

WHY DON'T JAK INHIBITORS REDUCE THE DISEASE BURDEN IN MYELOFIBROSIS?

*By John Crispino, PhD
Scientific Adviser*

With the discovery of JAK2 mutations and the recent approval of Ruxolitinib for individuals with myelofibrosis, there is a great deal of excitement and hope. However, there is also concern that, although the inhibitors are effective at reducing symptoms, they have not yet shown the benefit of reducing the disease burden.

Until recently, the reason why JAK inhibitors are not a more effective therapy has been a mystery. A new study by Ross Levine and colleagues, published in the prestigious journal *Nature*, provides a novel and compelling explanation for this limitation.

An Important Discovery About How JAK2 Works

Levine discovered that JAK2 mutant cells “persist” in the face of JAK inhibitors; that is, JAK2 mutant cells survive the onslaught of a drug rather than dying, and then re-emerge when the drug is removed. This phenomenon is different from chemical resistance shown by other cancers, where malignant cells acquire genetic changes that make them permanently resistant to a drug.

How do MPN cells achieve persistence if not by genetic means? The explanation seems complex, but is fairly straightforward when one understands how JAK/STAT signaling occurs. In order to understand persistence, one has to recognize that JAK kinases work as

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MF CHALLENGE UNDERWAY

By Barbara Van Husen

In the Spring issue of this newsletter, we described a major new research initiative aimed at halting and reversing bone marrow fibrosis in MF patients. This initiative, which we call The MF Challenge, has taken the first steps that we hope will lead to a significantly better prognosis for MF patients. We were fortunate to find a partner in the Leukemia & Lymphoma Society (LLS).

Grant Applications

In January 2012, we issued a Call for Proposals for the MF Challenge, seeking innovative projects that would test new concepts for halting and reversing bone marrow fibrosis. Applicants were encouraged to think ‘out of the box’ and push the frontiers of MF science in new directions.

The response was excellent; 22 proposals were received from researchers around the world. Applicants included seasoned MPN researchers and also investigators from other areas (such as pulmonary fibrosis) who brought new perspectives to this subject area.

The Grant Review Process

In order to bring a broad perspective to the grant review process, the MPN Research Foundation and LLS assembled a special review panel. Recognized experts in MPN science were recruited, as well as experts in other forms of fibrosis (particularly pulmonary fibrosis). We also recruited several panel members from the biotech/pharmaceutical industry to help identify proposals with commercial translation potential.

On June 1 the panel met to discuss each proposal in detail and establish composite scores for each proposal. The result was a list of projects ranked in order of scientific merit and potential.

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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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ARE WE THERE YET?

By Robert Rosen

“Are we there yet?” It’s a common refrain of children sitting in the back seat while driving to a defined destination, a family vacation or a visit with friends or relatives. Fortunately for children there is always a reasonable answer. We’ll be there in an hour, or a hundred miles, or after we cross the state line. It was easy.



At the MPN Research Foundation, we get the same question. Are we there yet? Where are the new treatments that we all so badly want? Is all this research doing anything, and specifically, what is the MPN Research Foundation doing to move things along?

For these questions, the answer is not as easy as the response to children in the car.

At a recent Foundation event one of our long-time supporters cornered me with the question: Where are we on the journey to better understanding, to better treatments? We’re happy to field these questions. Our organization was founded on principles of accountability and effectiveness. Our primary goal has always been funding research that might make a difference in the ever-fluid world of MPN science.

The metrics show that the MPN Research Foundation has funded 38 research grants (most for multiple years) with close to \$9 millions invested. We have supported new researchers with good ideas, many of whom credit us for keeping them in the field. We have enabled senior researchers to continue their good work. We have supported collaborative projects, and we have provided seed money for a project that ultimately won NIH funding of over \$30 million.

And we are now initiating a program to discover the underlying mechanisms for fibrosis in the bone marrow. (See article on page 1.) The journey does have defined destinations, but there are many miles still to go.



Support group coordinators from around the world gathered for a summit meeting in Chicago this past August.

MPN PATIENT SUPPORT GROUP COORDINATORS MEET IN CHICAGO

By Ann Brazeau

The MPN Research Foundation hosted a summit in Chicago on August 10th and 11th with patient support group coordinators from across the United States and abroad. Support group coordinators representing cities in the US came from California, Texas, Michigan, Illinois, Wisconsin, Massachusetts, Georgia, Ohio and Colorado.

Kaori Taki hosts a group near Tokyo, Japan, and traveled the farthest for the second time to participate in this meeting. Lisa Lacamel, the Vancouver coordinator, joined us for the first time.

The MPNRF provides ongoing support to the groups and is able to assist with recruitment, speakers, access to its website for meeting updates, access to brochures for distribution to cancer centers and hematology groups, and general information on forming a group as well as ongoing support when needed.

Speakers included Ann Brazeau, VP of Development and Michigan support group coordinator; Barbara Van Husen, President of the MPNRF; and Robert Rosen, Chairman and founder. Marge Blocks, Wisconsin coordinator, gave a wonderful presentation on the very basic science, indications and how to read a CBC and understand one's MPN

diagnosis. And Ron Anderson, coordinator from Los Angeles, recounted the history of the LA group.

A brainstorming session at day's end was useful in determining what the Foundation could do to better assist the groups and how the groups might assist the Foundation's efforts in the future. The MPNRF hopes to host these events every other year.

If you would like to form an MPN patient support group in your area, please contact Ann Brazeau at abrazeau@mpnresearchfoundation.org.

MF CHALLENGE UNDERWAY

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We are pleased to announce the 2012 grant recipients:

- Ann Mullaly & Benjamin L. Ebert, of Brigham & Women's Hospital
- Amit Verma and Zhizhuang Joe Zhao, of the Albert Einstein College of Medicine and University of Oklahoma Health Sciences Center
- Pearlie Epling-Burnett and Adam Mailloux, of the H. Lee Moffitt Cancer Center
- C. Arnold Spek, of the Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam

Funding for the 2012 grant awards will begin October 1, 2012. Mid-year and end of year progress reports will be reviewed by the review panel that evaluated the original proposals.

UPDATES

By Ann Brazeau

San Mateo Symposium – Bringing the Experts to the Patients

Last May, the MPN Research Foundation hosted a patient education symposium in San Mateo,

Dr. Jason Gotlib, from Stanford, shared current outcomes from their clinical trials and discussed other mutations and their possible roles in MPNs.

An open panel discussion allowed patients and caregivers ample time to ask numerous questions specific to their disease and treatments. To review the slides from this symposium, please visit our website at www.mpnresearchfoundation.org.



Dr. Ross Levine presents recent findings to patients, caregivers and family members at the San Mateo symposium.

California for the second time in the past three years. The location is a perfect setting for learning and sharing with other patients, caregivers, and family members.

Speakers this year had many updates as their respective research projects begin to reveal interesting outcomes. Dr. Ruben Mesa from the Mayo Clinic is collecting specific data on how patients feel over time on certain treatments.

Dr. Ross Levine of Sloan Kettering is focusing on genome sequencing and discovering ways to improve targeted treatments for MPN patients.

Dr. Laura Michaelis, from Loyola University, discussed the differences in male and female patients with MPNs and how important it is for physicians to pay attention to those differences. Dr. Michaelis is also a member of the MPNRF Chicago Roundtable.

Dr. Serge Verstovsek, from MD Anderson, shared data on current clinical trials of JAK2 inhibitors and other therapies for Myelofibrosis.

Midwest MPN Patient Symposium

On September 20th, the MPN Research Foundation hosted another educational symposium in Chicago. This was the first large scale program presented in Chicago and we hope to make it an annual event.

September 20th has also been named MF Awareness Day. Speakers at this event included three researchers from Chicago area academic institutions who are members of the Chicago Roundtable: Dr. John Crispino and Dr. Brady Stein from Northwestern University Feinberg School of Medicine and Dr. Laura Michaelis from Loyola University Medical Center. Other speakers included Dr. Ruben Mesa, Mayo Clinic, Arizona; Dr. Ross Levine, Sloan-Kettering; Dr. David Snyder, City of Hope; and Dr. Serge Verstovsek, MD Anderson Cancer Center.

These daylong symposia offer a great opportunity for patients, caregivers, and friends and family members to hear firsthand from the experts. For more information on upcoming symposia, visit the MPNRF website at www.mpnresearchfoundation.org.

HEROISM

By Mark Sanders

This chapter in my life began when I was 54 years old and living as a happily married, physically fit, professional firefighter for the city of Hammond, Indiana. As part of my annual physical, it was discovered that the sudden onset of shortness of breath, lethargy, and my engorged spleen (which I assumed to be a hernia) were all symptomatic of myelofibrosis. With a search of both the national and international bone marrow donors exhausted, and with no match in sight, my incredible doctor, Mark Litzow, became one of my personal heroes. He orchestrated the 9/10 match stem cell transplant that saved my life.



Mark Sanders, center, with stem cell donor John Fox and his wife Julie.

But of course, after surviving the transplant with great success, the question became “Whose stem cells were those?” An incredible part of the ‘Be The Match’ program is that after one year, they will exchange contact information between the recipient and the donor (if the donor is willing, of course). I had no idea that my donor had been as curious and excited about learning my identity as I was of learning his. One year had passed and my wife and I were waiting with great anticipation for more information from “Be The Match”, when we received a phone call... from the donor!

It’s tough to write the emotions that I had when he told me he was my donor and his name was John Fox. John and his wife Julie (who is also on the donor list) live in Raleigh, North Carolina. John had

A GOOD TIME TO BE ALIVE

By Shaun MaGruder

From the very moment that I found out that a research initiative had begun and that grants were being handed out to organizations to invent an ingenious way to tackle the war on fibrosis I immediately became ecstatic – I had always wondered why the medical community was not focusing on this front in addition to researching gene mutations.

Not only would we be tackling the war on fibrosis from a genetics perspective, but also from a second front. I am a firm believer that we will one day figure out a way to inhibit the process which causes the fibrosis within the marrow. In combination with current cyto-reductive therapies such as pegylated interferon along with an ingenious way of combating the fibrosis, I believe this disease could be kept at bay.

It is only a matter of time before this, like Polio and HIV, is merely a thing of the past. Words cannot express how grateful I am to the people involved in making this research opportunity possible – I am thankful from the deepest parts of my heart. As a combat veteran of the United States Army, I salute you!

HEROISM - continued

been on the bone marrow registry for 25 years and had never been contacted to donate! This giving, selfless, thoughtful and compassionate guy was my donor and without his cells, I doubt that I would be here today writing about him.

Of course my wife, Diane and I anxiously made the trip to Raleigh to meet John and Julie. It is impossible to capture the emotion in words... this man gave of himself to save my life. The Foxes are the epitome of what being a donor is all about: humble, giving, caring, gracious and beyond compassionate.

I have fought fires, helped save lives and loved my 20 years as a professional firefighter. But when life throws you into a tailspin and you reach up for help, it’s amazing to find such incredible people with their hand out to help you. Heroism is not in John Fox’s vocabulary, but it’s certainly in mine.

THE TROUBLE WITH K

By Delaney Halbert

I am a 37 year old female & mother of three. I was diagnosed with Essential Thrombocythemia in March of 2012.

The symptoms that cause me the most concern and debilitation are dizzy spells and headaches/pains. At my last visit with my hematologist, I brought up diet. I asked if there is anything I should add or avoid in my diet. He just said that a good diet is essential to everyone's good health. Although I hoped for a more substantive answer, I let my instincts be my guide and picked up an old but good habit, juicing.

I cleaned out the fridge, freezer and pantry of all the processed foods and loaded up on fruits, veggies and lean meats. It felt good to take charge and do so much for my body. At least twice daily, I was juicing. Each juice contained at least one of kale, spinach and broccoli.

The first week was fine. In fact, as you would expect, my energy improved. However, soon I started getting dizzy spells. By the end of the week, I also had bad headaches that made me feel like I was about to collapse or pass out.

I was frustrated by the return of the ET symptoms and suspected it was something I was ingesting that was amplifying the headaches, dizziness, etc. I found myself delving into reports of the medicinal effects of the foods I was consuming. Since the dark leafy greens are what I consume the most of, I started there. I typed in "Kale and blood clots" and WOW! Kale is rich in Vitamin K, which actually thickens the blood. This was all brand new information to me. I was blown away. I was taking in massive amounts of Vitamin K and, lo and behold, my symptoms were the worst ever.

On one hand, I was glad to have found this information so I can cut these out, but I was also upset that my questions about diet went unanswered by my doctor. To me, it's important for a physician to not just treat flare ups, but to also provide insights into how to eat well to take care of myself and not exacerbate the ET.

JAK INHIBITORS

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normal cell, the dominant form is a "homodimer" in which one JAK2 molecule associates with a second JAK2 molecule. In addition to JAK2, however, there are three other family members (JAK1, JAK3, and TYK2) that could each partner with a single molecule of JAK2 to form a "heterodimer."

Levine showed that JAK2 mutant cells switch from JAK2 homodimers to JAK2 heterodimers in the face of JAK2 inhibition. The disease persists, because signaling through JAK2 heterodimers is relatively insensitive to JAK inhibitors, including Ruxolitinib.

Toward the Next Generation of Treatments

While there is optimism that Ruxolitinib will prove to increase survival and reduce myelofibrosis, there is also awareness that other drugs, likely to be used in combination with a JAK inhibitor, are needed. Levine demonstrated that persistent cells are sensitive to HSP90 inhibitors, which are under investigation as a new therapy for MPNs.

In addition, he showed that other JAK inhibitors that bind inactive JAK2 (in a manner that is distinct from conventional JAK inhibitors) are able to reduce growth of JAK persistent cells. These latter results provide hope that the next generation of therapeutics will not only improve symptoms, but provide potent reductions in disease burden.

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