

MPD FOUNDATION® UPDATE

A PERIODIC NEWSLETTER FOR
THE MYELOPROLIFERATIVE DISORDERS COMMUNITY

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A BIRTH, A DEATH, AN ONGOING QUEST

By Robert Rosen

Simon, our second grandchild, was born last December. I cannot think of many events in a family's personal history that could be more joyful than this one: The relief of seeing a healthy infant, the exhausted pleasure on our daughter's face as she lay in the delivery room with her new son in her arms, the pride and excitement of the newly anointed grandparents.



Unfortunately, this milestone was tinged by an event as sad as the birth was happy. We received news of the nearly simultaneous death 800 miles away of one of our oldest friends, younger than we are, from metastasized breast cancer.

Both events, almost cosmic in coincidence, guaranteed to put me in a thoughtful mood about life and aging. As MPD patients we may find ourselves thinking about our health more often than we would like, wishing that our disease will remain treatable, and hoping for the breakthrough that will improve our chances for long life.

At the MPD Foundation, we see our mission as the promotion and support of science that will have the best chances of creating these breakthroughs. Rapid advances in understanding the genetic underpinnings of the MPDs are happening as we speak. We think we are on a good track, but then we read that the human genome is more complicated than originally thought, less likely to give up its secrets without more work than anticipated.

It always feels to us that each time we move two steps forward, some piece of news conspires to remind us that progress can be slow.

(continued on page 6)

THE STATE OF THE SCIENCE IN MPD RESEARCH

by John Crispino, PhD

At the MPD Foundation, we're patients and caregivers, not scientists. And we know that we can't keep up with – or understand – the latest research developments without the on-going, in-house help of a knowledgeable expert in the field.

So we are delighted to tell you that Dr. John Crispino has joined us as Scientific Advisor. Dr. Crispino is Associate Professor of Medicine, Northwestern University Feinberg School of Medicine, and specializes in research into the regulatory mechanisms governing normal and malignant blood cell development.

Following the American Society of Hematology (ASH) meeting in New Orleans last December, Dr. Crispino prepared the following summary of the latest and most significant research in the MPD field. Some of this is technical, but there is a tremendous amount of useful and encouraging information on developments in both clinical trials and basic research.

Clinical Research Highlights

- Data presented at ASH indicate that Incyte's INCBO18424 JAK inhibitor, known as 424, is effective at improving constitutional symptoms in MPD patients, including those with MF, Polycythemia Vera and Essential Thrombocythemia.
- There is optimism that the JAK inhibitor TargeGen 101348 will be shown to be a safe and effective therapy for MPDs. In a Phase I study with MF patients, this drug was associated with reduced spleen size and improved constitutional symptoms. More than half of MF patients treated with the TargeGen drug showed a reduction in JAK2 mutant allele burden. Dr. Ayalew Tefferi at the Mayo Clinic is initiating a Phase I/II study to test this agent in PV patients.
- Researchers are aggressively pursuing additional targets for therapeutic intervention. These include inhibitors of HSP90, HDAC, and P13K/AKT. These agents will likely be developed as drugs to be used in combination with JAK inhibitors.

Clinical Research in Detail

Incyte 424

Overall, this drug is well tolerated and appears to be very effective at providing symptomatic relief. Nearly 75% of patients who have enrolled in clinical studies continue to participate.

- Treatment with Incyte 424 leads to marked reduction in spleen size, slight drop in allele burden, decrease in peripheral CD34+ cells, significant improvement in constitutional symptoms, weight gain and improved walking. The response is durable and benefits do not diminish as long as the patient stays on the study.
- Although the drug is well tolerated in general, some patients experience anemia and thrombocytopenia (low platelet counts), particularly at higher doses. These side effects are readily reversible upon cessation of the drug.
- The benefits are independent of JAK2 mutation status. Patients with and without JAK2 mutations show similar responses. This observation (and other data) suggest that the drug is targeting something other than mutant JAK2. The best guess is that the drug interferes with production of inflammatory cytokines, possibly by inhibition of JAK1.

Data from Phase I/II trials in PV and ET patients:

- 424 was given to 73 patients with PV/ET who were not responsive to Hydroxyurea.
- The drug led to rapid and sustained reductions in spleen size, improved pruritus (itching), and decreased bone pain and night sweats.
- More than 90% of PV patients in this trial achieved normal hematocrit without phlebotomies, and more than half achieved a reduction in splenomegaly and a normalization of white counts and/or platelets.
- This preliminary data suggests that the drug will be useful in PV and ET patients.

Remaining issues for 424:

- There is no evidence that this drug reduces bone marrow fibrosis.
- It is too early to say whether this drug will reduce the risk of leukemic transformation.

TargeGen 101348

- Although the clinical study is still relatively new, it appears that this drug is well tolerated and effective at providing symptomatic relief. Moreover, it has the unique added benefit of reducing the JAK2 mutant allele burden.
- The drug has only been tested in MF, but the Mayo Clinic is opening a trial of PV and ET patients.
- Unlike Incyte 424 which targets both JAK1 and JAK2, TargeGen 101348 is a more selective JAK2 inhibitor. Perhaps this explains why the drug is more effective at reducing the allele burden.
- We expect to hear a more complete update at the 2010 ASH meeting, if not sooner.

Alternative Therapies

In addition to JAK kinase inhibitors, alternative approaches of interfering with mutant JAK2 signaling are being studied. Some of these new approaches appear to be promising. They include inhibitors of the HSP90 and HDAC pathways, which appear to lead to degradation of mutant JAK2 protein. Still other small molecules, which target downstream pathways that are activated by JAK2 mutants, are being evaluated for their activity in MPDs. Researchers suspect that combining these agents with JAK2 inhibitors may provide optimal benefits.

HSP90 Inhibitors

- HSP90 inhibitors interfere with the function of HSP90, a molecular chaperone that helps other proteins fold correctly. There are solid preclinical data to suggest that blocking HSP90 function leads to a selective destabilization and degradation of the JAK2 mutant protein.

HDAC Inhibitors

- Histone deacetylase (HDAC) inhibitors may have a two pronged effect in MPDs. First, they enhance the acetylation of H3/H4 histones and thus may counteract one interesting nuclear effect of the mutant JAK. Second, they increase acetylation of HSP90, which leads to reduced activity of the chaperone and instability of the mutant JAK or MPL proteins.
- Panobinostat (LBH589, Novartis) is an HDAC inhibitor currently in Phase I studies for MF.

Results are very preliminary, but researchers reported that 3 of 18 patients showed reduction in splenomegaly and one became transfusion independent.

PI3K/AKT/mTOR Pathway Inhibitors

- The PI3K/AKT/mTOR pathway is crucial for cell survival. Cells with mutant JAK or MPL appear to be more reliant on this survival pathway.
- RAD001, an mTOR inhibitor, is currently in a Phase I/II study in Italy. The drug appears to reduce abnormal STAT signaling. However it is too early to say whether this will be effective in patients with MPD.

Interferon Alfa

- IFN- α appears to preferentially target JAK2 mutant progenitors compared to wild-type JAK2 cells.
- Pegasys and ABT-737 cooperate to selectively target JAK2 mutant cells in PV specimens (Dr. Ron Hoffman).

Basic Research Highlights

- SNP arrays (which detect single nucleotide polymorphisms, or variations at a single site in DNA) have localized new genetic alterations in MPD clones to specific candidate regions. However more work needs to be done to identify specific genes whose mutations might contribute to the initiation or the progression of MPDs.
- New genetic alterations associated with leukemia transformation have been discovered. One such highlight was the identification of deletions of the gene Ikaros in MPD patients who progressed to acute leukemia. This discovery was made by Dr. Robert Kralovics, a grantee of the MPD Foundation.
- A more complete analysis of the frequency of TET2 mutations in MPDs was presented. It is clear that TET2 mutations occur in a wide spectrum of hematologic disorders and that they do not specifically associate with the MPDs. More research is needed to determine the extent to which TET2 mutations contribute to MPD initiation and progression.
- Several groups are gearing up to perform complete sequencing of genes in MPD specimens.

(continued on page 6)

SCARY NEWS FROM THE DOCTOR ...

and What Our Family Did Next

by JoAnn Mason

Our daughter, Jaclyn Mason, was diagnosed with Polycythemia Vera at age 17. It was scary news, indeed. Hematological malignancy? Blood cancer? Incurable? What would that mean for Jaclyn's future – and ours?



Jaclyn and JoAnn Mason.

At the time, we had never heard of myeloproliferative disorders. As parents, we were confused, frightened and eager for answers. We didn't know where to turn for help. We then discovered what many supporters of the MPD Foundation already know. When you feel most alone with these diseases, you suddenly discover you're not.

Fortunately, I met Celia Miltz, whose daughter has a related MPD. Through Celia I attended an MPD Foundation board meeting in 2008 and felt that this was the best place to focus our energies. I knew the Foundation would be a good partner, because they have funded some of the leading researchers in the field, and they know how to put their money where it does the most good.

Our family created the Jaclyn Mason Fund, to raise money for research and patient advocacy; and through the generosity of friends and family over this last year, we have been able to help fund several research grants. We hope to do the same in 2010 and beyond.

The desire to pursue better treatments and a possible cure for the myeloproliferative disorders remains an organizational and personal goal as our daughter continues to struggle with her disease, along with many other MPD patients.

Both Jaclyn and I are thrilled to be a part of the process and proud to be involved with an organization that is investing in the most cutting edge research in the field. Through the Jaclyn Mason Fund, we hope to contribute in a meaningful way to improving outcomes for MPD patients around

the world. Once again, we send our deepest appreciation to all those who have been so thoughtful and generous. To learn more or make a donation, please visit www.mpdfoundation.org and click on Jaclyn Mason Fund in the lower right corner of the page.

TREKKING THE JOHN MUIR TRAIL IN SEARCH OF A CURE

by Annette De Bow

I was diagnosed with JAK2 positive Polycythemia Vera in the summer of 2007, six months after the birth of my daughter. The next year was a blur of doctor visits and phlebotomies to decrease the number of red blood cells circulating in my body because my bone marrow is on overdrive. I also had to balance the joy of being a new parent with the shock and grief of my new diagnosis.

One thing I learned for sure: MPD patients like me need better treatments and, ideally, a cure. And we all need to help fund the research that will get us there.

This summer, I'm going to do my part. And I need your help. To help the MPD Foundation fund critical research, I will realize a long-held dream of hiking the John Muir Trail from Yosemite to Mount Whitney – all 211 spectacular miles. And I want you to be with me every step of the way.

Please sponsor part of my trek to help develop the medical breakthroughs I'm counting on to live long enough to dance at my daughter's wedding. To learn more about the trek, visit <http://trekforacure.com/index.html>. To make a donation, visit www.mpdfoundation.org, click on *Events* and scroll down to *Trek for a Cure*.

MPD Foundation Update is a periodic newsletter published by the MPD Foundation to provide members of the MPD community with information on current research and the Foundation's activities.

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HIGHLIGHTS OF RECENT EVENTS

by Ann Brazeau, Vice President of Development

Indiana Firemen Donate \$5000 to the Foundation

Firemen from Local 556 in Gary, Indiana, recently awarded the MPD Foundation \$5,000 for MPD research. Mark Sanders, his son Eric and coworker Mike Hull met with Bob Rosen and Ann Brazeau to hand over the check. Mark has myelofibrosis, and is anxious for new drugs or a cure.



Indiana firemen show their support for the MPD Foundation with a \$5,000 check. Left to right, Eric Sanders, Mark Sanders, Ann Brazeau and Mike Hull.

ASH 2009 Update

The MPD Foundation once again hosted a booth at the annual American Society of Hematology Meeting, last December in New Orleans. Attendance was down from last year's event; however, we were able to add new hematologists to our data base and will continue to have a presence at this and other conventions.

MPD Foundation Co-Sponsors New York Patient Symposium with Cancer Research & Treatment Fund

Dr. Richard Silver and the Cancer Research and Treatment Fund once again invited the MPD Foundation to co-host an MPD patient symposium in New York City last November. It was a huge success. Over 230 people attended this daylong symposium, which took place at the New York Athletic Club. Speakers included Drs. Tefferi, Mesa, Silver, Spivak, Barbui, Champlain, and Verstovsek; Robert Rosen, founder of the MPD Foundation; and board member David Boule.

UPCOMING EVENTS

MPD Foundation Reception in Rochester, Friday, May 7th

The MPD Foundation has been invited to host an MPD patient reception in Rochester, Minnesota in conjunction with Dr. Ruben Mesa's symposium "Living with a Blood Cancer." The reception will be on Friday, May 7th from 7 pm to 10:00 pm at the Kahler Grand Hotel/Marriott in the Elizabethan Room. All MPD patients attending Dr. Mesa's event are invited to join us for wine and appetizers. This reception is being generously sponsored by Incyte Corporation.

2010 MPD Foundation Bay Area Patient Symposium, Thursday, May 20th

The MPD Foundation is hosting a Bay Area Patient Symposium in San Mateo, California on Thursday, May 20th. Speakers include Drs. Ayalew Tefferi, Ruben Mesa, Jason Gotlib, and David Leibowitz. Joy Selak, author of *You Don't Look Sick* will also speak about living with a chronic illness. Space is limited, so register early at www.mpdfoundation.org/events.

2010 MPD Foundation San Diego Patient Symposium in September

Plans are underway for an MPD patient symposium in San Diego in September. Visit our website for more information as final details are confirmed for this event.



MPD Foundation President Barbara Van Husen talks with researchers Ayalew Tefferi and François Delhommeau (back to camera) at the ASH meeting.

FEEL THE NEED – FEED THE CURE

First Annual Fundraiser Gets off to a Snowy Start

by Ann Brazeau, Vice President of Development

Feel the Need – Feed the Cure was designed to help supporters of the MPD Foundation become active fundraisers by hosting food-themed events – big or small, plain or fancy – in their homes, at restaurants or anywhere else.

Originally, we hoped all the events would take place in February. But Nature had other ideas. Across the U.S., it was one of the snowiest Februaries on record. That kept a lot of people home.

So now we're extending the event for the entire year. That adds a lot of possibilities, from picnics to barbecues to tailgate parties to gatherings at the golf club – anything involving food. If you're interested in hosting an event, please let us know and we will guide you through the process. Just email abrazeau@mpdfoundation.org or visit our web site at www.mpdfoundation.org.

Because it was such a miserable month, we're particularly happy to thank some of the brave souls who were able to hold successful events.

Our Thanks to the 2010 Participants

Jay and Kari Schmidt own several Subway stores in Ohio. They decided to have a contest between the stores to see who could sell the most during the month of February, and then sent the Foundation a percentage of that store's sales. We gratefully received a check for over \$2000 that will go directly toward MPD research.

Dr. Susan Fello, PhD, an Associate Professor at Indiana University of Pennsylvania, hosted a luncheon with her colleagues at the university. Susan raised over \$400 and hopes to do even better next year.

And I pitched in with a French Food/French Film evening. Unfortunately, I chose the wrong evening. Snow and ice kept many from attending. Despite the weather, we managed to raise \$700.

Please think about joining us in this effort. What could be better than good food and good friends, getting together for a good cause?

THE STATE OF THE SCIENCE

(continued from page 3)

This method allows researcher to identify all of the genetic alterations in a given sample. The hope is that the sequencing will reveal new genetic mutations that initiate MPD or contribute to disease progression.

- Research aimed at developing advanced animal models of MPDs is moving ahead. At least two groups have created mice that harbor the JAK2 V617F mutation in their DNA. These animals develop a disease that very closely resembles human PV, and will be used as a tool to facilitate the development of new therapies for MPDs.

A BIRTH, A DEATH

(continued from page 1)

Many of our stakeholders have remarked that they would like more science content in these newsletters. We are happy to accommodate. In this issue we are publishing a summary, prepared by our new scientific advisor, Dr. John Crispino, of the salient MPD papers published at the American Society of Hematology meeting last December. These findings reflect the most current scientific thinking about the MPDs.

It's not hard to see how much is happening. It's heartening to see results from clinical trials of early JAK2 inhibiting drugs, and to learn about new promising mechanisms of action under intense investigation. In addition, by next year or even sooner, as the quest for new treatments picks up steam, we hope to see exciting results from therapies using drug combinations.

As always, the MPD Foundation is proud to be in the forefront of significant research projects in this ongoing continuum.

For more information or to make a donation, contact the MPD Foundation at:

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