

MPN RESEARCH FOUNDATION

CHANGE YOUR PROGNOSIS UPDATE

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PERIODIC NEWSLETTER FOR THE MYELOPROLIFERATIVE NEOPLASMS COMMUNITY

LIVELY EXCHANGES, NEW IDEAS AT THE 2015 MPN ROUNDTABLE

Since 2013, the MPN Research Foundation has hosted an annual Roundtable to bring together scientists from both academia and industry to discuss the state of MPN science and help provide guidance to the Foundation's grant programs.

It also provides an opportunity for Foundation academic grantees to showcase their work. And the conversations among the scientists (both academic and industry) have resulted in multiple collaborative efforts.

The 2015 MPN Roundtable was held on November 10, 2015 at the O'Hare Hilton in Chicago. The 48 attendees included scientists from companies that are members of the MPNRF Industry Advisory Board; academic scientists, including MPNRF grantees; a representative from LLS, the Foundation's partner in the MPN Challenge Grant Program; and MPNRF board members, staff and guests, of whom 8 are MPN patients or patient family members.

JAK2 IN THE CROSSHAIRS

Ross Levine of Memorial Sloan Kettering made the keynote presentation. His topic was JAK2 inhibition, and in particular new approaches to targeting the JAK2 mutation.

PRESENTATIONS BY 2014 MPN CHALLENGE GRANTEES

The 2014 MPN Challenge grantees made brief presentations of their work. Their projects cover a variety of unmet needs, such as investigating the mechanism by which interferon targets JAK2 stem cells; developing zebrafish with multi-colored blood to study clonal hematopoiesis in MPNs; and developing an MRI-based imaging system that measures bone marrow fibrosis, which could make invasive bone marrow biopsies unnecessary.

(CONTINUED ON PAGE 6)

IS THERE A CURE IN CRISPR?

There may or may not be, but the potential is so great that we're supporting CRISPR research in a number of ways.

It's hard to remember what CRISPR stands for, but relatively easy to understand its potential to revolutionize genetic medicine.

First, the basics: CRISPR stands for clustered regularly-interspaced short palindromic repeats. These are segments of prokaryotic (meaning without a nucleus) DNA containing short repetitions of base sequences.

THE POTENTIAL TO "FIX" MUTATED GENES

Their significance is that they make it possible to edit genes at the molecular level with the intent of "fixing" mutations that contribute to the onset of diseases or conditions like the MPNs.

There is a lot of discussion about the pros and cons of gene editing, and we want to reflect on the Foundation's position and investment up until now, as well as help clarify for those living with PV, ET and MF what the long- and short-term value of this will be for them.

(CONTINUED ON PAGE 5)



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MISSION The primary mission of the MPN Research Foundation is to stimulate original research in pursuit of new treatments — and eventually a cure — for myeloproliferative neoplasms (MPNs). In addition, the MPN Research Foundation promotes collaboration in the scientific community to accelerate research, and serves as a powerful patient advocacy group for patients and their families.

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CHANGE YOUR PROGNOSIS

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HOPE AND FRUSTRATION

By Robert Rosen

It's been about 15 years now since we funded our first grant, to Joe Prchal, the researcher with the audacious idea that he could find a gene that caused polycythemia vera. Dr. Prchal's ambitious research laid the groundwork for the discovery of JAK2V617F in 2005. The explosion of interest in the MPNs soon followed and the rest is history in the making.

In the early years we could hardly find anyone to apply for our grants. We once advertised in a hematological journal for grant applicants and received one inquiry. How times have changed. The journals are now full of articles about the genetic underpinnings of our diseases.

Yet the discouraging fact remains that only one new drug has been approved for myelofibrosis, our most serious condition. Although the drug is not a cure, there is data suggesting it may extend the life of some people with myelofibrosis. On the other hand, the drug is primarily a symptom reliever and not all people can tolerate its side effects. It is however an important advance and has alleviated misery in countless patients. For this we are extraordinarily grateful.

On the hopeful side there are many drugs and drug combinations currently in clinical trials. (See the article on page 5 for more information.) Application of CRISPR gene editing to MPNs is promising. We sponsored a CRISPR scientific forum at ASH to explore ways to proceed.

The scientists tell us that drug development takes a long time. But as patients, time is not necessarily on our side. We are frustrated that we are not closer to more success in the drug development pipeline, but hopeful that some of the current pipeline products and new mechanisms under investigation will prove to be effective in treating and perhaps one day curing these diseases. The MPNRF is passionate about pushing the process, intelligently and strategically, as fast as we can. We were there in the beginning and will continue to be there for the MPN community.

WE CAN'T DO IT WITHOUT YOU

Like it or not, MPNs are rare diseases, and they don't attract widespread publicity. So it's up to us in the MPN community – patients, family, friends and caregivers – to do everything possible to help develop new treatments and, one day, a cure. And we can do it – if we do it together. Please be generous.

MPNRESEARCHFOUNDATION.ORG

“The MPN Research Foundation has provided key support for virtually every major advance in the MPNs since 2000.” — Andrew Schafer, MD, Chairman of Medicine, Cornell Weill, Chairman, MPNRF Scientific Advisory Board



MPNRF IS THE ONLY NONPROFIT FOCUSED EXCLUSIVELY ON FUNDING MPN RESEARCH

PROVIDED SEED MONEY THAT LED TO OVER \$30 MILLION IN NIH GRANTS FOR AN INTERNATIONAL MPN RESEARCH CONSORTIUM



IN 2005 FUNDED \$2.25 MILLION FOR GARY GILLILAND, RONALD HOFFMAN AND AYALEW TEFFERI TO INITIATE RESEARCH USED IN DEVELOPING JAK2 INHIBITING DRUGS

HELPED LAUNCH NEW AND YOUNG RESEARCHERS WHO ARE NOW AMONG THE MOST PRODUCTIVE MPN INVESTIGATORS

AGGRESSIVELY FUNDED EARLY GENOMIC STUDIES IN MPN IN EARLY YEARS AFTER DISCOVERY OF JAK2



FUNDED THE DISCOVERY OF THE CALR MUTATION FOR MPN PATIENTS LACKING JAK2 MUTATION



FUNDED NUMEROUS MOUSE MODELS THAT SERVE AS PLATFORMS FOR MPN RESEARCH



PIONEERED THE USE OF ZEBRA FISH AS A SCIENTIFIC MODEL OF MPN DISEASE



PROVIDED EARLY FUNDING OF IMMUNOTHERAPY TRIALS FOR MPN PATIENTS



PROVIDED EARLY FUNDING OF CRISPR GENE EDITING RESEARCH IN MPNs



CREATED ANNUAL MPN ROUNDTABLE, A FORUM FOR OUR GRANTEEES AND BIOPHARMA TO EXCHANGE CUTTING-EDGE RESEARCH IDEAS



CURRENTLY FUNDING DEVELOPMENT OF ANTI-CALR THERAPIES

MPN RESEARCH FOUNDATION IMPACT STATEMENT

HIGHLIGHTS: DECEMBER 2015 ASH MEETING

by MPNRF Scientific Advisor John Crispino, PhD; Robert I. Lurie, MD; and Lora S. Lurie, Professor, Northwestern University

Do you find these ASH summaries useful? We write them with you in mind, so that you can be an informed participant in your care. We would love to hear your feedback. Please send us your comments at info@mpnresearchfoundation.org.

JAK INHIBITOR CLINICAL STUDY UPDATES

Pacritinib (CTI Biopharma): Dr. Vannucchi presented an update on the Phase 3 PERSIST-1 trial of this JAK2/FLT3 inhibitor in myelofibrosis. Pacritinib resulted in consistent reductions in spleen volume and the total symptom scores across subgroups of patients with low platelet counts. Due to concerns about mortality, the FDA placed pacritinib on full clinical hold; but patients currently benefitting from it will be allowed to continue treatment. Patients should contact their doctor for more information. We'll post updates as they become available.

Momelotinib (Gilead): This JAK1/2 inhibitor is currently in a Phase 3 clinical trial for treatment of myelofibrosis. In Phase 1 and 2 studies, it has been shown to reduce spleen size and symptom score and to provide an anemia benefit.

NS-018 (NS Pharma): Dr. Verstovsek and colleagues reported the results of a phase 1/2 study of NS-018, a selective JAK2 inhibitor, in patients with myelofibrosis. 56% of patients treated with a 300mg dose achieved a 100% reduction in palpable spleen size and an overall improvement in all assessed symptoms by 4 weeks.

NEW MECHANISMS OF ACTION AND CLINICAL UPDATES

PRM151 (Promedior): Dr. Verstovsek reported on the efficacy and safety of PRM151 in 13 patients. PRM-151 was well tolerated and led to improvements in hemoglobin levels and platelet counts as well as constitutional symptoms and spleen size. A phase 2 study is ongoing.

COMBINATION STUDIES

Ruxolitinib clearly provides a therapeutic benefit to patients, but is not a cure. Therefore, a number of investigators are testing ways to improve the activity of ruxolitinib by combining with other therapies.

5-azacytidine (AZA): AZA is a DNA methyltransferase inhibitor approved for treatment of myelodysplastic syndrome. Dr. Verstovsek and colleagues assessed the activity of the combination of AZA with ruxolitinib in patients with a variety of myeloid neoplasms, including myelofibrosis. About half of the 24 enrolled patients showed a response, with the majority of the myelofibrosis cohort achieving a significant reduction in spleen size. The main toxicity was myelosuppression – the suppression of the bone marrow's production of blood cells and platelets.

Interferon (IFN α 2): Since treatment with interferon is associated with inflammation, Hasselbach and colleagues investigated whether the addition of ruxolitinib, which is effective at suppressing inflammation, would benefit patients.

The combination was well tolerated and effective in a majority of patients, with reductions in symptoms, spleen volume and allele burden. In particular, the ability of the combination to ameliorate symptoms while simultaneously reducing the allele burden is very promising.

Sonidegib: This is a small molecule inhibitor of the hedgehog signaling pathway, which controls cell growth. Dr. Gupta presented data from a Phase 1b/2 study of the combination of sonidegib and ruxolitinib in patients with myelofibrosis.

Twelve of 27 patients achieved $\geq 35\%$ spleen volume reduction by week 24. There was a decrease in allele burden (9% median decrease) and reduction in fibrosis in two patients.

READING PATIENT STORIES IS A GREAT WAY TO LEARN MORE ABOUT MYELOPROLIFERATIVE NEOPLASMS (MPNs) AND HOW OTHERS HAVE COPED WITH THEIR DIAGNOSIS AND TREATMENT.

To tell your own MPN story or send in a photo, contact Raquel at rnunez@mpnresearchfoundation.org.



CLINICAL TRIAL HIGHLIGHTS

Research in the MPNs is starting to pay off, with multiple clinical trials underway. A complete list can be found on our website at www.mpnresearchfoundation.org/Clinical-Trials. The trials listed here may be of particular interest because they are testing new mechanisms of action and currently enrolling patients.

MYELOFIBROSIS PATIENTS

Aurora Kinase Inhibitor

Sponsor: Millenium Taketa Pharmaceutical
Contact: Brady Stein, bstein@nmff.org

PRM 151, an anti-fibrotic agent

Sponsor: Promedior
Contact: info@promedior.com

Imetelstat, a telomerase inhibitor

Sponsor: Janssen
Contact: <https://clinicaltrials.gov/ct2/show/NCT02426086>

Anti-PDL1, an immunological agent

Pending IRB approval
Sponsor: Celgene
Contact: Brady Stein, bstein@nmff.org

Glasdegib, a Hedgehog inhibitor

Sponsor: Pfizer
Contact: 1-800-718 1021

P1101, an interferon derivative

Sponsor: Pharmassentia
Contact: Rosenthal.Allison@mayo.edu

SL-401, an antibody against interleukin-3 receptor

Sponsor: Stemline
Contact: Serge Verstovsek, sverstov@mdanderson.org

LCL-161, an SMAC inhibitor

Sponsor: Novartis
Contact: Serge Verstovsek, sverstov@mdanderson.org

ACE-011, an anti-actin antibody

Sponsor: Celegene
Contact: Serge Verstovsek, sverstov@mdanderson.org

Nivolumab, an immune checkpoint inhibitor

Sponsor: BMS
Contact: Serge Verstovsek, sverstov@mdanderson.org

POLYCYTHEMIA VERA & ESSENTIAL THROMBOCYTHEMIA PATIENTS

RG7388, promotes tumor suppressor pathway P53

Sponsor: MPD-RC
Contact: Johon.mascarenhas@mssm.edu or Jill Kleczko (212 241 0573)

IS THERE A CURE IN CRISPR?

(CONTINUED FROM PAGE 1)

In the case of the MPNs, we view two uses for this technology:

As a means of creating improved cell lines and mouse models, with which to test scientific theories of the origin of MPNs as well as to test potential therapies; and as a route to better outcomes for stem cell transplants, the only cure, accessible to only a small percentage of people living with Myelofibrosis.

MPNRF decided in 2015 to explore the potential of CRISPR with three initiatives:

1. We reached out to CRISPR experts to discuss the potential of its use in MPNs and build awareness for the MPNRF grant program.
2. We solicited proposals for gene editing in the MPNs, culminating in awarding 3 multi-year grants that will produce better cell lines and mouse models with which to study MPNs.
3. We hosted a seminar at ASH – CREATE – which aimed to bring MPN clinicians together with CRISPR experts to understand the technology and to discuss the use of CRISPR for stem cell transplants. Rachel Haurwitz of Calico Biosciences and Ann Mullally of Brigham and Women's Hospital of Harvard University gave presentations.

To summarize, there is more work to be done before CRISPR will be a useful tool for MPNs. You won't be able to go to your doctor next year, or probably even in three years to have them "edit out" your mutated genes.

But MPNRF's investment has forced those who are enthusiastic about this technology to consider the MPNs, which, as a rare disease, are typically in the back of the line when it comes to investment.

We are eager to find what progress is made of this initial investment, in hopes that there is a path forward that realizes benefits to patients.

MPN RESEARCH FOUNDATION UPDATE

A periodic newsletter published by the MPN Research Foundation to provide members of the MPN community with information on current research and the Foundation's activities.

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LIVELY EXCHANGES, NEW IDEAS AT THE 2015 MPN ROUNDTABLE

(CONTINUED FROM PAGE 1)

2015 MPN CHALLENGE GRANTEES DESCRIBE THEIR NEW PROJECTS

Following lunch, the new 2015 MPN Challenge grantees introduced themselves and the goals of their new projects, which began in October, 2015:

- **Zhijan Qian and Wen-Shu Wu (University of Illinois)** will be testing the feasibility of correcting the JAK2V617F mutation using CRISPR gene editing technologies.
- **Zhaohui Ye (Johns Hopkins)** will be identifying common pathways in MPNs and targeting them with gene editing technologies.
- **Brady Stein (Robert H. Lurie Cancer Center, Northwestern)** will be testing PDL-1 inhibitors in a new clinical trial of MPN patients.
- **Camelia Iancu-Rubin (Icahn School of Medicine, Mt. Sinai)** will be defining the immunomodulatory properties of mutated calreticulin in MPNs, and testing compounds to address this target.
- **Susan Byrne for George Church (Harvard Medical School)** will be establishing isogenic human induced pluripotent stem cell lines containing CRISPR engineered MPN mutations.

IN THE WORKS: AN MPN PATIENT REGISTRY

Michelle Woehle, Executive Director of the Foundation, described the Foundation's commitment to begin building an MPN Patient Registry. This registry will begin with patient-entered data, and will be designed to ultimately record physician-entered data and to be compatible with shared electronic medical records.

DISCUSSION OF UNMET NEEDS

Each year, the Foundation strives to direct its research funding dollars to topics and investigators who can truly move the needle in MPN science. Andy Schafer and John Crispino led a lively discussion of unmet needs that merit our support:

- There is still not enough known about the basic mechanisms of MPNs. So we will continue to fund basic research.
- We need to support preclinical testing and help develop improved preclinical models to test novel therapies.
- The Foundation will work to develop new program project ideas and bring together expertise across academic and/or industry boundaries.

There is much to think about, much to do and much optimism for the future.

MPN ROUNDTABLE KEYNOTE ADDRESS BY DR. ROSS LEVINE.



HAVE FUN, RAISE FUNDS AND MAKE A DIFFERENCE



Dozens of MPN patients and family members helped fund MPN research in 2015. Some sold jewelry. Others hosted cocktail receptions. Some literally have climbed mountains. One family member registered for a 40-mile bike ride, and she did not even own a bike! We're inspired by the many ways you – our supporters – have gone above and beyond to help address unmet needs in MPN research. Thanks to your work, the Foundation raised nearly \$2 million last year.

ORGANIZE YOUR OWN EVENT

Organizing a fundraising event is a great way to have fun and support the MPN Research Foundation. The possibilities are endless! Consider:

- **Dinner party.** Ask your guests to donate what they would have spent on a meal and drinks at a restaurant.
- **Golf.** Ask your foursome to donate to the MPN Research Foundation. By giving what they would spend for a day on the links, they'll enjoy each other's company – and help us find a cure.
- **Neighborhood block party.** Set up games like bean bag toss, badminton or volleyball. Collect donations to play or entry fees for teams.
- **Garage sale or car wash.** Donate half the proceeds – and let your buyers know it!
- **Poker or bridge.** Split the winning pot with the MPN Research Foundation. Maybe the winner will donate back to the Foundation!

Some other crowd pleasers are a bake sale, wine tasting, pancake breakfast or lemonade stand. However you do it, make it fun and encourage your friends and family to help support MPN research. For more creative fundraising ideas or to learn more about Team MPN, the MPN Research Foundation's grassroots community fundraising program, please visit www.mpnresearchfoundation.org/Team-MPN-to-Fund-Research.

HOW TO JOIN TEAM MPN

First, come up with a fundraising idea that sounds fun and doable for you! Anything from a walk to a potluck dinner party or outdoor barbecue. Contact Bill Crowley at wcrowley@mpnresearchfoundation.org to find out how we can support your efforts and how the funds will be used.

Get the word out. We'll even help you create a fundraising web page for your event. Do it! As a member of Team MPN, you'll join a community of supporters who are determined to change the prognosis for people struggling with MPNs.



STRONGER TOGETHER: MPNRF JOINS MPN ADVOCATES NETWORK

MPNRF has always funded research globally as well as tried to assist patients around the world as much as possible. However, given our staff constraints, our ability to offer comprehensive assistance outside the United States has always been limited.

We thought we'd have to initiate something ourselves until we were clued in to the existence of the MPN Advocates Network.

Organized in 2015, the MPN Advocates Network was formed by representatives from the Netherlands, Spain and the UK with the goal of facilitating networking among MPN patient groups around the world.

MPNRF attended an MPNAN meeting in London in November 2015, where we discussed whether and how an international coalition could work together, and what goals were reasonable. Groups from Italy, Germany, UK, the Netherlands, Switzerland, Israel and the United States were represented. The representatives were all in agreement that an attempt at expanding the network was a worthy endeavor. We'll work out the details at another meeting in August 2016.

We hope that through this effort more patients will be connected with the information they need to manage their MPNs. While we continue to invest in research that will help MPN patients live longer, better lives, we also want to help people who are just being diagnosed, are newly experiencing symptoms or dealing with the host of issues that people with chronic cancers like MPN face.

If you're interested in this initiative we encourage you to check out www.mpn-advocates.net or send me a note at mwoehrle@mpnresearchfoundation.org.

WE'RE NOT ALONE. AND TOGETHER WE CAN CHANGE OUR PROGNOSSES.

Please be generous. And don't be shy about asking your friends to help out, too.

PARTNERS' CORNER: MPN ADVOCACY AND EDUCATION INTERNATIONAL



In 2005, Ann Brazeau began working at the MPN Research Foundation. Prior to that, she had worked with breast and prostate cancer patients and created outreach programs for those who were uninsured and underinsured. She enlisted physicians, nurses, and educators to participate in programs for these patient groups while bringing the "mountain" to those who could not afford quality care and pre- screening. Education and advocacy have been at the heart of her work for her entire career.



ANN BRAZEAU, (FAR RIGHT), PICTURED HERE AT A RECENT MICHIGAN SUPPORT GROUP MEETING WITH SPEAKER DR. MARIE HUONG NGUYEN FROM THE UNIVERSITY OF MICHIGAN.

While at the MPNRF, Ann wore many hats but was most comfortable with the patients and caregivers. Providing resources and programs to educate the MPN community became her passion. In 2013, her desire to focus all of her energy on education and advocacy led to the creation of MPN Advocacy and Education International. Since then, numerous programs have been presented across the country and two international programs will be held in 2017.

MPN Advocacy and Education International created Women and MPN and hosted its first program in San Diego last year. This year, it will take place on September 30th in NYC. They have also been working for over one year (pro bono) with Vietnam veterans who have MPNs and believe their exposure to Agent Orange could be the cause. MPN Advocacy and Education International hopes to add MPNs to the Veterans Administration's 'presumptive' list to ensure each veteran with an MPN receives compensation, quality care, and full benefits.

Like so many other organizations, including MPNRF, MPN Advocacy and Education International is dedicated to making a difference in the lives of those affected by myeloproliferative neoplasms. The resources available today and the sense of community among all the organizations, allows for greater outcomes for patients everywhere.