As I write this it is August and still high summer here in Chicago. This year we feel a rare seasonal hopeful-ness. Both our baseball teams are still roughly in contention for their division pennant races, and the angst normally associated with the Cubs swoon has not yet set in. My wife and I took two neighbor boys, young men actually, to see the Cubs last week. We had good seats and ample time to enjoy the slow elegance of the game in our role as spectators.

As patients we sometimes feel like spectators, ineffective in our hopeful waiting for the next scientific victory, observing but not influencing the pace of progress. We may feel this way, but the truth is more encouraging. The difference is this: fans at a baseball game cannot affect the outcome, but you as a patient can make a difference. You can be the game changer, a vector of force that pushes us closer to success.

As patients, we’re helping the scientists make progress.

Patients, their friends and families make the MPD Foundation. Without your support, there would be no MPD Foundation. We could not have funded the best scientists in the world to investigate our disease and advance the field of knowledge. You enable the foundation to function, to fund medical research and to support patients in other ways as they wrestle with issues related to an MPD diagnosis.

Since the decoding of the human genome, our knowledge of the biology of MPDs continues forward in leaps and bounds.
LARGE SCALE PEGASYS TRIALS TO OPEN THIS YEAR
By Ruben A. Mesa, M.D., Professor of Medicine, Mayo Clinic, Scottsdale, Arizona

MPD Research Consortium will launch two international trials to help define best-practice treatment for high-risk PV and ET

Pegasys (pegylated interferon - alpha 2a) has shown promise in early pilot studies. The goal of these large-scale international clinical trials is to help establish a current true standard of care for high risk PV and ET, and to determine the full impact of treatment on MPD symptoms, disease control, and perhaps disease progression.

The current therapy of essential thrombocytopenia (ET) and polycythemia vera (PV) consists of decreasing short-term risks of “vascular events” (i.e. blood clots or bleeding) with a long-term eye on potential progression of these diseases to either myelofibrosis or acute leukemia. Treatments to control those short-term risks include low-dose aspirin (for both ET and PV patients) and phlebotomy (mainly for PV). Patients at higher risk of blood clots or bleeding (age over 60, or prior “vascular event”) usually also take hydroxyurea (or anagrelide) to lower their hematocrit (or platelet count) to further decrease risk.

Interferon-alpha has been used (primarily in PV) to control counts, and according to non-randomized trials (by Dr. Richard Silver and others) might slow down progression of the disease to MF. Pegylated interferon alpha - 2a (Pegasys: Roche Pharmaceuticals) lasts longer than regular interferon, and generally needs to be injected only once a week. This is obviously more convenient for patients, and it also seems to lead to fewer side effects.

Two recent and important studies, one by Dr. Jean-Jacques Kiladjian from France and the other by Dr. Srdan Verstovsek from M.D. Anderson, have shown that this form of interferon in PV and ET a) was tolerable, b) helped control counts well c) seemed to decrease risk of blood clots and bleeding and d) decreased the relative amount of the mutant JAK2 burden in patients.

In order to determine whether Pegasys is indeed as beneficial as these initial pilot studies suggest, the MPD Research Consortium is undertaking two parallel studies on the use of Pegasys in patients with high-risk ET and PV. These trials will be available at 35 medical centers around the world, 12 in the United States and 23 in Europe (representing 11 separate European countries).

Two parallel studies
The first trial is a randomized study between the use of Pegasys versus hydroxyurea therapy in patients with high risk PV and ET. This large study measures the impact of therapy on MPD associated symptoms (i.e. fatigue, itching, night sweats), blood count control (i.e. phlebotomy or platelet count), side effects of treatment, and the JAK2 allele burden.

The second parallel study is also for patients with high risk PV and ET, but who have “failed” hydroxyurea due to either intolerance of the side effects or lack of response. This latter study is for patients who likely have had an MPD for a longer time than patients in the randomized trial.

These trials highlight the role of international cooperation for rapidly and successfully conducting important clinical trials to help patients with MPDs. Results will likely decide which current therapy should be considered the current “gold standard” for comparison to future therapies (such as JAK2 inhibitors).

Further information about these clinical trials (including participating centers and dates of opening) will be available this winter on the MPD Consortium website at www.mpdr-e.org or the MPD Foundation website at www.mpdfoundation.org.
The discovery of the JAK2V617F mutation has produced a promising candidate for molecularly targeted therapy in the majority of patients with myeloproliferative diseases. But...it’s not that simple.

Researchers have also discovered a mutation in the TET2 gene in some MPD patients; it also occurs in MDS and AML. But we know very little about the function of the TET2 gene or how it interacts with JAK2. In fact, we don’t even know how either of these mutations causes MPDs. In short, we’re looking for something far more complex than a simple biochemical on/off switch to disable the JAK2 mutation.

A unique analytical tool: the conditional knock-in mouse

For a number of reasons, we can’t find what we’re looking for by simply testing one potential JAK2 inhibitor after another in clinical trials on humans. It would be unacceptably risky and prohibitively expensive; it would take decades to run through all the possibilities; and it would ultimately delay the introduction of the more effective treatments that MPD patients need now.

What we need is a fast way to test large numbers of compounds in a way that accurately replicates what happens with MPDs in humans. And the exciting news is that at Harvard we have developed an effective analytical tool that does just that: a conditional knock-in mouse model. That’s a strain of mice with the JAK2 gene activated. (A knock-out model has the gene deactivated.) These mice have the JAK2 mutation present in their stem cells, and they express the mutation exactly as it is expressed in MPD patients.

This gives us a superlative way to understand what’s happening in the stem cells. We can also study combinations of mutations using other mice, and can recapitulate in mice what happens in patients. We can also create either disease-free or “in remission” mice. We are also developing TET2 conditional knock-out mice that can be crossed into the JAK2V617F knock-in mice, to better understand the role of TET2 in MPDs in humans, and how it might impact the therapeutic activity of JAK2 inhibitors. This is the most sophisticated model available today. Some labs, for example, inject human MPD cells into immunocompromised mice. This is a less precise model because of both the human cells and the immunocompromised mice.

What we can learn from our mice

By studying our conditional knock-in mice, we can develop an extremely accurate model of what will happen in MPD patients in various circumstances. We’re looking at basic questions such as, “How does the JAK2 burden influence disease development?”

“What is the relationship between JAK2 and TET2?”

“What are the consequences of these mutations in the context of the hematopoietic stem cell, which is the ultimate therapeutic target?”

But we never forget that patients want a cure, not a lesson in genetics. So we’re also looking for answers to the questions patients care about most: “Which cells can self-renew and create the disease?” and “How can we stop them?”

“What are the effects of various therapeutic agents on JAK2? On stem cells? And, most important, on the disease itself?”

There’s a long way to go before we discover a cure, but we can proudly say that we’re making progress far faster than would have been conceivable even a few years ago.
NYC Patient Symposium coming up November 4

The MPD Foundation and the Cancer Research and Treatment Fund will be co-hosting the 5th MPD Patient Symposium in New York on November 4, 2009. Guest speakers include Drs. Ayalew Telfer, Richard Silver, Ruben Mesa, Jerry Spivak, Richard Champlin, Tiziano Barbui, Srdan Verstovsek and Robert Rosen, from the Foundation. This day-long event will be held at the New York Athletic Club. Attendees will enjoy a unique opportunity to engage with guest speakers from the most prestigious cancer centers and share their experiences with fellow patients. For more information and to register, call 212-288-6604 or visit www.crt.org.

Over 150 Participate in the 4th Annual Al Bolea Memorial Ride

In 2006, Al Bolea passed away from myelofibrosis. Every year since, his friends and family have gathered to celebrate his life and raise money for MPD research by hosting a charity bicycle ride. Al was an avid cyclist. This year the ride, which took place near Boston, included a BBQ and raffle. Over 150 cyclists participated, topping previous years’ participation. In addition to making this annual ride a reality, Al’s family served and catered the BBQ.

The MPD Foundation greatly appreciates the effort the family has made to work with the Foundation to host this event. In addition, over 150 participants came out to support MPD, and together, the group raised more than $35,000. We are proud to have been able to present the Al Bolea Memorial Fund with over $15,000 to support MPD research.

MPD Patient Support Groups Continue to Flourish

There are now thirty MPD patient support groups, eight of which are out of the country and two online. The newest additions are in New York City, San Diego, Phoenix and New England. These groups offer a safe place for MPD patients and their families to share their stories and learn up-to-date information on MPD research, current drug therapies and clinical trials. Participants can hear from experts in the field either in person or through conference calls.

The MPD Foundation posts meeting information and collateral materials on its web site, assists with securing speakers and helps support groups use constant contact e-mails to reach out to patients in specific areas.

If you are interested in attending a support group meeting, please visit our website at www.mpdfoundation.org and click on “Patient Resources” for a list of cities and contacts. If you would like to learn more about forming a group, contact Ann Brazeau, VP of Development, at 312-683-7226 or abrazeau@mpdfoundation.org.

A Faster, Greener Way to Receive MPD Related News

Send your email address to: mwoehrle@mpdfoundation.org or just fill out the enclosed card to receive regular email updates on research, clinical trials, MPD community events and more.

EVENT UPDATES
by Ann Brazeau, VP of Development

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Thanks to you, we’re nearly $8 million closer to a cure

The goal is almost in sight, and with your continued support we’ll get there. Please be generous.

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

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

MPD Foundation
233 South Wacker Drive, Suite 375
Chicago, IL 60606
Tel (312) 683-7243 Fax (312) 332-0840
www.mpdfoundation.org