MPD Foundation
advancing research • empowering patients

UPDATE
A PERIODIC NEWSLETTER FOR
THE MYELOPROLIFERATIVE DISORDERS COMMUNITY
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WWW.MPDFOUNDATION.ORG

UNCERTAINTY

by Robert Rosen

As I age I find that the thrill of the new has given way to a certain apprehension. The culprit is change. I always welcomed change, the challenge of the unknown, the skill required and acquired during periods of adaptation. I think of my three children, all at critical points in their young adulthood, and somehow I am glad that I am not so young anymore. Something has crept into my psyche, a discovery that change doesn't quite thrill me like it did before. I have become increasingly aware of some vague but new discomfort with uncertainty.

This is definitely not a useful trait if you are a genetic scientist these days. At the MPD Foundation we have been reading endlessly about changing theories on the human genome, speaking with our scientific advisors at every chance. When we started the foundation, we were thoroughly enlivened by the possibilities of using the newly decoded genome to address Myeloproliferative Disorders. Scientists and dreamers worldwide shared these ambitious thoughts. But the genome had other ideas, and scientific papers revisiting the working of the genome appear with regularity. We find that truly understanding the genetic roots of most diseases will take years, or decades or generations. The story unfolds and what might have been certain is now tinged with uncertainty.

Tremendous progress has occurred. From a biological point of view, studies into the genome have provided enormous amounts of vital information, growing every day. From a medical point of view, progress is happening, but more slowly. There have been some huge successes. Gleevec, a treatment for CML, selectively kills cells with the mutated

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UPDATE: POLYCYTHEMIA VERA CLUSTER IN PENNSYLVANIA

By Ann Brazeau

In 2004, several people living on the same rural road in northeast Pennsylvania were diagnosed with polycythemia vera. Since then, the Pennsylvania Department of Health (PADOH) reviewed these cancer cases and those reported to the Pennsylvania Cancer Registry from the three counties (Carbon, Luzerne, and Schuylkill) surrounding what is known as the Tamaqua borough. PADOH discovered that although the overall cancer rate in the tri-counties was similar to that of other parts of the state, there were significantly more PV cases than expected. In October of 2006, The Agency for Toxic Substances and Disease Registry (ATSDR) was asked to assist with more in-depth studies of PV in those counties.

Polycythemia vera is estimated to occur in 1 of every 100,000 people each year. The median age of diagnosis for PV has been approximately 60 years, and males account for slightly more than half (58%) of the cases. (These statistics were taken from a 2010 report from the International Journal of Environmental Research and Public Health, ISSN 1660-4601.)

The same year the first Pennsylvania cases were discovered, 2004, the Janus-activated kinanse -2 (JAK2) mutation was discovered; it occurs in 95% of all PV patients. Before the discovery of the JAK2 mutation, PV was diagnosed using a complex series of clinical and laboratory tests. However, in 2008, the World Health Organization (WHO) updated the existing diagnostic methods and included the JAK2 mutation as a major diagnostic criterion for PV. This method of diagnosis was used by ATSDR to validate cases in their examination of what was appearing to be a cluster of PV patients in Pennsylvania.

The ATSDR investigation had three main goals: (1) to locate all cases of PV in Carbon, Luzerne, and Schuylkill counties, (2) to confirm the diagnosis of the PV cases using medical records and JAK2 diagnostic tools, and (3) to describe the characteristics of the PV cases. ATSDR found a statistically significant cluster of 15 PV cases. They also found that nearly half of the cases had not been reported to the Pennsylvania Cancer Registry. The presence of numerous environmental exposures in the tri counties – and the absence of other causes –make it possible for external factors to be at the root of the PV cases in the area.

Can Environmental Causes Be Behind Some Cases of PV?

In August 2008, ATSDR and PADOH organized a meeting with a panel of experts in Philadelphia. Medical researchers, environmental scientists, and public health professionals met to review the findings and recommend future studies. Four major research areas were identified: epidemiology, genetics/biomarkers, toxicology, and environmental analysis.

The PV cluster in Carbon, Luzerne and Schuylkill counties will require a great deal of assessment of a host of possible environmental influences including hazardous waste sites, industrial emissions and waste, and naturally occurring radiation sources as well as possible genetic risk factors. Because the area was allocated a substantial amount of federal funding to study the specific causes, comprehensive research can be conducted that will not only benefit the local community but the entire MPN (myeloproliferative neoplasms) community.

For this rural community in Pennsylvania, the increased benefits are evident with local physician awareness, the formation of a patient support group, access to PV patient clinical trials, a community JAK2 screening and follow-up study, testing of residential properties and nation-wide attention to an orphan disease that otherwise can go unnoticed.

The MPD Foundation has paid very close attention to this evolving story in Pennsylvania and has supported and assisted the Centers for Disease Control, researchers, and the patients in those counties. The Foundation provides resources to the patient support group and is available as needed to interact with federal agencies.

THE PROMISE OF NEXT GENERATION DNA SEQUENCING

by John Crispino, PhD, Scientific Advisor

Every cell contains DNA, the genetic material that serves as the body's blueprint. In general, cells of different tissues within the same individual contain identical DNA sequences. However, small, but potentially devastating changes can occur in DNA within specific tissues. For example, genetic mutations are acquired during the initial development of MPDs, and additional changes occur during the progression from chronic PV to myelofibrosis or acute myeloid leukemia.

Until recently, scientists have used candidate gene sequencing, array comparative genomic hybridization, genomic single nucleotide polymorphism, or copy number variation arrays to identify these disease-associated genes. These strategies contributed to the identification of mutations in *JAK2, TET2, ASXL1, IDH1, IDH2* and *MPL* among others.

Although these insights have helped researchers better understand the biology of MPDs, there is much more to be learned. Indeed, nearly 20% of myelofibrosis patients lack any of the known MPD associated disease mutations. Moreover, it has become clear that *JAK2* and *MPL* mutations alone are not sufficient to cause disease.

Perhaps the Next Great Leap in Biology is at Our Doorstep

With the advent of next generation sequencing technology, which allows scientists to sequence every base pair of DNA from an individual, we are on the verge of precisely defining the complete repertoire of genetic mutations that cause disease. Whole genome sequencing has emerged as the premier way to uncover novel disease associated mutations.

In recent landmark papers, Tim Ley and colleagues at Washington University in St. Louis reported the whole genome sequence of AML blasts from multiple individuals. In the first study, which examined the genome of one AML patient, they identified ten genes with acquired mutations. The second study, which examined the DNA sequences of an AML specimen and a matched normal skin sample, described 12 acquired mutations in coding sequences and 52 additional changes in regulatory regions of the genome.

Determining which of these alterations are relevant to AML remains a challenge. Other limitations to whole genome sequencing include the high cost and the requirement for sophisticated computational biology.

Nevertheless, there is tremendous optimism for this new technology. We anticipate that multiple research groups will propose to use one form of next generation DNA sequencing to learn more about the genetics of MPD in the upcoming grant competition. Stay tuned for an update next year.

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gene. The discovery of the mutated JAK2V617F in many MPD patients is a stunning advance, and the story of JAK2 inhibiting drugs is being written as clinical trials are ongoing. Already their value seems clear for Myelofibrosis patients, and new generations of these drugs continue in development by multiple biotech and pharmaceutical companies.

In one of the exciting new scenarios, the cost of sequencing, or analyzing every gene in an individual's genome has come down to affordable levels. The MPD Foundation is engaged in the investigation of full genome sequencing for a subset of the MPD population. In theory, this would allow MPD patients to be evaluated for common variations in their genetic makeup compared to a healthy population. It is reasonable to believe that this technology, over time, properly implemented, and with results intelligently evaluated will yield critically important information about the genetic roots of the MPDs.

We will continue to keep you advised on the progress of our researchers and new thoughts about full genome sequencing.

RESEARCH GRANT RECIPIENTS REPORT PROGRESS

In February 2009, the MPD Foundation announced its largest set of research grant awards. $1.8 million dollars in total were awarded to 8 grantees; four of these awards were for continuation of the MPD Research Alliance and four were awards to outstanding new researchers committing their energies to work related to MPDs. Each award was for two years, pending annual review and approval by the Foundation's Scientific Advisory Board (SAB).

Grantees are required to submit semi-annual progress reviews, which are reviewed by the SAB. Highlights from the second of these reviews (at the end of the first full year of funding) are as follows:

- **Benjamin Braun, MD, PhD (University of California at San Francisco)** is studying signaling pathways in hematopoietic stem cells, and in particular the potential contribution of RAS mutations to leukemic transformation at the stem cell level.
- **François Delhommeau, PhD, PharmD (Inserm, Paris)** has sequenced the genes of hundreds of MPD patients with a mutation in the gene TET2, and is now studying the function of this mutation. TET2 occurs in approximately 15% of MPD patients, and may be a mutation that predisposes an individual to develop an MPD.
- **Benjamin Ebert, MD (Brigham & Women's Hospital, Boston)** is sequencing MPD patient samples and has identified new genes that are mutated in some MPD patients' cells. His lab has also developed a mouse model that includes both JAK2 and TET2 mutations, to test these mutations both separately and in combination.
- **Ron Hoffman, MD (Mt. Sinai, New York)** is studying the effects of interferon on MPD cells, and the results of these studies are leading to the Phase 3 randomized trial of Pegasys, scheduled to start this Fall.
- **Robert Kralovics, PhD (Center for Molecular Medicine, Vienna)** is studying chromosomal abnormalities in MPD using SNP arrays. He has identified a number of potential tumor suppressor genes (including IKZF1 and other genes on chromosomes 7 and 13). He is now doing whole genome sequencing on hundreds of MPD patients searching for disease associated changes.
- **Josef Prchal, MD (University of Utah)** is also studying interferon and its effect on MPDs. He will be using the results of the Phase 3 Pegasys trial in his work. He is collaborating with investigators in France and at Baylor University in the U.S.
- **Dorothy Sipkins, MD, PhD (University of Chicago)** is interested in the marrow/microenvironment interaction with malignant cells. Using novel *in vivo* imaging techniques, Dr. Sipkins has documented the homing and engraftment of both MPD and control CD34+ cells, and is now investigating how CIMF and PV cells exploit and alter the bone marrow vascular niche. This could provide targets for future therapeutic research.
- **Ayalew Tefferi, MD (Mayo Clinic, Rochester)** has published eight papers documenting correlative and mutation incidence studies done using the tissue bank developed with MPD Foundation funding over the past four years. This database of patient specimens and associated clinical data has been an invaluable resource to investigators from multiple institutions as they validate their discoveries, and to drug developers testing new compounds.

Based on the approval of the Scientific Advisory Board, all eight of these grants have been approved for a second year. The MPD Foundation is pleased and proud to have invested in the work of these eminent scientists.

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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MPD FOUNDATION ANNOUNCES 2010 CHALLENGE GRANT PROGRAM

by Barbara Van Husen

The MPD Foundation is pleased to announce that it is seeking proposals from MPD researchers for the 2010 Challenge Grant Program. Proposals, which are due by September 1, will be evaluated by the Foundation's Scientific Advisory Board in the Fall, and an award announcement will be made no later than February 1, 2011.

Worthy projects will advance the understanding of mechanisms of action in the MPDs and/or contribute to accelerating the discovery and development of new treatments for MPD patients.

Grants will be awarded in two categories:

- **New Investigator Awards.** Two-year grants of $75,000 per year. These grants are aimed at emerging investigators who are considering a career related to research in the myeloproliferative disorders (MPDs) or established investigators in other fields who are interested in bringing their experience, skills and ideas to research in the MPDs.

Projects may be basic or translational research. The proposal should demonstrate an understanding of current science related to the MPDs and should build on that science to help provide a direction for future research. Projects deemed to accelerate the discovery of effective treatments for MPDs will be considered as having an advantage for New Investigator awards.

- **Established Investigator Awards.** Two-year grants of $150,000 per year. These grants are aimed at researchers with a demonstrated interest and history of achievement in MPD research. Projects can be either basic or translational research, as long as results will contribute to new understanding, new molecular targets, or new treatments for MPDs.

The MPD Foundation believes that active and meaningful collaboration among researchers with diverse expertise will accelerate the discovery of new mechanisms of action and the development of effective treatments for the MPDs. Preference will therefore be given to established investigator proposals made by collaborative groups of researchers, at a single or multiple institutions. An interdisciplinary approach will also receive favorable treatment.

For more information on the 2010 Challenge Grant program, please visit www.mpdfoundation.org

BAY AREA PATIENT SYMPOSIUM BRINGS THE EXPERTS TO THE PATIENTS

by Ann Brazeau, Vice President of Development

In May 2010, the MPD Foundation hosted an educational symposium for over 100 patients and guests in San Mateo, California. The setting was beautiful and the venue, which was provided by Tano Corporation, was perfect for this event.

Speakers included Drs. Ruben Mesa, Mayo Clinic, Arizona; Ayalew Tefferi, Mayo Clinic, Rochester; Jason Gotlib, Stanford; David Leibowitz, Palo Alto; Ann Mullally, Harvard; and Joy Selak, author of *You Don't Look Sick*. Each speaker brought informative, up to date information to the enthusiastic group.

The MPD Foundation will host another symposium in San Mateo in the spring of 2012.

Participants take a break from the Bay Area Symposium. From left to right: Kathryn Yates, Linda Van Houten, Susan Klepper, Lerma Swartz, Eric Swartz, Paul Goldstein.

STEPHANIE MILTZ MARRIES JASON CINDRIC IN FLORIDA

Stephanie Inspired the Miltz Family to Start Friends of ET Research

Stephanie Miltz is an inspiration, plain and simple.

She was diagnosed with ET at the unusually young age of 16. Her hematologist, the late Dr. Harriet Gilbert of New York, was an early advocate of interferon – now one of the front-line treatments for MPDs. Stephanie was on interferon for nearly three and a half years, and then on a combination of interferon and anagrelide. The interferon was very hard on her. But she managed it all amazingly well, and then made the inspiring choice to become a nurse!

Stephanie graduated from Marymount Manhattan College in New York City with a degree in Theater, and then from Florida Atlantic University in Boca Raton, Florida, with a degree in Nursing. She is currently pursuing her graduate degree at Florida Atlantic University as a Nurse Practitioner and will graduate in May 2011.

Almost from the time she was diagnosed, Stephanie worked with her parents, Celia and Don Miltz, to make a success of the fundraising golf tournaments the family organized on behalf of the organization they founded, Friends of ET Research. Friends of ET Research ultimately joined forces with the MPD Foundation to take advantage of the Foundation's Scientific Advisory Board, whose expertise helps the Foundation allocate its limited resources where they will do the most good. The Scientific Advisory Board consists of leading researchers in the field, and evaluates grant proposals using the same meticulous scoring system that the NIH uses.

Stephanie is in complete remission and has been without medications for four years now. Which brings us to the best news of all: On June 12, 2010 at 6 o'clock in the evening, Stephanie Miltz married Jason Cindric on the beach at Jupiter Beach Resort in Jupiter, Florida. A dinner reception immediately followed the ceremony.

Jason, the son of Yvonne and Andy Cindric of Mont Vernon, New Hampshire, is a graduate of Florida Atlantic University with a degree in Finance and is the owner of Living Ocean Designs, Inc., in Palm Beach, Florida.

Following a honeymoon trip to Kauai, Hawaii, Stephanie and Jason are living in Lake Worth, Florida.

Donations in honor of the couple will be gratefully accepted at **www.mpdfoundation.org**

UPCOMING EVENTS

REGISTER NOW FOR THE OCTOBER 25, 2010 SAN DIEGO MPD PATIENT SYMPOSIUM

On October 25, 2010, the MPD Foundation will be in San Diego to host an educational symposium at UCSD. Our keynote speaker, Dr. Catriona Jamieson, will share her extensive findings in stem cell research and MPDs. Additional speakers include Drs. Ross Levine, Ruben Mesa, Jamille Shammo and John Crispino. To register, visit our website at **www.mpdfoundation.org/events**

JOIN AN MPD PATIENT SUPPORT GROUP IN YOUR AREA

If you are seeking the support of other MPD patients and family members or want to learn more about your MPD, consider joining a support group in your area. The MPD Foundation provides support and resources to patient group coordinators across the country and abroad. Groups meet periodically throughout the year and bring speakers who are experts in the field to answer questions and share updates in research and clinical trials and offer a safe place for patients to share their stories.

If you would like assistance starting a group, please contact the MPD Foundation and we will help you get started. For current locations of MPD support groups, visit our website at **www.mpdfoundation.org/patientresources**

ANNETTE DE BOW FINISHES ONE MONTH TREK FOR A CURE, RAISES OVER $20,000!

Annette De Bow on the climb to Forester Pass on the John Muir Trail – 13,200 feet up.

"I have chosen to combine my adventurous spirit, drive and deep appreciation of nature to hike the John Muir Trail in the High Sierras to raise money to fund MPD research."

Polycythemia vera patient Annette De Bow completed a one month hike on the John Muir Trail in August, 2010, trekking over 220 miles to raise more than $20,000. Two years ago, when Annette was diagnosed with PV, she decided to confront the disease head on and wanted to do something that would make a difference for the future of all MPD patients.

The trek began in July and each week a new set of friends – including Audrey, another PV patient from Canada – joined Annette to hike different segments of the trail. Of her experience Audrey reports "It was so meaningful, just the actual doing of the hike and making it, standing on Silver Pass and knowing that we were there because we climbed it. Being reminded that this disease is not the end of the story. I will be forever grateful for the opportunity to have been able to be a part of such a special event."

Annette hiked six passes over 11,000 feet. That did not include the 14,500 feet to finish the last 1.9 miles to the summit of Mt. Whitney, on Friday, August 13th.

Another trekker, Kara, enthused on her segment of hiking with Annette and Audrey, "Annette and Audrey continue to be such an inspiration. They are both very driven, focused, and compassionate women that in the face of adversity had joined together to do something positive instead of being beaten down by circumstances or submitting to denial. I felt grateful to be a small part of the grand Trek for a Cure! We were at the top of the world!"

Annette lost eight pounds while hiking, but says she has gained it all back and is feeling great. She experienced some well-earned fatigue but felt it was not unusual given the work her body was doing each day. Getting back to civilization, cars, and grocery shopping is a bit of a culture shock, but Annette is happy to have accomplished such a great feat and, of course, thrilled to be home with her family.

The MPD Foundation extends its deep appreciation and congratulations to Annette and her friends and family for their support. Without the enthusiasm and commitment of individuals like Annette, the Foundation would not be able to support its research and outreach programs that are vital to the entire MPD community.

"Each week was a new adventure with an excited, strong and supportive team. We set off into the wilderness ready for what was coming our way."

For more delightful highlights and stories about Annette's Trek for a Cure, visit her blog at **www.trekforacure.blogspot.com**

Annette on Mount Whitney, with fellow hikers Bruce Gervais and Jim Wanket.

EXPANDING THE ROLE OF SOCIAL NETWORKING

by Michelle Woehrle

In an effort to reach a wider audience, as well as continue to increase public awareness about MPDs, the MPD Foundation is creating a larger online presence for itself through the use of such social networking tools as Facebook and blogging.

One of the most popular social networking sites, Facebook grants us access to its over 500 million active users. The MPD Foundation has utilized this site increasingly over the last year by creating a fan page as well as a Cause that users can donate to through Facebook. By linking up with our page, or becoming a "fan," Facebook users are able to broadcast their connection to the Foundation to all of their Facebook friends.

The MPD Foundation's Facebook page allows the organization to connect with the online MPD community in a more informal, personal way. It encourages fans to share their stories and interact with one another. The page is also an opportunity for the Foundation to share upcoming events, initiatives, and other exciting news with fans and others who may not receive our updates in the traditional way. It allows fans access to information updates in between newsletter publications.

The MPD Foundation is also promoting donations through its Facebook page by using the Cause application. This application allows users to promote charitable causes that are important to them, encouraging their friends to take an interest as well as donate. Fans may also set up a "Birthday Wish," requesting that friends make a contribution to their chosen cause in lieu of birthday gifts. The Cause feature allows advocates to take an active role in fundraising for the Foundation, and has resulted in hundreds of dollars in donations.

The MPD Foundation also launched its official blog in early June. The blog is a forum in which the Foundation posts articles and information that may not necessarily be published on its website. Like the Facebook page, it is an excellent source of information of interest to the MPD Community that is available between newsletters.

The posts may discuss such topics as how changes in health care legislation will affect MPD drugs, or relay the success of our patient symposia or meetings of medical minds. The blog will also feature patient profiles and stories in their own words, and encourages followers to comment on the posts and suggest other things they might like to see featured. It is a very useful tool for the MPD community to stay abreast on what the Foundation is doing. The blog may be accessed at **mpdfoundation.blogspot.com**

PUTTING THE FUN IN FUNDRAISING

by Juliana Gordon

Kacey Weiniger has raised almost $2,000 selling custom-made bracelets designed in memory of her grandmother, Louise Spitz Lehman, a former myelofibrosis patient who passed away before Kacey was born.

The idea started as a community service project for her Bat Mitzvah. Kacey says that she always felt as though she had missed out on knowing the amazing woman that her family describes; by raising money to find a cure for MPDs she hopes to save other children the loss of never knowing a grandparent.

The bracelets bear the message "LIVE LAUGH LOVE" and the words "Forever Louise." Kacey has experienced a very high demand for the bracelets, selling 650 of them with the help of family and friends. She has found the sales a great opportunity to spread awareness about MPDs, informing each buyer of the meaning behind the bracelets.

PLEASE NOTE OUR NEW ADDRESS

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