

MPD FOUNDATION UPDATE

A PERIODIC NEWSLETTER FOR
THE MYELOPROLIFERATIVE DISORDERS COMMUNITY

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FIRST UPDATE ON THE MPD RESEARCH ALLIANCE

“Are we there yet?” First, we had the big news about the discovery of the JAK2 mutation. Then we announced with great excitement the formation of the MPD Research Alliance. Now we’re waiting for news of a big discovery that will help us all lead longer, healthier lives. Are we there yet?

Not yet. But we’re a lot farther down the road than we were just six months ago. The MPD Foundation has awarded initial grants to the three leading MPD researchers who make up the core of the MPD Research Alliance. Their one and only mission is to collaborate in an accelerated push to develop new genetically targeted MPD drugs. We have high hopes that this alliance, and others like it, will lead to new treatments for the MPDs in the next five years.

No, we’re not there yet. But here’s what the Principal Investigators in the Research Alliance have accomplished in their first quarter of operations.

Three Lines of Investigation With a Single Goal

Dr. Gary Gilliland of Harvard is focused on gene discovery and compound identification. In his first quarterly report Dr. Gilliland announces some exciting progress – the discovery, far sooner than anyone expected, of a new mutation in 5-10% of JAK2 negative MF patients. (See “MPD Research Alliance Researchers Discover a New Mutation in Myelofibrosis Patients” on page 2.) Dr. Gilliland’s team is also investigating additional existing compounds that may inhibit the JAK2 mutation.

Dr. Ron Hoffman of the University of Illinois at Chicago is working on drug screening and preclinical testing, specifically developing a murine (mouse) model for testing

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MPD RESEARCH ALLIANCE RESEARCHERS DISCOVER A NEW MUTATION IN MYELOFIBROSIS PATIENTS

By Dr. Gary Gilliland, Ph.D., MD
Harvard Medical School

The discovery of the JAK2V617F mutation in many MPD patients has reinvigorated and revolutionized research into these diseases. We now understand that there is a cell growth pathway called the JAK-STAT pathway that is activated by the JAK2V617F mutation. This pathway normally serves as an “on-off” switch to generate specific types of blood cells as needed. The JAK2V617F mutation locks the switch in the “on” position, and results in the overproduction of white cells, red cells and/or platelets that are present in MPD patients. The discovery of the JAK2V617F mutation has fostered an intensive ongoing search for JAK2 inhibitors that can be tested in clinical trials.

The support of the MPD Research Alliance helped make possible this unusually rapid discovery.

However, a significant proportion of MPD patients, in particular those with ET or MF, are JAK2V617F negative. Investigators at Harvard Medical School and the Mayo Clinic, supported by the MPD Research Alliance, have recently made an exciting discovery of a new mutation in MF and ET patients that are JAK2V617F negative.

Finding a new mutation against the backdrop of the extraordinary complexity of the human genome is more daunting than searching for a needle in a haystack. However, we reasoned that the best place to begin the search would be to screen components of the JAK-STAT pathway for mutations. We used robotics to perform high-throughput DNA sequence analysis of each of the genetic components of the pathway, including genes for cytokine receptors that bind to JAK2 and are the initial trigger for the “on” switch.

Using this strategy, we discovered a mutation called W515L in the gene encoding the cytokine receptor MPL (also known as the thrombopoietin receptor) that is responsible for growth of blood cells that produce platelets. MPLW515L is present in approximately 5-10% of MF patients, and at a lower frequency in ET patients.

The findings were considered important enough to be accepted for publication by two high quality peer review journals. The Harvard group published them in the online access journal *PLoS Med*, and the Mayo Clinic group published in the journal *Blood*.

The discovery is significant for three reasons:

First, it provides an important proof-of-principle that it should be possible, with further work, to ultimately identify all of the mutations that cause PV, ET or MF.

Second, since MPL requires JAK2 for its activity, initial experiments indicate that JAK2 inhibitors are also effective in inhibiting the MPLW515L mutations.

Third, the pace of this discovery has been remarkably rapid, and is largely due to the synergistic interactions between investigators brought together by the support of the MPD Research Alliance.

References available upon request.



Left to Right—Dr. Ron Hoffman of UIC, Dr. Ayalew Tefferi of Mayo Clinic, and Dr. Gary Gilliland of Harvard

UIC RECEIVES \$20 MILLION NCI GRANT TO RESEARCH BLOOD DISORDERS

Excerpts from UIC news release of September 6, 2006, announcing the NCI grant to the MPD International Research Consortium

A \$19.6 million National Cancer Institute grant has been awarded to the University of Illinois at Chicago College of Medicine to advance basic and clinical research for incurable blood disorders.

It is the largest grant in UIC history.

Dr. Ronald Hoffman, Eileen Heidrick Professor of Oncology at UIC and principal investigator of the project, will lead an international team of scientists and physicians from 15 institutions in the United States, Canada, Italy and Germany to establish the Myeloproliferative Disorders Research Consortium.

“This is an important collaboration among more than 20 investigators who will share their expertise to study the cellular and genetic basis for specific myeloproliferative disorders,” said Hoffman. “The goal is to develop novel clinical treatment programs and to identify specific biomarkers that will be useful indicators of response to therapy and risk reduction in patients.”

The consortium will focus on two myeloproliferative disorders, polycythemia vera and idiopathic myelofibrosis. These disorders occur when certain types of blood cells are overproduced by the body, often leading to bone marrow failure.

The grant will fund six primary research projects and will allow the consortium to maintain an interactive Web site for investigators, an international tissue bank, and an online database to aid researchers in understanding the clinical differences among patients with myeloproliferative disorders.

Three of the research projects will deal with the cellular and molecular biology of polycythemia vera. Two of the research projects will address abnormal stem cell trafficking in myelofibrosis. A sixth project will embark upon clinical trials for each of the disorders.

Myeloproliferative disorders include chronic myeloid leukemia, polycythemia vera, essential thrombocythemia and idiopathic myelofibrosis. While much is known about chronic myeloid leukemia, the other disorders are among the least understood malignant blood disorders and the most understudied, Hoffman said.

Until now, medical advances for these disorders have been limited because the small numbers of patients at any single institution prevent the conduct of rapid clinical trials and only a handful of basic and clinical researchers worldwide specialize in these uncommon blood disorders.

Polycythemia vera is characterized by the production of too many red blood cells. The disorder can lead to the formation of blood clots, heart attack and stroke.

Idiopathic myelofibrosis occurs when abnormal blood stem cells in bone marrow cause too few red cells, and usually too many white cells and platelets, to be made. The only current therapy for the potentially fatal disorder is stem cell transplantation from a donor.

The Myeloproliferative Disorders Research Consortium comprises clinicians and researchers from UIC; University of Utah, Salt Lake City; Consorzio Mari Negri Sud, Santa Maria Imbaro, Italy; Georgetown University, Washington, D.C.; Istituto Superiore di Sanita, Rome; IRCCS Policlinico S. Matteo, Pavia, Italy; Johns Hopkins University School of Medicine, Baltimore; McGill University, Montreal; MD Anderson Cancer Center, Houston; Mt. Sinai School of Medicine, New York; New York University School of Medicine, New York; New York Blood Center, New York; Weill Medical College of Cornell University, New York; Ospedali Riuniti de Bergamo, Bergamo, Italy; and University Hospital, Freiburg, Germany.

The MPD Foundation was proud to award the Research Consortium two timely organizational grants that made it possible for this group to pursue the lengthy application process to the National Cancer Institute.

IN BRIEF

By Ann Brazeau
Associate Director, MPD Foundation

\$10 Million MPD Research Alliance Capital Campaign Off to a Good Start

In its second year, the MPD Foundation is making significant progress in reaching the five year, \$10 million Capital Campaign goal. The generous support from patients, their families and friends, continues to help us pave the way to future hope and promise for longer, healthier lives for MPD patients. We have received several significant multi-year pledges and are encouraged by the enthusiasm we continue to receive when meeting with individuals, other foundations and drug companies. However, much work remains to be done to achieve our goals and sustain the work of the Research Alliance. Please consider making a donation or pledge to help the MPD Research Alliance achieve its goals. (Important: Note our new address, on the last page of this issue.)

Friends of ET Research 7th Annual Golf Classic

The Friends of ET Research 7th Annual Golf Classic was held on September 11th in Carmel, New York. **Celia Miltz**, MPD Foundation board member, began hosting this golf outing after her daughter, **Stephanie**, was diagnosed with Essential Thrombocythemia. Nearly 200 people participated this year, raising over \$55,000 to help support the MPD Research Alliance. This annual event has raised over half a million dollars. A special thanks to Celia, Stephanie and all of the Friends of ET!



MPD Foundation Board member Celia Miltz (left) and daughter Stephanie at the 2006 Friends of ET Golf Outing in Carmel, NY.

Al Bolea MPD Memorial Bike Ride

Al Bolea passed away in September, 2005 from complications due to myelofibrosis. On September 9, 2006, the Al Bolea MPD Memorial Bike Ride took place with riders leaving Regis College in Weston, Massachusetts, to cycle up to 62 miles. We expect contributions from the event to total over \$36,000. **Tom Maglozzie**, one of the **Tappet Brothers** from the NPR Radio Show *Car Talk*, participated in the ride and sent the riders off from the starting point. The MPD Foundation extends its deep appreciation to **Naomi Wernick** and all of Al's friends and family members for the hard work and contributions to the MPD Research Alliance.

If you are interested in coordinating a fundraising event, please contact **Ann Brazeau**, Associate Director, at 312-683-7226 or by e-mail at abrazeau@mpdfoundation.org.



Al Bolea MPD Memorial Bike Ride Committee members including friends and family.

MPD Foundation Hosts First Midwest Research Alliance Patient Forum

The MPD Foundation hosted a Midwest MPD Research Alliance Patient Forum in May, in cooperation with the Leukemia & Lymphoma Society and the Illinois Department of Public Health. Over forty people attended. The forum focused on the specific goals of the MPD Research Alliance, which is being funded by the MPD Foundation. Guest speakers included **Dr. Ron Hoffman**, a leading MPD researcher and important contributor to the Research Alliance from the University of Illinois at Chicago, and **Dr. Michael Goldstein**, Associate Director for Clinical Education and Research at the Institute for Healthcare

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MY LIFE AS AN MPD PATIENT

By Woody Woodruff

MPDs are strange things to live with. They're progressive, but unpredictable. Over the nine years since I was diagnosed, I feel older and more fatigued, to be sure. But my spleen isn't any bigger than it was, and hydroxyurea is still keeping my counts under control. (I'm 64 and I have PV.)

I know that some MPD patients are much sicker than I am. Others run marathons or play basketball. So I'm not a typical MPD patient; basically, nobody is. Every one of us has a different story. This just happens to be mine.

Actually, the title of this is a little misleading. I don't live my life as an MPD patient. I live my life as a full-time advertising copywriter, husband, father, grandfather and early-morning dog walker. I exercise, but not as much as I should. I drink wine with dinner – red in the winter, and white in the summer. But you're not reading this newsletter to learn about stuff like that, so I made up a title that would make it seem like this article belongs here.

Anyway, let me tell you a little about my MPD, because that's one thing we all have in common. I was diagnosed with PV in 1997, by a really annoying internist who tested for everything when I went for my routine physicals. He noticed the high counts. Most internists aren't so alert, which is why many of us have strokes, heart attacks or other serious symptoms before anyone diagnoses us. So thanks to the internist, the events surrounding diagnosis were not very interesting. Nonexistent, really. Nothing happened except that I started seeing a hematologist/oncologist and having phlebotomies every couple of months. Since then, I've added hydroxyurea and baby aspirin to the regimen.

The phlebotomies were boring, too. I have great veins (How many people ever realize how important that can be?) so there was never any poking around or resorting to suction tubes.

Well, the first thing I did after diagnosis was head for Google. That took me to an old version of the Merck manual, which said that the life expectancy for untreated polycythemia vera patients was 18 months. Instant depression. The hematologist just

laughed at me. "You'll probably live close to a normal lifespan," he said. As I said, I'm 64 now, so I can say for sure that I won't die young. Not very young, anyhow.

But while we're on the subject, think about that Merck statement. If untreated patients are going to die after 18 months, why in heaven's name wouldn't the doctor treat them? Okay, maybe they're talking about undiagnosed PV. If it wasn't diagnosed, how would anyone know that the patient had had it for 18 months? Don't believe everything you read on the Internet.

I hope my life as an MPD patient remains uneventful. I like it that way.

Which brings me back to life expectancy. I don't know what mine is, but last year I bought a tractor with a front loader and a backhoe. I don't know how to use the backhoe very well, but I'm planning on staying alive long enough to learn. Oh, the tractor has nothing to do with my day job. My wife and I have a vacation place in the Catskills. It has old, falling-down stone walls all over, and I am teaching myself dry stone masonry (that means gravity holds the stones in place, not mortar) to restore the walls. It's good exercise, but some of the stones are too heavy to lift, so I needed the tractor to move them into place. Needed? My wife just laughs at that, but she's been pretty understanding.

One thing I like about stone walls is that they have extremely long life expectancies. Especially if you keep them in decent repair.

The one interesting thing I can say about my MPD is that I've met a lot of wonderful people because of it, especially Bob Rosen and the crew at the MPD Foundation. It's really great to play a role, however small, in an effort like the MPD Research Alliance that has a good chance of producing new and better treatments that can extend our life expectancies and improve the quality of life for those whose MPDs are so much nastier than mine has been so far.

I hope my life as an MPD patient remains uneventful. I like it that way.

CLINICAL TRIALS AT MD ANDERSON CANCER CENTER

Srdan Verstovsek, MD, Ph.D.

MPD Program Leader

MD Anderson Cancer Center

In the Summer 2005 UPDATE, Dr. Verstovsek wrote about opportunities to participate in clinical trials at MD Anderson. Some of those trials remain open to new patients, and some new ones have been started. Here's the latest.

Pegasys for PV and ET

Toxicity and inconvenience are the major obstacle in the use of interferon-alpha (IFN- α) therapy for patients with MPD. IFN- α is commonly injected under the skin 3 times a week or even daily. Upon the initiation of therapy, most patients experience flu-like symptoms such as fatigue, fever, chills, headaches, and lowering of blood cell count, disturbances of the gastrointestinal tract and musculoskeletal system. Long-term toxicities are

The great majority have normalized blood cell counts and spleen size, without major toxicities.

seen in many patients and present in different forms. Different preparations of IFN- α are now available. Roche Laboratories developed a semi synthetic form of long lasting IFN- α , or Pegasys, by attaching a PEG (polyethylene glycol) molecule to regular IFN- α . This significantly prolongs its presence in blood and provides extended activity over a week-long period of time.

The drug is conveniently given at home once a week by self-injection of a pre-filled syringe. Toxicities are less pronounced and happen less often. Patient compliance is enhanced due to convenience and better tolerance of side effects. The dose of Pegasys is adjusted in case of any toxicity as continuous treatment increases the patient's ability to achieve a response. Pegasys is currently being evaluated in a phase II study at M.D. Anderson for ET and PV patients. Twenty-eight patients have enrolled so far and the great majority have normalized blood cell counts and spleen size, without major toxicities. Starting dose is 180

micrograms per week; patients are required to visit MD Anderson every 6 months while on the study.

Revlimid (Lenalidomide) and Prednisone for MF

Thalidomide improves blood cell counts and reduces splenomegaly in selected patients with myelofibrosis, but at the expense of significant side effects. When given with prednisone (corticosteroid), these side effects are diminished and patients can tolerate a prolonged course of therapy. Revlimid is a more potent and less toxic analog of thalidomide that has recently been approved as therapy for myelodysplastic syndrome and multiple myeloma. We are currently recruiting MF patients for a clinical trial of Revlimid and Prednisone in combination. Because Revlimid has already been shown, on its own, effective in MF patients, this study is the usual patient's first choice (15 patients have joined in 2 months since study has opened). Early signs of improvements in patients' status have already been observed. Participants are required to visit MD Anderson monthly for the first three months and then once every three months while on the study.

Bortezomib (Velcade) for MF

Bortezomib is a biological agent that affects multiple signaling pathways that affect cell growth and survival and induce cell death inside malignant cells. Bortezomib also inhibits angiogenesis (new blood vessel formation) that is important for the persistence of disease. We are exploring the multiple potential effects of Bortezomib on the neoplastic process in MF, and are recruiting patients at the Mayo Clinic and at MD Anderson. The medication is given intravenously weekly four times every six weeks.

Dasatinib (Sprycel) for MF and PV

Dasatinib is a potent inhibitor of proteins in the cells called tyrosine kinases. If kinases are inhibited, the malignant cells may die off. Dasatinib has recently been approved for therapy of patients with chronic myelogenous leukemia. Since there are several known tyrosine kinases expressed in MF that might be affected by Dasatinib, we are conducting a trial to determine its efficacy in controlling, suppressing and eliminating the disease in patients with MF, PV and other similar

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CLINICAL TRIALS UPDATE

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diseases. This medication is taken by mouth twice a day, and is provided as long as there is a benefit for the patient.

Obatoclox for MF

The main characteristic of malignant cells is their resistance to normal cell death; their continuous proliferation is what causes the development of a clinical disease. Obatoclox is a synthetic small molecule that reinstates the malignant cell's ability to die by altering certain proteins important for this process. In clinical studies, this medication has been able to significantly improve blood cell counts in a proportion of patients. We are currently recruiting patients for a study investigating its potential to increase blood counts in MF patients with low blood cell counts. The medication is given every two weeks intravenously.

Sunitinib (Suniteb) and Bevacizumab (Avastin) for MF

Abnormal levels of bone marrow angiogenesis (new blood vessel formation) and circulating

angiogenic factors (factors that induce blood vessel formation) have been documented in patients with MF. The study of Sunitinib in MF is scheduled to open in September 2006, and the study of Bevacizumab will open during the fall.

GC-1008 for MF

MF is characterized by prominent fibrosis (scar tissue) in the bone marrow, which is associated with so called profibrogenic proteins. One of them, transforming growth factor-beta (TGF- β) appears to have a dominant role. GC-1008 binds to TGF- β and blocks its activity. A clinical study of GC-1008 in MF will open at MD Anderson this fall. This agent is given intravenously once every two weeks.

For additional information about the therapies for MPD at M.D. Anderson Cancer Center, visit <http://www.mdanderson.org/diseases/mpd/> or contact Dr. Verstovsek at (713) 745-3429 or sverstov@mdanderson.org.

RESEARCH ALLIANCE *(continued from page 1)*

promising MPD compounds on human cells imbedded in mice. UIC is studying stem cells responsible for the MPDs, and is receiving additional tissue samples for study from the Mayo Clinic.

Dr. Ayalew Tefferi of the Mayo Clinic is responsible for developing a tissue bank as a central repository and resource for the MPD Research Alliance. He has begun to share samples with the other MPD Research Alliance collaborators. So far he has provided over 1000 samples to Harvard, where they played a role in the discovery of the new mutation in JAK2 negative MF patients, and he is providing 50 chemotherapy samples to the University of Illinois to support Dr. Hoffman's preclinical testing of mouse models of the MPDs. Dr. Tefferi is also conducting preclinical testing of several novel drugs for MPD patients, including a promising JAK2 inhibitor, and is working to standardize diagnosis and response criteria for MPD patients.

The Road Ahead

We're clearly headed in the right direction; recent news stories have highlighted a trend among foundations to encourage collaboration among researchers more used to competing with each other. Dr. Gilliland, Dr. Hoffman and Dr. Tefferi have demonstrated the value of collaboration and its importance to the ultimate success of the MPD Foundation's goal: the development of new treatments that will improve the life expectancies and quality of life of MPD patients everywhere.

We always knew it was a worthwhile goal. Now we know we're on the right track. But we have a long way to go, and we need your support to get there. Please help in whatever way you can.

The MPD UPDATE will provide regular reports on the progress of the MPD Research Alliance, but to follow progress in between issues of the UPDATE, please visit us at www.mpdfoundation.org

THE RESEARCH ALLIANCE, THE RESEARCH CONSORTIUM: HOW TO KEEP THEM STRAIGHT

In 2006, there was a dramatic increase in funding for MPD research creating new hope for patients. Most of the funding was awarded in two distinct grants, both involving a collaboration of researchers. The MPD community is lucky to have these two grants. While they appear similar, they are different in the scope of research.

Separate but Complementary Goals

In this issue of UPDATE, we shared the good news that the **MPD Research Consortium** received a \$19.6 million grant from the National Cancer Institute to conduct a wide range of studies for MPD patients in the context of an international collaboration between noted MPD research scientists and physicians.

The MPD Research Consortium is focused on basic and translational research dealing with the cellular and genetic basis of two of the MPDs: PV and MF. In addition, the MPD Research Consortium will conduct clinical trials to explore novel treatment options for patients with PV and MF. Eleven clinical sites throughout North America and Europe will participate in these trials.

The **MPD Research Alliance** is focused entirely on drug discovery for three MPDs (PV, ET and MF) and will research new treatments for both JAK2 positive and JAK2 negative patients. It is working closely with pharmaceutical and biotech companies to test a wide range of compounds for efficacy and safety, and to help move them as quickly as possible into clinical trials.

Together is Better

Although the two organizations operate independently, both teams of researchers value the sharing of information. The willingness of MPD researchers to work together is a major departure from the way traditional research has been conducted and we are enthusiastic about the promise this new collaborative spirit offers.

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.

Update Editorial Staff

Woody Woodruff, Editor | Amanda Friedeman, Layout Editor

IN BRIEF (continued from page 4)

Communication. Dr. Hoffman discussed the current state of MPD research and project plans for the MPD Research alliance. Dr. Goldstein, who was recently diagnosed with polycythemia vera,



Mingjiang Xu and Ed Bruno of the UIC chat it up with a Forum attendee.

gave an informative presentation on the self-management of chronic diseases.

Northeastern MPD Patient Support Group Being Formed

The MPD Foundation receives many requests for information about patient support groups across the country. Recently, **Jay Humphrey**, an MPD patient from Rhode Island, has taken on the task of reaching out to other patients to coordinate a support group in Rhode Island, New Hampshire, Massachusetts, Maine and Connecticut. If you are interested in participating, please contact Jay at 401-640-1500, or by e-mail at wwhumphrey@aol.com.

If you are interested in starting a patient support group in your area, please contact **Ann Brazeau**, Associate Director, at 312-683-7226 or by e-mail at abrazeau@mpdfoundation.org for assistance.

We've Moved...

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

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