Awards were announced in December by MPN Research Foundation (MPNRF) for the 2022 Thrive Initiative which totaled $1.8 million in support of 11 research projects over two years.* The awards fill research funding gaps, some related to the pandemic, and are in addition to currently funded projects supported through our 2021-2023 MPN Challenge.

The awards include an exciting mix of seasoned, global MPN researchers to continue existing projects, as well as junior and established investigators with new ideas and perspectives to explore. Together, they help MPNRF pioneer the way for new research and treatments.

"Many are projects that otherwise might be left on the research bench without support," says Brandon Goetzman, chair of the MPNRF board’s Scientific Steering Committee. “Each project went through a rigorous peer review process, with final selections based on scientific merit.”

Awards are in three categories.

FOLLOW-ON SUPPORT AWARDS
To preserve and advance existing promising MPN research that might otherwise languish.

**Aberrant Megakaryopoiesis in the MPNs**
John D. Crispino, PhD, MBA, St. Jude Children’s Research Hospital
Ayalew Tefferi, Mayo Clinic, MN

The Crispino lab has long focused on the biology of the megakaryocyte (MK), the blood cell that produces platelets. Over production of MKs is a feature in essential thrombocythemia (ET) and expansion of atypical MKs contributes to fibrosis in myelofibrosis (MF).

- A major objective of this follow-on work is to better understand the factors that drive MPN MKs toward ET versus MF, and develop strategies to prevent or slow disease progression.
- This project focuses on a novel signaling axis called DYRK1A-NFAT as a key controller of aberrant (abnormal) MK production.
- The ultimate goal is to use this new information to develop therapeutic agents and strategies to prevent or inhibit aberrant MK development and related progression to MF.

MPN Research Foundation stimulates original research in pursuit of new treatments — and eventually a cure — for myeloproliferative neoplasms (MPNs).

mpnresearchfoundation.org
Harnessing the Immune System to Target Calreticulin Mutant MPNs
Marina Kremyanskaya MD, PhD
Cansu Cimen Bozkus, PhD
Icahn School of Medicine at Mount Sinai

This award supports the first US clinical trial to test a vaccine that could reverse the effects of a mutation associated with MPNs, in this case in the calreticulin (CALR) gene. CALR mutations are believed to be the genetic driver in about 30-35% of ET and MF patients.

+ All CALR mutations lead to a unique altered protein. This can be recognized as foreign by the immune system and is an ideal immunotherapy target.
+ Preclinical studies showed that mutated CALR can induce immune responses but the response in MPN patients was not as robust.
+ This research team has developed a vaccine that targets mutated CALR with the goal of enhancing the immune response in MPN patients.
+ It has the potential to eliminate the mutant malignant cells, leading to a reduction in tumor burden.

Analysis of Mutational Spectrum in Pediatric MPNs
Nicole Kucine, MD, MS
Weill Cornell Medicine

While MPNs are mostly diagnosed in people in their 60s or 70s, children and young adults are also diagnosed with MPNs.

+ The genetic factors contributing to disease onset and progression have not been well studied in the pediatric and young adult patient group.
+ Dr. Kucine has developed a database of children and young adults with MPNs. She will use this funding to continue to follow and expand this patient database to compare and contrast the role of genetics in this group versus what is already known about adults with MPNs.

Tracking MPN Fitness to Speed Development of Disease Modifying Agents for MPNs
Joseph Scandura, MD, PhD
Weill Cornell Medicine

Dr. Scandura is developing a new clinical measure called “MPN fitness” that can potentially predict major events, i.e., thrombosis, disease progression, and response to therapy.

+ MPN fitness refers to a mutated or abnormal cell’s ability to “out compete” a normal cell. The goal of this project is to further simplify the process of measuring MPN fitness, making it more user-friendly and robust for future clinical trials and further validation.
+ This work takes the field one step closer to more personalized predictive treatments for MPN patients.

JUNIOR INVESTIGATOR AWARDS
To provide an opportunity for junior investigators to compete exclusively with their peers and enhance their capacity for future funding in the MPN field.

Investigation of IL-1RAP in MPNs: Potential Novel Anti-Leukemic Therapy
Idorenyi Amanam, MD, MS
City of Hope National Medical Center

Immunotherapies address the need for a more personalized approach to cancer treatment, using the body’s own immune cells to fight cancer cells.

+ Immunotherapies involve T cells, which are shown to be effective in cancers such as leukemia.
+ High expression of IL1RAP (interleukin-1 receptor accessory protein) is associated with MPN accelerated and blast phases, and poor overall survival in acute myeloid leukemia (AML). Because IL1RAP is selectively overexpressed in MPNs, it appears to be an ideal therapeutic target.
+ Dr. Amanam’s group will use a “bispecific antibody” that binds to both IL1RAP on MPN stem cells and T cells. This allows them to kill cancer stem cells while reducing impact on healthy cells.

Development of Nanobody-Based Targeted Therapy for MPNs
Najla Arshad, PhD
Yale University School of Medicine

With up to 35% of MPNs driven by a mutated CALR gene, more specific targeted therapy is needed for this patient group.

+ Mutated CALR activates the cell surface thrombopoietin growth factor receptor (TPO-R, which helps develop platelets) and contributes to MPN disease.
+ The CALR mutated MPN cells also display tumor-associated peptides (small fragments of protein) on their surface, which this group plans to exploit by developing nanobody-based therapeutics against them.
+ Nanobodies are simplified antibodies that can readily target foreign cell surface proteins/peptides so that these cells can be eliminated.
+ This team plans to use nanobodies to target both the pathogenic mutated CALR - TPO-R interaction and MPN-associated cell surface peptides.
Role of Gas6-Axl-MERTK in MPN Thrombosis
Joan Beckman, MD, PhD
University of Minnesota, Twin Cities

Thrombotic events, such as blood clots, are a major concern for PV patients. Still, strong research projects on MPN-induced thrombosis are rare.

- Dr. Beckman, an expert in thrombosis research, is exploring a potential signaling pathway driving thrombosis in MPN patients.
- She is using unique preclinical models and mice with an MPN to test her hypothesis.
- This research has near-term implications. There is the potential for rapid translation of results into a clinical trial with an established late-stage investigational agent.

A New Mouse Model of the Early Phase of MPNs for Probing Disease Heterogeneity
Sahand Hormoz, PhD
Dana-Farber Cancer Institute

Recent studies have shown that the major MPN driver mutation, JAK2 V617F, which can lead to ET, PV, and MF, can occur in a hematopoietic stem cell years before an MPN is diagnosed. More understanding is necessary on the early phases of the mutation and its effects.

- This project seeks to develop a mouse model to study the factors that drive different disease outcomes in people who have this mutation.
- The model system, if successful, will enable the testing of new therapeutic strategies that can potentially delay or prevent the onset of disease.

Dissecting and Targeting Transcriptional and Epigenetic Regulation in Advanced Myelofibrosis
Ioannis Aifantis, PhD
New York University Grossman School of Medicine

Progressive fibrosis, or scar tissue of the bone marrow, is the cardinal feature of MF. Greater understanding of how and why this occurs is key to discovering and testing new treatments.

- As fibrosis progresses and bone marrow becomes less efficient, blood may be formed in the spleen (causing spleen enlargement).
- This team’s previous studies show that blood formation in the spleen is biased toward producing cancerous blood cells, with a reduction or lacking of normal blood cell formation.
- The project focuses on understanding the controlling factors for this and testing therapeutic approaches to MF.

The 2022 Thrive Initiative is made possible through the generous support of The Leukemia & Lymphoma Society, Shelley Spevakow of the SSASSY Foundation, the Susan Protter Estate, and several major individual and family benefactors who serve as champions for our collective mission.

*Year two funding of Thrive awards is contingent on satisfactory progress during year one. More on each project can be found here: www.mpnresearchfoundation.org/2022-thrive-initiative
An Important Time for MPNs: Highlights from American Society of Hematology 65th Annual Meeting

BY RAJIT RAMPAL, MD, PHD, MPNRF MEDICAL ADVISOR

This is a profoundly important moment in the treatment of MPNs.

We now have three FDA-approved JAK inhibitors – ruxolitinib, pacritinib, and fedratinib. We have combinations to offer, including a number of new drugs in late stages of clinical trials. And we may be able to sequence from one combination to the other. Compared to just a few years ago, this is huge.

Are we coming to the moment for MPNs where, like in breast cancer, a patient with advanced disease can be stable for several years because they can go from one treatment regimen to the next? I am certainly optimistic. I think that it is not an unreasonable thing to say that how we treat MPNs will be completely different in the next three to five years.

What is the basis of this optimism?

ASH MPN TAKEAWAYS

Momelotinib

There were many exciting advances in MPN research and treatment reported at the American Society of Hematology (ASH) Annual Meeting and Exhibition in December. Among these, came news of the anticipated 2023 approval of momelotinib for myelofibrosis. While it is similar to ruxolitinib in that it inhibits both JAK1 and JAK2, it has potential additional benefits.

With momelotinib, it appears we have a drug that can do the things that we expect the JAK inhibitors to do, i.e., shrinking spleens and improving symptoms, without the common side effect of reducing hemoglobin. Potentially increasing a patient’s hemoglobin, and maybe more importantly, converting transfusion-dependent patients to no longer require blood transfusions, that is an important development.

New Drugs Combined with Established Therapies

Many large phase 3 trials are looking at combination drug therapies, most often combining new drugs with JAK inhibitors. Among the primary questions is how do we know if positive results are related to the JAK inhibitor, like ruxolitinib, or the added drug.

Where we are now is looking at if these combinations work better than a single drug. That’s the first line that will be crossed in the coming one to two years, as these large phase 3 trials read out.
A randomized study, such as with pelabresib, now in a phase 3 trial with ruxolitinib, helps us get there. Two arms of patients will be directly compared. In this case, one group of patients gets only ruxolitinib and the other gets ruxolitinib plus pelabresib. The implication would be that if there is a difference, it would be attributable to the second drug. So far, this is one of the very encouraging drug combination trials for myelofibrosis.

Next the question becomes: How do the drugs get used, and do they get used in a sequential manner? For example, are patients started on ruxolitinib alone, then a drug like pelabresib gets added to the regimen if it’s not working well enough? The answer is that we still don’t know, and that’s where we have to go next.

**The Potential of Interferon in Combination Therapy**

Multiple forms of interferon have shown high rates of hematological and molecular responses in most patients with ET, PV, and some patients in the early phase of primary MF. But why it works for some people and not others, or why it stops working is poorly understood. That was the impetus for MPN Research Foundation’s 2017 creation of a global, multi-institutional collaboration to learn more about how interferon works.

At ASH 2022, Jean-Jacques Kiladjian, MD, PhD, Paris Diderot University, presented work from his studies of interferon over several years. Specifically, he reported on pegylated interferon (peginterferon alfa-2a) and ruxolitinib as a combination therapy.

The high-level takeaway is that the combination is reportedly safe. There isn’t randomized data yet, where half of patients get pegylated interferon alone and half get it with ruxolitinib.

Most interesting here is data reported that the level of mutation in some patients seems to be driven down more than we would expect with either drug on its own. That may indicate that the two are working together in certain patients. There’s more to be learned there, but we now know it seems to be safe.

**Cytopenia and Anemia – Potentially Reducing Transfusion Dependence**

With primary myelofibrosis, patients can present with anemia and/or with very low platelets. Cytopenia refers to either or both together. These people may require red cell transfusions, and sometimes platelet transfusions. Research on pacritinib – just approved last year – was re-analyzed and the findings offer potentially exciting news for this population.

Pacritinib is approved for first-line therapy in patients with very low platelet counts – less than 50,000. We had nothing to treat these patients before. As it turns out, pacritinib can do the same thing as momelotinib, inhibiting the same pathway (the ACVR1 pathway), leading to an increase in hemoglobin in some patients. And a proportion of patients taking pacritinib who were requiring red cell transfusions no longer needed them.

**A CALR Antibody**

Last, and anything but least, is one of the biggest stories coming out of ASH 2022 – news about a calreticulin (CALR) antibody. This is for people with MPNs who have a CALR mutation.

Researchers at Incyte have found a drug that can target the mutated calreticulin while avoiding normal cells. In mouse models, and some human cell lines, they saw that this drug, which is an antibody, was able to selectively deplete cells that had this calreticulin mutation.

It is a complete departure from how we have generally pursued MPNs, using an immunotherapy approach instead of an inhibitor. And it is early. Remember, all of the data that’s been presented was in mice and cells.

The next step is testing in humans, where we will actually get a real readout about what’s going to happen. It’s potentially a big leap forward. First, we need to study its safety, then if determined safe, it could move onto a phase 2 clinical trial. (See MPNRF-funded vaccine project in Thrive story on p.1.)

*Several studies reported at ASH are related to projects previously or currently funded by MPNRF. Some of these are highlighted on pages 6-7.*
Several research studies reported at ASH 2022 are projects by investigators currently or previously funded by MPNRF. They are a part of the MPNRF legacy of seeding and engaging impactful thought leaders to advance our understanding of MPNs.

Jyoti Nangalia, MBBChir
Wellcome Sanger Institute

The origins of adult blood cancers can be found early in life, including before birth. Dr. Nangalia’s team sequenced over 1000 clones from 10 JAK2 mutant MPN patients and used this information to build genetic “trees” for each patient and their mutations. This research may provide opportunities for earlier detection of disease risk and interventional strategies. Related to MPNRF 2019 MPN Challenge award.

Anandi Krishnan, PhD
Stanford University

Dr. Krishnan’s lab has identified a highly sensitive approach to profiling chronic progressive hematologic malignancies, such as MPNs, by looking at the RNA expressed by platelets. The goal is to use large cohorts of patients and machine-learning to better characterize disease features and enable predictions regarding outcomes based on this information. Work directly related to MPNRF 2021 MPN Challenge award.

Stephen Oh, MD, PhD
Washington University in St. Louis

Dr. Oh provided several updates, including work demonstrating RSK1 dependency in MPN progression to secondary AML. RSK1 (Ribosomal S6 Kinase 1) is involved in regulating cell survival and proliferation. In this case, an oral RSK1-4 inhibitor (PMD-026) was tested which is currently in phase 1/1b clinical trials for breast cancer. Dr. Oh and team demonstrated pre-clinical efficacy for this approach in blood cancers. Work directly related to MPNRF 2021 MPN Challenge award.

Bridget Marcellino, MD, PhD
Icahn School of Medicine, Mount Sinai

Dr. Marcellino’s work is focused on eliminating malignant stem cells with p53 as the major therapeutic target of interest. P53 is a gene that provides instructions for making a protein that acts as a tumor suppressor, regulating the growing and dividing of cells. She is studying two approaches to impact p53 levels, i.e., HDM2 and PPM1D. Results show that dual targeting of these proteins resulted in greater depletion of malignant cells. Work supported in part by MPNRF 2020 Progression award.

Linda Resar, MD
Johns Hopkins School of Medicine

Previous work by Dr. Resar showed that the protein HMGA1 is increased in MPNs and required for disease progression. Now she reports that HMGA1 represses certain genes and proteins needed for a related immune attack. She and her team also demonstrated that entinostat, an HDAC (histone deacetylase) enzyme inhibitor, is a possible pathway to reverse this process, potentially preventing disease progression. Entinostat has been studied with promise in several solid tumor cancers. Background science funded in part by MPNRF 2020 Progression award.

Nicole Kucine, MD
Weill Cornell Medicine

In one of the largest studies of pediatric MPNs to date, Dr. Kucine’s analysis included the mutational profiles of 29 young MPN patients. While fewer pediatric patients had multiple mutations compared to what is reported in the adult MPN population, some did show multiple mutations in childhood. Dr. Kucine’s commitment to understanding pediatric MPNs includes drivers of disease development, mutation acquisition over time, and the role of various mutations in MPN progression and outcomes. Work related to MPNRF 2022 Thrive Initiative award. See pages 1-3.

Shannon Elf, PhD
University of Chicago

Dr. Elf’s lab presented on type 2 mutant calreticulin (CALR) genes and the mechanism by which it loses its function as a molecular “chaperone,” affecting its normal interaction with other proteins. Mutant CALRs (type 1 and 2) eventually activate the MPL receptor, which serves as a disease driver in MPNs. The chemical chaperone tauroursodeoxycholic acid (TUDCA) was shown as a potential

Continued on page 7
I couldn’t just sit and wait for things to come to me,” says Doug Ahmer, who was diagnosed with primary myelofibrosis in 2016. In fact, he uses Google alerts with keywords and reads a lot from a variety of reliable sources, “so I can keep up to date on new drugs.” That’s how Doug, now in his mid-70s, came to be on a clinical trial, with results that have altered his daily living from needing a walker to enjoying a one-mile brisk stroll.

Doug lived with his wife in Washington state when his general oncologist began addressing his primary MF with a “watch and wait” approach. When he moved to Boise, Idaho, a new community hematologist/oncologist started him on the JAK inhibitor ruxolitinib. While his enlarged spleen initially reduced in size, two years later, it was larger than ever. His platelets dropped as low as 50, and his fatigue was overwhelming. It appeared that ruxolitinib was not the answer to his MF symptoms.

It was then that he came across information about a launching clinical trial to study the effectiveness of selinexor for MF. The drug is FDA approved for some forms of myeloma and lymphoma. An oral “selective” inhibitor, it leads to tumor suppression while largely sparing normal cells.

With other serious health issues, Doug knew he was not a candidate for a stem cell transplant. He was also considerably overweight and anemic at the time, which could limit his treatment options.

He would be one of the first patients to enroll in this phase 2 trial if he qualified and would have to travel to Huntsman Cancer Institute in Salt Lake City – a five hour drive or costly airline ticket. He considered his options carefully and jumped into the review process to see if he was eligible. And he was.

Today, more than three years later, Doug explains the difference in his life. “It has opened up my ability to be mobile. I don’t suffer from fatigue even close to what I had. That ‘I can’t take another step’ overlayed tiredness, that’s completely gone.”

He reports that his blood counts are all currently in the normal range. And while he still has fibrosis in his bone marrow, according to his most recent bone marrow biopsy, there is less evidence of fibrosis. The once weekly medication has a few very “manageable” side effects for him.

“If appropriate treatments aren’t working, clinical trials are the only way you can get more and better help,” Doug strongly believes. So he generously shares his clinical trial experience and urges others to explore all of their options.

“I wish I had more information that could give me better knowledge of where I’ll be. I’m feeling really good – too good to believe I’m at the end,” he says with raised brows. “I’m out there on the leading edge, paving the path.”

**CLINICAL TRIAL IS LIFE ALTERING FOR DOUG**

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**MPNR-FUNDED RESEARCHERS AT ASH – Continued from page 6**

**Ann Mullally, MD**
Dana Farber Cancer Institute and Brigham and Women’s Hospital

Dr. Mullally presented on MPNs as a paradigm for clonal dominance and myeloid, or blood cell, transformation. She discussed studies complimentary to Dr. Jyoti Nangalia’s that show the JAK2 V617F mutation can be in blood cell lineages many years before MPN diagnosis, offering data on how fast these and other clonal mutations in blood can progress (i.e., their relative fitness). She also presented data on mutated CALR and its potential as a tumor specific antigen. The goal is toward clonally selective targeting of MPN mutations that initiate disease. Dr. Mullally is the recipient of an MPNR Interferon Initiative award and a 2020 Progression award. The presented work is not related to this funding.
Clinical trials determine whether a therapy is safe and effective in treating a particular disease. Successful clinical trials are a critical part of the drug development process, helping to bring more prescription drugs to patients.

Trials are designed to test a medical treatment against a placebo (inactive look-a-like), other medication, or the standard medical treatment for a patient’s condition. The data collected both from healthy volunteers and those with the targeted disease are necessary for the Food and Drug Administration (FDA) and health authorities around the globe to review prior to approving any new therapy or a new use of a therapy approved to treat a different disease. The decision to participate in a clinical trial is one to consider carefully and discuss with your physician.

**Pelabresib/Manifest 2 (Phase 3)**
Sponsor: Morphosys
Diagnosis: MF
Notes: BET inhibitor combined with ruxolitinib for patients without prior experience with a JAK inhibitor.

**Bomedemstat (Phase 2)**
Sponsor: University of Miami, Imago BioSciences, Inc.
Diagnosis: PV and ET
Notes: For patients who did not benefit from one standard therapy, bemdemstat focuses on inhibiting LSD1 and improving blood counts. Must be able to travel to trial site in Miami, FL.

**ABBV-744 (Phase 1)**
Sponsor: AbbVie
Diagnosis: MF
More Info: [https://www.abbvieclinicaltrials.com/study/?id=M20-247](https://www.abbvieclinicaltrials.com/study/?id=M20-247)
Notes: BET inhibitor for patients currently or formerly on a JAK inhibitor. Trial has several study arms including ABBV-744 alone, in combination with ruxolitinib, or in combination with navitoclax.

**INCB000928 (Phase 1/2)**
Sponsor: Incyte
Diagnosis: MF
Notes: ALK2 inhibitor for transfusion-dependent patients or those with symptomatic anemia administered alone or in combination with ruxolitinib.

**TP-3654 (Phase 1/2)**
Sponsor: Sumitomo Pharma Oncology, Inc.
Diagnosis: MF
Notes: For higher risk patients who were ineligible for or did not previously benefit from a JAK inhibitor.

For a personalized list of trials that match your diagnosis and history, use the MPN Clinical Trial Finder on our website.
Visit mpnresearchfoundation.org/mpn-clinical-trials