

MPD FOUNDATION® UPDATE

A PERIODIC NEWSLETTER FOR
THE MYELOPROLIFERATIVE DISORDERS COMMUNITY

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TIME AND COMMITMENT

by Robert Rosen

Like many of you I spent hours riveted to the TV in August watching the Summer Olympics in China. As a weekend athlete myself, I continuously marvel at the unimaginably high level of performance exhibited by athlete after athlete, causing me to reflect on not only their skill levels, but the years of dedication, commitment and patience that laid the foundation for their successes. Although it is tempting to think that mere skill will prevail, we know that years of hard work are a precondition for success.



In case you haven't already guessed, the words of the paragraph above are intended as a metaphor for the state of MPD research, particularly in a world informed by the discovery of the JAK2 genetic mutation. Progress takes time and patience and hard work but is starting to pay off.

In the six months since our last newsletter, clinical trials in a number of new JAK2 inhibiting drugs have been launched. The MPD Research Alliance has supported and enabled much of this progress to occur in such a relatively short time frame.

MF patients have been the first to have access to some of these drugs, and as of this writing there are trials involving candidate drugs from at least four biotech companies. In addition early stage trials for PV patients and ET patients are now starting with at least one of these drugs, with more drugs to follow on this clinical path. We look forward to seeing published results by the time of the ASH convention in December.

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INVESTING IN THE FUTURE OF MPD RESEARCH

By Barbara Van Husen

Eight years, ago when the MPD Foundation was established, few researchers were focused on these little-known, underserved disorders. The small group of researchers who did concentrate on them struggled for funding and recognition, but their years of effort resulted in the stunning discovery of the JAK2 mutation in 2005.

Since that discovery, these researchers have been joined by an increasing number of scientists who have contributed to the wave of drug development activities we see today. These activities bring with them the hope that effective new treatments for the MPDs will become available over the next few years. But every new discovery brings with it a set of new questions, and the need for new researchers to tackle them.

Missing: Financial Support for Young Researchers

Unfortunately, new investigators (or those wishing to change their area of scientific focus) find it increasingly difficult to fund their endeavors. While scientific advances in the understanding of the human genome and other aspects of microbiology continue to expand rapidly, funding for new researchers is shrinking dramatically.

The National Institutes of Health, the largest source of scientific career development grants in the U.S., has seen applications increase but success rates for those applications fall for the last five years. In this funding environment, it is difficult for new researchers to make the commitment that will ultimately benefit MPD and other patients.

What the MPD Foundation is Doing to Help – Thanks to Your Generous Support

The MPD Foundation believes that we need to invest in tomorrow's researchers today to ensure that today's discoveries turn into tomorrow's treatments. For that reason, the MPD Foundation determined in 2008 to begin a New Investigator Award program aimed at

- Emerging investigators who are considering a career related to research in the MPDs

- Established investigators in other fields who are interested in bringing their experience, skills and ideas to research in the MPDs

A call for proposals for this new grant program was issued by the MPD Foundation in July, 2008. Early response to the call for proposals has exceeded our expectations; as we go to press, we have received an impressive 35 letters of intent. Full proposals are due in mid-October, so that our Scientific Advisory Board can review them in November, with grants to be awarded in early 2009.

The enthusiastic response confirms our belief that there is a need for this kind of career development program. If the program can bring one or more dedicated scientists to focus on the MPDs, we believe we can set the stage for future discoveries that will benefit us all.

The only down side is that we expect to receive more high-quality proposals than we can possibly fund; any additional help you can give us as the holiday season approaches will be much appreciated – and is likely to pay off handsomely if we can motivate just one young researcher to devote his or her career to finding better treatments for our disorders.

We look forward to announcing the results of the first set of grant awards in early 2009.

**YOUR DONATION
NOW COULD
CHANGE A YOUNG
RESEARCHER'S LIFE**

**And the lives of thousands of MPD
patients for years to come.
Please be generous.**

TWO WAYS TO GO

Clinical trials for a JAK2 inhibitor and Pegasys both under way at M.D. Anderson Cancer Center

By Dr. Srdan Verstovsek, MPD Program Leader, Leukemia Department, M.D. Anderson Cancer Center

JAK2 Inhibitor Clinical Trial now Open to Patients With PV or ET

Three years ago, several independent groups described a novel mutation in the gene encoding the cytoplasmic Janus kinase 2 (JAK2) in patients with MPD. This mutation is present in 50% of ET and MF patients and 97% of PV patients, and it makes the JAK2 protein active all the time.

JAK2 is an important protein inside the cell, as it transmits signals for the cell to grow. The JAK2 protein may be a major reason for the existence and progression of the myeloproliferative diseases, and JAK2 inhibitors might positively affect the disease.

Encouraging Results at M.D. Anderson Lead to Clinical Trial Expansion

M.D. Anderson Cancer Center is currently conducting several clinical trials of JAK2 inhibitors for patients with myelofibrosis. A Phase I/II study of the oral JAK2 inhibitor INCB018424 for patients with MF has accrued more than 100 patients so far and showed exemplary efficacy in reducing enlarged spleen/liver, reducing elevated white cells and platelets, and improving patients' quality of life. Interestingly, these benefits occurred regardless of the presence of the JAK2 mutation, and there were limited non-hematologic side effects. Based on these encouraging results the study of INCB018424 has just been opened to patients with PV or ET.

Specifically, it's a Phase II, open label, dose regimen ranging clinical study to determine the safety and efficacy of INCB018424 in patients with advanced polycythemia vera or essential thrombocythemia refractory to hydroxyurea.

Are You Eligible to Participate?

Like all clinical trials, this one has fairly strict criteria for patient eligibility. You must have PV or ET (irrespective of JAK2 mutation status) that is refractory to hydroxyurea or for which hydroxyurea is contraindicated.

You may not have used interferon alpha or anagre-

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The Pegasys Alternative: JAK2 Inhibitors Aren't Your Only Option

Interferon-alpha (IFN- α) therapy has been used for some time in treating patients with essential thrombocythemia (ET) and polycythemia vera (PV). Toxicity and inconvenience are major obstacles in its use; IFN- α is commonly injected under the skin three times a week or even daily.

Upon the initiation of therapy, most patients experience flu-like symptoms such as fatigue, fever, chills, headaches, lowering of blood cell count, and disturbances of the gastrointestinal tract and musculoskeletal system. Long-term toxicities are seen in many patients and present in different forms.

A different preparation of IFN- α is now available. Roche Laboratories developed a semi-synthetic form of long-lasting IFN- α , called Pegasys, by attaching a PEG (polyethylene glycol) molecule to regular IFN- α (PEG IFN α -2a).

This significantly prolongs its presence in blood and provides extended activity.

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 approved as therapy for Hepatitis B and C, at the dose of 180 mg/week.

The French "PV-Nord" group conducted a study of Pegasys in patients with PV, and recently reported results in 37 evaluable patients. All patients had responded to Pegasys at the 12 months evaluation, including 35 with complete hematological response (CR; normal blood cell count, no enlarged spleen, no phlebotomy; 94.6%). Neither

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PATIENT POWER

Forbes includes MPD Foundation in an article on the way patient groups are accelerating the development of new drugs.

We're not alone. The September 15, 2008 issue of Forbes features an article on a number of patient groups, and says, "Patient groups with an entrepreneurial bent have become the drug industry's new power brokers."

We can't exactly claim to be power brokers, but we're definitely part of the scene.

Along with a discussion of other patient groups, the article briefly describes MPDs and tells how in 1997 Robert Rosen called Robert Pritzker – they both happened to be seeing hematologists at the same clinic in Chicago – with the idea of starting the MPD Foundation.

Then it tells how the Foundation formed the MPD Research Alliance and gradually got three prominent researchers at different institutions to overcome their reluctance to share information and develop a genuine spirit of collaboration.

The article ends with the good news that there are now seven anti-JAK2 drugs in clinical trials.

"If you were told you have an incurable disease, you might be motivated to help find a cure." — Forbes, September 15, 2008

MPD FOUNDATION MEETS ALL 20 BBB CHARITY STANDARDS

The MPD Foundation proudly announces that we recently won approval to display the seal of the BBB Wise Giving Alliance, the nation's most experienced charity evaluator.



bbb.org/charity

"National charities that display the BBB Wise Giving Alliance seal can do so with pride," says Art Taylor, President and CEO of the Alliance. "Not only are they attesting to their organizations' adherence to sound standards, they are helping to increase donor confidence and strengthen public trust in giving."

RECENT AND UPCOMING EVENTS

*By Ann Brazeau
MPD Foundation*

MPD Patient Support Group Coordinators First Annual Symposium

The first annual MPD Foundation Patient Support Group Coordinators Symposium was held in Chicago, September 26th and 27th, 2008.

Coordinators from all across the country and from Japan, United Kingdom, Canada and Puerto Rico met in person for the first time to discuss how to improve outreach to MPD patients, the latest news on MPD research and current clinical trials, how to cope with living with a chronic illness and basic meeting planning strategies.

This two-day event included a recognition dinner as a way to thank these exceptional volunteers for their time, commitment and outreach to the many patients in their respective parts of the world.

October Educational Fundraiser: An Evening at the Detroit Institute of Arts

On October 9, 2008, 150 guests of Josephine Pompeo, a recently diagnosed myelofibrosis patient, will gather at the Detroit Institute of Arts to learn more about MPDs and what they can do to help.

A cocktail party, including entertainment by the famous Simone Vitale Band, will be followed by a sit-down dinner.

Guests will hear Josephine's story, her hematologist's explanation of the disease and a presentation from the MPD Foundation's Ann Brazeau.

This event will be a first in the Detroit area. Josephine also assisted with the formation of a Michigan patient support group several months ago, and already membership has grown to nearly 30 patients.

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LIVING WITH A BLOOD CANCER SYMPOSIUM AND RECEPTION

The MPD Foundation hosted a Patient Reception in conjunction with the Mayo Clinic's Living with a Blood Cancer Symposium in Chicago on May 2, 2008. Over 60 patients and family members attended the reception from all different parts of the US and from several other countries. This reception opened the door for new patients who had never before spoken to another MPD patient and presented a great opportunity to ask experts in the field specific questions about their disease.

Dr. Ronald Hoffman, a member of the MPD Foundation Research Alliance, and Dr. Ruben Mesa, from the Mayo Clinic, were on hand and accessible for questions and support.

A special thanks to TargeGen for generously sponsoring this reception.



Attendees socializing at the MPD Foundation reception.



From left to right: Robert Rosen, Sarah Dreller and Ann Brazeau at the reception table.



From left to right: Matt Weismantel, patient support group coordinator for NJ and PA, Susan Protter, patient support group coordinator for a new group forming in Manhattan, and Dr. Ronald Hoffman.

RECENT AND UPCOMING EVENTS

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Mesa Finishes Triathlon in 14 hours and 34 minutes for a Cure!

Dr. Ruben Mesa, a hematologist and MPD researcher from the Mayo Clinic, participated in the Ironman Wisconsin Triathlon on September 7th. Mesa swam 2.4 miles, cycled 112 miles and ran 26.2 miles in just 14 hours and 34 minutes. To date, he has raised over \$6000 for MPD research and awareness and the checks keep coming.

3rd Annual Al Bolea Memorial Bike Ride Helps Fund MF Research

The 3rd Annual Al Bolea Memorial Bike Ride took place in Massachusetts recently. Al Bolea lost a gallant fight against myelofibrosis in 2005. This year's ride through the Charles River Wheelman (CRW) bicycling group raised research dollars for MF. Al was a 16 year veteran with the CRW. The MPD Foundation greatly appreciates the many volunteers who help to make this event a success.

JAK2 INHIBITORS: A WORD OF CAUTION

By Dr. Ayalew Tefferi

Division of Hematology, Mayo Clinic, Rochester, MN

A cellular enzyme classified as a cytoplasmic tyrosine kinase (CTK), referred to as Janus kinase 2 (JAK2), has recently been shown to be involved in a series of mutations that have been described in PV, ET and PMF over the last three years. These mutations involve either JAK2 itself (e.g. JAK2V617F) or another protein called MPL, which is also involved in the JAK2-driven JAK-STAT cellular signaling pathway.

Among the JAK2 and MPL mutations in PV, ET and PMF, JAK2V617F is by far the most frequent; mutational frequency is estimated at over 95% in PV and 50% in ET or PMF. In contrast, the so-called JAK2 exon 12 mutations are rare and appear to be specific to JAK2V617F-negative PV (i.e. overall incidence in PV estimated at 3%).

What does JAK2 really mean to MPD patients?

At present, it is not clear if the presence of either a JAK2 or MPL mutation in either ET or PMF has prognostic relevance. Current information is equally inconclusive regarding the prognostic relevance of JAK2V617F allele burden in PV, ET or PMF.

JAK2 and MPL mutations cause PV- or PMF-like disease in mice. Despite this compelling observation, it is currently not clear as to how much JAK2 and MPL mutations contribute to the pathogenesis of PV, ET or PMF. In this regard, it is important to note that patients with PV, ET and PMF usually display activated JAK-STAT signaling regardless of whether or not they carry one of these mutations.

Therefore, JAK-STAT, and not necessarily a specific JAK2 or MPL mutation, is now considered a rational target pathway for drug development in PMF, PV and ET. In other words, most anti-JAK2 clinical trials include patients who are either positive or negative for one of the aforementioned mutations.

JAK2 Inhibitor clinical trials: What are the hidden risks to ET and PV patients?

A number of anti-JAK2 drugs have undergone pre-clinical testing and some have already been introduced into clinical trials. However, it is important to understand the natural history of PV, ET and PMF well before committing patients to unknown risks associated with experimental drugs.

For example, low-risk patients with ET or PV do not require cytoreductive therapy and their median survival exceeds or approaches 20 years. Similarly, although high-risk patients with ET or PV require cytoreductive therapy, they are currently well managed by treatment with hydroxyurea, low-dose aspirin and phlebotomy in case of PV.

Therefore, it may be inappropriate to include patients with either ET or PV in early phase clinical trials using anti-JAK2 drugs before their short-term and long-term safety is well documented. Furthermore, one has to demonstrate convincing evidence that such drugs might affect the natural history of the disease before considering their use in ET or PV; in other words, one has to show that molecular and biological markers of disease are favorably affected during ongoing clinical trials in PMF. In the end, FDA approval for use in either ET or PV will probably require demonstration of superiority over hydroxyurea in a controlled setting.

Survival is significantly shorter in PMF compared to both PV and ET; life expectancy in intermediate to high risk patients with PMF is estimated at less than 5 years. In addition, quality of life in PMF is severely compromised by splenomegaly, anemia and constitutional symptoms.

Therefore, such patients are reasonable candidates for Phase I and Phase II JAK2-targeted clinical trials. A positive outcome in this setting, especially if accompanied by favorable biologic activity (e.g. reduction of JAK2V617F mutant allele burden), might be adequate to warrant registration studies in PMF that are not necessarily controlled.

A number of JAK2 selective kinase inhibitors are currently being tested in humans. The results of some of these studies have been reported in meeting abstracts only and one should wait until the

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JAK2 INHIBITOR CLINICAL TRIAL

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lide within 7 days or hydroxyurea within 1 day of enrollment. All other cytoreductive therapies or investigational medications must be discontinued within 28 days of enrollment.

Other criteria also apply. For details, contact Dr. Srdan Verstovsek, the Leukemia Department's MPD Program Leader at M.D. Anderson Cancer Center, at sverstov@mdanderson.org or 713-745-3429. For information on other clinical trials at M.D. Anderson, visit <http://www.mdanderson.org/diseases/mpd/> and click on "clinical trials."

For additional information about JAK2 inhibitors (including eligibility criteria for participation in clinical studies), and all other available studies for MPDs at M.D. Anderson Cancer Center, visit our website at <http://www.mdanderson.org/diseases/mpd/> (Click on "clinical trials" and associated trial number).

OFFICIAL NAME CHANGE: MPDS ARE NOW MPNS

by Dr. Ayalew Tefferi

Division of Hematology, Mayo Clinic, Rochester, MN

According to the revised 2008 World Health Organization (WHO) classification system, the name "myeloproliferative disorders (MPD)" has been changed to "myeloproliferative neoplasms (MPN)." This new WHO category of MPNs includes the four classic diseases we usually think of as MPDs – chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) – plus three new ones: chronic neutrophilic leukemia, chronic eosinophilic leukemia and mastocytosis.

The National Cancer Institute defines neoplasm as "an abnormal mass of tissue that results when cells divide more than they should or do not die when they should. ... Also called tumor." As we all know too well, MPN patients have more than enough cells that divide more than they should, but tumors aren't part of the picture.

Neoplasm means (correct definition to come)

Editor's note: Regardless of the WHO decision, the MPD Foundation has no intention of changing its name any time soon.

THE PEGASYS ALTERNATIVE

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thrombosis nor hemorrhage was reported. Only one case of a serious side effect was reported (grade 3 skin rash, on a scale 1-4).

During the whole study period (median follow up of 31 months), treatment was stopped due to mild toxicity (grade 1-2) in 9 (24%) patients.

Pegasys as a JAK2 Inhibitor

Pegasys also reduced the presence of the JAK2 V617F mutation. Sequential blood samples available in 29 patients showed a measurable V617F decrease in 26 (90%) patients.

Median V617F decreased from 45% before Pegasys, to 22%, 17%, 5%, and 3% after 12, 18, 24, and 36 months, respectively. Molecular CR (JAK2 V617F undetectable) was achieved in 7 patients.

Those results show that Pegasys yields high rates of hematological and molecular response in PV with limited toxicity, and could even eliminate the JAK2 mutated clone in selected cases.

M.D. Anderson Study of Pegasys

Pegasys is currently being evaluated in a Phase II study at M.D. Anderson Cancer Center, Houston, TX, for patients with advanced ET and PV.

A total of 76 patients have been enrolled and treated thus far (36 ET, 40 PV). After a median follow-up of 2 years, 85% of patients have responded. In 5 of 41 (11%) evaluable patients with serial bone marrow samples, V617F became undetectable. So far only 7 patients (9%) stopped therapy due to therapy-related toxicities.

Pegasys results in remarkable clinical activity with an acceptable toxicity profile in advanced, previously treated, patients with ET or PV.

Clinical responses are frequently accompanied by significant reduction of JAK2 V617F allele burden, which becomes undetectable in a proportion of patients, suggesting selective targeting of the malignant clone.

JAK2 INHIBITORS: A WORD OF CAUTION

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studies are completed and fully published before making any conclusions.

In the mean time, I recommend that patients contact the individual centers that are involved in anti-JAK2 clinical trials to get more information about eligibility and logistics.

Dr. Ayalew Tefferi is dedicated to both the scientific method and the well-being of MPD patients. He is deeply involved in finding and proving the efficacy of better treatments, both at the Mayo Clinic and as a founding member of the MPD Foundation's Research Alliance.

WE NEED A CURE.

**THE MPD RESEARCH ALLIANCE
NEEDS YOUR HELP TO FIND ONE.**

Please be generous.

MPD
FOUNDATION
www.mpdfoundation.org

TIME AND COMMITMENT

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We know that one drug, INCB018424, has shown activity in MF patients, even those who are JAK2 negative. Published reports show that the drug is effective in MF patients at reducing spleen size and appears to provide clinically meaningful reductions in fatigue, night sweats and pruritus. Ongoing early stage clinical trials are designed to understand the drug's mechanisms of action and establish the optimal dosing regimen for larger later stage trials, Phase II and Phase III. It will take more years of testing to make informed evaluations as these drugs work their way through the clinical trial pipeline.

Nevertheless, preliminary results have been sufficiently favorable that one trial has been expanded to include patients with ET and PV. (See article on page 3.) We will be interested to see how this drug and other JAK2 inhibitors perform with PV and ET patients.

In addition to the JAK2 inhibitors, some studies are showing highly favorable results from the use of Pegasys, which is written about on page X of this newsletter. We may need to direct more resources to understanding the mechanics of this drug. Many informed researchers feel that there is another mutation, upstream of JAK 2, which merits attention.

I suspect we will need patience, as well as continued commitment to the kind of leading edge research that has brought us to this point. An enormous amount of progress has happened in recent years, and it is our committed goal to continue the forward momentum.

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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