NEW NAME, NEW GRANTS

By Robert Rosen

If you look carefully, you’ll notice that in this issue we’re introducing a new name for our organization: MPN Research Foundation. Over the last year our board of directors has wrestled with the increasingly frequent use of the acronym MPN (myeloproliferative neoplasm) in place of MPD (myeloproliferative disorder) throughout the scientific community. So, in order to keep up, we have officially changed our name. An article on page 5 explains the scientific community’s reasons for making the change.

Growing up in a leafy suburban setting, I absorbed some of the outdoor culture that comes with raking leaves and mowing the lawn in a wooded back yard. When our first child was born, long after I moved out, my father nailed a sign on an oak tree proclaiming a part of the yard to be Rebecca Park. The sign remained in place until their deaths 37 years later.

As I watched those backyard trees grow and mature, that old metaphor about mighty oaks starting out as little acorns became meaningful to me. Like those acorns, MPN Research Foundation grants fund the seeds of research ideas. These ideas incorporate the strong possibility of growing into a body of work that will stand tall and strong in our medical community.

Our New Investigator grant program is intended to nurture young scientists who will bring fresh new ideas to us.

Some years ago, one of our younger investigators was at a career crossroads, unsure of whether there would be funding available to continue his research in the MPNs. Although he

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The December, 2010 American Society of Hematology Annual Meeting again proved to be an exciting event with an impressive number of presentations on the Myeloproliferative Neoplasms. There is an ever growing interest in the disease with more and more researchers jumping into the field. We expect that this will translate to new insights into the biology and new therapies in the near future.

**JAK Inhibitors Move Closer to FDA Review**

The most exciting news from ASH 2010 involved the march of small molecule JAK inhibitors towards FDA review. The Phase 3 COMFORT trial of the lead JAK inhibitor, INCYTE 018424 (aka 424), in patients with myelofibrosis is nearly completed. Phase 1/2 data presented by the clinical investigators, including Drs. Ayalew Tefferi and Srdan Verstovsek, were published in the *New England Journal of Medicine* in September 2010.

This report showed that 424 is effective at inducing marked reductions in spleen size and significant improvement in constitutional symptoms. At the ASH meeting, Dr. Verstovsek and colleagues also reported promising results of 424 in patients with PV or ET who are refractory or intolerant to hydroxyurea. They observed durable normalization of hematologic parameters, resolution of splenomegaly and alleviation of symptoms in the majority of patients. The word on the street is that INCYTE will be seeking FDA approval for use of 424 in PMF this calendar year.

Promising results for two other JAK inhibitors were presented. Dr. Animesh Pardanani reported that TargeGen 101348 is well tolerated and effective in control of constitutional symptoms and splenomegaly. This JAK inhibitor even appeared to reduce allele burden in some patients. Despite the recent acquisition of TargeGen by Sanofi, it appears that 101348 will continue to be developed for MPN.

Dr. Pardanani also presented data from a Phase 1 study of CYT387, a small molecule JAK1/2 inhibitor, in PMF. This drug led to decreased spleen size and improvement in constitutional symptoms in most patients. Intriguingly, CYT387 also led to marked improvements in anemia: 5 of 9 patients experienced a >50% reduction in transfusion requirement.

Together, it is becoming clear that currently available JAK2 inhibitors differ in their toxicity and therapeutic activity profile and one cannot make general conclusions about the utility of these agents in MPNs based on experience from one individual drug.

**Beyond JAK2: Other Pathway Inhibitors**

In addition to JAK inhibitors, reports of several other pathway inhibitors were presented at ASH. These alternative therapies include HSP90 inhibitors, such as PUH71 under study by Dr. Levine, HDAC inhibitors, including vorinostat (Merck) and LBH589 (Novartis), and PI3K/AKT pathway inhibitors, such as RAD-001 and BEZ235. These inhibitors show varying degrees of efficacy in pre-clinical studies and some are in early phase clinical trials. These drugs may be useful in combination with JAK inhibitors.

Two other drugs were highlighted: pomalidomide and Pegasys. Dr. Tefferi presented data suggesting that low-dose pomalidomide is effective in the treatment for anemia associated with JAK2V617F-positive myelofibrosis, especially in the absence of marked splenomegaly. Pomalidomide also appears to improve thrombocytopenia in most subjects with baseline platelets <100 x 10^9/L but is not active in controlling disease-associated splenomegaly.

Separately, a phase 2 study presented by Quintás-Cardama and colleagues reported that PEG-IFN-α-2a is active in advanced, previously treated PV and ET patients. Unlike JAK inhibitors, clinical responses achieved with Pegasys are frequently accompanied by significant reduction of JAK2V617F allele burden, which becomes undetectable in a proportion of patients. The main drawback to this therapy is that 30% of patients were taken off study after a median
The MPN Research Foundation has just announced its 2011 research grants. The six recipients are all, in different ways, pursuing the same bad guys: the handful of mutations, among the 25,000 or so genes in the human body, that are responsible for causing myeloproliferative neoplasms.

Once those mutations are discovered, researchers will try to develop medicines that inactivate them and, at long last, control or even cure the diseases.

$150,000 Established Investigator Awards

The MPN Research Foundation awarded three $150,000 Established Investigator Awards, each renewable for a second year if the investigators’ first-year results show promise.

**Dr. Shaoguang Li**, at the University of Massachusetts Medical School, is trying to confirm the identification of the gene Alox5 as a target for the treatment of polycythemia vera, one of the three classic MPNs. Alox5 is a promising target, because its presence is essential for the development of a related blood disease, chronic myelogenous leukemia; its loss prevents the disease from developing.

**Dr. Robert Kralovics**, at the Center for Molecular Medicine, Austrian Academy of Science, is attempting to decipher the genetic complexity of myeloproliferative neoplasms through genome sequencing.

**Dr. Benjamin Ebert** and **Dr. Ross Levine**, at Harvard Medical School and Memorial Sloan Kettering Cancer Center, will use whole genome sequencing to identify variant forms of genes that contribute to MPD pathogenesis.

$75,000 New Investigator Awards

The MPN Research Foundation also provides grants to new investigators, in the hope of encouraging them to devote their careers to research in the MPNs. These grants may also be renewed for a second year.

**Dr. Toshiaki Kawakami**, at the La Jolla Institute for Allergy and Immunology, is studying a series of genes whose absence in mice is known to cause tumors and myeloproliferative neoplasms. He hypothesizes that the same thing happens in humans, and if it does, the discovery could lead directly to new therapeutic targets for MPN drug development.

**Dr. Wei Tong**, at the University of Pennsylvania School of Medicine, is trying to determine the ways in which a protein called LNK down-regulates JAK signaling. JAK2 is basically an on-off switch whose malfunction is present in many MPNs. LNK normally regulates the JAK2 switch to prevent myeloproliferation; mutated versions fail to turn off the signaling.

**Dr. Saghi Ghaffari**, at the Mount Sinai School of Medicine, is investigating a different signaling mechanism whose failure may be responsible for myeloproliferation. This is important because the JAK2 mutation is not present in all MPN patients; there must be at least one other mutation to account for those cases.

Each research project was selected for the direct impact it could have on patients, either in the short term or by opening new avenues for productive research in the future, and for its potential to leverage the Foundation’s limited funds by producing, over time, benefits far exceeding the initial investment.
There I was, cruising down the highway of American Life when three vein clots in my gut forced me on a detour I never saw coming. I was living a great life at the age of 42: my husband and two middle-school children were healthy, smart, and fun; we were “pregnant” with our adoption application submitted to the Chinese government; my job running a nonprofit housing organization was my passion; and my community service through local, state, and national nonprofits was also very rewarding. Life was hectic, there was always more to do than time to do it, and I thrived!

The first detour began in the Fall of 2007. I felt run down, but I struggled with anemia all my life, so it wasn’t too unusual. Suddenly my stomach bloated and became painful. There’s a dramatic story but here’s the ending: hubby got me to the hospital and an emergency surgery saved my life: portal, mesentery, and splenic veins were clotted; 90 cm of small intestine was necrotic and removed. The Hem/Onc diagnosed the thromboses due to Protein C and Factor XII deficiencies (JAK2 test was not performed). My discharge instructions were to stay on warfarin indefinitely.

This detour had speed bumps and dead ends. I returned to work but couldn’t resume my normal 10-12 hour work days plus kids’ activities. It was all I could do to put in 6-8 hours at work. After consulting with my husband, I retired from the position I had held for 12 years in September, 2008.

We also had to accept that the child we sought for our family through adoption would not come to be. The feeling of loss for the daughter I dreamed of since I was in college continues today.

Not ready to quit work completely, I did as much consulting work as my body and brain could handle in 2009. But the fatigue worsened. I wanted naps. I started forgetting far more than my usual.

The second detour occurred in September, 2009, with another medical emergency: hematocrit at 69.1, very high blood pressure, severe ankle & leg swelling, vision problems, migraines. The internist believed it to be Polycythemia Vera.

Hello, Polly

Two years after the clots, I was diagnosed with Polycythemia Vera. I’m JAK-2 positive. My treatment regimen is Hydrea daily with occasional phlebotomies.

It’s important for humans to be able to name what ails us. At last, I could tell people I had to leave my career because I had Polycythemia Vera. It sounds more impressive than “I was so exhausted and forgetful all the time. I couldn’t keep up.”

I personify PV and call her Polly. Since she is of me and in me, I talk to her as I deal with the side effects and impacts on my life. “C’mon Polly, let’s get these groceries unloaded and then we’ll lie down for awhile.” (You’ve never talked to your car when it’s low on fuel?)

The third detour came up quickly last March, 2010. I had to quit work mid-project for a client because I didn’t have the stamina and concentration necessary to fulfill the assignment. That was a big blow to my psyche, not to mention my bank account.

I felt like a failure. And I felt robbed by Polly. She forced me to put my Wonder Woman cape into storage. But she will not take my sense of humor! As my family and I adjust to a “new normal” we use the traffic light system as code for how I’m feeling and what they can expect from me:

“Green light” day means I’m feeling good and can do everything as normal. “Yellow light” day means that I’m fatigued and can do some things but need some naps and cannot do optional errands and outings. “Red light” day means I’m exhausted and feeling poorly; I’m in bed or on the sofa all day – no energy to cook or clean or help anyone.

My mother taught that driving different ways home makes the journey more interesting. If Polly is my GPS life navigator, I can count on a future of “recalculating route.”

Marina lives in Duluth, Georgia with her husband Robert and their two teenagers. She is a member of the Atlanta MPD Support Group. She updates her blog (when she’s not too tired) at: www.funnymama.blogspot.com
CHICAGO MPN ROUNDTABLE CREATES NEW ERA OF OPEN COMMUNICATION

By Michelle Woehrle

In 2010 (before changing our name) the MPD Foundation began playing host to a gathering of MPN specialists in the Chicago area, recruiting doctors from Rush, Northwestern, University of Chicago, University of Illinois at Chicago, and Loyola. This group, now known as the Chicago MPN Roundtable, was conceptualized as a way to draw clinicians and researchers from local hospitals and universities into a discussion about patient care, recruitment for research and the potential of inter-institution collaboration.

The Chicago MPN Roundtable members are working on the following projects:

**MPN/MDS Rounds.** Roundtable co-chairs Laura Michaelis and Brady Stein (Loyola and Northwestern, respectively) together with member Jamile Shammo (Rush) are working with the MPN Research Foundation and Aplastic Anemia & MDS International Foundation to host an information session for clinicians in the Chicago area. These sessions, known as MPN/MDS Rounds, offer doctors access to the latest research and best practices for clinical care.

**Access to Ongoing Research.** A goal of the Chicago MPN Roundtable is to create a central point of contact for Chicago area patients interested in considering a clinical trial.

**Collaborative Publication.** The Chicago MPN Roundtable is working on ideas for collaborative research and publication. The group has drafted a proposal for a retrospective research project on MPN that will involve multiple local institutions working together for a joint research project.

The Chicago MPN Roundtable will benefit the MPN patient community by reducing barriers to communication between institutions as well as disseminating information to clinicians that could improve their care. We’re proud to be a part of this and hope to create a good model for establishing MPN Roundtables elsewhere.

WE HAVE CHANGED OUR NAME TO KEEP UP WITH THE SCIENCE

The MPD Foundation is now the MPN Research Foundation. But don’t worry; you’ll still be able to reach us at our current web address and email addresses, at least for the foreseeable future.

Why the change? Because in 2008 the World Health Organization (WHO) developed a new classification system for the Myeloproliferative Disorders (MPDs), and in the process changed the official designation to Myeloproliferative Neoplasms (MPNs). They also added a handful of new blood diseases to the category, such as chronic neutrophilic leukemia, chronic eosinophilic leukemia, hypereosinophilic syndrome and the not-very-helpful “MPNs, unclassifiable.”

However, the three diseases that have always been our concern – polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF) – are still considered the “classic” Philadelphia chromosome-negative [Ph(−)] myeloproliferative neoplasms. Our focus will remain on funding research to find a cure for these three diseases.

The word “neoplasm” actually defines our diseases far more precisely than “disorder” did. Neoplasia (Greek for “new growth”) means the abnormal proliferation of cells – in our case, one or more lines of blood cells. Many kinds of neoplasia result in lumps or tumors, either benign or malignant. They are called neoplasms, too, and are a good deal more common than our blood cell neoplasms; so friends may think you’re using the term “neoplasm” incorrectly. You won’t be.

But whatever we call it, we still need to cure it. We’re trying hard – you can read about our new research grants on page 3 of this newsletter. And we still need all the help you can give us. Please be generous. Write your first check today to the new MPN Research Foundation.

www.mpdfoundation.org
San Diego Symposium Brings the Experts to the Patients

The MPN Research Foundation hosted a patient educational symposium in San Diego on October 25th at the UCSD Moores Cancer Center in La Jolla.

Our keynote speaker, Dr. Catriona Jamieson, MD, PhD, is an Assistant Professor in the Medicine Hematologic Malignancies Program and Director of Stem Cell Research at UCSD. She discussed the possibility of using combination therapies for MPN patients since one drug may not manage all the symptoms.

Other speakers were Dr. Ross Levine, MD, a physician scientist at Memorial Sloan Kettering, New York; Dr. Jamille Shammo, MD, FASCP, Division of Hematology/Oncology, at Rush University Medial Center in Chicago; Ron Anderson, Patient and support group coordinator in Los Angeles; Dr. Ruben Mesa, MD, Professor of Medicine and Director of the Acute and Chronic Leukemias Program in the Division of Hematology-Oncology at the Mayo Clinic, Scottsdale, Arizona; Dr. John Crispino, PhD, Associate Professor of Medicine in the Division of Hematology/Oncology at Northwestern University’s Feinberg School of Medicine, the MPN Research Foundation’s scientific advisor and a member of its Chicago Roundtable.

After the presentations, patients formed groups specific to their MPN. A clinician/researcher joined each group and answered questions from individuals. Patients were able to share their stories and get feedback from the experts and fellow patients.

The MPN Research Foundation will continue to provide patient symposia throughout the year.

We extend a special thanks to our sponsors, Incyte Corporation, Sanofi-Aventis and Cytopia/YM Biosciences.

New York Symposium in November 2011

The Cancer Research and Treatment Fund has once again invited the MPN Research Foundation to co-host a patient education symposium in New York, this one on November 2, 2011. Details will be on our website as we complete speaker selection, location and additional logistics.

MPN Research Foundation Visits Cancer Centers to Grow Awareness & Partnerships

The MPN Research Foundation has begun to make personal visits to Cancer Centers across the country. These visits are specifically geared to engage the hematologists who see MPN patients. We want clinicians to know who we are, what we do and how we can assist their patients by connecting them to patient support groups, materials, providing educational symposia and general support. A clinician/researcher joins us to bring physicians up to date on diagnosis, current treatment protocols and updates on clinical trials. If your cancer center or hematology group would be interested in this two hour presentation, please contact Ann Brazeau at abrazeau@mpdfoundation.org.

Help Us Fund MPN Research

You can make a difference in your life and the life of a loved one by helping the MPN Research Foundation continue to fund meaningful MPN research. Please consider making a donation or an annual or monthly pledge. Don’t overlook the possibility that your company may have a matching gift program; whatever you donate to the MPN Research Foundation might be matched by your employer. Commemorative gifts and memorials are particularly meaningful ways of giving. Or you may want to ask your financial advisor for help establishing a planned giving program. Finally, you can combine generosity with fun by hosting a fundraising dinner or other event. For more information, please contact Ann Brazeau at abrazeau@mpdfoundation.org or at 312-683-7226.
Many MPN patients are struggling to get insurance coverage for their medicine. This is because most treatments prescribed are not FDA approved for MPNs and are considered ‘off label.’ Hydrea, Pegasys and IntronA are FDA approved drugs, but are not FDA approved for MPNs.

Approximately half of all anticancer drugs are prescribed off-label, meaning they are for indications other than those referenced in the United States Food and Drug Administration approved label. Some managed care organizations and private health insurance plans have declined to reimburse the cost of drugs used ‘off-label’ to treat cancer on the ground that these uses are “experimental” or “investigational.”

The Fee-for-Service Medicare program recognizes certain published compendia as authoritative references to identify medically accepted, unlabeled uses of drugs in anticancer treatment regimens. Some insurers refer to compendia when making policy decisions, thus creating a strong financial incentive for manufacturers to obtain a favorable compendium recommendation.

In the pharmaceutical industry, a compendium is a comprehensive listing of drugs. It typically includes a summary of the pharmacologic characteristics of each listed drug or biological; information on dosage; and, often, recommended uses for specific diseases. The current recognized compendia for off-label cancer drugs are: American Hospital Formulary Service Drug Information (AHFS-DI), National Comprehensive Cancer Network (NCCN) Drugs and Biologics, Clinical Pharmacology, and Thompson Reuters- DrugDex.

The accepted compendia contain listings of FDA Approved drugs. For each drug, there is also a list of cancer diseases that are considered favorable for off-label use. A disease gets added to the drug compendia for off-label purposes based on a review process that includes evidence from peer review journals, phase II studies, support from the drug company and physicians. The compendia listings serve as a strong guide, but not requirement, for insurance companies in considerations for coverage of off-label cancer drugs.

Of the four compendia, only two of them mention Hydrea for off-label use in Polycythemia Vera and none mention Pegasys which is growing in use among PV patients. Hydrea is typically universally reimbursed for all MPNs due to its compendia listing and relative low cost. This is not the case for Pegasys. Many MPN patients are experiencing insurance denials for Pegasys. Pegasys is a pegylated form of Interferon alpha made by Roche. It is FDA approved for Hepatitis C and as a result of its efficacy and tolerance in MPN phase II studies it is being prescribed more often in treatment for MPNs. While some patients are fortunate to have Pegasys approved upon initial prescription by their physician, many are being denied coverage immediately or after one year of treatment because it’s not FDA approved for MPNs.

A little history –
A key policy question of the late 1980s and early 1990s was whether medical insurance should cover unlabeled uses of drugs. Because health insurance policies generally excluded payment for experimental treatments, insurers denied claims for unlabeled uses of drugs. After several attempts in the preceding years, Congress, in the Omnibus Budget Reconciliation Act of 1993, amended Title XVIII of the Social Security Act, which governs Medicare, to address this issue. The provision required Medicare to cover off-label uses of anticancer drugs included in certain standard medical compendia.

Congress subsequently adopted a compendia-based system for determining coverage of off-label uses of all drugs reimbursed by Medicaid. When Congress created a new Part D outpatient prescription drug benefit for Medicare beneficiaries in the Medicare Modernization Act of 2003, the compendia-based coverage determination was again the model. Managed care medical directors, pharmacy benefits directors, and other health care professionals also reference the Compendium when making decisions that impact patient access to appropriate therapy. Private insurers often follow Medicare’s lead in paying for drugs. Thus, in a variety of legislative
of 9 months, with half of these cases due to toxicity.

**Advances in Basic Science**

Along with these important advances in clinical research, there were a number of important basic science discoveries presented at the meeting. For example, several groups reported new insights into the role of the TET2 gene, which is mutated in 5-15% of MPN patients. Dr. William Vainchenker, one of the first to identify JAK2 mutations in MPN, reported that animals that lack TET2 develop an MPN within 2 months of birth. The animals show increased white blood cell count, decreased red cell and platelet numbers and profound splenomegaly. This observation strongly suggests that TET2 mutations directly contribute to the phenotypes of human MPN.

Another exciting area of research involves the identification of mutations in known epigenetic regulators, such as ASXL1 and EZH2, which are mutated in 13-20% and 7-10% of MPN patients. Although the precise contribution of mutations in these genes to the pathology of MPNs is unknown, epigenetic changes frequently lead to differences in gene expression and could facilitate abnormal growth or survival of blood cells.

In summary, there is reason to be optimistic that new therapies will be available in the near future. In the event that JAK inhibitors are not curative, drugs that can be combined with JAK inhibitors are under development. The recent surge in clinical and basic research should soon be translated to improved quality of life for people with MPNs.

**INSURANCE COVERAGE FOR MPN TREATMENTS**

Contexts, Congress has strongly endorsed the value of the recognized medical compendia for ascertaining the medical appropriateness of off-label uses of cancer drugs.

**What does all this mean for MPNs?**

Some of the more common treatments for MPNs include IntronA, Hydrea and Pegasys. None of these are FDA approved for MPN and thus are being prescribed off-label. The MPN Research Foundation is currently looking into encouraging drug companies to apply for compendia listings.