MPN PROGRESSION RESEARCH NETWORK
LEADING A GLOBAL COMMUNITY

MPN Research Foundation's unique research mission takes shape in multiple ways. High on our list of priorities is leading a global community to work collaboratively to better understand, treat, and prevent MPN disease progression.

MPN disease progression is considered by patients, clinicians, and drug makers to be a major area of question. For people living with essential thrombocythemia (ET), polycythemia vera (PV), or myelofibrosis (MF), it keeps their minds spinning at all hours. "Will I progress and how will my doctor know?"

An initial result of the PRN was to fund six pilot projects in 2021, each focused on a specific question to be addressed, in part through the collaboration and sharing of data and/or biological samples. They are now complete or near completion and are summarized on pages 3-5.

MORE PATIENT INFORMATION NEEDED

One major challenge to overcome in this disease community is that studies of progression lack sufficient numbers of patients or years of follow-up to address our long-term objectives. Working toward a solution, MPNRF, through the PRN, took a deep exploratory dive into the complex undertaking of creating a large MPN patient observational database.

"We are at a critical juncture," explains MPNRF Chief Executive Officer Kapila Viges, "where the disease landscape, regulations, and technology have all evolved to bring this within reach." She adds: "We took a cross-stakeholder approach, a thread that runs through our entire research strategy. We gathered input from patients, clinicians, researchers, and biopharma industry leaders."

With broad insights from this comprehensive group of global experts, including leaders of multiple institutional MPN patient database models, MPNRF studied the challenges, restrictions, and success stories of building and maintaining such a patient database.

With best practices and lessons learned gathered from different parts of the world, an innovative strategy and implementation plan for a large-scale patient observational database is in the works — a very exciting and potentially groundbreaking step to help answer your questions about MPN disease progression. Stay tuned in 2024!

FACT

MPNs can progress to a more aggressive blood cancer.
PV progresses to MF in less than 20% of patients over their lifetime.
ET progresses to MF approximately 10% of the time. MF transforms to acute myeloid leukemia (AML) in about 20% of patients.

Treating physicians want more evidence and consensus of what MPN progression looks like. Drug makers want better definitions and more data to convince regulators how drugs can intervene in the chain of events that might cause MPN disease to progress.

This is an area that MPNRF has regularly funded since its creation. However, simply funding research proposed by the community is not how we operate. Throughout our 24-year history, we have asked the question: What are the larger goals our research investments can achieve?

When we established MPN Progression Research Network (PRN) in 2020, it was with the vision of building a global community to address how to slow, stop, and possibly reverse MPN progression.

MISSION

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

mpnresearchfoundation.org
PATIENT IMPACT COUNCIL TO PLAY INTEGRAL ROLE IN MPNRF

A revitalized MPNRF Patient Impact Council recently launched with a new approach to actively advocate for the patient voice and perspective in all aspects of our work to promote research advances and therapies with meaningful patient benefits.

Created with very clear objectives and activities, the council includes individuals representing diversity in MPN experiences, diagnosis, skills, community connections, geographic locations, and demographics. Members include those living with ET, PV, MF, and acute myeloid leukemia, as well as those who have undergone bone marrow transplantation or are caregivers.

“Ultimately, a Patient Impact Council not only serves as a moral imperative, but also a practical necessity to focus our research on meaningful advancements in healthcare that directly benefit those they intend to serve – patients.”

— Sara Douglas, Associate Director of Patient Engagement

Members of the council will work collaboratively with MPNRF staff and its funded research teams, including providing feedback to help inform MPNRF’s research strategy and priorities. Other responsibilities will include:

- Offering feedback on specific research projects, including MPN Challenge awards, to increase patient relevance.
- Contributing to the creation of understandable research project descriptions.
- Offering the patient perspective to MPNRF, biopharma, and potentially regulatory agencies on clinical trial protocols, patient-facing documents, and unmet needs for treatments and education.
- Serving as ambassadors for MPNRF through various communications and events.

The MPNRF Patient Impact Council members below will lend their critically important lived experience and patient voice to the collective efforts of our global MPN community:

Kyle Bonder | Transplant Caregiver New York, NY
Ignacio Edenburg | MF Miramar, FL
Ben Hohenbrink | MF Bluffton, OH
Tyler Parsons | PV St. Louis, MO
Diana Turner | PV Chicago, IL
Bridget Broaden | ET Belleville, IL
TJ Houppert | ET Fairport, NY
Andrea Spica | ET+Transplant Dallas, TX
Ned Weinschenker | MF Providence, UT
Jean Diesch | PV Gibsonia, PA
Robert Greenbaum | ET+AML+Transplant Holly Springs, NC
MJ Tooxy | PV Ellicott City, MD
Joan Yatsko | MF+Transplant Linfield, PA
EVALUATION OF TP53 PATHWAY REGULATORS IN PROGRESSION OF MPN

Bridget Marcellino, MD, PhD, and Ron Hoffman, MD
Icahn School of Medicine at Mount Sinai, New York, NY

If we imagine our genes as a set of instructions for how our body works, sometimes there are typos (mutations or deletions) or extra words (increased expression), which can make things go wrong, causing diseases to progress.

Dr. Marcellino and her team are studying a specific cellular stress response network in the body which is associated with cancer, the TP53 pathway, to understand its role in the advancement of MPNs. TP53 is a tumor suppressor gene that helps repair damaged DNA of diseased cells, or eliminate the cells, but this pathway seems to be compromised in MPNs.

This study is shedding light on how this important pathway — responsible for suppressing tumor cells and protecting us — can go awry. It is important to investigate the potential mechanisms that might be responsible for the dysfunction of this pathway to further understand how it facilitates the progression of MPN disease.

Importantly, a large, multi-institutional database is being developed for this study, housing clinical and molecular information from more than 2,000 patients.

MORE

+ Using blood-forming stem cells from MPN patients, the research team aims to validate if the genes MDM2, MDM4, and PPM1D can serve as biomarkers (indicators) for TP53 pathway dysfunction, which could provide insights to medical practitioners about potential disease progression in specific patients.
+ Such a large database is essential to analyzing enough patients to make concrete conclusions.
+ By providing a clearer understanding of how MPNs might progress, studies such as this can help in the development of better treatments and disease management strategies.

TARGETING THE HMGA1 EPIGENOME IN MPN PROGRESSION

Linda Resar, MD, Alison Moliterno, MD, and Leslie Cope, PhD
The Johns Hopkins University School of Medicine, Baltimore, MD

Operating much like an on and off switch, epigenetic regulators are naturally occurring proteins that control expression of genes involved in cell growth and behavior. Dr. Resar’s group discovered HMGA1 as an epigenetic “key” required to “unlock” the genome and activate gene networks required for chronic MPN to progress to myelofibrosis or leukemia. In this study, her team is investigating how HMGA1 becomes activated in MPN and what happens after HMGA1 is activated, in order to develop new therapies to prevent MPN progression.

They found that HMGA1 is activated by the JAK2 mutation and, in turn, HMGA1 flips on multiple gene pathways that foster MPN progression, including bone marrow fibrosis. In some cases, HMGA1 unlocks gene networks that disrupt cell growth and behavior, leading to leukemia. More recent work also suggests that HMGA1 turns off genes that allow the immune system to attack mutant MPN cells. They are now searching for pathways that could be disrupted with therapy to prevent fibrosis and leukemia development while stimulating the immune system to attack the mutant MPN cells.

This extensive study — including collaborations with five institutions and seven researchers — advances our understanding of HMGA1’s intricate role in MPN progression, providing solid groundwork for developing targeted therapies to inhibit it.

MORE

+ Preliminary research also indicates HMGA1 is linked to excessive platelet production and may contribute to blood clotting complications seen in MPN patients.
+ In experimental models, reducing HMGA1 levels in cells from MPN patients not only stops the growth and spread of the disease, but also makes these cells more responsive to the JAK inhibitor ruxolitinib.
+ The continuation of this research is crucial to unlocking new and more effective treatment avenues for MPN patients.
INTERROGATING THE SPATIAL ARCHITECTURE OF MPN DISEASE PROGRESSION

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

In this investigation of MPN patient bone marrow, researchers are taking highly detailed images of marrow samples, identifying the spatial arrangement of various cells in it, and analyzing what is happening in each individual cell to better understand how MPNs progress. This insight will provide a deeper comprehension of MPN's underlying mechanisms, potentially leading to the development of more effective therapies.

The team created a special mix of markers to identify different types of cells in samples from MPN patients across disease progression. The markers also identified signals these cells send out, to understand each cellular "player" and their specific roles.

Imaging mass cytometry, a powerful analytical technique, was used to look at individual cells and allowed a view into which cells might be causing an MPN to get worse. Certain white blood cells called CD14 positive monocytes were observed to release signals (TNF and other cytokines) that could be problematic. In patients with MF, other unique characteristics were found in the bone marrow, including protein markers that hint at disease progression. They were also able to see that as MF worsens and potentially changes to AML, certain markers in the cells increase, which might be a sign of the disease progressing.

The study’s methodologies – including the image analysis and use of single-cell technology – are set to pinpoint abnormal cell populations that could be driving MPN progression.

Collaboration has been key, with additional MPN patient samples and analytical support shared from other institutions in addition to data analysis support. As more patient samples are analyzed, the researchers are studying if these findings hold true for a larger group.

MORE

* The researchers developed and fine-tuned multiplex imaging antibody panels and image analysis system to identify various blood-forming stem and progenitor (descendent) cell populations that can be identified by presence of crucial cytokine and signaling biomarkers on them (specifically TNF, IL-6, pS6, and pCREB).
* These cells could be contributing to or potentially driving MPN progression, especially those that show NFkB hyperactivation, which is not affected by ruxolitinib.
* MF patient bone marrow analysis revealed collagen fibers, pCREB and pS6 protein markers, blood and platelet forming cells in abundance. Patients advancing to leukemia displayed pCREB, pERK and pSTAT5 proteins in their blood forming cells, suggesting that they might be instrumental in progression.
IDENTIFYING AND VALIDATING ACTIONABLE BIOMARKERS IN MPN

Ann Mullally, MD, Brigham and Women’s Hospital, Boston, MA
Rebekka Schneider, MD, PhD, University Hospital RWTH Aachen, Germany and Erasmus MC Cancer Institute, Amsterdam, The Netherlands

The project is focused on two potential biomarkers of MPN progression, SLAMF7 in a type of white blood cells called monocytes, and CXCL4 in blood and bone marrow cells. Monocytes were found to be increased in numbers in MPN patients with essential thrombocythemia and polycythemia vera and might be responsible in progression to MF. These monocytes exhibit high expression of the signaling molecule called SLAMF7 which can be targeted with a drug elotuzumab. Dr. Mullally’s group proposes that SLAMF7 and a cell surface marker protein CD14 could potentially be used as biomarkers of progression to MF. Dr. Schneider is investigating CXCL4 as a potential biomarker for initiation of bone marrow fibrosis and progression.

Previous studies demonstrated higher gene expression of CXCL4 in bone marrow from both mice and patients, and the absence of CXCL4 enhanced the MPN phenotype in mice, including reduction in the number of monocytes and fibrosis. Bone marrow samples from more than 250 patients are being analyzed. CXCL4 protein analysis (ELISA) has been performed on ~400 patients including 56 controls and shows progressively higher levels of CXCL4 during fibrotic progression.

The two research groups are collaborating on integrating the SLAMF7 and CXCL4 data to understand how the blood forming cells and the surrounding bone marrow microenvironmental cells “talk to each other” to advance the disease. This will enable the identification of novel and targetable biomarkers at various stages of progression and therefore potentially allow physicians to intervene early on.

MORE

- Dr. Schneider’s previous research indicated higher gene expression of CXCL4 gene in bone marrow samples from mice and human patients. Of note, the absence of CXCL4 rectified the MPN traits in mice.
- CXCL4 is also being evaluated as a potential blood biomarker of fibrotic progression in MPN patients.
- The integrations of results from these studies could provide pivotal insights that might steer improvements in future diagnostic and therapeutic strategies for MPNs.

CHARACTERIZING THE ROLE OF INHERITED GENETIC VARIATION IN MPN DISEASE PROGRESSION

Vijay Sankaran, MD, PhD
Boston Children’s Hospital, Boston, MA

Given that secondary acute myeloid leukemia is more aggressive than primary AML, there is a clear need to further understand the inherited genetic features that could lead to more responsive prevention of MPN progression to AML. The studies are utilizing very large populations, first to examine the overlap between germline genetic variants that predispose one to the development of MPN or AML, and second to look at the genetic variants that could make individuals with MPN more susceptible to transformation to AML.

The team’s most recent results indicate that inherited genetic variants that increase the risk for acquiring MPNs also contribute to the risk for progression. This offers valuable insights that could shape future preventative measures and targeted treatments for affected individuals.

MORE

- Dr. Schneider’s previous research indicated higher gene expression of CXCL4 gene in bone marrow samples from mice and human patients. Of note, the absence of CXCL4 rectified the MPN traits in mice.
- CXCL4 is also being evaluated as a potential blood biomarker of fibrotic progression in MPN patients.
- The integrations of results from these studies could provide pivotal insights that might steer improvements in future diagnostic and therapeutic strategies for MPNs.

- One key challenge noted is the frequently late diagnosis and data base coding of an MPN, leading to inaccuracies regarding “time to AML” and survival analyses.
- The large genetic pool from multiple international databases enabled the identification of a number of new genetic loci (locations within a gene or another DNA segment) which may be associated with MPNs.
- According to this study, 7% of MPN patients progress to AML in ~5 years of diagnosis, leading to decreased survival. ■
Funded continuously by the National Institutes of Health (NIH) since 2006, the MPN Research Consortium (MPN-RC) is an interactive group of laboratory and clinical scientists from 12 institutions throughout North America.

With its global impact and renewed funding for another five years, the MPN-RC will continue to work in a coordinated fashion to develop therapeutic strategies intended to improve the survival of patients with MPNs, according to Ronald Hoffman, MD, who has been at the helm of this initiative since its inception and has a long history with MPNRF as a valued advisor.

MPNRF was a founding supporter of what was then called the Myeloproliferative Disorders Research Consortium. Rick Winneker, PhD, MPNRF Director of Research Strategies, represents MPNRF on the consortium’s External Advisory Board.

The overall goal of the MPN-RC is to maintain a multi-institutional research group that merges the skills and efforts of its scientifically diverse membership to generate the scientific foundation for novel therapeutic strategies. Data from both basic and clinical research is utilized as a platform and rationale for a rigorous evaluation through well-constructed, independent investigator-initiated phase I/II clinical trials pursued at multiple institutions.

“In addition to providing greater understanding about the pathogenic mechanisms underlying MPNs, or how and why these diseases develop,” adds Dr. Winneker, “the MPN-RC addresses unmet clinical needs of MPN patients.”

Myelofibrosis has become the major focus of research and clinical development for the consortium. In the most current NIH application, Dr. Hoffman writes: “We have chosen to focus our efforts on MF since it is the MPN with the shortest survival and at present, allogeneic hematopoietic stem cell transplantation is the only approach which substantially alters its natural history.” Dr. Hoffman is director of the Myeloproliferative Disorders Research Program, which he founded in 2007 while at Mount Sinai, where he continues his work as a physician/scientist specializing in MPNs.

World renowned for his research in the MPN arena, Dr. Hoffman has an extensive background spanning some 30 years, including both laboratory-based stem cell research and hands on care of patients with hematological malignancies.

During the last decade, MF patients have received enormous clinical benefit from the widespread use of the JAK1/2 inhibitor, ruxolitinib, which is the first drug approved for the treatment of MF patients. Unfortunately, this drug (and others in the class) does not substantially halt disease progression and offers minimal improvement in survival. The limitations of this class of drugs can be attributed to an inability to eliminate MF hematopoietic stem cells (HSC) and/or fully disarm the bone marrow microenvironments that support these cancerous cells.

“To improve MF patient survival,” Dr. Hoffman writes, “we hypothesize that drugs capable of effectively depleting MF HSCs but sparing their normal counterparts be utilized. These drugs would act by directly targeting malignant HSCs and/or by correcting their tumor promoting micro-environments.”

“In its simplest terms,” explains Dr. Winneker, “the MPN-RC has put together a ‘bench to bedside’ strategy to eliminate MF HSCs. Lessons learned from these studies will also be useful to scientists and clinicians studying a large number of other cancers.”

The MPN-RC projects and supportive cores are led by an all-star cast of academic research and medical thought leaders in the MPN field, including: John Crispino, PhD; Amylou Dueck, PhD; Marina Kremyanskaya, MD, PhD; Ross Levine, MD; Bridget Marcellino, MD, PhD; John Mascarenhas, MD; Ruben Mesa, MD; Anna Rita Migliaccio, PhD; and Raajit Rampal, MD, PhD.
After a medicine has been demonstrated to be safe in Phase 1 and achieves the intended result in Phase 2, then Phase 3 trials are implemented, often to compare it against another course of treatment. Together, these steps play a vital role in ensuring patient access to potentially more effective treatments.

Phase 3 trials involve large, diverse patient populations in order to collect the most comprehensive data on the drug’s performance and any potential side effects. The results are integral to determining whether a new treatment should be approved for widespread use, helping agencies such as the US Food and Drug Administration (FDA) make informed decisions to protect public health.

The decision to participate in a clinical trial is one to consider carefully and discuss with your physician.

**Luspatercept (ACE-536)/INDEPENDENCE (Phase 3)**

**Sponsor:** BMS/Celgene  
**Diagnosis:** Myelofibrosis  
**Notes:** For patients with primary myelofibrosis (PMF) or post-ET MF or post-PV MF requiring blood transfusions. Must also be on continuous JAK2 inhibitor therapy.  
**More Info:** [https://clinicaltrials.gov/study/NCT04717414](https://clinicaltrials.gov/study/NCT04717414)

**Navtemadlin (KRT-232)/BOREAS (Phase 2/3)**

**Sponsor:** Kartos  
**Diagnosis:** Myelofibrosis  
**Notes:** A novel oral small molecule MDM2 inhibitor called navtemadlin is assessed for the treatment of PMF, post-PV MF or post-ET MF patients who no longer respond well to JAK inhibitor therapy. A novel method of action in MF is MDM2 inhibition.  
**More Info:** [https://clinicaltrials.gov/study/NCT03662126](https://clinicaltrials.gov/study/NCT03662126)

**Imetelstat/IMpactMF (Phase 3)**

**Sponsor:** Geron  
**Diagnosis:** Myelofibrosis  
**Notes:** For treatment of patients with intermediate-2 or high-risk MF who are relapsed/refractory to JAK inhibitor treatment. Patients should not be a candidate for further JAK inhibitor treatment.  
**More Info:** [https://clinicaltrials.gov/study/NCT04576156](https://clinicaltrials.gov/study/NCT04576156)

**Rusfertide/VERIFY (Phase 3)**

**Sponsor:** Protagonist Therapeutics  
**Diagnosis:** Polycythemia vera  
**Notes:** To determine safety and efficacy of rusfertide in treating patients with PV in maintaining hematocrit control and in improving symptoms of PV. Must have had at least 3 phlebotomies due to inadequate hematocrit control in 6 months before starting the study or at least 5 phlebotomies due to inadequate hematocrit control in 1 year before starting the study.  
**More Info:** [https://clinicaltrials.gov/study/NCT05210790](https://clinicaltrials.gov/study/NCT05210790)

**Ropeginterferon Alfa-2b (P1101)/SURPASS ET (Phase 3)**

**Sponsor:** PharmaEssentia  
**Diagnosis:** Essential thrombocythemia  
**Notes:** To compare the efficacy, safety and tolerability of two different dose regimens of ropeginterferon as compared with anagrelide. The study is for second-line therapy for ET patients who have had a suboptimal or failed response to hydroxyurea.  
**More Info:** [https://clinicaltrials.gov/study/NCT04285086](https://clinicaltrials.gov/study/NCT04285086)

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**2024 MPN CHALLENGE RESEARCH AWARDS RFA NOW OPEN**

The 2024 MPN Challenge awards funding cycle opened its Request for Proposals (RFA) November 6th. MPN research pioneers, medical innovators, and researchers new to the study of MPNs are invited to apply. All supporters of MPN research and practice advancement are encouraged to share this opportunity with colleagues in their own institutions and broader communities.

Whether you are in the realms of cutting-edge science or patient-centered care, this is your opportunity to catalyze change and propel developments in the field. We strongly encourage junior investigators to apply for funding.

Proposals are due January 30th, 2024. Peer review begins April 18th. Notifications of awards are expected May 6th-7th.

Visit [MPNResearchFoundation.org](https://www.mpnresearchfoundation.org) and go to the RESEARCH tab.
OUR PROGRESS PERPETUATES OUR NEED

Your investment in MPN research is as urgent as ever.

PAST. PRESENT. PROGRESS. Our research focus sets us apart. The consistency of our focal point – past and present – has contributed to groundbreaking progress through a better understanding of ET, PV, and MF and the development of more and better treatments. As a result, many patients can look forward to an improved prognosis.

This would not be possible without your continued support. Thank you for making a donation today!

Including us in your ‘giving thanks’ and end of year giving plans is an investment in critical MPN research.

A holiday gift of MPN research is also a meaningful way to honor or memorialize a loved one, or someone in the MPN community whose dedication has impacted you or your family.

WE HAVE A NEW ADDRESS!

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