

MF CHALLENGE EXPANDS REACH AND IMPACT IN 2014

When we began the MF Challenge in 2012, our focus was simple: to identify the cause(s) and potential treatments for fibrosis in the bone marrow, the key characteristic of myelofibrosis (MF). We began this program because in spite of the current high level of activity in MPN research, there were important questions that remained unanswered – and the most urgent were those associated with MF, the most virulent of the MPNs.

However, we have realized that much of the research focused on MF overlaps research for PV and ET. In fact, it's frequently hard to tell where one begins and the other ends. In all cases research is focused on some malfunction in the bone marrow, and discoveries in one area are highly likely to impact all the MPNs. As a result, we are renaming our grant program the **2014 MPN Challenge**.

The Big Question: What Causes Fibrosis?

The goal of the 2014 MPN Challenge is both to continue to search for the factor(s) that induce(s) fibrosis in bone marrow, and to identify new avenues of research that will strengthen the overall understanding of the cause(s) and potential treatments for all of the MPNs (ET, PV and MF).

Five Top Research Areas

We are requesting proposals in the following areas:

1. Fibrosis and the Bone Marrow Niche
2. CALR Mutation
3. Reducing MPN Allele Burden
4. Selective JAK2 Inhibition
5. Immunotherapy

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REPORT FROM ASH DECEMBER 2013

By John Crispino, PhD, Scientific Advisor

This year's American Society of Hematology (ASH) meeting provided a bittersweet update on the progress of JAK inhibition therapy in the MPNs. As many readers already know, the Sanofi JAK inhibitor, which had completed Phase 3 trials and was well on its way to the FDA for consideration, has been removed from the clinic. This disappointing news was accompanied by optimism, however, for the next generation of inhibitors.

Apart from news of this class of drugs, several groups reported on new potential therapies that would work alone or in combination with a JAK inhibitor. There were also several exciting new basic research discoveries, with the most notable being the discovery of a mutation in a gene encoding a protein named Calreticulin in the vast majority of ET and PMF patients who lack a JAK2 or MPL mutation.

BASIC SCIENCE DISCOVERIES

Discovery of New Mutation Explains Most Non-JAK / MPL MF and ET

Although JAK2 mutations were discovered seven years ago, and MPL mutations soon thereafter, the genetic changes associated with JAK2/MPL negative cases of the MPNs have remained elusive. At this ASH meeting, the laboratories of Dr. Robert Kralovics (with support of the MPNRF) and Dr. Tony Green reported mutations in Calreticulin (CALR) in the vast majority of JAK2/MPL negative ET and PMF cases.

CALR is a protein that controls the stability and folding of other proteins in a cell. While it remains unclear how the mutations lead to MPNs, they may act similarly to

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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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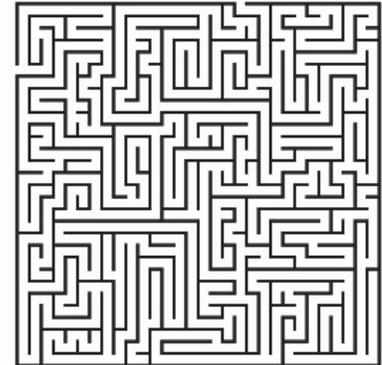
Hugh Rosen, PhD

The Scripps Research Institute

WHERE WE ARE NOW AND WHERE WE ARE GOING

By Robert Rosen

As a kid my parents would frequently bring me puzzle books, which I would devour and which were always preferable to homework. A maze was always my favorite. You could see the beginning and easily see the end, but getting there was the challenge.



I feel like the state of MPN Science today is akin to finding yourself in the middle of the maze. When we started the foundation we saw the opening. That was easy. There was a vast uncharted territory of unmet scientific needs. Any forward movement was sure to advance the science. We knew little else.

Now the maze looks different. We've advanced through twists and turns, the dead ends and the opening corridors. We generally can see where the end might be and what would constitute successful navigation towards scientific advancement, better treatments and a cure.

A correct choice at one junction led to the discovery of the JAK2 mutation. Another turn led us to the CALR mutation discovery. We feel hopeful that each correct move will bring us closer to the end. Happily we get JAK 2 inhibiting drugs, and multiple new treatments in the pipeline.

Other turns take us to new mechanisms of action. The CALR discovery shows a new mechanism of action with a high probability of translation to a new treatment. PRM151 and Imetelstat are in clinical testing. The MPNRF is funding preclinical testing of a new (for MPNs) drug that is currently showing good activity that might lead to early clinical trials.

Some forays appear to be headed in the right direction but leave us with disappointment and false hopes. Drugs like SAR302503 fail clinical trials even after early successes, others are slow to get off the ground, and still others are based on faulty assumptions. We are only partway down these passages and don't yet know where they will lead.

We acutely sense where the maze is leading, we turn left and then right and we move towards our goal. We are helping our scientists find their way through the labyrinth, slowly but surely making their way to improved health for us all.

FAMILIES FUNDING RESEARCH

By Jo Ann Mason

When our daughter Jaclyn was diagnosed with Polycythemia Vera (PV) she was in her teens. We knew very little about the disease or what it might mean for the future. We felt very alone and lost and not sure what to do. After doing some research, I discovered the MPN Research Foundation. The Foundation very quickly reached out and gave us information about Jaclyn's diagnosis. While PV has been a challenge for our family, Jaclyn continues to do well.

I felt it was important that we do our part in supporting the MPN Research Foundation's efforts to fundraise and advocate for new treatment options and a cure. With the help of our many friends, we have raised substantial funds for Polycythemia Vera research, and we can report a significant step forward.

Revealing the Potential of Alox5

Dr. Shaoguang Li from the University of Massachusetts received a sizable grant, and the results of his research are very encouraging.

Dr. Li's research has targeted an enzyme, labeled Alox5. By using a drug already approved by the FDA for asthma, Dr. Li's research with laboratory mice showed that the drug weakens PV. This discovery may lead to a new treatment option for patients like Jaclyn.

Because of sequestration cuts and a very competitive funding process from the National Institutes of Health and National Cancer Institute, Dr. Li had few options to get his research funded. This breakthrough would not have been possible without the support of the MPN Research Foundation.

2011 GRANTS RESULT IN MAJOR DISCOVERIES

Toward the end of 2013 we completed a final review of our 2-year grants awarded in 2011, and we are pleased to say that this group of grants has been truly productive.

As discussed in this newsletter, one 2011 grant (to Robert Kralovics of Vienna) resulted in the discovery of a gene mutation (CALR) that occurs in virtually all JAK2-negative ET and MF patients. This opens up exciting new avenues for research and the hope that therapies based on this discovery can be made available to patients.

In addition, our 2011 grants have identified at least one other new candidate drug for PV patients, which is currently finishing preclinical testing in preparation for clinical trials in humans. This drug, which is already FDA-approved for other diseases, is an example of bringing advances in one area of medical research to bear on the MPNs.

As the MPN Challenge proceeds in 2014 we hope to further accelerate the transfer of information across groups of scientists for the benefit of all.



Jo Ann Mason and Dr. Srdan Verstovsek, Director of the Hanns Pielenz Clinical Research Center for Myeloproliferative Neoplasia at MD Anderson Cancer Center.

THE MF CHALLENGE FORUM: Bringing Academia and Industry Together to Discuss Unmet Needs in MPN Science

In 2012 the MPN Research Foundation, with the Leukemia & Lymphoma Society (LLS) as partner, instituted the MF Challenge, a grant program focused on understanding the causes of bone marrow fibrosis in MF patients, and identifying ways to halt and reverse it. In 2012 and 2013 the MF Challenge awarded eight Concept Grants aimed at bringing new ideas, approaches, and investigators to the subject of bone marrow fibrosis.

To date, the results are encouraging, and we will continue to seek new approaches in this area until outstanding questions are resolved. But in 2013 we began to realize that with the growing number of investigators working on this issue, we had a unique opportunity for discussion of fibrosis, combination therapies, and other yet-unmet needs in MF research. We also recognized that both academia and industry have a high interest in working collaboratively on this topic. We determined to bring these parties together.

First MF Challenge Forum Highlights Opportunities for Collaboration

In November 2013, the Foundation hosted the first MF Challenge Forum, a meeting to highlight work being done for the MF Challenge and to identify opportunities for collaborative work on MF treatments. Participants in this meeting included MF Challenge grantees (from both 2012 and 2013), other academic experts, and representatives from biotech and pharmaceutical companies with

an investment in the future of MF research.

The meeting was lively and productive. David Scadden of the Harvard Stem Cell Institute delivered a keynote speech that focused on interactions in the bone marrow niche. MF Challenge grantees presented initial results of their grant projects. And the entire afternoon was devoted to identifying areas of research that, if pursued aggressively, could accelerate MPN research and deliver new treatments.



Robert Rosen addressing the MF Challenge Forum.

Perhaps even more interesting were informal conversations among academic scientists and their counterparts in biotech and pharmaceutical companies, which will, we hope, result in some productive partnerships moving forward. Feedback from attendees was unanimously positive, and suggestions for making the meeting even more effective were gratefully received by the Foundation.

As a result of this discussion the Foundation has aimed its 2014 grant programs at a specific list of scientific targets with a potential big bang for the buck. And plans for the 2014 Forum are underway.

MF CHALLENGE EXPANDS

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Based on the response to MF Challenge RFPs in 2012 and 2013, MPNRF and LLS are encouraged to believe that “paradigm-shifting” strategies can be identified in many areas of cancer and basic biology research, which can be brought to bear in the search for MPN treatments.

These new strategies, in combination with currently emerging treatments, could truly change the course of these diseases.

Depending on the response to this RFP (i.e., if multiple proposals of sufficient potential to merit an award are received), we anticipate funding up to 10 awards in calendar year 2014.

MDS/MPN ROUNDTABLE BRINGS CHICAGO CLINICIANS TOGETHER

The MDS/MPN roundtable provides an opportunity for Chicago based clinicians to come together to discuss topics in the field of MDS/MPN medicine.

The 3rd roundtable, held at Rush University Medical Center, Chicago, featured a lively discussion about the role and timing of allogeneic stem cell transplantation in Myelofibrosis. We heard a Myelofibrosis case presentation from Dr. Andy Dalovisio. Next, Dr. Jamile Shammo gave a detailed approach to MF diagnosis and therapy. Dr. Toyosi Odenike followed with a presentation of Ruxolotinib and other treatments and strategies for myelofibrosis.

The intense dialogue at this meeting is a clear indication of clinicians’ interest in receiving information about different approaches to MDS/MPN medicine.



Michelle Woehrle, Deputy Director, MPN Research Foundation and MF patient Patrick Corcoran at OneVoice Against Cancer meeting in Washington, D.C.

NEW WAYS FOR US TO BE HEARD

By Michelle Woehrle and Patrick Corcoran

Our mission to push MPN research forward and find a cure for PV, ET, and MF has brought us to places we never expected, most recently the halls of Congress. In early 2014 we joined One Voice Against Cancer (OVAC), a coalition of organizations whose goal is to increase cancer research funding at the federal and state level. As part of this group, we have participated in several Lobby Days and meetings, providing the unique perspective of PV, ET and MF patients, caregivers, and researchers.

On March 12th, MF patient Patrick Corcoran and MPN researcher Dr. Michael McDevitt (Johns Hopkins) participated in the Grassroots Lobby day. They met with Congress members about their experience in the trenches of MPN.

The goal of this work is to promote the cause of MPNs in a way that hasn’t been done before. With new MPN drugs being brought to the FDA for evaluation, we feel we need to be part of these conversations. In addition, as we learn more we hope to be in a position to request additional funding for MPN research. We’re still in the formative stages of this work but hope to report back on positive movement later this year.

REPORT FROM ASH DECEMBER 2013

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activated JAK2 and MPL signaling in other MPN cases. Researchers are investigating how the mutations drive the disease and ways to inhibit the activity of the mutant protein.

Preclinical Insights Into Novel Therapies

Several groups reported other targets that may provide novel and effective therapies for the MPNs. Dr. Levine reported that a small molecule under development by Novartis inhibited the hedgehog signaling pathway, which is activated in MPN patients, and enhanced the anti-tumor activity of ruxolitinib in a mouse model.

Dr. Wen and colleagues demonstrated that targeting aurora kinase A, which leads to maturation of megakaryocytes, proved effective in both the MPL and JAK2 mouse models as well as MPN patient samples.

Finally, Dr. Li (funded by the MPNRF) reported that targeting Alox5, an enzyme involved in inflammation, attenuated PV in the JAK2 mutant mouse model.

Insights Into Leukemic Transformation

Tsuruta-Kishino and colleagues reported that loss of the tumor suppressor p53 cooperates with JAK2 V617F to promote leukemic transformation of MPN to acute leukemia. Importantly, data from Dr. Levine's group confirm this finding and further demonstrate that p53 loss is a frequent event in patients who transform to AML. This is a critical area of research that may lead to new strategies to prevent this progression.

JAK INHIBITORS

Ruxolitinib (Jakafi; Incyte): Dr. Mesa provided the 3-year update of patients in the COMFORT-I trial. The results show that ruxolitinib continues to show efficacy in reducing the constitutional symptoms in patients with myelofibrosis, including a durable spleen response.

Fedratinib (SAR302503; Sanofi): Dr. Pardanani

presented Phase 3 data that fedratinib showed significant improvement in splenomegaly and constitutional symptoms among myelofibrosis patients. Unfortunately, several patients developed serious neurological side effects, most closely resembling Wernicke's encephalopathy, a syndrome characterized by confusion, memory loss and imbalance. Due to these adverse events, Sanofi has suspended all clinical studies and has discontinued development of the drug.

However, there is optimism that other agents will show efficacy in patients who are resistant or intolerant to ruxolitinib.

Momelotinib (GS-0387 formerly CYT387; Gilead): Dr. Pardanani reported that this JAK inhibitor provides a durable spleen response, but more importantly continues to show the ability to confer transfusion independence to a substantial number of patients. In this study 68% of patients who were transfusion dependent achieved independence. The phase 3 study, which randomizes patients to momelotinib versus ruxolitinib treatment, is now open.

Pacritinib (SB1518; Cell Therapeutics): Results from a phase 2 trial, led by Dr. Verstovsek, showed that Pacritinib therapy led to a significant reduction in spleen size and was equally effective in patients with <100,000/mL platelets. A phase 3 study is currently recruiting patients.

BMS-911543 (Bristol-Myers Squibb): Dr. Pardanani reported that, similar to other JAK inhibitors, BMS-911543 induced rapid improvement in constitutional symptoms and splenomegaly. The drug was also effective in patients who were previously treated with a different JAK inhibitor. There was a modest decrease in JAK2 mutant allele burden in some patients.

LY2784544 (Lilly): This is a JAK2 selective inhibitor that reportedly shows dose dependent selectivity for JAK2 V617F signaling. Dr. Prchal presented data from a Phase 1 study in patients with PV, ET or MF that showed improvements

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in constitutional symptoms and spleen size in over 50% of patients. Overall, the drug was well tolerated, with GI and hematologic toxicities. There was an improvement in bone marrow fibrosis in some patients.

INCB039110 (Incyte): Dr. Mascarenhas presented data from a Phase 2 study of this JAK1 inhibitor in myelofibrosis. Since JAK1 mediates cytokine signaling and growth factors that are implicated in myelofibrosis, it may be another useful target for therapy. The drug was well tolerated and provided an improvement in spleen size and constitutional symptoms. Importantly, it preserved mean hemoglobin levels. This suggests that it may be a feasible alternative to a JAK2 inhibitor.

NON-JAK INHIBITORS

Telemorase Inhibitors

Dr. Tefferi presented data from a phase 1 study of Imetelstat (Geron Corporation), a telomerase inhibitor, in myelofibrosis. In the study of 33 patients, with 22 patients included in the efficacy analysis, four patients met criteria for complete remission and a fifth met criteria for partial remission. Of note, the complete responders displayed reversal of bone marrow fibrosis and 2 patients had evidence of molecular remission. Several patients became transfusion independent and others showed reductions in mutant allele burden. This study is exciting because it suggests that Imetelstat, unlike JAK inhibitors, may have significant disease altering activity.

Other Therapies

Given that JAK inhibitors do not cure patients, there is a rush to develop second agents that have disease-altering activity alone or when used in combination. These second agents include histone deacetylase, HSP90, Lox, and PI3K inhibitors. Furthermore, a recombinant protein named PRM-151 (Promedior) is under development as an anti-fibrotic agent.

MPNRF RESEARCHER FINDS MISSING GENE

We have always tried to put our research dollars where they will do the most good for MPN patients. This time, we scored a bullseye.

Funded by the MPN Research Foundation, Dr. Robert Kralovics, PhD, of the Research Center for Molecular Medicine in Austria, discovered the missing gene mutation responsible for MPNs in the vast majority of JAK2-negative patients.

That's a big deal, because it provides a new target for drug development. It also, for the first time, makes accurate diagnosis a sure thing; previously, it was largely a process of eliminating other possibilities.

It's also the beginning of a whole new era in MPN research, because no one yet knows exactly how the gene, Calreticulin (CaR), leads to MPNs.

Hear About His Discovery From Dr. Kralovics Himself

Recently Dr. Kralovics sat down with the MPN Research Foundation and gave a simple, understated description of his momentous discovery. Hear it in his own words at www.mpnresearchfoundation.org/Video-Updates.

The MPN Research Foundation has provided key support for virtually every major advance in MPN research since 2000.

– Andrew Schafer, MD, Director of the Richard T. Silver, MD Myeloproliferative Neoplasm Center at Weill Cornell and Chairman, MPN Research Foundation Scientific Advisory Board.

NOT A WARRIOR

By Lina

The use of the words “warrior” or “fighter” in reference to cancer patients baffles me. There are two implications with these words that bother me most.

First is the implication that this is a “battle” with an opponent who fights fairly. This is not true. Cancer does NOT follow any particular regulations. It does not conform to accepted rules of engagement. Cancer is mean. Cancer plays dirty. Cancer is not a fair fight.

Frankly, cancer is a jerk. Cancer is the bully on the playground, who is twice your size, steals your lunch money, and pushes you in the dirt. Cancer is an invisible thief who breaks into your life and steals your energy, your health, your peace of mind. But to me, cancer is not a battle.

Second is the implication that those who “lose the battle” against their cancer did not fight hard enough. This is also not true.

I am sure that there are those who disagree with this. That for some, approaching cancer as a battle to be won is comforting and reassuring. What I think we can agree on, though, is that cancer is cruel. It can hurt every aspect of your life. But it is a situation in your life from which you can learn. From which you can grow. From which you can draw strength.

Some of my biggest life lessons have come from cancer. I learned a lot about myself through my experiences, and it has truly made me who I am today. But I am not a warrior. My situation is not a battle. It is my life. I am myself; a patient, a wife, a sister, a daughter, a friend. And I am me.

As always, you are your own best advocate. Be assertive, be persistent. If you do not take care of yourself, who will?

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YOU’D BETTER HAVE A WILL IF YOU WANT YOUR WAY

By Bill Crowley

It’s almost impossible to overstate the importance of estate planning, regardless of the size of your estate or your stage of life. A few examples of what happens when you don’t plan carefully:

When Sonny Bono died in a skiing accident in 1998, he did not have a will or estate plan. His surviving wife had to petition the probate court to be appointed administrator, and had to deal with multiple claims against his estate.

Supreme Court Chief Justice Warren E. Burger prepared his own will (consisting of only 176 words), and neglected to address several issues that cost his estate over \$450,000 in taxes.

Actor Heath Ledger died with an out-of-date plan that didn’t include his companion, actress Michelle Williams, or their daughter, Matilda Rose. Luckily, his family agreed to provide for Matilda Rose, but not without some family disharmony.

If you don’t have an estate plan, you need one regardless of the size of your estate. If you want to include the Foundation as part of your estate to help find a cure for MPNs, we can help you. To learn more about this support option, call Bill Crowley at (312) 683-7226.

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