

## WHERE DO WE GO FROM HERE? 2012 ASH MEETING SUMMARY

*By Barbara Van Husen*

It's hard to believe today that in 2000, when the MPN Research Foundation began its work, MPNs were largely ignored by the scientific community. They were often under- or misdiagnosed, and the first Internet patient discussion groups were frustrated by the lack of understanding among clinicians and the lack of treatment alternatives.

It was in this world that the MPN Research Foundation made its first grant in 2000.

In 2005, when the JAK2 mutation was discovered, things really took off. And the MPN Research Foundation was ready to move this discovery forward by funding the preclinical testing that is now leading to FDA approved treatments that were only a dream a few years ago. With a total of 38 grant awards totaling almost \$9 million, the Foundation has been a powerful force in MPN research.

### **The MPN World Has Changed – But Not Enough**

But as rapid as this progress has been, we all know the work is far from done. Emerging drugs improve patient conditions but do not (yet) alter the course of the disease. Patients are still concerned about disease progression and the potential for conversion to acute leukemia. And the only true cure is still bone marrow transplant, a high-risk procedure that is not available to all MPN patients.

On the positive side, there are now many academic researchers working on these questions. And with FDA approval of new drugs for MF, industry is now mobilizing to invest in MPN science. (See article on page 3.)

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*By John Crispino, PhD  
Scientific Advisor*

The December 2012 ASH meeting provided important updates on clinical trials for JAK inhibitors as well as insights into novel alternative therapies. In addition, there were several exciting pre-clinical advances that suggest new targets for therapies for the MPNs.

### **Ruxolitinib Delivers Modest Increase in Survival**

Ruxolitinib, a dual JAK1/JAK2 inhibitor, has been on the market for over a year and has shown efficacy in reducing the constitutional symptoms in patients with myelofibrosis. However, it has been unclear whether Ruxolitinib alters the natural history of the disease, provides a survival advantage, reduces the allele burden, or improves bone marrow fibrosis.

An update on the Phase III COMFORT trials provided some exciting news. Most importantly, the survival advantage reported at the 2011 ASH meeting has been confirmed in the extra one year follow-up: patients taking Ruxolitinib show a modest, but significant, increase in overall survival.

In addition, the Ruxolitinib response has been durable and there is evidence of gradual reductions in allele burden. The drug may extend survival by reducing cachexia, which is associated with weight loss, loss of appetite, fatigue and other symptoms commonly seen in myelofibrosis.

Despite the good news, it remains unclear to what extent the drug halts or reverses bone marrow fibrosis. Moreover, the most frequent adverse events reported include anemia or thrombocytopenia. Preliminary Phase Ib data, however, suggest that lower doses of ruxolitinib are effective at reducing spleen length and generally well tolerated in myelofibrosis patients with low platelet counts (between 50,000 and 99,000).

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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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## MY AWESOME DAD

*By Molly Rosen Guy*

In the summer of 1997, in between my sophomore and junior year of college, I remember walking across Wells Street Bridge in Chicago with my Dad – Robert Rosen. He was talking about some numbness he'd been experiencing in his fingertips.

"I don't know what's going on," I remember him saying. "I've seen a bunch of doctors, but no one seems to have any idea." He seemed very scared.



Molly Rosen Guy and daughter Sunny.

A few months later, during Thanksgiving dinner, my Dad told me and my two siblings that the numbness had traveled to his toes and gotten much worse. He told us he'd been bouncing around from doctor to doctor, and no one had been able to tell him what was wrong. I remember hearing the word leukemia, a lot of whispering, I remember seeing mascara tears on my Mom's pillow. Needless to say, it was a really terrible time in the Rosen family.

I grew up with a Dad who worked in real estate, who left the house every day at dawn in a tight tie, with a packed briefcase. He was not (much like every other member of both my immediate and extended family) – a nonprofit guy, a science guy, a medicine guy, or a numbers guy, to say the least. He was a pragmatic, 9-5 businessman who spent his days making deals and bossing people around in a crisp starched shirt. Very different from the Dad I have today.

In the past thirteen years, I've watched my Dad grow the MPN Research Foundation from a teeny, tiny little seed of nearly nothing into an esteemed research and advocacy organization that has awarded almost nine million dollars to promote, fund and support the most innovative and effective research into the causes, treatments, and potentially the cure

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## WHERE DO WE GO FROM HERE?

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### Time to Reassess/Recalibrate/Refocus

As the MPN world, once so quiet and empty, becomes more filled with activity, the MPN Research Foundation felt the need to review its activities to determine what our mission should be in the years to come. The results were clear:

- The Foundation **must continue to fund innovative research**, especially with new investigators, until effective treatments are delivered to patients. Reduced funding by NIH and other sources makes our dollars, focused specifically on MPNs, critical.
- The Foundation should work to **bring scientists, clinicians, industry and patients together** to identify unmet needs and opportunities, and to disseminate information broadly and clearly.
- The Foundation should move aggressively to **raise the funds needed** to have a significant impact on the advancement of research.

So the MPN Research Foundation is now rededicating itself to its roots: **to stimulate original research in pursuit of new treatments and eventually a cure for MPNs**. To accomplish this, we must increase our fundraising significantly. Without this investment, we believe important areas of research will be missed, and the potential MPN scientists of the future will direct their energies elsewhere.

We are also determined to bridge the gap between academic science and the biotech and pharmaceutical companies that ultimately deliver solutions to patients. We have high expectations for the resulting acceleration of progress.

### **Please Join the Many MPN Patents, Family Members, Friends and Caretakers Who Are Helping Us Help MPN Patients Everywhere**

The MPN Research Foundation looks forward to the day we can stop sending fundraising letters, close the door, and turn off the lights. But although there is much to be hopeful for, that day is not here yet. Please join our many contributors throughout the MPN community by making a donation to the Foundation at **[www.mpnresearchfoundation.org](http://www.mpnresearchfoundation.org)**.

## BIOTECH AND PHARMACEUTICAL COMPANIES JOIN IN FUNDING MORE MPN RESEARCH

*By Barbara Van Husen*

One of the biggest challenges facing the MPN Research Foundation in its mission to broaden and accelerate MPN research is raising enough dollars to really make a difference.

We have historically relied on donations from individuals, more specifically MPN patients, families and friends, to make our grants.

We have long considered the potential of raising money from industry – specifically the biotech and pharmaceutical industries – to augment the funds we have available for research. We are therefore happy to announce that two major pharmaceutical companies (Incyte Corporation and Sanofi Oncology) have agreed to join our research effort by donating funds that will be used to augment the money we raise from individuals.

MPN Research Foundation will provide no goods or services in return for these donations, and the companies will not be involved in the solicitation or review of grant proposals or in the selection of grants to be awarded. For details, see our formal commitment to product and company neutrality at [www.mpnresearchfoundation.org/Corporate-Sponsors](http://www.mpnresearchfoundation.org/Corporate-Sponsors).

We will recognize these companies as donors to our grant programs, and hope that over time more companies will join the ranks as Industry Partners of the Foundation.

We also hope that our increasingly collegial relationships with these companies will allow us to actively bridge the gap between academia and industry, so that the research we fund actually reaches the patients we support as new and effective treatments.

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Another update presented data from a Phase II study of Ruxolitinib in PV. This small study demonstrated that Ruxolitinib provided a sustained improvement in patients resistant or intolerant to hydroxyurea. Effects included improvement in constitutional symptoms, modest decreases in the allele burden, and impressive reductions in peripheral blood counts.

### **Cytosia (Now Gilead Sciences) JAK Inhibitor Shows Durable Benefits**

An extended study of the Phase II trial of CYT387 reported safety and efficacy data, which confirmed last year's report that the JAK inhibitor provides benefit to patients with myelofibrosis. Specifically, patients displayed a durable response with symptomatic improvement and a reduction in spleen volume.

Unlike Ruxolitinib, CYT387 provided a benefit to patients with anemia in this trial: among the 33 patients who were transfusion dependent, nearly 70% achieved a minimum of a 12-week period without transfusions and some remained transfusion free for more than 2 years. Overall, there was a 48% anemia response rate. This update provides optimism that CYT387 will confer an important therapeutic benefit in myelofibrosis. Nevertheless, a Phase III trial is required to confirm the anemia response in a much larger cohort of patients.

### **Sanofi (Formerly TargeGen) JAK Inhibitor May Benefit Patients With Low Platelets**

SAR302503 continues to show promise in clinical studies. Results from a Phase II study confirmed activity in reducing splenomegaly and improving constitutional symptoms. The most common hematologic side effect is anemia.

Surprisingly, SAR302503 treatment was associated with a low incidence of thrombocytopenia. This curious finding suggests that the drug will be useful in patients whose platelet counts are low. Data from an ongoing Phase III trial should be released in 2013.

### **PI3K Pathway Inhibitors Enhance Performance of JAK2 Inhibitors**

There were several presentations regarding the use of PI3K inhibitors. These drugs target a signaling pathway that is related to, but distinct from, JAK/STAT.

In one presentation, pre-clinical studies demonstrated that a class of these compounds known as "Pan-PI3K" inhibitors showed the best synergy with Ruxolitinib. Mice treated with one of these compounds, GDC0941, in concert with Ruxolitinib showed drastic reductions in spleen weight and decreased growth of endogenous erythroid colonies (ones that do not rely on cytokines due to activated JAK/STAT signaling).

In an impressive related study, the PI3K inhibitor BEZ-235 was shown to strongly cooperate with Ruxolitinib in MPN cell lines, primary patient samples and in animal models of MPNs.

Together these results provide a strong rationale for opening human trials to test the combination of PI3K pathway and JAK inhibitors.

### **HDAC Inhibitor Shows Benefits, Problems**

Histone deacetylases are enzymes that modify the structure of DNA and also control the stability of some cellular proteins. This year, the results of Phase II trials of this class of drugs in PV and ET patients were presented.

In one study, a Phase II trial detailed the activity of the drug Vorinostat as a single agent. Vorinostat normalized white blood cell and platelet counts in many patients and also showed a significant reduction in allele burden. However, more than 50% of the patients dropped out of the study due to side effects.

Nevertheless, the observation that the drug was effective at reducing the tumor burden suggest that combining it with a JAK inhibitor and using it at a lower dose may be beneficial.

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### **HSP90 Inhibitor Reduces Fibrosis in Animal Models**

HSP90 is a protein that regulates the stability of proteins. A previous study demonstrated that HSP90 inhibition led to a selective degradation of the mutant form of JAK2 and to reduced disease burden in a mouse model of MPN.

A new report presented at this meeting revealed that the HSP90 inhibitor PU-H71 cooperated with a JAK inhibitor to provide pathologic improvement, a reduction in fibrosis and reduced JAK/STAT signaling without increased side effects in animal models. These results provide a strong rationale for combination studies of HSP90 and JAK inhibitors.

### **LOXL2 Inhibitor Shows Promise**

LOXL2 is a protein that has been implicated in cancer progression and fibrosis including that of the bone marrow. A conversation between the MPN Research Foundation and Gilead Sciences revealed that the company is developing a LOXL2 inhibitor that may be a promising agent. Stay tuned for more information.

### **Pomalidomide Modestly Effective in Reducing Transfusion Dependency**

This drug acts as an immunomodulator that shows efficacy in multiple myeloma. In addition to papers that described its use in myeloma, there were multiple presentations regarding its use in the MPNs.

Previous reports have suggested that pomalidomide improves anemia and reduces the need for red blood cell transfusions in patients with myelofibrosis. This year's meeting included two reports of trials that combine a low dose of pomalidomide with the corticosteroid prednisone.

In both cases, pomalidomide showed modest efficacy with some patients becoming transfusion independent during the study. A Phase III trial is underway.

### **PRM151 Effect on Bone Marrow Fibrosis to Be Studied**

This is a drug under development by Promedior, a biotechnology company seeking to develop new treatments for fibrosis, such as idiopathic pulmonary fibrosis.

In a discussion with the MPN Research Foundation, the company revealed that it plans to open a study of this investigational drug in bone marrow fibrosis.

It is believed that the drug works by regulating monocyte-derived cells that contribute to the fibrotic process. Stay tuned for updates on clinical studies of PRM151 in the MPNs.

### **Telomerase Polymorphism and Therapeutic Benefit**

Telomerase is an enzyme that repairs the ends of chromosomes after cell replication. Studies have revealed that telomerase is hyperactivated in tumor cells.

Two studies at the meeting reported on telomerase in the MPNs. In one paper, the company '23 and me' reported the identification of a new polymorphism (a difference in the DNA sequence among different individuals in a population) associated with the MPNs in TERT, the gene that encodes the telomerase reverse transcriptase.

Although it is unclear how this variant would contribute to the MPNs, the observation is interesting because of the existence of a telomerase inhibitor under development by Geron Corporation.

Imetelstat, a first in class telomerase inhibitor, is under study in a Phase II trial in patients with ET who are refractory or intolerant to prior therapy. In this small trial, Imetelstat showed robust activity against the megakaryocyte lineage, with significant reductions in platelet counts in the majority of patients.

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A reduction in JAK2 mutant allele burden was also seen in the majority of JAK2 V617F positive cases. Although it remains unclear why the drug appears to selectively affect platelet-producing cells, the Phase II data suggest that the drug may have efficacy in ET.

### Scientific Talks of Note

Dr. Jerry Spivak of Johns Hopkins University discovered that MPL, the receptor for thrombopoietin and regulator of megakaryocyte production, is required for PV in mouse models.

This result is surprising in that MPL is generally not associated with red blood cell production. It is likely that the requirement for MPL is at the hematopoietic stem and progenitor level. This observation suggests that reducing the activity of MPL, perhaps by reducing thrombopoietin levels, may have therapeutic benefit in the MPNs

Multiple presentations described the use of next generation sequencing to identify novel mutations in the MPNs. Although these talks did not discuss the identities of new mutations, we should be optimistic that potential new targets for therapy will be revealed in the near future.

#### **MPN Research Foundation Update**

is 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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## HATS OFF TO DR. JOHN CRISPINO!

*By Robert Rosen*

Dr. John Crispino, scientific advisor to the MPN Research Foundation, was recently invested as the Robert I. Lurie MD and Lora S. Lurie Professor of Medicine at the Northwestern University Feinberg School of Medicine, and as associate director of education and training at the Lurie Comprehensive Cancer Center of Northwestern University.

We've known about John's impressive qualifications for years, and his contributions to the foundation are invaluable. Over the past decade Dr. Crispino and members of his lab have made many important contributions to improve the understanding of mechanisms of normal and malignant blood development.

John, congratulations from all of us at the MPN Research Foundation.





Jaclyn and JoAnn Mason

## ELEGANT RECEPTION HONORS MPN RESEARCH FOUNDATION DONORS

*By Ann Brazeau*

Last October, JoAnn and John Mason hosted a reception in honor of their many friends and colleagues who have so generously supported the MPN Research Foundation for several years. JoAnn, a Board member, has made an enormous impact on fundraising, specifically for polycythemia vera research.

The evening began with brief comments from Robert Rosen, founder and chair of the Foundation, Barbara Van Husen, president, and JoAnn.

JoAnn's daughter, Jaclyn, was diagnosed with PV in her teens. Since then, JoAnn has become actively involved in fundraising and advocating for better treatment options and hopefully a cure.

The Masons have raised substantial funds for polycythemia vera research, including a sizable grant to Dr. Shaoguang Li from the University of Massachusetts, who has been studying MPNs since 1996.

The support from the Masons and their friends and colleagues is already making a difference for the future of MPN patients. The reception was a wonderful way to acknowledge those supporters.

## WE'RE TIRED OF FATIGUE!

80% of blood cancer patients rank fatigue above pain as their chief complaint. Ever since the work of Dr. Ruben Mesa, Joyce Niblack and others was published six years ago, the extent and nature of Myeloproliferative Related Fatigue (MRF) have been known and stratified.

But little has been done to explore means to relieve that fatigue. Now The Fatigue Project, a cooperative program among patients, caregivers, and healthcare professionals, has come together to do something about it. The first step was a preliminary survey to provide information on patient-developed strategies to overcome fatigue.

Then Dr. Ruben Mesa at the Mayo Clinic and his team, including Matt Clark, PhD, Dr. Robyn Emanuel, and Amy Lou Dueck, PhD, supported by Dr. Claire Harrison of Guy's and St. Thomas' in London and Zhenya Senyak and psychiatrist Dr. Michael Goldstein of MPNforum, developed a formal questionnaire to be distributed on-line.

Their ultimate goal is to gather enough information to design a clinical trial to test interventional alternatives.

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## MY AWESOME DAD

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for ET, PV, and MF. He balances his roles as both chairman and patient with equanimity and open-mindedness.

He no longer wears a suit to the office, although he runs the Foundation with the same rigor and intensity he brought to his corporate life. Through working with the MPN community, my Dad has become a softer, more teachable version of the Dad I grew up with. He's learned to learn, and listen. Quite a far cry from being the real estate guy in a tie who had no clue why his fingers were numb.

It's been awesome to watch – both as his daughter, and as a recently elected MPN Research Foundation board member.

Happy springtime. Sending light and love to all of you and your families. Thanks for letting me part of your journey.



## ANNETTE DE BOW HITS THE TRAIL ONCE AGAIN!

Annette De Bow taking a rare break on the trail.

*By Raquel Nuñez*

When Annette De Bow hit the John Muir Trail in the High Sierras in her first mountain trek the summer of 2010, she didn't know what to expect. What she did know was that she had to start taking an active role in her own health.

Annette was diagnosed with Polycythemia Vera in the winter of 2008, six months after the birth of her daughter. After a year of coming to grips with PV, which she describes as “the joy of being a new parent combined with the shock and grief of a diagnosis,” Annette set her sights on contributing to efforts to find a cure. She became an advocate for her future. And Trek for a Cure was born.

Annette chose to combine her love of the wilderness with her need to take an active role in efforts to seek medical solutions to the rare disorders collectively called MPNs. In 2010 she took to the mountains, hiking the 240 miles of the John Muir Trail through the High Sierra for a little over 30 days. Friends and family joined her on the trail in shifting groups, each hiking for four days to a week.

Audrey Hicks, also diagnosed with PV, flew in from Canada to join Annette on the trail. Many more enthusiastically supported Annette's trek, and by the time she reached the summit of Mount

Whitney, the culmination of her expedition, she had raised \$30,000 to support the MPN Research Foundation's initiatives to find a cure for MPNs.

Annette is once again dusting off her hiking boots, heading into the wilderness and towards a cure for MPNs. This summer she will hike 190 miles from Lake Tahoe to the Yosemite Valley over a three week period. She wants you to join her.

Annette hopes to recruit more patients diagnosed with MPN's to participate in the trek. And with the second Trek for a Cure, she finds her thoughts and feelings run deeper. She told us, “I live with PV every day of my life, but it is not how I define myself. I feel revitalized in the wild country, and I feel invigorated knowing that together with many supporters we can contribute to finding a cure for my disease. I am not walking alone; many will be hitting the trail with me, supporting my efforts to make a positive contribution.”

If you don't think you are quite up to the hike, you can still support Annette every step of the way by making a donation at [www.trekforcure.com](http://www.trekforcure.com). At the site you can read more about the hike and about Annette's own story, and see photos from previous hikes. You can also sign up for a segment of the hike. Or click the donation button from the comfort of your home. You can also email Annette at [Annette@trekforcure.com](mailto:Annette@trekforcure.com).