

# MPN RESEARCH FOUNDATION

CHANGE YOUR PROGNOSIS

# UPDATE



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PERIODIC NEWSLETTER FOR THE MYELOPROLIFERATIVE NEOPLASMS COMMUNITY

## SPECIAL SCIENCE EDITION

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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.

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## OUR MISSION HAS NEVER BEEN CLEARER

Michelle Woehrle, Executive Director



Michelle Woehrle

This spring, during our 20th year, the world as we all know it was up-ended with the spread of Coronavirus, or Covid-19. What at first seemed like a distant issue soon changed the way most of the United States and the world lived and worked, received healthcare, education, shopped, and moved. Nothing was unscathed, and that includes the MPN research community. I am writing this mid-April, where the extent to which these changes will remain part of our new normal is still unclear.

What has never been unclear is that our mission – funding research in pursuit of better therapies and eventually a cure – is more important than ever. National budgets and research funding focus will likely be overwhelmingly focused on Covid-19 or preparing for the next pandemic that could so cripple the global economy. Once again, after a decade of seeing a relative increase in attention on MPNs from academic and industry scientists, we are concerned that the well of interest will dry up for the new kid on the block.

Where will that leave the people living with PV, ET and MF? MPN patients are often initially misdiagnosed, or have their

symptoms or concerns about progression or health events such as heart attack, stroke or blood clots not adequately addressed by doctors who are used to seeing acute cases of leukemia or other heme malignancies in overly busy practices.

As long as MPNRF exists, there will be a funding stream for a MPN clinician researcher community to support and treat those living with the disease. We haven't been taken down by the pandemic, and it won't slow our progress answering the questions that remain unsolved. So, while we are so grateful as the world seeks to solve this and future global health crises, our focus remains unchanged and unhindered.

Now is not the time for us to stop or slow down. We hope that you take hope and inspiration from reading this publication. We hope you walk away feeling confident and assured that those living with an MPN will always have a strong ally in the MPNRF. We were there when no one was looking into MPNs, and we will be there pushing for better outcomes for our patients no matter what. ■

The MPN Research Foundation would like to acknowledge the generous sponsorship of Sierra Oncology and Bristol Myers Squibb, for this special edition of the *MPN Update*.



## MISSION

The primary mission of the MPN Research Foundation is to stimulate original research in pursuit of new treatments — and eventually a cure — for myeloproliferative neoplasms (MPNs). In addition, the MPN Research Foundation promotes collaboration in the scientific community to accelerate research and serves as a powerful patient advocacy group for patients and their families.

[MPNRESEARCHFOUNDATION.ORG](http://MPNRESEARCHFOUNDATION.ORG)

# REPORTING GREAT PROGRESS FOR 2017 CHALLENGE GRANTS

Rick Winneker, PhD, Director of Scientific Strategies

The MPN Research Foundation exists primarily to fund research. To date, over \$15 million has been awarded to 75 research projects focused on innovative science and treatment options needed to improve outcomes for patients with an MPN. The Challenge Grant program was launched in 2012 as our main research funding mechanism. In 2017, we funded five Challenge grants for 2 years. A brief summary for these very successful projects is below:

**Angela Fleischman, MD, PhD**  
University of California, Irvine  
*Inflammation as a Driver of Clonal Expansion in Myeloproliferative Neoplasm*



The goal was to define how chronic inflammation drives the emergence of hematopoietic stem cell clones with MPN disease driver mutations while exhausting non-mutated cells. Dr. Fleischman showed that inflammatory stimuli provide a selective advantage for JAK2 mutated cells and that an inexpensive anti-oxidant supplement, N-acetylcysteine (NAC), reduces thrombosis and extends life in a mouse model of MPN. She is now planning to test NAC in a clinical trial and opened a trial to study how a low inflammatory diet may impact inflammation, symptoms, and blood counts in MPN patients.

**James Griffin, MD**  
Dana-Farber Cancer Institute  
*Inhibition of deubiquitinating enzymes (DUBs) as a novel targeted therapy for JAK2-dependent myeloid malignancies*



JAK2 inhibition has been shown to be an effective therapy for MPN patients. However, current JAK2 therapies inhibit both the mutated and non-mutated

JAK2 protein. The goal was to achieve selective degradation of the mutant JAK2 protein by identifying drugs that inhibit a specific protein that normally stabilizes the mutant JAK2. Compounds were identified that can lead to degradation of mutant JAK2 and cause selective killing of mutant JAK2 expressing cells. This represents a completely novel way to inhibit mutated JAK2. Further optimization of these potential new drugs is now ongoing.

**Rebekka Schneider, MD**  
Erasmus University Medical Center  
The Netherlands  
*Functional and molecular dissection of the fibrotic transformation and clonal selection in MPNs*



The altered bone marrow (BM) microenvironment and inflammation play a key role in fibrotic progression but no specific markers for the early diagnosis of BM fibrosis have been defined. These studies identified the cells responsible for fiber deposition and revealed two potential therapeutic targets, which will be tested as novel therapies in ongoing experiments. One of these proteins also found in the blood might be a marker for early diagnosis of fibrosis.

**Vivian Oehler, MD; Marie Bleakley, MD, PhD**  
Fred Hutchinson Cancer Research Center  
*Characterizing myeloproliferative neoplasm neoantigens and T cell responses for therapeutic application*



"Neoantigens" are novel therapeutic targets derived from mutated proteins that are

shared among MPN patients. A neoantigen discovery platform was developed to identify both candidate neoantigens and the T cells that specifically respond to those neoantigens. Candidate neoantigens with therapeutic potential were identified and produced from known or likely disease driver mutated proteins. If successful, new therapies targeting these neoantigens should allow for eradication of the malignant MPN progenitor cell while sparing normal cells.

**Stephen Oh, MD, PhD**  
Washington University, St. Louis  
*Leveraging NFkB Pathway Dysregulation for Therapeutic Benefit in MPNs*



These studies have further characterized the inflammatory NFkB pathway and its impact in MPN patients. This pathway appears to be relatively insensitive to ruxolitinib. Dr. Oh confirmed that the drug pevonedistat inhibits this pathway and restricts growth of an MPN cell line and patient cells. Pevonedistat also inhibits production of multiple inflammatory cytokines. A phase 1 clinical trial of pevonedistat in combination with ruxolitinib in MF patients is now underway. Additional preclinical studies with pevonedistat alone and in combination with ruxolitinib are ongoing.

These completed grants have led to the opening of new clinical trials, the identification of new therapeutic and diagnostic targets and potential new therapies. We couldn't be more pleased. ■

# PATIENTS ARE JOINING THE RESEARCH EFFORT THROUGH DATA SHARING

Lindsey Whyte, Registry Manager



In 2017, we launched myMPN ([mpnresearchfoundation.org/myMPN-Register](http://mpnresearchfoundation.org/myMPN-Register)), giving patients a chance to influence the direction of MPNRF-funded and other research by reporting their health experiences online.

By contributing personal experiences, including symptoms and medical events at regular intervals, longitudinal data is collected for analysis and presentation at scientific conferences and meetings. The anonymous data is made available upon request to approved researchers for use in their studies, and participants in the registry are notified of studies and clinical trials they might qualify for.

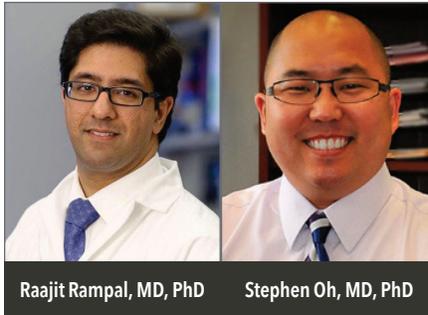
To date there are over 1,200 myMPN participants in the U.S., and data collection in other English-speaking countries is on the horizon. Scientific posters and papers that have been presented at industry conferences illustrate the value of data collected so far, validating the registry as a tool for ongoing data collection and analysis.

The online portal means that participants can report their experiences from the convenience of their own home at any time. In addition to submitting novel abstracts for scientific conferences and to journals, myMPN data is also used in Foundation-sponsored meetings to support decision-making and guide discussions with our academic and biopharma partners.

With your help, we're using the power of patient data to make the MPN research community even stronger. ■

# ANNOUNCING THE INAUGURAL MPN DISEASE PROGRESSION SUMMIT

Rick Winneker, PhD, Director of Scientific Strategies



Raajit Rampal, MD, PhD

Stephen Oh, MD, PhD

Last September, the Foundation hosted a meeting in Maryland where patients talked to stakeholders about the burden of their disease. Despite a variety of disease-related symptoms and treatment-related side effects that impact their lives significantly, it was nearly unanimous that progression to a more serious or aggressive state was a major concern.

MPN disease progression has always been an area of interest for our research funding; however, this Fall we will be shining a greater light on this topic by holding our first MPN Disease Progression Summit meeting. Our goal is to launch a long-standing network of clinicians and researchers working collaboratively to improve outcomes and quality of life for patients through the prevention and treatment of disease progression.



## Our objectives for this first meeting are:

1. Further develop the vision, scope and structure of this collaborative network of researchers
2. Present and discuss key areas of unmet medical and research needs that can be addressed collaboratively in the near term
3. Present pilot projects for funding in 2020
4. Develop an outreach communication plan for this and future meetings

A distinguished and diverse group of clinicians and researchers from the US and seven other countries have already expressed interest in attending. Drs. Raajit Rampal (Memorial Sloan Kettering Cancer Center) and Stephen Oh (Washington University, St. Louis) have agreed to be co-organizers of the meeting.

If successful, we plan to make the meeting annual, and serve as the hub to develop research partnerships and communicate progress to the broader MPN stakeholder community. ■

# INTERVIEW: KRIS VADDI

**Kris Vaddi is the CEO and Founder of Prelude Therapeutics. He has served on the selection committee for MPNRF's annual grant program and was one of the researchers who discovered and helped develop Jakafi, which was the only available treatment for MPNs for many years. Kris is also a member of our Scientific Advisory Board.**



Kris Vaddi

**MPNRF:** How did you end up in medical research? Why did you become a scientist?

**Kris Vaddi:** I grew up in a small town in India, where my father was the first physician with a full-time medical practice. He had a consulting room at home where he would see patients at all hours. I spent time as a child observing his work, and became very interested in the field of medicine. However, I realized in my early teens that my interest lay in the tools he was using to treat his patients, rather than the work of being a doctor. I studied the brochures that sales reps left behind and was fascinated by the pharmaceutical industry. It was suggested that I study medicine for a career in pharmaceutical research. I attended medical school in India and came to the US to attend graduate school and pursue a career in the pharmaceutical industry.

After completing my PhD, I found a post-doctoral position at DuPont Merck Pharmaceutical Company and worked in drug discovery in a newly emerging area of research. I had a great experience and decided to pursue the career of a pharmaceutical scientist.

**MPNRF:** Can you share a defining moment or turning point in your work as a scientist?

**KV:** While I was at Incyte, I started a discovery program targeting JAK-STAT pathway. After

3 years of work, we discovered a number of JAK1 and JAK2 inhibitors that were active in preclinical models of blood cancers and rheumatoid arthritis. As we were advancing our lead molecule, INCB18424 (now known as Jakafi), we learned about the discovery of JAK2V617F mutation in MPNs and decided to initiate a clinical trial in myelofibrosis.

In 2007, we treated the first patient with Jakafi. A couple of weeks later we received news that the patient had a dramatic improvement. Reading that note and learning about how something I championed for 5 years had such an impact on a patient was the single most cherished moment in my career to date. I was very fortunate to be part of the team that helped Jakafi get approved for myelofibrosis and PV and have a positive impact on so many patients. I truly consider my work on Jakafi as a defining career moment.

**MPNRF:** What do you enjoy most about your work in research?

**KV:** I really love to follow the molecules that chemists make to develop drugs. Witnessing the fascinating transition of a small molecule drug that starts as an interesting lead to ultimately become an approved drug is

something I was fortunate to experience. I really enjoy being part of the team that shepherds molecules through various phases of testing, ending with successfully completing clinical trials to become a drug.

**MPNRF:** What gets you up in the morning? What motivates you?

**KV:** As a young scientist, I couldn't wait to get back to the lab to continue the experiments I started the day. As I advanced in my career and spent more time in developing strategies and guiding teams in drug discovery, I became more interested working on multiple projects simultaneously and learning more about the biotech business. After 14 years at Incyte, I realized my true passion is to build companies to champion the discovery of new drugs based on emerging understanding of cancer. I started Prelude Therapeutics in 2016. For the past 4 years my focus has been on building the company and advancing the molecules we discover into clinical trials. After 25+ years in drug discovery research, I still get up every morning excited to see what our work in the labs and in clinical trials uncovers that day. The opportunity to bring hope to patients and make a real impact on their and their loved one's lives is exceptionally motivating and rewarding. ■

