

MPN RESEARCH FOUNDATION

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UPDATE

VOLUME XX, NO. 3 FALL 2021

NEWSLETTER FOR THE MYELOPROLIFERATIVE NEOPLASMS COMMUNITY



MPN INTERFERON INITIATIVE: RESULTS OF A THREE-YEAR GLOBAL PROJECT

Rick Winneker, PhD
Director of Scientific Strategies

In real world usage and in clinical trials, multiple forms of interferon (IFN) have shown high rates of hematological and molecular responses in most patients with essential thrombocythemia and polycythemia vera and in some patients with early phase myelofibrosis. This is great news but there is still much to learn. After much anticipation, we are thrilled to announce the results of our Interferon Initiative.

The Interferon Initiative brought together global interferon experts to study its underlying mechanism of action, and to better define the patient/disease profile that can predict both response to treatment and resistance to therapy. This understanding can help to validate the use of newer, more disease-specific forms of the drug, as well as new approaches to combine IFN with other therapies. It also remains promising to define new signaling pathways that can be modulated to enhance the drug's potential therapeutic benefits.

While the reasons for different responses to IFN remain obscure, we know they are largely related to elusive mechanisms interferon uses on a molecular level to eliminate the JAK2 mutant clone – a mutation present in the majority of patients with an MPN. This set the basis for the projects pursued in this initiative.

RESEARCH TEAMS AND PROJECT SUMMARIES

Working closely with MPNRF staff, the principal investigators of our four active projects gathered to discuss their work on a quarterly basis, then presented annual project updates to a distinguished international

group of academic advisors to track progress, solicit feedback and promote collaboration.

The project descriptions and findings are summarized below. For more details, including publications and abstracts, see the full report on our website.

Overcoming Resistance to Interferon in MPN Stem Cells

Ann Mullally (Brigham and Women's Hospital, Boston, MA, US); Steven Lane (QIMR Berghofer Medical Research Institute, Brisbane, Australia); and Michael Milsom (German Cancer Research Center, Heidelberg, Germany)

Secondary mutations in MPN stem cells were explored to determine if they mediate resistance to IFN. Also examined were why MPN stem cells are preferentially sensitive to IFN, and what the key genetic drivers of resistance to IFN are in MPN patients.

Overall results provide insights into molecular response and resistance to IFN and provide additional understanding for its clinical use in MPN patients. Specifically, while DNMT3A was considered a candidate for a secondary mutation that leads to IFN resistance, preclinical work did not show that anticipated result. Studies are ongoing to evaluate two other candidate genes. In an unrelated preclinical study, it was shown that IFN, in contrast to



MPN INTERFERON INITIATIVE

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MISSION

THE MISSION OF THE MPN RESEARCH FOUNDATION IS TO STIMULATE ORIGINAL RESEARCH IN PURSUIT OF NEW TREATMENTS — AND EVENTUALLY A CURE — FOR MYELOPROLIFERATIVE NEOPLASMS (MPNs).

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MPN RESEARCH FOUNDATION

180 N. Michigan Avenue
Suite 1870
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mpnresearchfoundation.org

* DECEASED

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THANK YOU TO OUR SPONSORS:



ANNOUNCING OUR 2021 MPN CHALLENGE AWARDEES

The MPN Research Foundation's **MPN Challenge** was created to stimulate innovative and clinically relevant research that has the highest potential for near-term patient impact. We do this by expanding our understanding of both the basic biology of MPNs and what is driving the establishment and progression of disease. For 2021, we remain focused on addressing critical gaps slowing the development of new therapeutic approaches.

A call for proposals was issued earlier this year and we received 22 highly promising proposals representing institutions from the US, France, Israel, and Australia. A peer review panel of MPN thought leaders convened in September and deliberated the final recommendations to the MPNRF Science Steering Committee.

The MPNRF Board of Directors approved the following investigators to each receive a two-year award, funded to a maximum of \$100,000 per year.



+ **Sara Buhrlage**, James Griffin, Jarrod Marto and Ellen Weisberg (Dana-Farber Cancer Institute): "**JOSD1 as a novel targeted therapy for JAK2V617F dependent myeloproliferative neoplasms.**" Dr. Buhrlage's project is being supported in part by The Leukemia & Lymphoma Society.



+ **Anandi Krishnan**, Jason Gotlib, Holden Maecker and James Zehnder (Stanford University): "**Platelet, blood and plasma signatures of MPN subtype-specific risk.**"



+ **Bridget Marcellino** and Cansu Cimen Bozkus (Icahn School of Medicine at Mount Sinai): "**Characterization of immune landscape and determinants of immune dysregulation in myeloproliferative neoplasms.**"



+ **Stephen Oh** (Washington University, St. Louis): "**Functional interrogation of an aberrant DUSP6-RSK1 signaling axis driving MPN pathogenesis.**"



+ **Josef Prchal** (Huntsman Cancer Institute), Jihyun Song (University of Utah), Perumal Thiagarajan (Baylor College of Medicine), Tomas Ganz (University of California, Los Angeles) and Victor Gordeuk (University of Illinois): "**Role of iron deficiency in thromboses of polycythemia vera.**"

We are delighted to support these dedicated investigators over the next two years and follow their progress towards impactful findings. The MPN Research Foundation remains committed to advancing disease knowledge that will lead to promising new therapies and better outcomes for MPN patients. ■

a JAK2 inhibitor, was able to deplete dormant mutant MPN stem cells, perhaps explaining its ability to induce molecular remission in some patients. Next-generation sequencing also was performed on MPN patient samples to evaluate the association between complete clinical-hematologic response at 24 months and a molecular response, with either recombinant interferon-alpha (IFN α) or hydroxyurea.

Mechanism of Action of Interferon Alpha in MPN Therapy

Jean-Luc Villeval and Isabelle Plo (INSERM/Gustave Roussy/University of Paris-Saclay, France)

Focused on the mechanism of action of IFN, hypotheses were tested on the interplay between mutant JAK2 and IFN signaling, and on a potential role of a specific nuclear structure called PML-nuclear bodies. The activity of IFN was evaluated in JAK2 versus CALR mutated cells, and an algorithm was developed to predict the long-term IFN response in patients.

This work indicates that the long-term molecular effect of IFN depends on both the driver mutation type and IFN dosage. It was learned that the JAK2V617F mutation sensitizes IFN pathway signaling much better than CALR mutations, and that the hematological and molecular response induced by IFN in mice may benefit from combination with a JAK2 inhibitor. Also, based upon results seen in mice, the combination of IFN with arsenic trioxide may be more effective than IFN alone in eliminating MPN stem cells in patients with a JAK2V617 mutation. A clinical trial is being planned.

Novel Agents for the Treatment of Malignancies

Leonidas Plataniotis (Northwestern University Feinberg School of Medicine, Chicago IL)

Novel proteins that participate in the generation of the IFN response in MPN cell lines and patient samples were identified and characterized. Biological effects of targeting these candidate IFN response proteins also were explored.

These studies provide the basis for future development of compounds that target these IFN response proteins, which may prove effective in the treatment of MPNs. Specifically, two new potentially interacting proteins were identified in a JAK2 mutant expressing cell line. Their gene expression is increased in the blood of MPN patients compared to healthy controls. It was shown that inhibition of these proteins enhances the anti-tumor effects of IFN against MPN cells.

Using a Vascular Niche Platform to Develop Interferon-Based Strategies to Eradicate MPN Stem Cells and Phenotypes

Joseph Scandura (Weill Cornell Medicine, New York, NY)

The goal of this project was to measure the strength or fitness of MPN stem cells to overrun normal stem cells and develop ways to weaken them. A "cell-based blood formation factory" was created that allows stem cells to be grown and evaluated in the laboratory. This platform offered an opportunity to quickly and robustly assess the relative expansion of MPN and normal stem cells simultaneously in a well-controlled experimental setting.

Results suggest that this important model may be used to help predict both negative MPN events, such as progression, and desired events, such as response to drug therapy, including IFN. Overall, this platform may be applicable to speed up and simplify the discovery of agents with the potential for disease modifying activity.

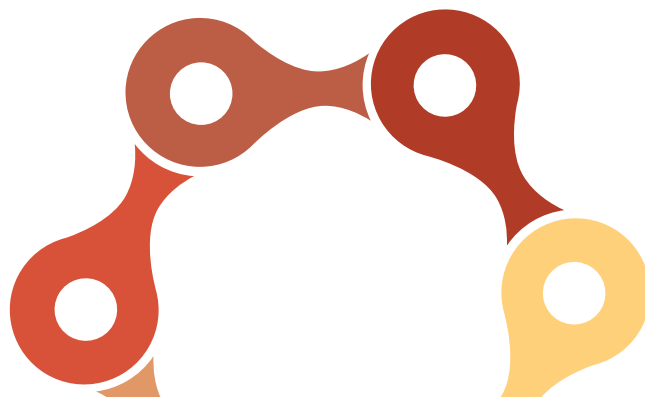
IN SUMMARY

Each of the developments resulting from the Interferon Initiative is integral to our understanding of how interferon works and doesn't work in MPNs. We are now better positioned to understand the role of secondary mutations on IFN resistance and relapse, and we are closer to optimizing IFN treatment strategies based on a patient's specific driver mutation, allele burden and overall genomic profile.

Much of the Interferon Initiative's work will continue beyond the scope of this specific funding, as the effort has positioned these investigators for future funding opportunities. ■

PROJECT SUPPORT

- + MPN Research Foundation
- + MPN Australian Alliance
- + Cancer Research & Treatment Fund
- + PharmaEssentia



TO BE (A GUINEA PIG) OR NOT TO BE: PARTICIPATION IN A CLINICAL TRIAL

MY PERSONAL EXPERIENCES

Ned Weinshenker

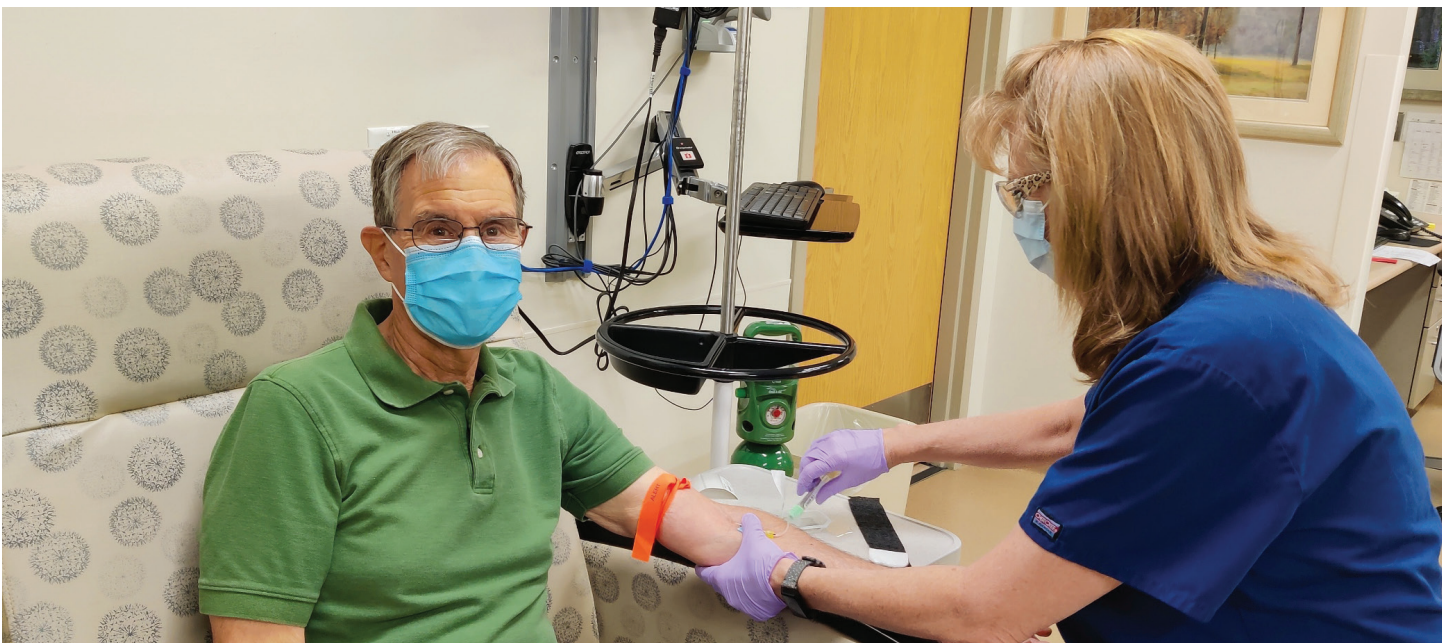
In November 2018 I was diagnosed with Primary Myelofibrosis (PMF). Since it is such a rare disease, like most people diagnosed, I knew nothing about it. I immediately set out to learn as much as possible so that I could be in a good position to participate in the decisions regarding my prognosis and care. Personally, I have found that the more I know about an issue the less anxious I am. I am not one to put my head in the sand and hope for the best.

PMF is a cancer that patients seem to experience differently regarding the constitutional symptoms and the underlying disease (genetic factors). When I realized that I was most likely not a candidate for stem cell transplant due to age, I considered other options. I noted that the only drug approved for treatment at the time, Jakafi, only dealt with constitutional symptoms and spleen volume reduction so I started to look at new therapies that were in clinical trials. The listing of clinical trials on the MPNRF website was a fantastic resource to get me started.

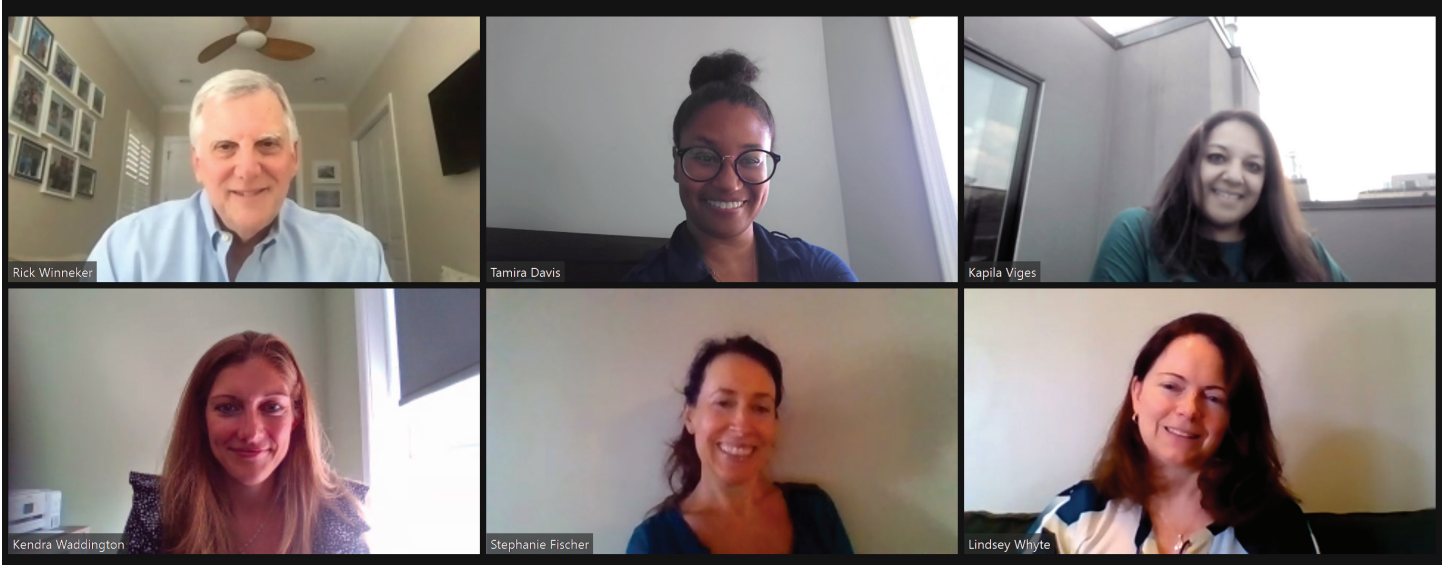
As I reviewed all of the studies, the one that struck me as the most promising for me was the drug CPI-0610 from Constellation Pharmaceuticals. I collected all the information I could find and brought it to my doctors for review. I set it up in a chart with all the possibilities and the pros and cons of each. The doctors reviewed it with me and agreed with my conclusion that this trial would be

the best opportunity at that time as the first few patients were starting to see a positive effect on the underlying disease. The other major factor in my decision was that this was an "open label" study, meaning I would know that I would be receiving the active drug and not a placebo. The only downside was that the closest clinic to me was UCLA Medical Center, 850 miles away from my home in Utah. With my doctor's agreement I was able to apply for the study and after meeting the entrance requirements, I started on therapy in March 2019. I am still in the study and will continue as long as it is showing efficacy. I follow the literature to see what other studies are in progress in case this drug starts to decline in efficacy.

I have worked in the pharmaceutical and medical device field for a large part of my career and know the importance and value of well-run clinical studies. Participating in any study that can generate data that will be helpful to eventually fully understand this disease and to develop potential therapies and cures is important – not only for me but for future patients. Knowing how important complete data is for a clinical trial I am extremely diligent about following the dosing schedules and filling out the daily diaries. I hope by providing my experiences it will encourage other MPN patients to consider clinical trials. ■



THE ENGINE BEHIND THE FOUNDATION



It is an exciting time at the MPN Research Foundation! Not only are there promising new therapies on the horizon for MPNs, but also a new energy inside the foundation.

We continue to focus on our future and how we can best advance MPNRF's research mission while elevating its institutional legacy of thought leadership.

We are a group of passionate, committed individuals who feel fortunate to work to serve this community. Working remotely and across time zones, we look forward to paving the path for the next chapter of the foundation.

While research is exponentially expanding our knowledge – and a better quality of life for people living with MPNs – there is much more yet to be done. To meet our aspirational goals, we move forward

as a team with more specialized expertise, driven to continually increase our impact, effectiveness and results. Every day, we are mindful that patients are at the center of the MPNRF and its important mission is in our collective hands.

THE MPNRF TEAM

Kapila Vigés, Chief Executive Officer

Rick Winneker, Director of Scientific Strategies

Kendra Waddington, Director of Development

Stephanie Fischer, Director of Patient and Biopharmaceutical Industry Engagement

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To receive our monthly digest, *Under the Microscope*, and other timely communications about what's happening in the MPN community, visit us on the web at mpnresearchfoundation.org

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CLINICAL TRIAL HIGHLIGHTS

With the help of patients who choose to participate, clinical trials determine whether a therapy is safe and effective in treating a particular disease. Trials are designed to test a medication or other medical treatment against a placebo (inactive look-a-like), other medication, or the standard medical treatment for a patient's condition. Data collected in clinical trials are necessary for the Food and Drug Administration (FDA) to review prior to approving any new therapy or a new use of a therapy previously approved to treat a different disease.

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

IMPactMF - Imetelstat (Phase 3)

Sponsor: Geron

Diagnosis: Myelofibrosis

More Info: www.clinicaltrials.gov/ct2/show/NCT04576156

Notes: For high-risk patients who did not benefit from previous therapy, this trial focuses on improving overall survival.

9-ING-41 (Phase 2)

Sponsor: Actuate Therapeutics

Diagnosis: Myelofibrosis

More Info: www.clinicaltrials.gov/ct2/show/NCT04218071

Notes: For patients with advanced disease. 9-ING-41 is an anti-cancer and anti-fibrotic given alone or in combination with ruxolitinib.

Bomedemstat (Phase 2)

Sponsor: Imago BioSciences

Diagnosis: Essential Thrombocythemia

More Info: www.etclinicalstudy.com

Notes: For patients who have high platelets and did not benefit from at least one standard therapy, bomedemstat focuses on inhibiting LSD1.

Selinexor (Phase 2)

Sponsor: Karyopharm Therapeutics

Diagnosis: Myelofibrosis

More Info: www.clinicaltrials.gov/ct2/show/NCT04562870

Notes: For higher risk patients who did not benefit from ruxolitinib. Selinexor was previously approved by the FDA for another blood cancer.

Continuous Positive Airway Pressure (CPAP) (Phase 1)

Sponsor: University of Utah

Diagnosis: Polycythemia Vera or Essential Thrombocythemia with obstructive sleep apnea (OSA)

More Info: www.clinicaltrials.gov/ct2/show/NCT03972943

Notes: OSA is estimated to affect 30% to 50% of patients with PV and ET. Individuals with OSA stop breathing during sleep. The CPAP provides pressurized air that keeps upper air passages open during sleep.

FOR MORE ON CLINICAL TRIALS VISIT: MPNRESEARCHFOUNDATION.ORG/MPN-CLINICAL-TRIALS