



UPDATE

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NEWSLETTER FOR THE MYELOPROLIFERATIVE NEOPLASMS COMMUNITY

CALR mutation: celebrating 10 years since discovery

Evolution of personalized/individualized medicine

Drug discovery relies on resources and collaboration beyond the boundaries of the laboratory. When MPN Research Foundation was founded in 1999, meaningful research on the blood cancers now collectively known as myeloproliferative neoplasms was scarce, including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF).

Established with a mission to stimulate original research in pursuit of new treatments — and eventually a cure — MPNRF has since played a key role funding some of the most important work over the last 20 years, including the discovery of a mutation in the calreticulin gene (*CALR*). The Foundation's very first grant in 2000 funded initial laboratory work specifically exploring genetic drivers critical to the identification of MPNs. This grant is representative of the spirit of MPNRF as it contributed to a practice-changing moment in hematologic cancers.

In 2013, two seminal papers were published back-to-back in the same issue of the *New England Journal of Medicine*, describing mutations that had been identified in *CALR* in a subgroup of patients with ET or MF. These mutations appeared to be mutually exclusive of the Janus kinase 2 (*JAK2*) and thrombopoietin receptor (*MPL*) mutations, which are found in the majority of ET and MF patients. The *CALR* gene encodes a protein called calreticulin, which is believed to play a role in protein folding, calcium regulation, gene activity, cell proliferation, migration, adhesion, and apoptosis.

Using different strategies, the two teams of researchers demonstrated that in its mutated state, *CALR* is a major driver of MPN in patients *without* *JAK2* and *MPL* mutations. In one paper, a team led by Robert Kralovics, PhD, performed exome sequencing on samples from 6 patients and identified insertion or deletion mutations of *CALR* in all of them. Targeted sequencing was then conducted on a large cohort of patients with both MPNs and other myeloid cancers.

Concurrently, a team led by Jyoti Nangalia, MBBS, PhD, who is now a member of MPNRF's Scientific Advisory Board, performed exome sequencing on samples obtained from a large cohort of 151 patients with MPNs. The large patient sample provided an unprecedented view of the mutational landscape in MPNs, allowing for *CALR* mutations to be identified in patients with ET or primary MF without *JAK2* or *MPL* mutations.

"There were so many memorable moments — from that special day of discovery, to calling one of our patients in July 2013 to kindly donate another blood sample so we could confirm the mutation," Dr. Nangalia recalls. "I remember thinking she was likely the first person in the world with a confirmed *CALR* mutation and a cause for her disease. Then, to implementing the test in clinic at the hospital within a few months, and testing all our historical patient samples to confirm their diagnosis."

These two new studies filled a large gap in the current knowledge of the genetic origins of MPNs, by identifying the most common mutation in

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MISSION

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

mpnresearchfoundation.org

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patients without *JAK2* or *MPL* mutations, but the papers were the culmination of years of investigating the genetic complexity of these disorders.

Since the initial discovery of the *CALR* mutation and its relationship to MPNs 10 years ago, research has continued. Detection of *CALR* mutations has been embedded in the World Health Organization and other international diagnostic guidelines.

The discovery of this mutation has had a major impact, according to Ann Mullally, MD, a physician-scientist at Brigham and Women's Hospital/Dana-Farber Cancer Institute, associate professor of medicine, Harvard Medical School, who is also a member of MPNRF's Scientific Advisory Board.

"First of all, I think it's very important in definitively making a diagnosis of MPN," she says. "Prior to the discovery of this mutation, we would see patients who looked like they had MPN and then do a biopsy. The biopsy results looked like MPN, but we really didn't have a mutation that was causative for the disease and so there was always some question as to whether they truly had MPN or not."

That paradigm changed with the discovery of the *CALR* mutation, which is the second most common mutation after *JAK2*. "Its presence is very definitive for making a diagnosis, since the mutation is not found in other diseases," says Dr. Mullally. "So, I think that [discovery] was very, very, very important."

Knowing the type of mutation also helps in determining prognosis. "We know that there are differences as to whether you have MPN with this mutation versus MPN with the *JAK2* mutation, for all different types of complications and prognosis," Dr. Mullally explains. "In and of itself, just being able to identify whether somebody has the mutation can already be very helpful in terms of counseling patients about what you know their risks are."

Perhaps most exciting, ongoing research has yielded promising future implications for patients, as *CALR* represents a new therapeutic target and raises the possibility of new treatment approaches that are more personalized to the patient, compared to the current one-size-fits-all approach to MPNs, whatever the identified driver mutation(s). Rare disease research, however, takes time.

Ten years after its discovery, we are now moving into clinical trials directly targeting *CALR*.

Dr. Mullally notes that a clinical trial of a mutant specific *CALR* antibody designed to target this mutation was presented at the 2022 American Society of Hematology Annual Meeting. And the first US-based clinical trial began in 2023.

"The 10-year anniversary of the discovery of the *CALR* mutation is really a time for everybody to kind of take stock," says Dr. Mullally. "The MPN Research Foundation has been really instrumental in this and the amount of research that's been going on all around the world is really impressive, to understand how this mutation causes disease."

She adds that much of the work is highly collaborative. "This involves not only what happens in the laboratory but what happens in the clinic, clinical research, and patient observations."

A research team led by Marina Kremyanskaya, MD, PhD, Icahn School of Medicine at Mount Sinai, first developed a vaccine that targets mutated *CALR* with the goal of enhancing the immune response in MPN patients. In a project funded by an MPNRF 2022 Thrive Initiative award, *Harnessing*

the Immune System to Target Calreticulin Mutant Myeloproliferative Neoplasms, she and her colleagues began initial testing of the vaccine in a clinical trial in MPN patients.

Today, two companies are investigating *CALR*-targeted treatments in current clinical trials, with potential to be available to patients if approved in the coming years.

MPNRF has awarded more than \$18 million for blood cancer research since it was founded, including supporting researchers doing preclinical testing and funding very early full genome sequencing projects at a time when the human genome project first suggested this might be feasible. Today, some of the investigators who received the Foundation's earliest awards are now leaders in the field. ■

Clots = Clogs

Why cardiovascular risk reduction is important to the MPN community

"The cardiovascular system is a plumbing system with a lot of pipes, and like any plumbing system it's best if they are clear – no clogs," explains Ellen Ritchie, MD, an MPN specialist at Weill Cornell Medicine in New York City. "And we know that MPN patients are at high risk for thrombosis (blood clots)."



For people living with essential thrombocythemia, polycythemia vera, and myelofibrosis, this underscores the importance of reducing other cardiovascular risk factors that can lead to heart attack or stroke.

Dr. Ritchie spoke at the Annual Women and MPNs conference, organized by MPN Advocacy & Education International late last year.

While cardiovascular events often accompany MPNs and contribute significantly to morbidity and mortality, the reasons remained unclear until research in recent years offered some insight.

"Recent research provides us with insight into the connection between cardiovascular disease and its complications and MPN. This information is essential in helping us assess and manage risk factors in MPN patients," according to Gaby Hobbs, MD, Massachusetts General in Boston, one of the authors in a 2022 study published in the journal *CardioOncology*, titled *Cardiovascular Disease in Myeloproliferative Neoplasms*.

The need for more research in this area also supports the need for more and better data about MPN patients. (See progression research story on page 5.)

Some of what we know about MPNs and cardiovascular disease

- ✦ People who have ET or primary MF and a *JAK2* mutation have about twice the risk for arterial thrombotic events (clots in arteries) compared with non-*JAK2* mutations.
- ✦ People who have PV with the *JAK2* mutation are at increased risk for venous thrombosis (clots in veins), including those that lead to major organs such as the liver and spleen.
- ✦ Knowing your mutations can help inform your care team's evaluation of cardiovascular risks, beyond your medical and family history.

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Who develops which MPN and why?

Research begins to offer some answers



It is known that JAK2 mutations are found in “healthy” people around the world, particularly in older individuals. Most of them don’t acquire characteristics of myeloproliferative neoplasms. The question is why do some people with the mutation develop an MPN while others don’t.

Researchers from the Wellcome Sanger Institute, the University of Cambridge, and other collaborators combined three key data sets to answer this and other related questions in a recently published study in the monthly journal *Nature Genetics*, titled: *Inherited polygenic effects on common hematological traits influence clonal selection on JAK2^{V617F} and the development of myeloproliferative neoplasms*.

There was previously little understanding of why a minority of people with mutated *JAK2* genes go on to develop MPNs – the group of rare chronic blood cancers that includes essential thrombocythemia, polycythemia vera, and myelofibrosis. Also unclear were the factors that influence blood heterogeneity in MPNs, including the differences in gene mutations, such as *JAK2*.

“This study aims to understand how the DNA that people are born with can affect the type of MPN they might develop, or indeed, the type of MPN they are less likely to develop,” explains Jyoti Nangalia, MBBS, PhD, of Wellcome Sanger Institute and the Wellcome-MRC Cambridge Stem Cell Institute at the University of Cambridge. She is co-senior author of the study and also a member of the MPN Research Foundation Scientific Advisory Board.

“I hope that in the future this information will help us predict which individuals are most likely to develop MPN if they are found to have a *JAK2* mutation, and the type of MPN they may be predisposed to,” Dr. Nangalia adds.



Physicians use blood tests to help diagnose and manage MPNs, including the number of circulating blood cells (red cells, white cells, and platelets), and the presence and prevalence of any identified genetic mutations.

In the published study, the authors describe their work specifically:

“By analyzing two large MPN disease cohorts and the UK Biobank (UKBB), we provide new insights into the interaction between germline polygenic variation involved in basic hematopoiesis and clonal selection on somatic driver mutations in blood and describe how this interaction can influence the phenotype of subsequent blood cancer.”

In other words, blood cells with the MPN driver mutations also need the right genetic environments to ultimately lead to an MPN diagnosis.

The authors conclude: “Our results highlight an independent and causal new component of the overall susceptibility to clonal disease and provide a new framework for considering an individual’s genetic background in the context of their clinical presentation.”

Earlier work by Dr. Nangalia et al was funded by MPN Research Foundation through a 2019 MPN Challenge™ award. The study *Origins of MPN: Understanding the timing of acquisition of driver mutations and dynamics of clonal expansion*, received global attention for its new evidence that *JAK2* mutations can be identified from birth and earlier.

The new study published in January 2024 is related. “Previously MPNRF has funded our work exploring when in life the mutations that cause MPN are acquired. This study now sheds light on why such mutations result in overgrowth of bone marrow cells in some individuals more than others,” says Dr. Nangalia.

In *Nature Genetics*, the researchers report combining information on the known somatic driver mutations in MPN, inherited genetic variants, and genetic risk scores from individuals with MPNs.

- ✦ The goal was to obtain a more complete picture of how these variants combine to cause blood disorders.
- ✦ They found that the inherited variants that cause natural blood cell variation in the population also impact whether a *JAK2* somatic mutation will go on to cause MPN.
- ✦ They also found that individuals with an inherited risk of having a higher blood cell count could display MPN features in the absence of cancer-driving mutations, thus mimicking disease. ■

Progression Research Network Summit

Moving objectives forward

The Progression Research Network's 4th Summit, organized by MPNRF, provided a forum for updates and discussion of the global expert group's work on MPN disease progression. Included on the agenda was progress toward the feasibility and development of a large MPN patient real-world evidence database.



"We have completed a feasibility study and now have a roadmap that allows us to take a long-term view, while demonstrating near-and mid-term value of a registry," says MPNRF CEO Kapila Vigés. "These efforts are complex and have a history of both success and setbacks. We want to be thoughtful about learning from past challenges while staying on an aspirational course to impact the field of MPNs."

Simultaneously, the group is working on developing a consensus statement on State of the Science in MPN Progression. It will further define progression, biologically and clinically, as well as the need for clinical trial endpoints to address disease progression.

Discussions were held at the Summit to answer some of these questions:

- ✦ How do we currently define progression in the classical MPNs and what are we missing?
- ✦ Can these definitions be suitable as clinical trial endpoints for progression?
- ✦ Can we further define the value of currently used endpoints (i.e., symptoms, spleen, transfusion independence) using real-world evidence or phase 3 clinical trial data as it relates to overall survival or progression-free survival?
- ✦ Do we have any biomarkers that are available and validated today to prognosticate progression?
- ✦ Are there novel endpoints, (i.e., variant allele fraction reduction, megakaryocyte spacing, or peripheral blood CD34+ cells) that should be evaluated?
- ✦ Are there published data sets or real-world evidence that we could try to meta-analyze?
- ✦ Can we design a multi-center biomarker-driven observational study?

A part of the Summit was dedicated to presentations on what was learned from the 6 projects initially funded by Progression Research Network in 2020. These highlights were previously reported in detail. ■

Progression Research Network projects

Characterizing the Role of Inherited Genetic Variation in MPN Disease Progression

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

Identifying and Validating Actionable Biomarkers in MPN Progression

Ann Mullally, MD, Brigham and Women's Hospital, Boston, MA;
Rebekka Schneider, MD, PhD, University Hospital RWTH, Aachen, Germany

Evaluation of TP53 Pathway Regulators in Progression of Myeloproliferative Neoplasms

Bridget Marcellino, MD, PhD, Icahn School of Medicine, Mount Sinai, New York, NY

Interrogating the Spatial Architecture of MPN Disease Progression

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

MPN Stem and Progenitor Cell Clonal Fitness as Predictors of Progression

Joseph Scandura, MD, PhD, Weill Cornell Medicine, New York, NY

Targeting the HMGA1 Epigenome in MPN Progression

Linda Resar, MD, The Johns Hopkins University School of Medicine, Baltimore, MD



Crossing the globe and decades

A drug's long development history

With development roots around the globe, momelotinib was approved in September of last year by the US Food and Drug Administration (FDA) and recently in the United Kingdom and European Union. It is the newest option available for the treatment of intermediate or high-risk myelofibrosis, and the only drug approved for MF-related anemia.

While it may seem like momelotinib appeared on the treatment scene quickly, it actually has a long drug development history that traces back to 1999, the year Cytopia, Ltd. was founded. An Australian biotechnology company, Cytopia's chief scientific officer, Dr. Andrew Wilks, is credited with discovering JAK 1 and JAK 2 a decade earlier with his colleagues at Ludwig Institute for Cancer Research.

A JAK inhibitor, momelotinib works differently than other drugs in its class, such as ruxolitinib, and has shown to help prevent or reduce anemia and therefore the need for transfusions, in addition to treating other classic MF symptoms.

Momelotinib was discovered and initially developed under Dr. Wilks' leadership before it was acquired in 2011 by YM BioSciences, Inc., a drug development company headquartered in Toronto. Dr. Nick Glover, former president and CEO of Sierra Oncology, previously led YM, where he and his team advanced momelotinib through Phase 1/2 studies. That's when the drug was first reported as showing anemia benefits. YM was acquired by US-based Gilead Sciences in 2013; momelotinib was acquired from Gilead by Vancouver-based Sierra Oncology in 2018.

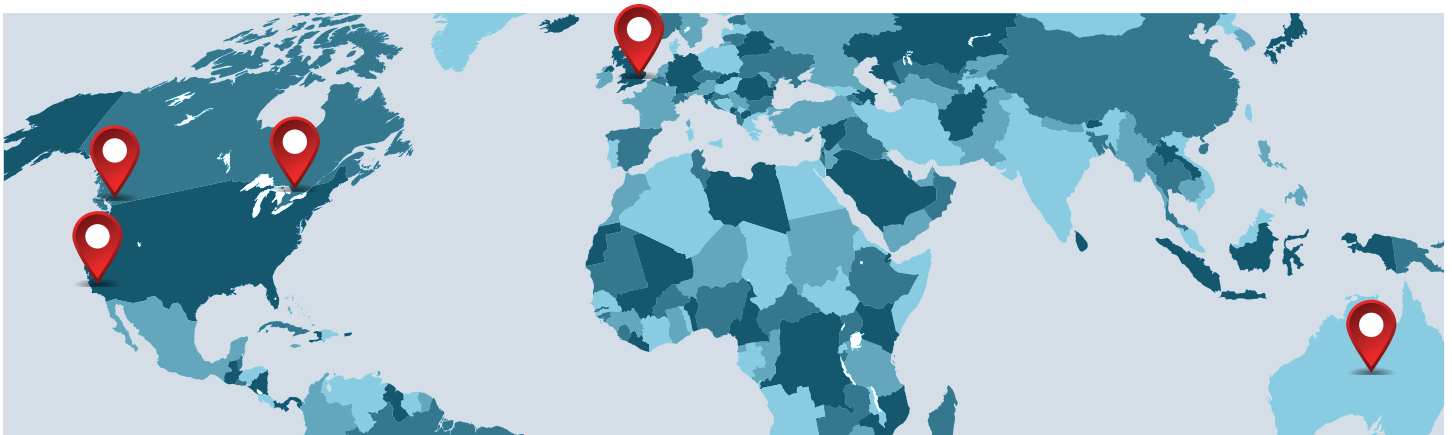
The final home on momelotinib's long international development journey became London-headquartered GSK, when it acquired Sierra

+ MOMELOTINIB: an oral drug featuring inhibitory ability along 3 key signaling pathways, including JAK 1, JAK 2 and activin A receptor, type I (ACVR1). Inhibition of JAK1 and JAK2 may improve constitutional symptoms and splenomegaly (enlarged spleen). Inhibition of ACVR1 leads to a decrease in circulating hepcidin, a protein which is elevated in myelofibrosis and contributes to anemia.

in 2022. It is now marketed as Ojjaara in the US (Omjjara in EU) for primary myelofibrosis or secondary myelofibrosis in adults with anemia (post-polycythemia vera and post-essential thrombocythemia). To date, it is the only medicine approved for both newly diagnosed and previously treated myelofibrosis patients with anemia.

Myelofibrosis patients with anemia often require transfusions and reportedly more than 30% will discontinue treatment because of it. Patients who are transfusion dependent have a poorer prognosis and shortened survival.

Momelotinib's road to approval was longer than might be expected. But if the result is that transfusions can be prevented or limited in a significant proportion of MF patients, then the investments by industry, researchers, clinicians, and the patients who participated in clinical trials were a collective success. ■



Clinical trial highlights

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 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 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.

Ruxolitinib + Abemaciclib (Phase 1)

SPONSOR: Memorial Sloan Kettering Cancer Center in collaboration with Eli Lilly and Company and Incyte Corporation

DIAGNOSIS: Myelofibrosis (MF)

NOTES: For patients with primary MF or post-PV or post-ET MF. Must have been taking ruxolitinib for at least 12 weeks and kept the same dose for the last 4 weeks. At the time of screening, must be taking either 10mg or 15mg of ruxolitinib twice a day. In addition, must have inadequate response to ruxolitinib.

MORE INFO: <https://classic.clinicaltrials.gov/ct2/show/NCT05714072>

DISC-0974 (Phase 1/2)

SPONSOR: Disc Medicine, Inc.

DIAGNOSIS: Myelofibrosis (MF)

NOTES: For patients with anemia of MF. Must be on stable dose of JAK inhibitor (except momelotinib) and/or hydroxyurea, or, if taking any other treatment for MF, stable for at least 28 days prior to being considered for study.

MORE INFO: <https://classic.clinicaltrials.gov/ct2/show/NCT05320198>

PXS-5505 (Phase 1/2)

SPONSOR: Syntara

DIAGNOSIS: Myelofibrosis (MF)

NOTES: For treatment of patients with primary MF or post-ET or post-PV MF who are not eligible for stem cell transplantation.

MORE INFO: <https://classic.clinicaltrials.gov/ct2/show/NCT04676529>

INCA033989 (Phase 1)

SPONSOR: Incyte Corporation

DIAGNOSIS: Essential Thrombocythemia (ET) or Myelofibrosis (MF)

NOTES: Study to determine safety and dose of INCA033989 in treating patients with ET or MF. This is a monoclonal antibody directed against mutated CALR.

MORE INFO: <https://classic.clinicaltrials.gov/ct2/show/NCT06034002>

Ropeginterferon alfa-2b-njft (P1101) (Phase 2)

SPONSOR: PharmaEssentia

DIAGNOSIS: Essential Thrombocythemia (ET)

NOTES: For treatment of patients with ET who have not been treated with interferon, have not had cytoreductive treatment, or pre-exposed to hydroxyurea and/or anagrelide.

MORE INFO: <https://classic.clinicaltrials.gov/ct2/show/NCT05482971> & <https://exceedet.com/hcp/>

Clots = Clogs – Continued from page 3

- ✦ Among patients hospitalized for a heart attack, those with MPNs have an increased risk of in-hospital bleeding but a decreased risk of in-hospital death or cardiac arrest compared with patients without MPNs, according to a study published in *JACC: CardioOncology* in 2023.
- ✦ Nutrition is a low-risk approach to reduce inflammation and symptoms in MPNs, while potentially reducing risk of heart disease. A study by Angela Fleischman, MD, University of California, Irvine, supported by MPNRF, showed how the anti-inflammatory Mediterranean diet was feasible for MPN patients.

- ✦ Patients report less fatigue and bone pain when they make heart-healthy lifestyle changes, such as eating a healthy diet and staying physically active.
- ✦ The hypothesis that anti-inflammatory therapies can provide cardiovascular benefit in patients with MPNs still requires rigorous evaluation in clinical trials, according to the *CardioOncology* study authors.

The more we learn about thrombosis and cardiovascular risks in MPN patients, the more we are able to study how to prevent them. Research is the key to identification and subsequent clinical trials of new and better solutions. ■



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