MPNRF AWARDS PILOT GRANT FOR NEW GENOMIC BASIS STUDY

Rick Winneker, PhD

Following on our promise to invest in research that would lead to better understanding and prevention of progression from PV/ET to MF, the MPN Research Foundation has made its first strategic investment in this area to Dr. Ann Mullally (Twitter: @MullallyLab) and colleagues at Dana-Farber in Boston. Through a one-year pilot grant, we are providing funds to Dr. Mullally and Dana-Farber’s Center for Prevention of Progression (CPOP) initiative to study the genomic basis for MPN disease progression.

Using a panel of 100 genes commonly mutated in myeloid disease, the Dana-Farber team has already sequenced more than 1,000 MPN patients. Our support was used to hire a data research specialist, Nish Patel, to integrate the clinical and pathological data from each patient’s health record with this new genomic information and enter it into their database to not only better understand MPN disease progression, but also to generate new hypotheses for laboratory testing.

“This support represents an important commitment to understand the role of genomics in promoting MPN progression and, most importantly, to use this information to develop early intervention strategies to prevent progression.” – Dr. Ann Mullally

Speaking this week, Dr. Mullally said:

“I am thrilled to receive this support from MPNRF. It represents an important commitment to understand the role of genomics in promoting MPN progression, and most importantly to use this information to develop early intervention strategies to prevent progression in patients with MPN.

Approximately five months since the initiation of this funding, we have made outstanding progress. Working with Dr. Coleman Lindsley, a leading expert in the genomics of myeloid disease, and MPN physician Dr. Marlise Luskin, together with database project manager Kevin Copson and data research specialists Anne Charles, Mariana Villalobos-Ortiz, Nish Patel, we have finalized the MPN-specific content extracted from the medical record and the clinical-pathological-genomic integration effort is well underway.

Our expectation is to complete this in the next six months and share our findings with the MPN research community soon thereafter. In the short-term, this data will provide comprehensive genomic information on all MPN subtypes, i.e. ET, PV and MF. By capturing information on patients with all forms of MPN and at all stages of disease (e.g. newly diagnosed, at progression, etc.), we expect to uncover new insights into the role genomics plays in the clinical variability we observe between MPN patients, and also advance the understanding of why MPN remains stable in some patients and progresses in others. We will immediately take the most interesting findings to the laboratory with the goal of developing new treatments to prevent or delay MPN.

www.mpnresearchfoundation.org
progression. Our longer-term goal is to expand this cohort of MPN patients prospectively to many thousands of patients, who we plan to follow for decades into the future so that we can continue to learn more about MPN progression and ultimately prevent it.

Since we are in Massachusetts, the analogy that comes to mind is the Framingham Heart Study, which began in 1948, is still going strong, and arguably has taught us more about heart disease than any study in the history of medicine. Our hope is that we can build on this initial pilot funding from MPNRF to expand the scope and goals of this important project on MPN progression.²

Funding for this project is also provided by the Susan Ann Protter Research Fund, which you can read more about on Page 8 in this newsletter, as well as the Robert Rosen Memorial Fund.

This project reflects a larger interest for the Foundation in understanding progression from ET/PV to MF. In addition to our MPN Challenge grants and other targeted funding of progression research, our next goal is to spearhead the creation of an "MPN Progression Research Network." We plan to launch this network this year and build it over time through annual meetings. Ideally, every researcher focused on MPN progression would eventually be a participant, sharing their data and seeking collaborative solutions to accelerate progress.

Our commitment to preventing disease progression is clear. Dr. Mullally’s project, along with several new MPN Challenge grants and a recently announced one year pilot grant to Dr. Belinda Guo in Western Australia, all focus on an important aspect of disease progression and demonstrate that we are not waiting, but are already starting to invest in this critical area of research.

Lindsey J. Whyte, Longitudinal Research Project Manager

A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes. (Gliklich, Dreyer, and Levy 2014)

In 2016, the FDA came out in support of real world data (RWD) such as that collected in patient registries like myMPN. Specifically, real world data could be used to improve the efficiency of clinical trials, in label expansion (identifying new populations suitable for a drug), dosing, and post-market monitoring of ongoing safety of approved drugs. Sources of RWD besides patient registries include claims data, electronic health records (EHR) and data collected from wearable devices such as Apple watches or fitness trackers.

The FDA’s willingness to accept RWD is a huge step in the right direction for patients and patient advocacy organizations. It empowers patients to tell it like it is. What’s interesting to me is that patient registry data is put in a similar bucket with EHR and insurance claims data! What are the differences and similarities between these sources of data?

EHR tells part of the patient’s story – the part that the clinicians enter, while claims data tells
While there were no major breakthroughs at this year’s American Society of Hematology (ASH) meeting, hundreds of presentations focused on all aspects of MPN research. There was a high level of clinical trial activity reported, featuring both well-known and relatively new therapies and several new drug mechanisms entering trials or in preclinical development.

In a phase 2 study, the JAK2/IRAK1 inhibitor pacritinib was well tolerated and demonstrated clinical activity in high risk, heavily pre-treated myelofibrosis (MF) patients with extreme thrombocytopenia. The phase 3 PACIFICA study for this drug is currently enrolling MF patients with fewer than 50,000 platelets. Interferon continues to be an exciting area of study. One study reported the 4 year follow up data of the PROUD-PV trial of ropeginterferon alpha-2b. This drug showed superior activity as compared to hydroxyurea or the best available therapy and had a sustained reduction in the allele burden, a measure of the extent of the disease.

Other clinical studies of novel single agents or combinations included a phase 2 study combining navitoclax with ruxolitinib in patients with MF. Overall, this drug combination was well tolerated and displayed preliminary clinical benefits that may stimulate advanced trials. The MANIFEST Phase 2 study of CPI-0610 showed that patients who had prior exposure to ruxolitinib with a sub-optimal response were eligible to enroll into one of two groups: CPI-0610, a monotherapy, or the combination of CPI-0610 with ruxolitinib. At 24 weeks, improvements in spleen volume reduction, symptom score, transfusion dependence, and bone marrow fibrosis were seen with the drug combination study and were well tolerated.

Additional clinical trial results for high risk MF patients were presented, including ruxolitinib plus pomalidomide; Img-728, a drug that targets a regulator of gene expression named LSD1; LCL161, a SMAC mimetic that targets molecules that allow for survival of malignant cells in patients; metformin, focusing on bone marrow fibrosis and disease progression; luspatercept in patients with MF-associated anemia and tagraxofusp, a CD-123 targeted therapy. Clinical study designs were presented for two new drugs, KRT-232, an MDM2 inhibitor designed to increase or stabilize p53 levels and PU-H71, a chaperone inhibitor which enhances the degradation of mutant JAK2 protein levels when combined with ruxolitinib.

Presentations on the basic biology of the MPNs and preclinical development of new therapies included research further describing the functions of normal versus mutant forms of calreticulin, the contributions of gene regulatory factors such as HMGA1, and the role of cytokines such as IL-1b in development and progression of the MPNs. Several new therapeutic targets (HDAC11 PRMT5, PPM1D) and novel inhibitors in preclinical development (palbociclib, a CDK6 inhibitor, RMC-4550, a SHP2 inhibitor, obatoclax, a pan-Bcl-2 inhibitor) were also presented.

Overall, more clinical trials of new drugs and multi-center studies to better predict disease progression are all very positive signs of progress on multiple fronts. This is needed to develop more personalized therapeutic strategies and improve outcomes for patient with MPNs. If you would like to see a more detailed summary of research from ASH, please visit our website: www.mpnresearchfoundation.org/19-ASH-Meeting-Report.

With this survey the MPN Research Foundation wants to learn more about what kind of information you want to see from us and how you want to receive it. Please visit the link below to complete the survey electronically. Thank you in advance for your help!

1. How do you prefer to receive updates from the MPN Research Foundation?
   A. Monthly email digest — MPNRF | Under the Microscope
   B. Our fall and spring newsletters
   C. Social media channels (Facebook, Twitter, Instagram)
   D. Other — Please explain

2. Would you like the amount of research in our biannual newsletters to:
   A. Increase
   B. Decrease
   C. It’s satisfactory

MPNRF.ORG/SURVEY
Research on myeloproliferative neoplasms has picked up heavily over the last few years. There are several MPN clinical trials under way. The trials listed below are currently enrolling patients and may be of interest. A complete list can be found on our website: www.mpnresearchfoundation.org/Clinical-Trials.

The trials listed below may be of interest as they are currently enrolling patients:

**9-ING-41 in Myelofibrosis**
- **Sponsor:** Actuate Therapeutics Inc.
- **Contact:** Francis J. Giles, MD fgiles@actuatetherapeutics.com
- **Diagnosis:** Myelofibrosis
- **Status:** Not Yet Recruiting

**CPAP Treatment**
- **Sponsor:** University of Utah
- **Contact:** Catherine Cromar Catherine.cromar@hci.utah.edu
- **Diagnosis:** CALR Gene Mutation Essential Thrombocythemia JAK2 Gene Mutation MPL Gene Mutation Obstructive Sleep Apnea Syndrome Polycythemia Vera
- **Status:** Recruiting

**Momelotinib**
- **Sponsor:** Sierra Oncology, Inc.
- **Contact:** Ashwin Swami, MD, MBA aswami@sierraoncology.com
- **Diagnosis:** Primary Myelofibrosis Post-polycythemia Vera Myelofibrosis Post-essential Thrombocythemia Myelofibrosis
- **Status:** Recruiting

**Vactosertib**
- **Sponsor:** Weill Medical College of Cornell University
- **Contact:** Joseph M Scandura, MD PhD jms2003@med.cornell.edu
- **Diagnosis:** Myeloproliferative Neoplasms
- **Status:** Recruiting

**PRT543**
- **Sponsor:** Prelude Therapeutics
- **Contact:** CANN.REFMAL605@SarahCannon.com
- **Diagnosis:** Relapsed/Refractory Advanced Solid Tumors Relapsed/Refractory Diffuse Large B-cell Lymphoma or Mantle Cell Lymphoma Relapsed/Refractory Myelodysplasia Relapsed/Refractory Myelofibrosis
- **Status:** Recruiting

**Pacritinib**
- **Sponsor:** CTI BioPharma
- **Contact:** Sirin Artan Kahrs, MD sartankahrs@ctibiopharma.com
- **Diagnosis:** Primary Myelofibrosis Post-polycythemia Vera Myelofibrosis Post-essential Thrombocythemia Myelofibrosis
- **Status:** Recruiting

What services insurance companies cover or deny. A visit to your doctor for symptoms such as fatigue and itching will likely only appear as a “doctor visit” unless the clinician included detailed notes, and those notes are included in the data dump and analysis. Similarly, insurance claims data shows that a visit was made. No detail will be included about the reason for the visit. Data from wearable devices provides insight into the activities (or inactivity) of patients, and sometimes details like heart rate, calories burned and, if the user records details in a linked app, intake of food and beverages include calorie and fat counts.

Generally, the RWD mentioned above are passively collected data sources. Patients are not aware that their data is being used for means other than that which it was originally intended for (clinician record keeping, claims processing or fitness/food tracking). In fact, unbeknownst to the patient those data are de-identified, mined, and used for many different purposes; both commercial and research.

Meanwhile, detailed quality of life and health event data collected through a registry like myMPN is entered by the patient, and used exclusively for research and to move treatments for a disease forward faster. It will likely have a more complete accounting of the true patient experience.

In summary, patient reported data is the most powerful and complete of all RWD sources in informing the decisions of research, regulatory bodies and drug companies!

So don’t forget to log in to myMPN and update your profile with the latest on how you are feeling and any recent health events, so that the value of the data continues to grow! If you haven’t yet started with myMPN, there’s no time like the present – visit the registry at www.myMPN.org or www.mpnrf.org/mympn-register.
The MPN Interferon (IFN) Initiative is a multi-year program launched in December 2017. The goal is to work collaboratively to understand how IFN works in achieving remissions in some MPN patients, and why it doesn’t work in others. This should lead to better patient selection for IFN therapy and possibly new therapeutic strategies. This initiative has four active projects. Investigators work closely with MPNRF staff and a distinguished group of academic advisors to track progress, get feedback and promote collaboration. The third year of this initiative is now underway. Below is a brief summary for each project:

**Overcoming resistance to interferon in MPN stem cells**

Ann Mullally, (Boston MA) Steven Lane, (Brisbane, Australia) and Michael Milsom, (Heidelberg, Germany)

Model systems of myelofibrosis have been developed to study the effect of IFN treatment on hematopoietic stem cells. Secondary mutations found in some MF patients such as DNMT3a can be introduced in these models to study the impact on IFN resistance. Patient samples from a study of 24 months of IFN treatment have been sequenced for 100 commonly mutated genes in myeloid disease. Distinct patterns of response to IFN in JAK2-mutant MPNs as compared with CALR-mutant MPNs were found. DNMT3a mutations were the most frequent acquired mutations at 24 months and enriched in patients treated with IFN.

**Mechanism of action of interferon alpha in MPN therapy**

Jean-Luc Villeval, and Isabelle Plo, (Villejuif Cedex, France)

Multiple approaches are being employed to better understand how IFN works and which drugs may work best in combination. For example, which JAK2 inhibitors might work best with IFN and why, and data to support the use of arsenic in combination with IFN. New model systems and patient samples are being used to understand why patients with JAK2 mutations respond better to IFN than patients with CALR mutations.

**Novel agents for the treatment of malignancies**

Leon Platanias, (Chicago IL)

The goal is to identify proteins present in IFN signaling complexes that are also up-regulated in MPN patients, which might represent new therapeutic targets to enhance the effect of IFN. Several proteins have been identified and studies are ongoing to characterize the impact of knocking down these proteins on the IFN response in cell lines and patient samples. The plan is to examine whether gene expression levels or mutations of these proteins correlate to the IFN response in patient samples. Ultimately, targeted inhibitors of these proteins will be used or developed to further characterize their impact on the IFN response.

**Using a vascular niche platform to develop interferon-based strategies to eradicate MPN stem cells and phenotypes**

Joseph Scandura, (New York, NY)

A cell-based blood formation factory has been established to study the development of mature blood cells from stem cell precursors. The system has been used to evaluate the impact of IFN treatment on blood cell lineages directly in the culture system using individual patient samples and will now be used to evaluate various drug combinations with IFN and/or the selective knockout of relevant genes.

---

**myMPN**

A research program designed to collect information over time from patients living with Essential Thrombocythemia, Polycythemia Vera and Myelofibrosis

ET, PV and MF patients are invited to share their diagnosis, ongoing symptoms and changes in health status via surveys in myMPN. The information provided can be used by researchers to develop better treatments for MPNs AND by patients in doctor appointments to bring them up to date on symptom burden and quality of life.

Visit myMPN.org today to get started
**MPN PATIENT BILL OF RIGHTS**

This Bill of Rights helps establish and promote awareness of core elements that are crucial to quality MPN care. It is our hope that patients will use this document to learn about their disease and participate actively in their care.

### AS AN MPN PATIENT, YOU HAVE THE RIGHT TO:

1. **Receive a Clear, Understandable Diagnosis, and to Seek a Second Opinion from an MPN Specialist.**

2. Ask your doctor to communicate your treatment plan (and its potential implications) in a way you understand.

3. Be informed as to how your diagnosis and treatment may impact your reproductive health.

4. Access medications and treatments deemed appropriate by your doctor, not your insurance.

5. Find sources of financial information and assistance, understand how your insurance company prioritizes care, and how you can submit multiple appeals if your insurance denies a test, treatment or appointment.

6. Access accurate information from reputable sources including academic institutions, healthcare professionals, patient advocacy organizations, online patient communities and elsewhere.

7. Keep your doctors informed about symptoms affecting your quality of life, and receive information directed at improving those symptoms.

8. Include your caregiver(s), family, and friends in consultations with healthcare teams.

9. Disclose or not disclose your diagnosis to your employers and prevent or stop unlawful discrimination or judgment due to your condition.

10. Access clinical trial information and participate in those trials if you meet the eligibility criteria.

**LEARN MORE AT MPNRESEARCHFOUNDATION.ORG**

Created in partnership by The MPN Research Foundation, MPN Advocacy & Education International, The Leukemia & Lymphoma Society, MPN Education Foundation, Patient Power, Cancer Care, National Organization for Rare Disorders, Cancer Support Community, and PV Reporter.
DID YOU KNOW THAT CHARITY EVENTS HELP DRIVE DONATIONS?
Help The MPN Research Foundation create awareness, encourage charitable giving and plan a DIY fundraising event to support members of the MPN community.

JOIN THE FIGHT. JOIN TEAM MPN.
Team MPN members participate in marathons, triathlons, art shows, bake sales, cycling events, long-distance hikes - anything - all to support MPN research! You can even pledge your birthday in lieu of presents. It’s simple and your event’s donations can make an impact on funding research and helping us connect patients in the MPN community.

4 EASY STEPS
STEP 1: COME UP WITH AN IDEA THAT SOUNDS FUN AND DOABLE FOR YOU!
Is there an athletic event you’ve been eyeing and you need a cause? Maybe you don’t want to participate in an athletic event. Do you want to organize a bowling game for charity? Maybe plan a bake sale or host a game night at your home? Tired of the same old birthday celebration? Pledge your birthday to MPNRF and have friends honor you with a donation to us. Lots of possibilities to host and raise awareness.

STEP 2: CONTACT PAM SOTO TO LET US KNOW WHAT YOU’RE PLANNING AT PSOTO@MPNRF.ORG
Once you have picked a date and decided on your event, be sure to email us so we can start planning.

STEP 3: EASILY CREATE YOUR ONLINE FUNDRAISING PAGE
We will create a personalized fundraising page so you can tell your own story and collect pledges for the Foundation. We partner with you to set up all the details including messaging, photos, and a donation link. After your event, we share information on how the funds will be used.

STEP 4: COMMUNICATE AND NETWORK - SPREAD THE WORD!
Post and Re-Post! The Foundation is constantly posting on social media about news and ways people can support our efforts. Comment and repost as much as possible so your friends and family can see the great work we do.

So, let’s go...Create a Team MPN Event and raise funds for research and the MPN Community! If you are interested, please contact Pam Soto, Director of Individual and Major Giving at psoto@mpnrf.org or 312.683.7249.

MPNRF WELCOMES NEW MEDICAL AND SCIENTIFIC ADVISORS AS JOHN CRISPINO STEPS DOWN

Michelle Woerle, Executive Director
MPN Research Foundation is excited to announce the addition of two new Medical and Scientific Advisers. Raajit Rampal, MD, PhD of Memorial Sloan-Kettering Cancer Center and Robyn Scherber, MD of University of Texas Mays Cancer Center will carry on where John Crispino, PhD, leaves off in advising the Foundation on programmatic and strategic matters. Dr. Crispino is moving from Northwestern University to St. Jude Children’s Research Hospital, where he will continue his research activities including work on the potential benefits of Aurora-Kinase inhibition for patients with myelofibrosis. Dr. Crispino will remain a close friend and advisor to MPNRF and will retain his position on our Scientific Advisory Board.

Over the years, Dr. Crispino has worked alongside MPNRF’s leadership, including Bob Rosen, Dr. Andy Schafer, Weil Cornell and our Scientific Advisory Board (SAB) on seven annual MPN roundtable meetings and multiple grant reviews, in addition to other MPNRF-led scientific meetings focused on topics such as CRISPR gene editing and immunotherapy. Since 2009, he has helped mold the direction of many Foundation projects, and we wish him continued success at St. Jude.

“It’s been an honor advising the Foundation over the past 10 years,” says Dr. Crispino. “In that time, we have witnessed many advances in our understanding of the molecular basis of the MPNs, but we remain short of our goal of providing a cure for patients. I look forward to continuing to aid the Foundation in its mission to foster research in this disease.”

With John’s departure, the Foundation has decided to expand the role of scientific advisor to include both clinician and basic/translational research perspectives. Two individuals were quickly identified who could take on this role. Raajit Rampal and Robyn Scherber have both been assisting the Foundation in some capacity already; Dr. Rampal as part of the Foundation’s vetting of projects related to progression in MPN, and Dr. Scherber as the co-PI of the myMPN patient registry.

They will be working alongside the Foundation’s SAB, chaired by Dr. Schafer, and be available to the Board and staff for strategic direction around programs or questions raised by our stakeholder community.
Described by her close friends and family as adventurous, brave, and generous, Susan Protter would live more than twenty years with her MPN. But she wasn’t one to let the grass grow under her feet. As a native New Yorker, she enjoyed an active lifestyle. Her father taught her to sail at a young age on the Long Island Harbor on his 43-foot schooner, fittingly named after his daughter. As an adult Susan frequented the NYC Opera, enjoyed hosting out of town family, meeting up with friends as often as she could, and of course, traveling.

“She loved to travel the world, but she wanted adventure,” says her cousin, Dr. Steven Nemerson. “She went to the Middle East and Africa and always wanted to get to know the people where she traveled, especially meeting those who were less fortunate and of other cultures. It was interesting to her that others around the globe who didn’t have certain luxuries were still so happy.”

As a young adult, Susan got into the publishing industry and then transitioned into representing writers, eventually becoming one of New York’s first independent literary agents. She represented hundreds of authors throughout her career.

However, in 2012, Susan began to juggle a steady stream of doctor appointments as her health declined. She would undergo an aortic valve replacement, back surgery, treatment for kidney cancer, which later reemerged in the lungs and brain, and then deal with the effects of being legally blind. Yet Susan’s will remained strong, and she proved that she could adapt to changing conditions; perhaps a lesson embedded within her from those early days on the Long Island Sound with her father. When she lost her eyesight, it was no surprise that she taught herself braille and later join the New York Braille Society.

At the end of her life, Susan left a multi-million dollar donation to the MPN Research Foundation to continue the study of MPNs.

“Given her lifelong commitment and sense of generosity to people who are less fortunate, this cause became very meaningful to her,” Steven added. “She felt that the MPN Research Foundation was very helpful in providing insight to her doctor for her treatment.”

Julia Cooper-Smith, Susan’s close friend of over 40 years and fellow literary agent says of her late friend, “She was very courageous and faced her illness amazingly, but she knew there wasn’t enough research being done in MPNs. I think she wants her gift to the Foundation to, in the short term, make patients more comfortable and in the long term improve another person’s chances of beating this cancer.”

Steven recalls a funny moment that characterizes Susan’s personality. “We were all going out for milkshakes in the city and my daughter was pushing Susan in her wheelchair. Before we knew it, Susan went flying out of the wheelchair when my daughter hit a bump in the sidewalk. We were all horrified, but Susan just laughed, she handled it like a good sport. She managed her illness with humor and courage.”

“There are uncommon disorders,” says Steven. “Researchers are still learning about them, and the interesting thing is, it’s not as though they all have the same genetic cause and manifestation. A patient’s complications are different, the spectrum of intensity is different, and we know the longer a patient lives with an MPN, generally the worse their symptoms become.

The treatments for MPNs is pretty crude, compared to other cancers that have more refined therapies. MPNs are notoriously underfunded and there’s a lot left to be learned. For example, are there environmental influences? There’s still a lot of work to be done, and this isn’t just an older person’s disease. We’re now seeing that it’s more common than previously thought among children, and young adults.”

Susan provided for this research in her last will and testament. Her bequest is already supporting important work such as a new grant to Dr. Ann Mullally for her work on progression through Dana-Farber’s Center for Prevention of Progression (CPOP) initiative, and much more to come.

The Foundation’s plan is to honor Susan’s wishes to hit at both the immediate and long-term needs of people living with an MPN. Her generosity affords us flexibility to fund beyond our current limitations and hopefully make dramatic gains on the quality of life and options for people with an MPN.

In short, Susan’s gift will change the world.

By remembering the MPN Research Foundation in your estate plans, you will help all of us find a cure for MPNs. We understand that including the MPN Research Foundation in your will represents a deep commitment. With a gift through your estate, you will be supporting our efforts until we find a cure.

We can provide you with the language to include the Foundation in your Will. We can also talk with you or your financial advisor about a wide variety of options. For more information, contact William Crowley at 312-683-7226 or wcrowley@mpnrf.org.