

MPD FOUNDATION® UPDATE

A PERIODIC NEWSLETTER FOR
THE MYELOPROLIFERATIVE DISORDERS COMMUNITY

VOLUME V, NO. 2 SPRING, 2007
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2007: A YEAR OF PROMISE FOR MPD PATIENTS.

The discovery of the JAK2V617F mutation in 2005 has triggered a cascade of events that promises to usher in a new era for MPD patients: new drug candidates, clinical trials, and better treatment options for MPD patients, even those at greatest risk.

The MPD Foundation relies heavily on its scientific advisory board to evaluate progress reports submitted by our MPD Research Alliance (RA) researchers. In a vote of encouragement and support, one of our SAB members ended a recent meeting with the comment that the work of the RA has exceeded expectations.

The MPD Research Alliance is now moving into its second year of funding and research with positive momentum. Drug companies have been contacting our researchers to test existing compounds for effectiveness against MPDs, demonstrating that the collaborative aspect of the RA provides a platform to move the state of the science forward at a faster pace.

We are hoping to see at least two clinical trials of new MPD drugs this year.

Our model of a strict focus on collaboration and drug development is paying off. Although no clinical trials have been formally announced yet, we know that Dr. Ron Hoffman and Dr. Mingjiang Xu, of the University of Illinois at Chicago, are preparing to initiate a Phase I/II trial of a promising compound by the end of 2007.

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ON NORMALCY

by Sarah M. Dreller

Recently I saw Montel Williams interviewed about his struggles with MS. He talked about the kinds of lifestyle changes he'd made to counteract the degenerative nature of the disease and the success he'd had maintaining a semblance of normalcy. All of this he related in the most matter-of-fact language, referring to "my illness" as if it were "my dog" or "my car."



Sarah Dreller, PV patient, and husband Clark Christensen

What struck me more than the words he used, though, was his composure. This was difficult, intimate stuff he was sharing with the world and yet he was impressive in every way—no undeserved arrogance, no desire to be pitied, no defeatist attitude. When the interviewer told him that she would never have known he was sick, he was genuinely, modestly appreciative.

Although I have never been a Montel fan, I felt a strong psychological connection with him during that ten-minute segment. Three years ago, I fainted when the hematologist told me I had PV. But that night I resolved not to be the pale, weak, confused sick person of my imagination. I researched doctors for my second and third opinions, joined an online support group, and sought out a therapist specializing in serious illness. I also bought fresh new makeup and wore it regularly, made good use of my gym membership, and allowed myself a bit of private time every day to grieve for the loss of my healthy, carefree youth.

After a few years I finally gathered the personal strength to talk about my situation openly with my family, friends, and colleagues—hiding it from everyone seemed like denial rather than true acceptance. These days the biggest compliment someone can give me is the one the interviewer offered Montel, that is, based on outward appearances you wouldn't know I have a potentially life-threatening medical condition.

"People say they wouldn't know I have a potentially life-threatening medical condition."

PV Wasn't the Only Problem

Stoicism has its disadvantages, I've learned. Between September 2003 and June 2004, I complained to every doctor and nurse I met that I was experiencing increasingly problematic chest pains. At one point I collapsed and was taken to the hospital in an ambulance, only to be lectured on the importance of stress reduction and sent home. Eventually, after I started collapsing about twice a day, a cardiologist agreed to see me. He sent me directly from his office to the local hospital's intensive care unit for heart failure patients.

There, I foolishly refused a wheelchair, still for some reason believing it was in my best interest to appear OK. Since I walked into the unit and they were understaffed, the nurse in charge downgraded me to a different floor without consulting my doctor. After an angiogram the following day, which determined that one of my major arteries was 99% blocked and I was starting to suffer heart damage as a result, I finally received the attention I needed and deserved.

After endless tests, no one can tell me definitively why this happened. It could have been a side effect of the Agrylin I was taking, or it might be something entirely unrelated and undiscoverable with current technology. That means, of course, that it could happen again. So, among the most important lessons I took away from that ordeal—and one I continue to struggle with to this day—is to make sure my body language supports my words. No confident smiles if I'm really in pain.

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JAK2 V617F: QUANTITY MATTERS!

by Alison Moliterno, MD

Assistant Professor

Department of Medicine, Division of Hematology

Johns Hopkins University

In the two years since the initial reports of JAK2 V617F, much has been learned about how this genetic lesion is related to MPDs. The JAK2 V617F breakthrough has also stimulated larger investigative efforts in the genetic basis of MPDs, leading to discoveries of new lesions in the JAK2 gene and in thrombopoietin receptor gene in JAK2 V617F-negative MPD patients.

Recent findings in the JAK2 V617F-positive MPDs

Finding JAK2 V617F in 95% of patients with PV, 50% of patients with ET, and 50% of patients with IMF was not surprising given their shared clinical, laboratory and molecular characteristics and their propensity to evolve from one MPD subtype to another.

Surprisingly, it is clear now that some of the variation between PV, IMF and ET patients who harbor JAK2 V617F is in fact related to how much JAK2 V617F they have.

Surprisingly, it is clear now that some of the variation between PV, IMF and ET patients who harbor JAK2 V617F is in fact related to how much JAK2 V617F they have. For example, patients with ET who test positive for JAK2 V617F have levels that are much lower than either PV or IMF patients, and in some ET patients, the JAK2 V617F proportion of cells in the bloodstream makes up only the minority of cells. The importance of measuring the amount of JAK2 V617F was highlighted at the 48th Annual American Society of Hematology Annual Meeting this past December, during which an abstract showcasing a tight association between the amount of JAK2 V617F and important clinical features in PV was selected as a plenary paper.

Our own work shows that gender plays an important role in JAK2 V617F. We have found that



Dr. Alison R. Moliterno from Johns Hopkins

women harbor lower JAK2 V617F percentages than men in both PV and ET, and that women with ET are slower to convert to PV than men. These findings suggest the behavior of JAK2 V617F positive stem cells is different in a female genetic background. Ongoing studies are addressing further gender-based differences, and are determining whether quantitative assessment of JAK2 is helpful in defining thrombotic risk and other important disease-related complications.

New Genetic Lesions in the JAK2 V617F-negative MPDs

The discovery of JAK2 V617F has led to intense scrutiny of both the JAK2 gene and related genes that control cell growth. The result has been the identification of genetic lesions in the thrombopoietin receptor in about 5-10% of patients with IMF. The February 1st issue of the New England Journal of Medicine reported that several new mutations in the JAK2 gene have been discovered in patients with clinical syndromes similar to PV. These genetic changes all seem to all confer excess growth signals along a common biochemical pathway.

Looking Forward

Identifying the genetic causes of the MPDs is a true breakthrough on many levels. First, it allows targeted drug development to specifically suppress the growth of diseased cells. Second, recognition that the amount of the mutation may be important

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PEGASYS STUDIES

by Srdan Verstovsek, MD, Ph.D.

MPD Program Leader

The University of Texas M D Anderson Cancer Center

Interferon-alpha (IFN- α) has been used for many years to treat polycythemia vera and essential thrombocythemia. Although the treatment can be very effective, the IFN- α is barely detectable in serum after 24 hours and therefore it must be injected multiple times a week. Side effects are a serious problem for many users as well. To overcome these limitations, two forms of pegylated IFN- α have been developed, PEG-IFN- α -2a (Pegasys®, Roche) and PEG-IFN- α -2b (PEG-Intron®, Schering-Plough). Both result in a sustained absorption and reduced clearance from the body. This allows for administration only once a week. Unlike PEG Intron, Pegasys stays mostly in the blood circulation. Since blood volume differs a little among individuals, Pegasys can be administered as a uniform fixed dose (e.g. 180 μ g) rather than based on body weight.

PEG Intron has been evaluated in several clinical studies for ET and PV patients, and showed similar efficacy but no better tolerance than historical experience with conventional IFN- α . Two trials, however, have been conducted recently using Pegasys and the results might be of interest to PV and ET patients. A French group “PV-Nord” reported results in 32 PV patients followed up for



Dr. Srdan Verstovsek of
M D Anderson Cancer Center

at least 12 months. Only 2 were off the therapy, while 27 were in complete remission (normal blood cell count and no splenomegaly) and 3 had a partial response. The overall response rate was therefore 94%. No cases of thrombosis or hemorrhage were reported. Only one patient had a serious side effect, a skin reaction. Furthermore, 24 of 27 patients tested experienced a decrease in the % of cells in their blood with JAK2 mutation, from a mean of 49% to a mean of 27%, including one patient with no longer detectable mutant JAK2.

Our experience at MD Anderson is similar. In an ongoing study for ET and PV patients, 39 out of 40 evaluable patients responded, with 35 being in complete remission. So far only 3 patients are off the study because of side effects.

We conclude that Pegasys appears to be an effective and tolerable medication for PV and ET patients.

YEAR OF PROMISE *(continued from page 1)*

At the beginning of the RA grant we committed to include all MPD patients, JAK2 negative as well as JAK2 positive, in the research we support. In fact, there is some evidence that JAK2 inhibitors may be effective for patients who do not have the JAK2 mutation.

We are pleased to report some important work for patients with myelofibrosis.

RA researchers have developed a mouse model with myelofibrosis stem cells, and they are contin-

uing to work on the characterization of this stem cell. We hope to see tests on three candidate therapeutic molecules this year, and we may see some clinical trials for MF patients, using one or more of these drug candidates, in 2007.

We continue to be enthusiastic over the pace of progress and the noticeable increase in the number of academic and drug company researchers participating in this field.

To support patients who are interested in trying new drugs, we plan to launch a program on our web site to provide information about clinical trials of new MPD drugs and links to the institutions that are running these trials.

IN BRIEF

by Ann Brazeau, Associate Director

Capital Campaign Update

To date, the MPD Foundation has raised over \$1.8 million for the MPD Research Alliance. Total giving doubled from last year. Two major events raised over \$100,000 and we received several multi-year pledges. Over the last year, our database has grown substantially. Not only did the number of new donors grow, but there was a significant increase in the amount given by current donors.

2006 Events

The Al Bolea Charity Bike Ride in Boston raised over \$40,000. All proceeds were directed to the MPD Research Alliance. The second annual event will take place on August 26, 2007, with a fundraising goal of \$60,000.

The Friends of ET Golf Outing brought in a total of \$70,000. This highly successful event has made substantial contributions to the MPD Foundation over the last nine years.

2007 Upcoming Events

Team Wind-Mullers will be participating in a marathon in California to raise money for the Research Alliance. To date, over \$50,000 has been raised and the amount increases daily. This event takes place on April 29th, 2007 in Big Sur. Check out their web site and make a donation at www.firstgiving.com/windmullers.

Lisa Smith-Batchen, a friend of an MPD patient, will be running in the Badwater Ultramarathon this

July to raise money for the MPD Foundation's Research Alliance. Lisa will be the only woman in the world to do this marathon for the second time. Lisa Smith-Batchen is an elite ultra-runner and is considered to be one of North America's top endurance athletes. This event will give MPDs and the Foundation great media exposure. For more information, visit our web site under upcoming events.

The MPD Foundation and the Cancer Research and Treatment Fund will co-host the 2007 Annual MPD Patient Symposium in New York City on November 7th.

Fundraising Plans for 2007

The MPD Foundation relies heavily on significant donations from patients and their families and friends. We continue to seek multi-year pledges to support our long range research commitments. The Foundation also supports patients and family members who are able to host events in their area. There are many ways to raise money, including marathons, walkathons, bike rides, bowling tournaments and golf outings. You might also work for an organization that matches gifts to charities.

If you are interested in hosting a fundraising event, the MPD Foundation will provide materials and place information on our website. Please contact Ann Brazeau, Associate Director at 312-683-7226 or e-mail at abrazeau@mpdfoundation.org. For more information about upcoming MPD fundraisers, visit our website at www.mpdfoundation.org and click on Upcoming Events.

QUANTITY MATTERS *(continued from page 3)*

to defining the unique MPD will enhance both the diagnostic approach to the MPDs, and will aid in designing clinical trials for JAK2 inhibitors. Finally, the recent discoveries that JAK2 V617F-negative MPD patients have mutations in genes

that participate in the same biochemical pathways lends credence and hope to the concept that JAK2 inhibitors will help more than just the JAK2 V617F-positive patients.

The support of the MPD Foundation has been crucial to the success of both our own investigative efforts and those of investigators across the globe.

MPD FOUNDATION INITIATES RELATIONSHIP WITH THE FDA

With the expectation of new candidate drugs for MPD patients, we recently initiated an effort to create a relationship with the FDA. Our purpose is to learn how we can most effectively collaborate as patient advocates to accelerate the drug approval process if and when new drugs are available for clinical trials. Recently, we met with several leaders of the FDA who are responsible for oncology drug approvals, including hematological drugs. These are the same people who helped accelerate the approval process for Gleevec several years ago.

We are pleased to report that our meeting at FDA headquarters outside Washington, DC was well received. We made a presentation on the state of MPD research and the prospects for new drug development. The scientists from the FDA were highly receptive to our comments and assured us that the clinical pathway to approvals for an effective kinase inhibitor would not be complicated.

We were delighted to have established such a good working rapport in our first meeting. We will con-



Bob Rosen attends meeting at the FDA in Rockville, MD

tinue to do what we can to facilitate the development of new drugs for the MPD community and will update you on our progress.

ON NORMALCY *(continued from page 2)*

That Endless, Annoying Itch

These days I often think of my PV as a permanent parasite: it takes and takes forever, and I get nothing constructive in return. For example, it seems like I itch all the time, not just after a shower but also when I'm changing my clothes or even when I'm wearing a skirt and the wind blows a little. With experience I've constructed all sorts of coping strategies that work pretty well, ranging from good leather boots for protecting my legs in public to having my towel as close as possible to the shower so that I can dry off immediately.

But, in the meantime my husband and I have expended an enormous amount of energy tracking down and purchasing different types of soaps, antihistamines, towels, moisturizers, robes made of

100% cotton...the list goes on and on. It truly makes me sad when I think of all the great things we could have done together instead.

Learning to Treat PV as "Normal"

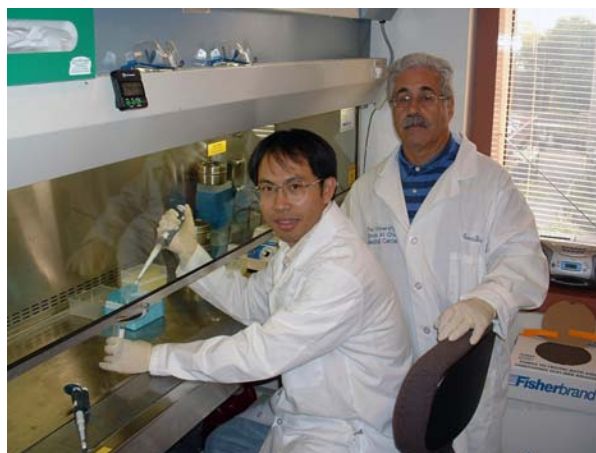
Under these time-consuming, expensive, and emotionally demanding circumstances, living in dignified co-existence with my PV and its complications is a real challenge. However, I've come to view my response as a core self-defining project, as important to me as nurturing strong family relationships and maintaining intellectual curiosity. This illness is never far from my mind, and I'll admit that every once in a while there's a day in which I don't think about very much else. But, I've decided that generally treating it as a "normal" part of my life—as just another facet of who I am—is the key to my long-term happiness.

CLINICAL TRIALS OF ERLOTINIB PLANNED FOR JAK2V617F-POSITIVE MPDS

by Mingjiang Xu, MD, PhD
University of Illinois Chicago

Thanks to the support of the MPD Foundation, Dr. Ron Hoffman and I, at the University of Illinois Chicago, and Dr. Joe Zhao at the University of Oklahoma, recently found that Erlotinib (Tarceva) effectively inhibits JAK2V617F activity and PV JAK2+ progenitor cell growth. Erlotinib is a kinase inhibitor that inhibits the epidermal growth factor (EGF) induced kinase activity (EGFR). Erlotinib has been used in the treatment of non-small-cell lung cancer with mutation of the EGFR.

Recently, we reported that Erlotinib is also a potent inhibitor of JAK2V617F activity. In vitro colony assays revealed that Erlotinib at μM concentrations effectively suppresses the growth and expansion of PV hematopoietic progenitor cells, while having little effect on normal cells. Furthermore, JAK2V617F-positive cells from PV patients show



Researchers Mingjiang Xu and Ed Bruno of the University of Illinois at Chicago

greater susceptibility to the inhibitor than their negative counterparts (J. Biol. Chem. in Press, published online December 18, 2006).

We are planning a clinical trial (Phase I/II) of Erlotinib in the treatment of JAK2V617F-positive PV and other myeloproliferative disorders for 2007.

MPD RESEARCH ALLIANCE UPDATE

The first year of the MPD Research Alliance has exceeded our expectations. Dr. Gary Gilliland, in collaboration with researchers around the world, made significant progress in identifying new genetic targets for drug development, identifying several new MPD-related mutations which occur in non-JAK2 MPD patients. He remains committed to the principle that the responsible mutation for all MPD patients will ultimately be discovered.

In collaboration with Dr. Ayalew Tefferi of the Mayo Clinic, he further characterized these mutations in human alleles and in mice, developing models which have been and will be used to assess which therapeutic agents will work best against these mutations. Dr. Gilliland and Dr. Tefferi also collaborated with drug companies that have candidate compounds that inhibit the JAK2 mutation; as a result of this work, JAK2 inhibitors have been through preclinical testing in Dr. Gilliland's and Dr. Tefferi's laboratories, and at least one (and pos-

sibly two) are targeted for clinical testing in 2007. Three additional clinical leads from two highly regarded drug companies have also been identified, and are targeted for preclinical testing in 2007.

Dr. Ayalew Tefferi has worked closely with Dr. Gilliland on the testing described above, a significant accomplishment both researchers credit to their participation in the MPD Research Alliance. To support this work, Dr. Tefferi has created a comprehensive laboratory database for tissue samples collected at the Mayo Clinic, and has used this growing tissue bank and database as a base for pre-clinical testing. One of the major discoveries of this collaborative testing is that JAK2 inhibitors appear to also effectively inhibit cell lines transformed by non-JAK2 mutations, suggesting broad applicability of JAK2 inhibitor therapies to many MPD patients regardless of their JAK2 status. Dr. Tefferi plans to continue aggressive preclinical testing of additional JAK2 small molecule inhibitors in collaboration with drug companies who are approaching our researchers on an "almost weekly basis".

ANNOUNCING THE HARVARD FAMILY STUDY OF MYELO-PROLIFERATIVE DISEASE (MPD)

By Martha Wadleigh, Ross Levine and Gary Gilliland

There are rare families in which more than one individual in the family has polycythemia vera (PV), essential thrombocythemia (ET) or myelofibrosis (MF). Because these are rare diseases, a cluster of two or more individuals in a family suggests that there could be a genetic link, or possibly a shared exposure, that contributed to the development of MPDs. Families with MPD can thereby provide extremely important information about its causes.

In this Harvard study that has recently been approved by our Institutional Review Board (IRB), we will collect detailed information from families in which more than one member has PV, ET or MF. We will also request specimens of blood and a swab from inside the mouth to prepare DNA from each individual participating in the study. We will then use this information and material to better

understand the root causes of MPDs, in part through the use of sophisticated analysis of the DNA using high-density single nucleotide polymorphism arrays that will allow us to search the genome for these potential culprits. We hope that these studies will shed new light on MPDs, and enable us to develop new treatments.

Does more than one person in your family have an MPD?

In this study, it is important to study family members with MPD, as well as family members that do not have MPD. If you have two or more individuals in your family with MPD, and you and your family would be interested in participating in the study, or obtaining more information about the study, please contact:

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MPD RESEARCH ALLIANCE UPDATE

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Dr. Ron Hoffman concentrated in Year 1 of the MPD Research Alliance on the identification of the stem cell which underlies MF. Using this MF stem cell, Dr. Hoffman developed mouse models which allow the testing of candidate compounds against human cells in immuno-deficient mice, a complex testing platform which may be critical in the future for ensuring that these compounds are effective against human disease. This year two therapeutic agents will be tested using the MF stem cells. Dr. Hoffman is now expanding his work to characterize the stem cells associated with PV and ET.

All three of the MPD Research Alliance researchers have published extensively on the work done in their laboratories during the first year of the MPD Research Alliance. And all three look forward to continued acceleration of the pace of their research in the upcoming year.

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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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