expands.

- + **Take an entrepreneurial approach.** As a foundation, we must be 'opportunistic', pursuing emerging trends or needs that may be off the beaten path.

MPN Research Foundation looks forward to the day when all needs are met, research is fully funded, and MPN patients can live full, disease-free lives. Until then, we will aggressively pursue innovative research in pursuit of better treatments – and ultimately a cure. ■



MPN Research Foundation Annual Roundtable Meeting

"WE DEVELOPED A WORKING HYPOTHESIS WHICH WE REVIEWED WITH OUR CONSTITUENT PATIENT, ACADEMIC RESEARCHERS, AND BIOPHARMA PARTNERS. THE RESULT WAS AN OVERARCHING STRATEGY THAT HAS DIRECTED OUR EFFORTS IN RECENT YEARS."

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MPN RESEARCH FOUNDATION UPDATE

A periodic newsletter published by the MPN Research Foundation to provide members of the MPN community with information on current research and the Foundation's activities.

MPN RESEARCH FOUNDATION

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HELPING DOCTORS AND MYELOFIBROSIS PATIENTS MAKE THE TOUGH DECISION ABOUT STEM CELL TRANSPLANTATION

By Ed Bartholemy and Dave Boule



Roni Tamari, MD



Raajit Rampal, MD, PhD

The decision to undergo a stem cell transplant is incredibly difficult. Transplantation is the only curative treatment currently available to myelofibrosis patients, and can offer cured patients a normal life expectancy. However, about 50% of patients who undergo a transplant die within five years and many grapple with very difficult complications. Currently, there is no reliable way to identify which patients will be cured by a transplant and which will suffer serious complications or death. Patients and doctors facing this very difficult decision deserve high-quality, comprehensive information about the individualized prospects for a successful transplant.

At the 2019 MPN Research Foundation Roundtable, Ed Bartholemy, an MPNRF Board member whose wife has myelofibrosis, and Dr. Raajit Rampal, a Memorial Sloan Kettering Hematologist/Oncologist, discussed the need for a large, comprehensive study addressing this issue. Earlier studies have attempted to explore these questions about transplantation information, but were limited by small sample sizes and came to conflicting conclusions. The Roundtable discussion led to the development of this project, a large, multicenter study led by Dr. Raajit Rampal and his colleague Dr. Roni Tamari, a stem cell transplantation specialist at Memorial Sloan Kettering, in collaboration with the MPN Research Foundation.

"Although several studies have attempted to understand the factors that may increase or decrease a patient's odds of having a favorable outcome, evaluation of large datasets is needed," noted Rampal and

Tamari. "With the support of the MPN Research Foundation, the MPN research community has initiated this important collaborative effort to study the impact of molecular mutations on transplant outcomes in patients with myelofibrosis."

This project will study if the presence of specific molecular mutations and number of mutations are associated with survival, relapse, graft vs. host disease (GVHD, a serious complication in stem cell transplantation), and toxicities post-transplant. It will also study which patient-, disease-, and transplant-specific factors affect these outcomes.

The study will bring together data from about 15 transplant centers in the United States and Canada. The goal is to include data on 700-800 transplant patients in a single database, a significantly larger sample than prior studies were able to assemble. The data will be accessible to researchers at all of the contributing centers for future studies, and research collaboration across institutions will be encouraged.

The project will create a comprehensive database with details on transplant patients and their outcomes, including:

- + molecular mutations and genomic alterations;
- + demographic data about the patients, such as age and gender;
- + clinical data about the patient and their disease, both at the time of diagnosis and immediately pre-transplant;
- + the donor type, including whether the donor is related or unrelated, matched or mismatched, or if cord blood was used;
- + the protocols used for the transplants, such as the conditioning regimen to prepare the patient for transplant, GVHD

preventative measures, and stem cell source; and

- + transplant outcomes, including survival, incidence of relapse, changes in marrow fibrosis, incidence of GVHD, and cause of death for deceased patients.

Any of the patients' identifying data are removed to protect privacy. These data will then be studied in an effort to identify molecular markers and other characteristics of transplant patients which can be used to better predict transplant outcomes. This kind of information would enable patients who have a greater probability of a successful transplant to pursue this curative treatment more confidently and perhaps earlier in their disease, when transplant outcomes are better. Those with lower probability of a successful transplant would be able to pursue other therapies.

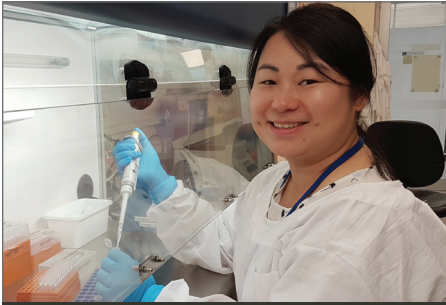
"We strongly believe that these type of collaborations across multiple institutions and involving data from hundreds of patients are likely to give us some of these sought-after answers," Drs. Rampal and Tamari said.

This study is different from the MPN Challenge Projects that the MPNRF typically funds. Most notably, the Foundation is actively involved in this study, doing outreach to get transplant centers on board and providing help with project management. Additionally, both the time frame of this project and the funding cost for the Foundation are less than a typical two-year Challenge Grant. The Foundation tries to maintain the flexibility to be opportunistic in developing or funding these kinds of projects as needs arise, in addition to our signature programs.

This type of multicenter study requires collaboration between institutions, presenting both legal and logistical hurdles. For the MPN Research Foundation, this study will serve as a pilot project to evaluate the feasibility of larger multicenter data-sharing research projects for MPNs in the future. ■

MPN RESEARCHER SPOTLIGHT: AN INTERVIEW WITH BELINDA GUO, PhD

Interviewed by Lindsey Whyte, Written by Jillian Weeks



Belinda Guo, PhD

MPNRF's mission is to promote novel research into MPNs, particularly through funding of new researchers and innovative approaches. Dr. Belinda Guo of the University of Western Australia is one such trailblazer in the field of MPN research. A recipient of the Gunn Family National Career Development Fellowship for Women in Hematology, Dr. Guo's research focuses on the application of next-generation sequencing technology to create novel approaches for the earlier detection of hematological malignancies.

In 2018, Dr. Guo received a grant from the Ruby Red Foundation in Australia to support her research exploring the potential role of platelets as a marker of fibrotic progression, which could lead to the development of a blood test to detect underlying bone marrow fibrosis. MPNRF and the Ruby Red Foundation came together in 2019 to further support this investigation through a jointly-funded project entitled "Platelets as a novel marker for progression in myeloproliferative neoplasms." This potentially ground-breaking initiative is slated to end in December 2021.

We spoke with Dr. Guo to learn more about what motivates her innovative work and how funding from organizations like MPNRF can help drive groundbreaking discoveries for patients.

MPNRF: Can you give us a brief overview of your project?

Belinda Guo (BG): Broadly, our work focuses on the progression of MPN from a relatively chronic state to the more aggressive myelofibrosis states. This project aims to identify easily detectable changes in the blood's platelets that can be used to monitor

patients and tell us if and when the disease may be progressing to that fibrotic state. We hope this work will provide timely and accurate information for patients and their doctors to assess their risk and possibly begin treatment earlier to stop that progression.

MPNRF: How did you end up in medical research, and what brought you to study MPNs?

BG: I've been interested in science from a young age, as my parents were in the fields of biology and botany. My curiosity grew and I became fascinated by human diseases, how they work, and different ways that researchers can manipulate certain systems to create a solution or a cure. To me, that work felt like science fiction and I knew that's what I wanted to do when I got older. I was introduced to MPN research by my postdoctoral mentor, Wendy Erber. Wendy is a hematopathologist with a longtime interest in MPNs, and she was part of one of the original groups that discovered the JAK2V617F mutation. Her dedication and enthusiasm as a researcher really drove me to champion this research and look for ways to improve patients' outcomes.

MPNRF: How has funding from the Ruby Red Foundation and MPNRF influenced the course of your research?

BG: Because MPN is a relatively rare disease, working in Perth alone really restricts the number of patients we're able to recruit to our study, which limits the overall applicability of our findings. This continued funding from the Foundation is helping to take our work to the next level, building an international collaboration with doctors at St. Jude Children's Research Hospital and Mount Sinai Hospital. We've been able to take the workflow we've developed and analyze samples from patients in the U.S. to determine whether our findings are applicable in a broad setting and how we can improve. It's also allowed us access to mouse models of MPN, which gives us an elegant way to assess changes in these markers from the beginning of the disease through its progression.

MPNRF: What motivates you to go to work every day? How do you like to spend your time outside of the lab?

BG: The whole idea of applying knowledge and different techniques to answer a question is like a puzzle, so it keeps me engaged and on my toes. It doesn't feel like work to me – it's something fun that I look forward to doing every morning. As far as time outside of work, the latest phase is jigsaw puzzles. I find them extremely calming and soothing because I know each piece definitely has a place and I just have to be patient to see where it goes.

MPNRF: How has the COVID-19 pandemic affected your work, and what lessons have learned through that experience?

BG: The main impact of the pandemic on our research has been in the progress. We haven't had to change the scope of the project itself, but there have been some delays in patient recruitment and collection of samples during lockdowns and restrictions. The biggest lessons have been in being flexible and always having backup plans in place – now when we design and plan experiments, we always consider potential ways it could be interrupted, by the pandemic or any other reason. The very last lesson would probably be, "don't panic." I've learned over the last year that things will go wrong and we just need to find the best way to get around them.

MPNRF: Finally, do you ever get to meet with MPN patients in person? How does that impact you?

BG: Our lab is very focused on applied research, so all of our projects involve input from other researchers as well as clinicians, patients, and patient networks. Prior to the pandemic, I was able to meet with patients and get firsthand accounts of their experiences. I had the pleasure of attending a Ruby Red Foundation event where we had lunch with patients and were able to discuss our research but also hear about their journeys. Developing that empathy and understanding their key concerns is a huge motivator for me, especially when we face obstacles in research. Knowing that what we're doing and what we aim to achieve could change someone's life for the better one day has a huge impact in driving my research. ■

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CLINICAL TRIAL HIGHLIGHTS

MPNRF tracks clinical trials for potential therapies for ET, PV and MF and shares information about opportunities to participate in trials with the patient community. 2021 is a record year with several advanced stage trials and many new investigational drugs. Currently there are 10 Phase 3 trials for MF, a long list of phase 1 and 2 trials and a growing number of trials for ET and PV in various phases, as well. Additional information can be found on our website at: mpnresearchfoundation.org/mpn-clinical-trials/.

Ropeginterferon alfa-2b (Phase 3)

Sponsor: PharmaEssentia Corporation
Diagnosis: Essential Thrombocythemia
More Info: www.SURPASSET.com

Luspatercept (Phase 2)

Sponsor: Bristol Myers Squibb/Celgene
Diagnosis: Myelofibrosis with anemia
More Info: www.bmsstudyconnect.com

TL-895 (Phase 2)

Sponsor: Telios
Diagnosis: Myelofibrosis
More Info: www.clinicaltrials.gov/ct2/show/NCT04655118

KRT-232 BOREAS (Phase 3)

Sponsor: Kartos Therapeutics
Diagnosis: Myelofibrosis
More Info: www.boreas-trial.com/

Itacitinib LIMBER-213 (Phase 2)

Sponsor: Incyte
Diagnosis: Myelofibrosis
More Info: www.clinicaltrials.gov/ct2/show/NCT04629508



The MPN Research Foundation would like to acknowledge the generous sponsorship of Abbvie, Sierra Oncology and Sumitomo Dainippon Pharma Oncology, for this special edition of the *MPN Update*.

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