

# MPN RESEARCH FOUNDATION

## CHANGE YOUR PROGNOSIS

# UPDATE

VOLUME XXI, NO. 3 FALL 2022

NEWSLETTER FOR THE MYELOPROLIFERATIVE NEOPLASMS COMMUNITY



## DRS. JOSEF & JAROSLAV PRCHAL

# BLOOD BROTHERS



Jaroslav Prchal, MD, PhD



Josef Prchal, MD

*Growing up in Czechoslovakia four years apart, Josef and Jaroslav Prchal didn't always agree on things. And that's still true today.*

Yet, independently and together, these two physician/scientists have made practice-changing marks on the global red blood cell landscape – and particularly on polycythemia vera (PV) – both in the research laboratory and medical clinic.

Jaroslav (Jeff) Prchal, MD, PhD, and Josef (Joe) Prchal, MD, went to medical school and began their early research careers in Prague as medical students. When the Russians invaded in 1968, they took separate physical routes to leave their homeland, each following their shared interest in disorders of blood and stem cells to different parts of North America.

Joe, professor in the Division of Hematology and Hematologic Malignancies at University of Utah, continues his now world-renowned blood cancer research through the Prchal Research Lab in Salt Lake City. And he still makes time to see patients, with a specialty in myeloproliferative neoplasms (MPN) and rare red cell diseases.

Jeff, as a young physician scientist at University of Toronto, is credited with the seminal discovery of first growing red blood cells in the

laboratory flask, working with his mentor, Dr. Arthur Axelrad. Jeff was developing an assay for polycythemia vera when seeing a suspected PV patient gave him the opportunity to test his scientific system to evaluate the presence or absence of the blood disorder, using his own bone marrow as a control. This led to the first specific, accurate test for PV, still used today.

This discovery of the specific characteristics of PV bone marrow provided the foundation for demonstration some 30 years later, in the Paris lab of William Vainchenker, that these unique behaviors in PV depend on an abnormal JAK2 protein.

Jeff is now the head of the Oncology Department at St. Mary's Hospital Center in Montreal. He closed his research lab in the 90's to focus on clinical care and administration.

### YES AND NO!

With such parallel careers, it is natural to ask if they ever worked together. The brothers' initial responses: Joe says 'no' while Jeff says 'yes.' Both are technically correct. Joe quickly adds that "he has greatly benefitted from Jeff's formative initial discovery and technical expertise," confirming that they have collaborated both formally and informally numerous times over the years.

When, for example, Joe found that some of his patients were incorrectly diagnosed as having PV, including by well-respected hematologists, Jeff flew to his lab in Birmingham Alabama to help investigate. He taught Joe's lab how to grow red cells in test tubes, and in the process identified a different blood disorder in these patients, with similarities and distinct differences to PV. Together they established that unlike PV, this other disorder was from an inherited defect, rather than one acquired.

Continued on page 4

### MISSION

MPN RESEARCH FOUNDATION STIMULATES ORIGINAL RESEARCH IN PURSUIT OF NEW TREATMENTS — AND EVENTUALLY A CURE — FOR MYELOPROLIFERATIVE NEOPLASMS (MPNS).

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**MPNRF HOSTS SPOTLIGHT SESSION AT 2022 TEXAS MPN WORKSHOP**

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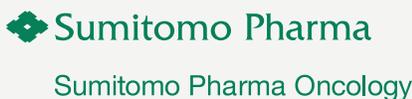
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**THANK YOU TO OUR SPONSORS**



**TEXAS MPN WORKSHOP**  
San Antonio, Texas

August 26-27 2022

*The Texas MPN Workshop brings together hundreds of international MPN experts to discuss new research and therapy options currently available and in various stages of development.*

This year, MPN Research Foundation participated in the third annual August conference in San Antonio, Texas, organized by Dr. Ruben Mesa, Mays Cancer Center at UT Health San Antonio MD Anderson, and Drs. Srdan Verstovsek and Naveen Pemmaraju, University of Texas MD Anderson Cancer Center in Houston.

MPNRF Chief Executive Officer, Kapila Vigas, and Director of Scientific Strategies, Rick Winneker, helped develop and moderate an MPNRF Spotlight Session, entitled *MPN Disease: From Pathogenesis to Progression*. The session featured two investigators recently funded by the foundation: Dr. Linda Resar, Johns Hopkins University School of Medicine (2020 Progression Pilot Award); and Dr. Catriona Jamieson, University of California, San Diego (2019 MPN Challenge Award). Both presentations focused on emerging targets for MPN progression.

Two other MPNRF-funded projects were represented as part of the workshop. Dr. Angela Fleischman, University of California, Irvine (2017 MPN Challenge Award) presented her research on *Inflammation, Dietary Factors, and the MPN Microenvironment*. Dr. Stephen Oh, Washington University School of Medicine (2021 MPN Challenge Award) presented his work on *Targeting an Aberrant DUSP6-RSK1 Signaling Axis Driving MPN Disease Development and Progression*. ■

# 3RD MPN PROGRESSION RESEARCH NETWORK SUMMIT



**“DISEASE PROGRESSION CONTINUES TO BE A LEADING CONCERN FOR MPN PATIENTS AND CAREGIVERS. CLINICIANS ARE LOOKING FOR MORE PREDICTABLE INDICATORS. AND, DRUG DEVELOPERS NEED RECOGNIZED OUTCOMES TO MEASURE THE EFFECTIVENESS OF THERAPIES. SITTING AT THE INTERSECTION OF THESE KEY STAKEHOLDERS, THE MPN RESEARCH FOUNDATION IS TAKING BOTH A NEAR-TERM AND LONG-TERM VIEW OF HOW WE CAN HELP ADVANCE THESE OBJECTIVES.”**

*Kapila Vigas, MPNRF Chief Executive Officer*

MPN Research Foundation established MPN Progression Research Network (PRN) in 2020 with the vision of building a community of participants, notably researchers and clinicians, and including patients, patient advocates, and biopharma representatives. The intent was to work collaboratively to improve outcomes for people living with myeloproliferative neoplasms (MPNs), through research on the prevention and treatment of disease progression.

Based upon our historical engagement with this community, it was clear that a greater emphasis on understanding and addressing disease progression needed to be a major priority.

In this spirit, the first PRN Summit (2020) was used to discuss the state of the science, establish the overall objectives of the network, and provide a forum to propose and fund highly collaborative short-term projects focused on progression. These projects are nearly complete and outcomes will be highlighted in a future Update issue.

One challenge to overcome in this rare disease community is that too often, studies of disease progression lack sufficient numbers of patients or years of follow-up to address our long-term objectives. As part of the second annual PRN Summit (2021), which focused mainly on developing strategies to address the network objectives, the need for a large MPN patient observational database was discussed. The third annual PRN Summit (2022) addressed obstacles and potential solutions to creating and maintaining such a large patient database, in part, by

exploring current best practices and lessons learned from ongoing academic center databases that exist in different parts of the world.

The goal now is to use all of this information, advice, and ongoing research to finalize a strategy in the near future. Stay tuned for more in 2023.

## **LONG-TERM OBJECTIVES OF THE PROGRESSION RESEARCH NETWORK**

- + Further define potentially actionable MPN disease progression criteria through the study of clinical parameters and biomarkers of disease.
- + Develop and further validate predictive indicators of progression to enable earlier detection, more informed monitoring, and better individualized intervention decisions.
- + Define new clinical endpoints, primary or surrogate, to be recognized in clinical trial design.
- + Develop new care guidelines and communicate with the MPN stakeholder community

MPNRF gratefully acknowledges financial support for the Progression Research Network Summit and its ongoing related PRN activities from: CTI BioPharma, Geron, Incyte, Kartos Therapeutics, Novartis, PharmaEssentia, Protagonist Therapeutics, Sierra Oncology, and SMP Oncology. ■

So, while they didn't train or run research in the same institutions, the brothers have always spoken frequently about their unique work. "We collaborated and benefited from different views of the clinical problem at hand," says Joe, "at times utilizing separate and complimentary approaches to what appeared a puzzling clinical situation."

They have published important papers together, including 25 peer-reviewed manuscripts, most in the journal *Blood* and also in other prominent medical journals, including *Nature*, *Science* and *Lancet*, in addition to co-authoring a number of reviews/ editorials and textbook chapters on PV.

In fact, Joe has published more than 400 peer-reviewed papers, in most of which he was senior or first author. He was a founding member of the NCI-funded Myeloproliferative Disorders Consortium; is a consulting editor for the *Journal of Clinical Investigations*, *Blood Cells, Molecules, and Disease*; served on the editorial board of *Blood*; and for several years was the editor of the American Society of Hematology (ASH) publication *Hematologist*. He is one of the editors of the 7th to 10th editions of *Williams Hematology* and *Williams Hematology Manual*.

"Much of my work, including discovery of the molecular basis of Chuvash polycythemia, the first recognized disorder of hypoxia inducible factors (HIF) pathway,

was based on Jeff's seminal discovery," says Joe. "I do very opportunistic research," he adds. "When I get intrigued by something, most of it based on seeing or consulting on the patient, and if it doesn't make much sense, I'm trying to find why."

As an early pioneer in MPN research, Joe was the recipient of the first MPN Research Foundation grant 20 years ago, and he has had a guiding relationship with the work of the foundation ever since. He initially set out to find the mutation(s) that cause PV. As part of the 2002 MPNRF-funded research, he and his team actually found the PV's chromosome location at the *JAK2* gene, contributing to the important discovery that *JAK2* is the most common mutation in MPNs. His work, and the independent work of Jaroslav, also contributed to the knowledge that a mutation of a single blood stem cell causes PV.

The younger Dr. Prchal (Joe) says he always listens carefully to his older brother, though they still disagree on some basics.

## **IS MPN CANCER?**

Joe prefers to refer to MPNs as myeloproliferative disorders or a clonal disorder. His explanation is that MPN clones make virtually normal cells, while cancer mutations make the cells grow fast, but result in abnormal, useless cells. Only when MPNs transform to acute leukemia they transform

to cancer, he says. Jeff, on the other hand, agrees with the World Health Organization's 2008 reclassification that yes, MPNs are chronic cancer diseases.

"The prevailing dogma is that the (mutated) clone expands and replaces the bone marrow. And I don't believe that," Joe explains. "That clone just produces protein(s) in a single stem cell, which makes the other stem cells, the normal cells, still there... they are asleep, or dormant." Among his many findings is that "some drugs may change the situation in MPNs, wherein all red, white blood cells and platelets are made by a single cell. For example, in some people after interferon treatment, the normal stem cells wake up and start making normal blood cells again."

Within Joe's long list of professional recognitions and awards for scientific accomplishments is an ASH 2017 Henry Stratton Award for outstanding contribution to the fundamental understanding of a broad range of red cell disorders. He was also named an MPN Hero in 2021.

His life-long goal, "to try to make new discoveries that are meaningful," keeps Joe Prchal perpetually focused. "Our diagnosis is much more accurate than before... We know MPNs are caused by mutations, but we still don't have an ability to eradicate or prevent it."

In other areas of MPN investigation, Joe presented at the ASH 2021 annual meeting, *Iron Deficiency in PV Increases HIF Activity and Transcription of Prothrombotic Genes*. He suggested that repeated phlebotomies augment iron deficiency, which increases the level of hypoxia inducible factors (HIFs) that increase pro-thrombotic genes, which then has the potential to increase risk of thrombosis (blood clots). The work is connected to MPNRF funding for a new 2021-2023 Challenge award on the "Role of iron deficiency in thrombosis of PV."

He credits MPNRF with taking risks in research that other major funding institutions are often not interested in taking – finding



the gaps and not being so invested in immediate successes that potentially important findings are missed.

Joe is also involved in research about the genetics of MPNs. His lab was the first to show that in some families several relatives develop MPN, but often not the same one. "They must be born with a genetic predisposition that greatly increases the chance of acquiring MPNs' mutations," he explains. "The ongoing work of many labs is now trying to identify what that genetic predisposition is."

As both brothers frequently mention their extraordinary mentors – global leaders in blood research Drs. Ernest Beutler, Arthur Axelrad, John Adamson, YW Kan – they believe that their successes were only possible because they were in the right laboratory with the right people early in their careers. They are not simply thankful, but committed to give the same opportunity to today's young physician/scientists interested in exploring hematology.

Together, they are currently forming the Prchal Research Foundation. Their goal is to identify promising young individuals in Czech Republic whom they plan to sponsor, allowing them to visit the top labs in North America. Likewise, accomplished hematology researchers from the US and Canada will be identified who may benefit to visit laboratories with special expertise in Prague or elsewhere in Czech Republic.

Jeff, who is accustomed to getting in on the ground floor of clinical and research projects, went to his brother's presentation when Joe won the prestigious Czech Neuron Prize for Medicine and Biology in 2021. As it is accompanied by a significant financial award, he suggested using those funds, and his own contribution to it, to create and sustain this new foundation.

"I followed the advice of my older brother, faithfully," adds Joe. ■

## SOLE2SOUL FOR MPN RAISES MORE THAN \$50K FOR RESEARCH



**Trekking more than 30 miles over three August days in the Canadian Rockies, a team of 20 Sole2Soul for MPN participants raised a total that currently exceeds \$82,000 for MPN research, including more than \$50,000 toward projects funded by MPNRF.**

In a collaborative effort with Cure Media, MPNRF and the Canadian MPN Research Foundation each fielded teams which included patients, care partners, and advocates. In addition, biopharmaceutical sponsors (PharmaEssentia, GlaxoSmithKline, and Incyte) had representatives participate in the event, providing them with a rare opportunity to experience the day-to-day life of MPN patients and care partners.

MPNRF gratefully acknowledges the collaboration of these partners and the dedication and physical commitment by each participant.

Jaroslav Prchal, MD, of St. Mary's Hospital, Montreal, an avid hiker/climber, joined the effort, inspiring trekkers with stories along the trail about the early days of MPN research and the promising pipeline of MPN therapies.

The MPNRF team included: Molly Rosen, daughter of MPNRF founder and MPN patient Robert Rosen; Lisa Gould, MPNRF

board member and daughter of an MPN patient; Kerry Fraser, former NHL hockey referee and MPN patient; Jimmy McCrossin, MF patient, and his wife Robyn McCrossin; PV patient Gary Linehan and friend Paul Sleight; and James Livermore, ET patient.

"When exchanging our goodbye hugs and sharing final words amongst each other, I was struck by those shared by a fellow hiker," wrote Robyn McCrossin. He said: 'I know this doesn't make any sense because your husband is not here, but we feel like we know him and we all love him.'"

**"TO ALL OF YOU WHO CARRIED OUT THE TASK OF HIKING THE MOUNTAINS OF WATERTON, I LOVE YOU FOR MAKING ME FEEL LIKE A MEMBER OF THE TEAM AND NOT LEFT BEHIND."**

*Jim McCrossin*

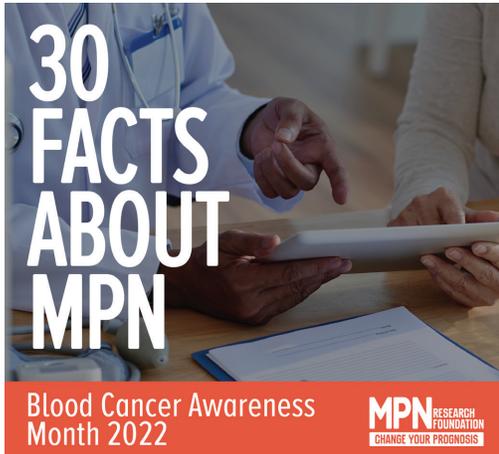
She added: "Another goal of this trek, besides raising money, was to begin building a community so that patients with these rare conditions do not feel alone. I would say, mission accomplished."

To learn more about the opportunity to support the efforts of these participants, go to [MPNResearchFoundation.org/news](https://MPNResearchFoundation.org/news).

**"CANCER DOES NOT DEFINE THE SOLE2SOUL FOR MPN™ TEAM. OPTIMISM, HOPE, COMPASSION, EMPATHY, RESOLVE, TENACITY, CAMARADERIE & JOY DEFINE US."**

*Gary Linehan*

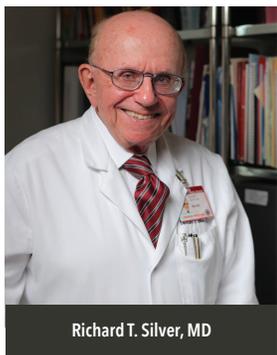
# BLOOD CANCER AWARENESS MONTH



*Throughout September, Blood Cancer Awareness Month, MPN Research Foundation promoted a campaign of 30 FACTS about MPNs.*

Visit our website and search "30 FACTS" to read and share them with family, friends, and care partners. ■

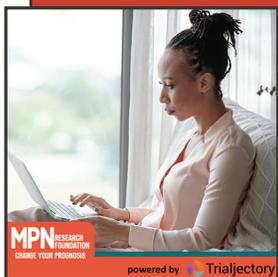
## HONORING AN MPN PIONEER



Richard T. Silver, MD

In honor of MPN Awareness Day, September 8th, MPN Research Foundation featured a profile on Dr. Richard T. Silver, Director Emeritus, Silver MPN Center at Weill Cornell Medicine in New York City. You can read about his extraordinary research and clinical career, and what keeps him actively engaged in the MPN community into his 90s, by visiting our website. ■

## PERSONALIZED CLINICAL TRIAL FINDER



Launched earlier this year, MPN Research Foundation clinical trial finder - powered by Trialjectory – easily and quickly matches an MPN patient to trials they may qualify for based on the diagnosis and other information that they enter. After filling out a short profile the patient may receive links to trial sites and a list that they can share with a doctor who manages their MPN.

Trialjectory provides live support in multiple languages. Get started today at [www.mpnresearchfoundation.org/mpn-clinical-trials](http://www.mpnresearchfoundation.org/mpn-clinical-trials).

## 2022 THRIVE INITIATIVE

*A call for applications for the 2022 Thrive Initiative successfully resulted in a total of 45 diverse research proposals from around the world.*

The initiative was designed to address current MPN funding gaps, in some cases related to pandemic shut downs or delays. Collaborative projects were encouraged that included multiple researchers and/or institutions.

The proposals spanned all four eligibility categories:

- + New researchers not previously engaged in MPN research
- + Junior investigators focused on MPNs
- + "Follow-on" projects, to pick up where a prior award left gaps
- + Awards for clinical translational projects

The collective goal is to move toward finding more effective treatments and potentially cures for MPN patients.

A 20-member expert peer review panel ranked the proposals and MPNRF Scientific Steering Committee made award recommendations as of this printing.

Thrive research is made possible by the Leukemia & Lymphoma Society. All MPNRF research is enabled by the Susan Protter Estate and several major individual and family benefactors who serve as champions for our collective mission. ■

**STAY INFORMED!**

**MPN** RESEARCH FOUNDATION

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# CLINICAL TRIALS PAVE WAY TO NEW DRUG TREATMENTS

**Research and trials are rapidly accelerating our understanding of chronic MPNs and how to treat them. As a result, we gain ground every year toward new, better treatment options for people living with essential thrombocythemia, polycythemia vera, and myelofibrosis.**

MPN clinical trials have gone beyond JAK inhibitors and are now looking at new targets and therapeutic pathways that will expand the universe of options for patients. This is especially promising for patients who could not tolerate JAK inhibitors or they stopped working.

While only a few MPN drug treatments are now approved, hundreds of clinical trials are underway across the globe. Many people living with an MPN find clinical trials offer a better treatment option for their disease symptoms either after current therapies failed or were not fully effective.

In addition to therapies that have been used for MPNs for years, such as hydroxyurea, peginterferon alfa-2a, and anagrelide, newer medications approved for MPNs include: ruxolitinib, fedratinib and pacritinib for myelofibrosis; and ruxolitinib and ropeginterferon alfa-2b for polycythemia vera.

These approvals took years, dedication and funding, and the commitment of valued patients who participated in their trials. With their help, clinical trials determine whether a therapy is safe and effective in treating a particular disease.

## ABOUT CLINICAL TRIALS

Clinical trials are designed to test a treatment either against a placebo (inactive look-a-like), another medication, or the current standard medical treatment for a patient's condition.

The goal is to understand as much as possible about its effects.

Data collected in clinical trials are necessary for review prior to approval of a new therapy, or for the new use of a therapy previously approved to treat a different disease. The decision to participate in a clinical trial is one a patient should consider carefully and discuss with their physician.

A few highlights of the many MPN trials currently underway appear below.



## CLINICAL TRIAL HIGHLIGHTS

### Sapablursen (Phase 2)

**Sponsor:** Ionis Pharmaceuticals, Inc.

**Diagnosis:** PV

A Phase 2 trial for patients who are phlebotomy dependent. Sapablursen (IONIS-TMPRSS6-LRx) uses Ionis' investigational ligand-conjugated antisense (LICA) technology to reduce the frequent need for phlebotomy by reducing excessive red blood cell production. It does this by inhibiting the liver protein TMPRSS6, which leads to an increase in the hepcidin hormone production that reduces iron absorption and recycling in the body.

**More Info:** <https://clinicaltrials.gov/ct2/show/NCT05143957>

### Pacritinib/PACIFICA (Phase 3)

**Sponsor:** CTI BioPharma Corp.

**Diagnosis:** MF

For patients with very low platelets (<50,000) who

have had no or limited exposure to a JAK2 inhibitor. Pacritinib (VONJO™) was approved by the FDA for MF. CTI is required by FDA to describe a clinical benefit in a confirmatory trial and will do so based on the results of the ongoing PACIFICA trial.

**More Info:** <https://clinicaltrials.gov/ct2/show/NCT03165734>

### PXS-5505 (Phase 1/2a)

**Sponsor:** PharmAxis Ltd

**Diagnosis:** MF

For intermediate- or high-risk MF patients who are not currently taking a JAK inhibitor. PXS-5505 is a pan-LOX inhibitor that has shown reduction in fibrosis in pre-clinical models.

**More Info:** <https://clinicaltrials.gov/ct2/show/NCT04676529>

### Imetelstat/IMpactMF (Phase 3)

**Sponsor:** Geron Corporation

**Diagnosis:** MF

For high-risk patients who did not benefit from previous therapy this trial of imetelstat focuses on improving overall survival compared to the best available therapy.

**More Info:** <https://clinicaltrials.gov/ct2/show/NCT04576156>

### Selinexor/XPORT-MF-034 (Phase 1/2)

**Sponsor:** Karyopharm Therapeutics Inc

**Diagnosis:** MF

For patients who have not previously received a JAK inhibitor selinexor is combined with ruxolitinib in this trial. Selinexor is a XPO1 inhibitor that was previously approved by the FDA for another blood cancer.

**More Info:** <https://clinicaltrials.gov/ct2/show/NCT04562389>

### TL-895 (Phase 2)

**Sponsor:** Telios Pharma, Inc.

**Diagnosis:** MF

TL-895 is a tyrosine kinase inhibitor for patients who did not benefit from prior therapy and who are intolerant or ineligible to receive a JAK inhibitor.

**More Info:** <https://clinicaltrials.gov/ct2/show/NCT04655118>. ■

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## CELEBRATE YEAR END WITH AN INVESTMENT IN MPN RESEARCH



*MPN Research Foundation is just that – a privately funded foundation dedicated to the research and outcomes that will change the life and prognosis of people who live with essential thrombocythemia, polycythemia vera, and myelofibrosis.*

Since our founding 22 years ago, we have remained laser-focused on identifying and funding research gaps that can offer clues to unanswered questions. Our research investments to date total more than \$17 million and have played an instrumental role in many of the major findings that have helped us understand more about what causes MPNs, their progression and treatment.

As our work continues, our patient-centered research takes place in laboratories around the globe, by world-renowned blood cancer investigators, as well as those who bring a fresh approach and new questions to the MPN research community.

From preventing disease progression to exploring potential new drug therapies that expand treatment options, MPNRF proudly funds peer-reviewed, often multi-institutional proposals, that may lead to near-term and/or long-term results that improve patients' lives.

At the same time, the foundation plays a unique role in bringing the collective MPN community together – researchers,

patients, advocates, and biopharma – to facilitate our shared purpose. Among our key objectives: keeping the patient voice top of mind throughout the drug exploration and development process.

Please consider being a part of our impact by investing in MPN research as we close out 2022. Giving Tuesday, on November 29th, is an upcoming opportunity to kick off your end-of-year giving. Your tax-deductible donation makes a difference towards advancing our mission and the fight against MPNs.

*With gratitude,  
MPN Research Foundation Board of Directors*