MPN RESEARCH FOUNDATION UPDATE

VOLUME XXIII | NO. 2 | SUMMER 2024

NEWSLETTER FOR THE MYELOPROLIFERATIVE NEOPLASMS COMMUNITY

2024 MPN Challenge™ awards announced

Selected from among 45 qualified applicants, our six 2024 MPN Challenge™ recipients represent a diverse group of investigators from around the world. Over the next two years, they will investigate research areas with the potential to advance our knowledge of myeloproliferative neoplasms (MPNs) and make a meaningful impact on the lives of patients and their caregivers.

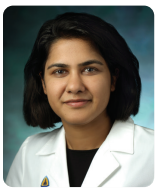
"The competition for 2024 MPN Challenge was intense, with numerous proposals demonstrating high scores," says Christina Persaud, RN, BSN, CCRP, senior manager of research programs for MPN Research Foundation. "This reflects the exceptional quality and innovation driving advancements in the field."

Focus areas for this year's research awards include: the biology of disease progression; spatial analysis of the bone marrow microenvironment toward personalized therapeutic development; strategies for earlier intervention and/or prevention of MPNs; and harnessing the immune system to improve long-term outcomes for patients.

> ***"MPN Research Foundation has a history of executing a robust peer review, leveraging scientific experts. A major change to this year's process, patient and caregiver reviewers provided the patient's perspective in influencing the deployment of our dollars into MPN research. I am personally very excited about the potential for near-term clinical impact."***
>
> **– Brandon Goetzman, MPN Research Foundation Board of Directors and chair of the Science Steering Committee**

Each recipient will receive a two-year grant of $200,000. They are required to make regular progress reports to receive full funding. The 2024 MPN Challenge awards are generously supported by the Susan Ann Protter Research Fund, alongside our community of committed funders.

2024 MPN Challenge™ projects



Immunotherapeutic targeting of SLAMF7 in myeloproliferative neoplasms

◀ Tania Jain, MBBS | Johns Hopkins University

A novel approach to treating myelofibrosis (MF) uses pioneering engineered T-cell therapy called chimeric antigen receptor (CAR) T-cells. The effects of inhibiting fibrosis-inducing cells by developing CAR T-cells directed at SLAMF7 as the therapeutic target will be studied in this project.

Identification of genetic and biological markers of risk of relapse in myelofibrosis patients undergoing hematopoietic stem cell transplantation

◀ Jonas Jutzi, MD, PhD | Brigham and Women's Hospital
Gabriela Hobbs, MD | Massachusetts General Hospital
Peter van Galen, PhD | Brigham and Women's Hospital

The project aims to understand why ruxolitinib use during and after stem cell transplantation improves outcomes in myelofibrosis patients, by analyzing genetic changes and the drug's impact on the immune system. The goal is to find ways to make stem cell transplantation safer and improved for patients with MF in the future and to use this information to prevent relapse.

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MISSION

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

MPN RESEARCH FOUNDATION

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Exploiting the anti-cancer antibody response in MPN patients and mouse models for the development of new immunotherapeutics

◀ Robert Kralovics, PhD | Medical University of Vienna

The goal is to capture all of the different antibodies made by MPN patients that can bind to MPN cancer cells, beyond just mutated calreticulin (CALR), identify the cancer-specific features they bind to, and generate artificial antibody formats that have the potential to trigger selective killing of MPN cancer cells.

Immunogenic clearance of senescent neutrophils to prevent pathogenic cell-cell interactions in MPN

◀ Simón Méndez-Ferrer, PhD | University of Cambridge
Jose Antonio Perez Simon, MD | Institute of Biomedical Research of Seville

The goal is to establish the potential of a new biomarker on the surface of neutrophils for early prediction of disease pathogenesis and progression and as a potential therapeutic target in MPNs. The outcomes of this research will further pave the path for better prediction and clinical testing of innovative therapeutic strategies, taking advantage of the potential of our own immune system to fight disease, and improve patient quality of life and treatment outcomes.

Neutrophil tissue factor and molecular biomarkers of MPN-related chronic kidney disease

◀ Brandi Reeves, MD | University of North Carolina at Chapel Hill
Steffen Koschmieder, MD, PhD | University Medical Center RWTH Aachen

This study aims to understand why chronic kidney disease (CKD) happens in people with an MPN. One major focus of this research is on neutrophil derived tissue factor in MPN patients and its role in CKD. This innovative study will be the first to explore why CKD happens in MPNs and will pave the way for rational treatments and improved patient outcomes.

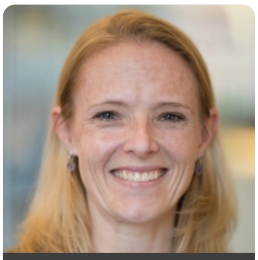
Spatial transcriptomic analysis of the bone marrow landscape: a novel approach to improve AI-based assessment in MPN

◀ Daniel Royston, MBChB, BMSC, DPhil, FRCPath
Rosalin Cooper, PhD | University of Oxford

The goal is to develop new and improved artificial intelligence (AI) tools to better diagnose and provide more information about what goes wrong in the bone marrow of MPN patients. It will help to find out which appearances in the bone marrow are important when planning treatment and importantly, allow the care team to decide which new treatments may be most effective in MPNs. Another goal is to work closely with patient groups to help MPN patients better understand the results of their bone marrow biopsies. ■

Understanding cells' garbage disposals

A tale of two related MPN Challenge™ projects



Sara Buhrlage, PhD
Dana-Farber Cancer Institute

Not everyone has doctoral-level initials after their name. So how do you describe a highly technical scientific exploration to an interested lay audience? We spoke with Sara Buhrlage, PhD, a biochemist at Dana-Farber Cancer Institute, for a real-world exercise in describing the potential impact of her complex laboratory work funded by MPN Research Foundation.

"Cells, including cancer cells, have a 'garbage disposal' system that destroys proteins that are no longer needed," Dr. Buhrlage explains. "My lab identified a novel strategy for treating MPNs that prompts cancer cells to degrade mutant JAK2 while not affecting wild-type JAK2 (normal JAK2). We believe this approach will have fewer side effects and be better tolerated than currently available therapies."

GLOSSARY TERMS

- **ENZYME:** proteins capable of enacting chemical reactions such as breaking down or forming new proteins.
- **PATHOGENISIS:** the origin and development of a disease.
- **PRINCIPAL INVESTIGATOR (PI):** a person in charge of a scientific research grant or clinical trial; managing laboratory operations, funding, and research aims.
- **PROTEIN HOMEOSTASIS:** a state of equilibrium in the creation and destruction of proteins that a cell will attempt to maintain.
- **UBIQUITIN:** a small protein that plays a crucial role in a cell's activity.
- **UBIQUITINATION:** the process of enzymes attaching a ubiquitin protein to another protein, marking that protein for destruction, transport, or other fates.

In a nutshell, making sure that the mutant version of the JAK2 protein is marked for destruction could help blood stem cells take out the trash. But we wanted you to understand how and why her work is important, including the project funded through a 2021 MPN Challenge™ award titled: ***JOSD1 as a novel targeted therapy for JAK2V617F dependent myeloproliferative neoplasms***.

"Identification of new targets and treatment approaches for MPN is important for understanding the full mechanism of disease pathogenesis [+], as well as for bringing new differentiated treatment options to patients," according to Dr. Buhrlage.

"Our work demonstrates that mutant JAK2 ubiquitination [+] and degradation is differentially regulated compared to wild-type JAK2 and that this can potentially be leveraged for development of new therapeutics in the future. Specifically, we identified that the deubiquitinase (DUB) JOSD1 (an enzyme [+]) removes ubiquitin from mutant JAK2 that marks the protein for degradation. We thus believe that JOSD1 represents a potential new drug target for MPNs."

As a scientist trained in chemistry, Dr. Buhrlage focuses on chemical probes and prototype therapeutics that home in on deubiquitinases, a family of enzymes identified as promising drug targets for multiple types of cancer. She considers herself fortunate to team up with colleagues and combine her expertise in DUBs and protein homeostasis [+] with specialists in a variety of disease areas, including MPNs.

Her lab's work in the MPN field is in collaboration with fellow Dana-Farber scientist Jim Griffin, MD, who was funded through a related MPN Challenge award in 2017. Titled ***Inhibition of deubiquitinating [+] enzymes as a novel targeted therapy for JAK2-dependent myeloid malignancies***, this project included Dr. Buhrlage as a key participant. It is uncommon for two related projects to receive funding by MPNRF, especially under the leadership of different principal investigators (PIs) [+]. In this case, Dr. Griffin was PI for the first project, while Dr. Buhrlage serves as PI for the current one.

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The progression of these two funded studies illustrates how the more we learn, the more questions we have, along with a need for in-depth answers.

The 2017 project sought to develop a strategy for directly targeting the JAK2-V617F mutated protein while leaving the wild type JAK2 protein alone. This is important even today because the existing JAK2 inhibitors don't differentiate between the healthy JAK2 protein and those with the MPN driver mutation. Enter 2021 and Dr. Buhrlage's Dana-Farber team begins to provide some new insights and ideas, with support from MPNRF and The Leukemia and Lymphoma Society. Once they identified how the JAK2 protein is marked for destruction, they described the potential to develop a target to stop only MPN-mutated cells.

"My collaboration with Jim was one of the first I established when I started my lab and it has been one of the most productive, leading to multiple publications and joint funding," says Dr. Buhrlage. "In addition to being a great scientific collaborator, he has been a supportive mentor." She elaborates on the importance of strong mentorship and support by established faculty when starting a lab: "This is critical for success. There are so many aspects of being a PI that you do not learn during graduate school and post-doctoral training."

Dr. Buhrlage is thriving in a hospital environment, where she enjoys "the dedication of the clinicians to provide the best possible care to their patients, while also being committed to research to bring better treatments and outcomes."

Back to research, she adds that to identify additional targets and strategies, further studies must explore the cellular players that interact with JAK2 and ubiquitin. Modifying the cellular "cross-talk" between these proteins has a wealth of potential. In the meantime, her laboratory work has led her to create a new commercial enterprise, called Entact Bio. ENTACS (enhancement-targeting chimeras) are described as molecular matchmakers. These small molecule drugs act as key regulators of protein function by bringing beneficial target proteins and deubiquitinases together.

The start-up's website explains it this way:

> ***"What if we could enhance proteins to restore health? Most cancer drugs are designed to block the activity of oncogenic (potentially cancer causing) proteins that drive disease. Few treatments work by enhancing the activity of proteins, such as tumor suppressors, that can protect from disease."***

Dr. Buhrlage is clearly excited about the potential for MPNs and a number of other cancers. "My hope is that our research will lead to a more personalized approach to therapy for MPN patients." ■

CITATIONS:

Sara Buhrlage, James Griffin, Jarrod Marto, et al. (Dana-Farber Cancer Institute): *JOSD1 as a novel targeted therapy for JAK2V617F dependent myeloproliferative neoplasms.*

Yang, J., Weisberg, E. L., Liu, X., et al. (2021). *Small molecule inhibition of deubiquitinating enzyme josd1 as a novel targeted therapy for leukemias with mutant JAK2.* Leukemia, 36(1), 210–220. https://doi.org/10.1038/s41375-021-01336-9.

MPN Roundtable™ 2024 brings together patients, researchers, clinicians, industry

Traditionally, MPN Roundtable™ is a small gathering carved out for candid conversations about where MPN research has succeeded, the gaps that remain, and possible new approaches and next steps to get us closer to more and better treatments, and ultimately cures for MPNs. The meeting isn't recorded intentionally, to encourage open communication between researchers, the biopharma industry, clinicians, and others in the MPN community.

This year, over two spring days in Chicago, some of the most prominent voices in the room were MPN patients.

MPN Research Foundation Board of Directors Chair Barbara Van Husen remembers the first Roundtable event well (2012). "The scientists said they had never been to a meeting like this, where across the table was a colleague who was approaching the same problems, possibly in completely different ways, yet they had not ever spoken."

This year, that unique value was magnified by the personal experiences and priorities of people directly affected by essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF).

"You are here to help chart a course for future research, each with a unique role and relationship to the MPN community," MPN Research Foundation CEO Kapila Viges said in welcoming the diverse group. "We need to understand what we're learning from patients and keep their journey front and center, continuing to inform where we go next." And while the organized program was robust, she encouraged individuals to

find time to interact with each other, particularly the patients at the center of our shared mission.

"The MPN landscape is changing every year, sometimes every month," she continued. "We're small but mighty — we have committed over $20 million to 105 projects, 98 investigators, in 9 countries. It may not seem like a lot but consider that it is almost all from private donations, from patients, families."

The impact of MPN Research Foundation is well documented. Projects have included a broad range of research investigations, from identification of disease drivers and disease progression to understanding why some patients and not others respond to interferon, and more. "Today we have more options for patients, but we're still not there. Our work is not done."

MPN Research Foundation sits at the intersection of patients, academia, and industry. "We take this position very seriously," Viges said, "... bringing each perspective together early in the discovery process."

With significant time built in for discussion, highlights of the MPN Roundtable included the following:

- **Specific insights from patients on living with ET, PV, and MF.** Individual and group comments addressed a number of challenges: accessing reliable, up-to-date information, including from primary care physicians (PCPs) and community hematologists; misdiagnosis and delayed treatment; moving clinicians' priorities beyond symptom management to disease modification; the inequity of access to the most current care and clinical trials; the importance of coordination between a PCP and MPN specialist; and more.
- **A keynote presentation on the status of using artificial intelligence to take the subjectivity out of bone marrow biopsies in MPNs**, making them more meaningful and reproducible. This work, presented by Daniel Royston, MBChB, FRCPath, Dphil, University of Oxford, (a 2024 MPN Challenge™ award recipient), has implications for earlier, more accurate diagnosis, and monitoring of disease progression.
- **Announcement of 2024 MPN Challenge™ awards**. See page 1 for details.
- **Updates by several recently funded MPNRF researchers**, including Stephen Oh, MD, PhD, Washington University School of Medicine in St. Louis, a 2021 MPN Challenge awardee. Earlier this year, Dr. Oh and colleagues reported on a gene called *DUSP6*, confirming its relationship with *JAK2*. "We think of it as a critical driver of disease progression," he shared, along with further progress in the investigation of *DUSP6* as a druggable target for MPN treatments.
- **A panel led by Ronald Hoffman, MD, Mount Sinai, on the National Cancer Institute-funded MPN Research Consortium.** The consortium funds multi-site projects and maintains an MPNRF-supported tissue bank for use by research institutions nationwide. "Our progress has been stupendous," said Dr. Hoffman. "If we can do as well in the next 20 years, in 20 years, patients will have their malignant clones eliminated by new classes of drugs." The consortium works closely with but independently of pharmaceutical companies to transition drugs into phase 1/2 clinical trials. "Jakafi® was a transformative drug. It improves symptoms... but patients continue to progress. We're trying to develop new classes of drugs that deplete MPN stem cells, that not only improve patient symptoms, but improve overall survival." ■

SEPTEMBER IS BLOOD CANCER AWARENESS MONTH

Follow us on social media and watch your email for our month-long campaign with patient-focused updates, current research insights, and how you can help support MPN Research Foundation and the future of groundbreaking research.

International MPN experts gather in France:

ESH 10th Translational Research Conference on MPNs

When more than 200 MPN scientific and clinical experts from 32 countries come together, deep knowledge and unique insights are shared through novel scientific presentations. Interactions then lead to critical discussions and sometimes new ways to process, evaluate, and expand research. In addition, experts discuss how these new approaches might translate in the clinic to help patients.

This was the case for the ESH 10th Translational Research Conference on MPNs held late April in Mandelieu-La Napoule, France. The European School of Hematology (ESH) promotes and facilitates access to cutting-edge knowledge in hematology and related disciplines, including new developments in the fields of basic, clinical, and therapeutic research. Their international conference highlights new data on the cellular and molecular biology of MPNs and their diagnosis and treatment.

Many of the conference presenters and attendees are currently funded by MPN Research Foundation or have other historical ties. This includes the chairs of the meeting: Ross L. Levine, MD, Sloan Kettering Memorial Cancer Center; Jean-Jacques Kiladjian, MD, PhD, Université Paris Diderot; and Jyoti Nangalia, MD, PhD, Cambridge, UK.

MPN Research Foundation is committed to filling unmet research needs among all stakeholders in the MPN community, including supporting global information sharing, which broadens our individual knowledge and perspectives.

Highlights of presentations and discussions included:

- Updates on diagnosing MPNs including the question: "Is triple negative essential thrombocythemia really ET?"
- Influencers that determine the strength, known as fitness, of MPN mutated cells and how they outperform normal cells, resulting in mutated cell proliferation and disease.
- If and how the *JAK2V617F* mutation responds differently to inflammatory clues, what drives inflammation and disease progression in MPNs, and how to target it with therapies.
- Transplantation and the immunosuppressive role of ruxolitinib in the high incidence of secondary skin cancers.
- Characterization of disease progression over longer periods, i.e., 10 years, including the impact on DNA, such as mutational changes, and the role exposure to chemotherapy has on production of mutations.
- Platelet-based dosing of medications for anemia [✚] and thrombocytosis [✚].

GLOSSARY TERMS

- **ANEMIA:** state of not having enough healthy red blood cells or hemoglobin to supply oxygen to the body.
- **CYTOKINES:** small, protein-based molecules that signal and influence cells in the immune system; examples include interleukins and interferons.
- **FIBROSIS:** fibrosis in bone marrow is a disruptive increase of the connective tissue structures called fibrils; its severity is used as a prognostic tool in the clinic.
- **OVERALL SURVIVAL (OS):** total length of time a patient is alive after receiving a diagnosis or starting treatment for an illness, frequently used to assess treatment success.
- **PROGRESSION-FREE SURVIVAL (PFS):** length of time a patient with a disease can live without it getting worse during and after treatment; also called progression-free mortality; used to determine how well a new treatment works in clinical studies.
- **THROMBOCYTOSIS:** when too many platelets are produced by the body.
- **VARIANT ALLELE FREQUENCY (VAF):** number of cells within a cancer cell population that carry a specific genetic mutation (allele); the frequency of some allele can be predictive of specific symptoms or prognoses.

- Need for longer clinical trial studies beyond the standard 24 weeks, while harnessing the ability to analyze existing data.
- Updates on ongoing late-stage trials, some with exceptional results, plus learnings from novel drugs considered "better agents" because they show early anti-clonal effects.
- Benefits and dangers of over comparing MPN treatments to chronic myeloid leukemia (CML) and other more aggressive blood cancers.
- Need for study of deeper benefits of treatments, i.e., overall survival (OS) [✚], progression-free survival (PFS) [✚], fibrosis [✚], cytokines [✚], and variant allele frequency (VAF) [✚].
- What we can learn about real-world response to treatment and progression from 10 years of data since ruxolitinib, i.e., durability, consistency in VAF, and why patients discontinued. ■

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 larger 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.

Pacritinib + Talazoparib (Phase 1)

SPONSOR: Fox Chase Cancer Center
DIAGNOSIS: Essential Thrombocythemia (ET), Polycythemia Vera (PV), or Myelofibrosis (MF)
NOTES: For patients with MPNs, such as ET, PV, or MF, who have progressed on or are intolerant to JAK2 inhibitors, i.e. ruxolitinib.
MORE INFO: https://clinicaltrials.gov/study/NCT06218628

Givinostat Hydrochloride (Phase 3)

SPONSOR: Italfarmaco
DIAGNOSIS: Polycythemia Vera (PV)
NOTES: For patients with *Jak2V617F*-positive high-risk PV. Patients must be at least 60 years old and/or have prior thrombosis.
MORE INFO: https://clinicaltrials.gov/study/NCT06093672

Imetelstat vs Best Available Therapy (Phase 3)

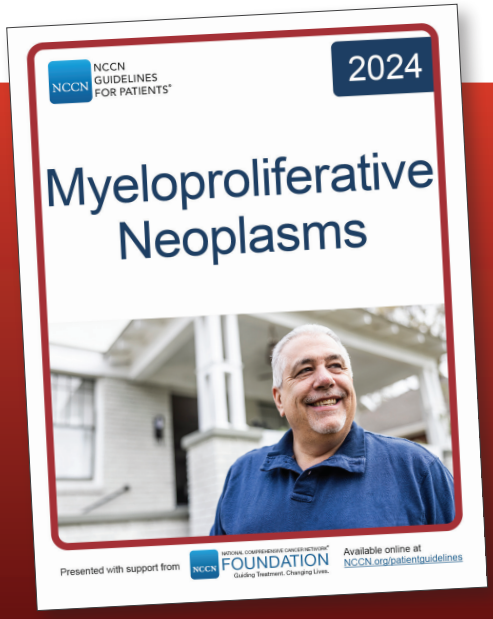
SPONSOR: Geron Corporation
DIAGNOSIS: Myelofibrosis (MF)
NOTES: For patients with intermediate-2 or high-risk MF who have not responded to JAK inhibitor treatment.
MORE INFO: https://clinicaltrials.gov/study/NCT04576156

INCB000928 With or Without Ruxolitinib (Phase 1/2)

SPONSOR: Incyte Corporation
DIAGNOSIS: Myelofibrosis (MF)
NOTES: For patients with MF who are transfusion dependent or have symptomatic anemia.
MORE INFO: https://clinicaltrials.gov/study/NCT04455841

Bomedemstat vs Best Available Therapy (Phase 3)

SPONSOR: Merck Sharp & Dohme LLC
DIAGNOSIS: Essential Thrombocythemia (ET)
NOTES: For patients with ET who have an inadequate response to or are intolerant of hydroxyurea.
MORE INFO: https://clinicaltrials.gov/study/NCT06079879



UPDATED NCCN MPN PATIENT GUIDELINES AVAILABLE

The *NCCN Guidelines for Patients®: Myeloproliferative Neoplasms* is a comprehensive, plain language resource kept up to date by an expert panel of national leaders in the MPN field, including a patient representative. The 75-page document was just updated for 2024 and is available to view and download at no cost through our website.

The guidelines for patients are based on the most current go-to guidelines for clinicians. They cover the basics of each MPN, then provide significant details about the condition, range of symptoms, prevention of complications, latest treatments, recommended tests for diagnosis and monitoring, and much more. Also included are lists, questions, medical terms, and personal note areas. Each section finishes with key points for a useful one-page summary.

mpnresearchfoundation.org/news/mpn-patient-guidelines-updated-by-nccn

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SUMMER COVER-UP REMINDER

MPN treatments can increase risk of skin cancer!

Several studies have confirmed the association of some JAK inhibitors with increased risk of non-melanoma skin cancers (NMSCs). One study published in a January 2024 issue of the journal *Blood* reports on just how serious the risks might be, specifically among patients living with MPNs. The researchers encourage vigilance, monitoring, and education across the MPN patient and practitioner community.

Non-melanoma skin cancers include basal, squamous, and Merkel. Melanoma is a cancer that develops in the skin's melanocytes, cells that produce melanin, which determines the skin's pigment.

Benefits of JAK inhibitors need to be balanced against potential toxicities, the authors suggest. They emphasize the importance of patient counseling about the risk of skin cancer before starting JAK inhibitor therapy and suggest close dermatological monitoring during treatment.

CITATION:

Rampotas, A., Carter-Brzezinski, L., Somervaille, T. C. et al., (2024). Outcomes and characteristics of nonmelanoma skin cancers in patients with myeloproliferative neoplasms on ruxolitinib. *Blood*, 143(2), 178–182. https://doi.org/10.1182/blood.2023022345