

MPD FOUNDATION® UPDATE

A PERIODIC NEWSLETTER FOR
THE MYELOPROLIFERATIVE DISORDERS COMMUNITY

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IT'S ABOUT THE SCIENCE

by Robert Rosen

The Microbe Hunters, a book I read in early adolescence, left a lasting impression on me. Compellingly written, it contained brief histories about early medical scientists like Pasteur, Leewenhoek, and Walter Reed. I was captivated by the energy and passion that these pioneering researchers brought to their work. Their reliance on rigorous scientific investigation to advance the field was a common denominator.



When we started the MPD Foundation, its basic mission was to redress the woefully inadequate amount of money and attention being devoted to MPD science. "It's about the science," we thought, and we had high hopes that science could show us the way.

MPD scientists are now delivering, and progress is undeniable.

One announcement after another seem to have punctuated our world these last couple of years. More than three years ago we had the amazing discovery of the JAK2V617F genetic mutation, followed by the race to develop JAK2 inhibiting drugs. Next the data on Pegasys arrived initially from European labs and then was confirmed by American scientists. Peg indeed has the power to reduce the JAK2 allele burden and lessen many of the clinical symptoms of PV patients. Somewhere along the way we learned about the MPL mutations found in many MPD patients, and now, as described elsewhere in this newsletter, the electrifying but puzzling discovery of the TET2 gene.

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MPD FOUNDATION AIDS KEY RESEARCHERS IN DISCOVERY OF NEW MPD GENE MUTATION

Researchers have recently discovered a novel tumor suppressor gene – TET2 – that is inactivated in MPD patients. The collaborative work between two of our Research Alliance investigators – Dr. Gary Gilliland and Dr. Ayalew Tefferi – has already yielded three papers on TET2 mutations, two of them just published in *Leukemia*. And Dr. Francois Delhommeau, recipient of a 2009 MPD Foundation New Investigator grant, first announced the TET2 discovery last December at the ASH Convention.

An important discovery, but what does it mean?

A group of researchers at several institutions in France noticed that there were two subsets of MPD patients with the JAK2 V617F gene mutation. One group, with a high percentage of the JAK2 V617F mutation, experienced an early expansion of the malignant clone. The other, with low percentages of the mutation, experienced later expansion. In searching for the cause of the difference, the researchers discovered a new gene mutation, TET2 (Ten-Eleven Translocation-2), which precedes the JAK2 mutation and promotes its early expansion.

The researchers found that TET2 mutations – deletions, frame shifts, stop codons or conserved amino-acid substitutions – occur in approximately 14% of MPD patients. They also discovered that TET2 probably behaves as a tumor suppressor gene. The gene may have key functions in hematopoiesis (the formation of blood cells) and hematopoietic stem cell production.

Could TET2 lead to a cure?

Dr. Gary Gilliland, of Boston's Brigham and

Women's Hospital and an MPD Research Alliance investigator, thinks that the link of TET2 to stem cell production may open many doors to understanding the MPDs. That's because stem cells are the key to a cure, not just to new treatments to control our symptoms or prevent disease progression. Still, it will take considerable time and work to understand how TET2 works, and how it fits with JAK2.

Dr. Ayalew Tefferi, of the Mayo Clinic in Rochester, Minnesota and another MPD Research Alliance investigator, notes that TET2 by itself does not appear to be the answer regarding the molecular pathogenesis of PV, ET and MF. To learn more, he and his colleagues need to sequence the entire genome in their 1000 samples from patients with PV, ET and MF. "We are ready to do that, and we have the patient samples," he said. "However, such a project is very expensive and we simply do not have the funds to do it as quickly as we would like to. If we did have adequate funds, we could do it tomorrow!"

Three researchers funded in part by the MPD Foundation contributed to the article "TET2 mutations and their clinical correlates in polycythemia vera, essential thrombocythemia and myelofibrosis," in the March 5, 2009 issue of *Leukemia*: Dr. Ayalew Tefferi, Dr. Gary Gilliland and Dr. Francois Delhommeau. They concluded that "The presence of mutant TET2 did not affect survival, leukemic transformation or thrombosis in either PV or PMF. ...TET2 mutations occur in both JAK2V617F-positive and -negative MPN, are more prevalent in older patients, display similar frequencies across MPN subcategories and disease stages, and hold limited prognostic relevance."

That's it. An important advance in the science, without doubt, but one whose implications remain to be explored.

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.

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

NEW GRANT INITIATIVES FOR 2009

This year – despite the economic chaos – the MPD Foundation has expanded its research grant program, committing \$1,800,000 to critical new research in the cause and treatment of MPDs.

First, we are continuing to support the MPD Research Alliance, a collaborative effort of leading MPD researchers aimed at accelerating the development of new treatments for these disorders. We have awarded two-year grants, each totaling \$300,000, to the three current members of the Research Alliance, as well as to a new member of the alliance, Dr. Josef Prchal:



Gary Gilliland PhD, MD
Brigham & Women's
Hospital, Harvard.
“Genetics and Therapy of
Myeloproliferative Disorders.”



Benjamin Braun, MD, PhD
University of California,
San Francisco.
“Oncogenic Ras in Leukemia
Stem Cells.”



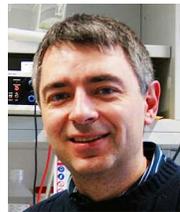
Ronald Hoffman, MD
Mt. Sinai School of Medicine.
“Use of Stem Cells Derived from
the Philadelphia Chromosome
Negative Myeloproliferative
Disorders as a Chemotherapeutic
Target.”



**Francois Delhommeau,
PhD, PharmD**
Saint-Antoine Hospital, Paris.
“Characterization and Function of
a New Tumor Suppressor Gene in
Myeloproliferative Disorders.”



Josef Prchal, MD
University of Utah.
“Define Somatic Mutations that
Precede JAK2 Mutation in PV
Patients & Monitor Their Changes
in Response to Pegasys.”



Robert Kralovics, PhD
Austrian Academy of
Sciences, Vienna.
“Genomic Approaches for
Disease Gene Identification in
Myeloproliferative Neoplasms.”



Ayalew Tefferi, MD
Mayo Clinic.
“Continued Development of
Clinical Database-Linked Cell
and Serum Bank of Patients with
Myeloproliferative Disorders.”



Dorothy Sipkins, MD, PhD
University of Chicago.
“In Vivo Imaging of PV and
CIMF CD34+ Progenitor Cell
Interactions with Bone Marrow
Microenvironment.”

ON THE LOSS OF TWO GOOD FRIENDS

Since our last newsletter, two good friends of the MPD Foundation have passed away. One was a leading MPD researcher, the other a leading MPD activist. We will deeply miss them both.

Dr. Ernest Beutler

Dr. Ernest Beutler served the Scripps Research Institute for more than 30 years, and as the first head of the Scientific Advisory Board of the MPD Foundation he was a constant source of wisdom, guidance and good humor.

He was a physician as well as a scientist, author of more than 800 scientific papers in leading journals as well as numerous monographs, book chapters and major presentations before groups such as the American Society of Hematologists; many of his topics, though hard for the layman to understand, have helped relieve patients' symptoms and improve the quality of treatment. Equally important, he always took the time to explain the scientific issues to MPD Foundation board members as we tried so hard to make decisions about which research efforts to support.

A member of the Skaggs Institute for Chemical Biology at the Scripps Institute, Dr. Beutler – Ernie to everyone – was also a member of the National Academy of Sciences, the Institute of Medicine and the American Academy of Arts and Sciences. He also served as President of the American Society of Hematology.

Joyce Niblack

Joyce Niblack may have been the truest friend the MPD community will ever have. She was always there, to answer questions, reassure patients and share information on the latest developments in the field.

She worked with the late Dr. Harriet Gilbert to publish the first MPD patient newsletter.

She founded and managed the MPD-Net online support group, which under her guidance grew to have more than 2500 subscribers worldwide.

She founded the CMPD Education Foundation and was a founding member of the board of directors of the MPD Foundation.

She was a strong advocate of the notion that patients should take an active role in managing their diseases, and she organized the biennial Mayo/CMPD Education Patient Conference around the then-revolutionary concept that doctors and patients would all gain from talking together and sharing both scientific developments and personal experiences.

Joyce even helped advance scientific knowledge in the field. More than a thousand MPD-Net subscribers sent blood samples to Dr. Gary Gilliland at Harvard, at her request. He used the results to shape one of the first publications about the importance of the JAK-2 genetic mutation in the myeloproliferative disorders. And she collected quality of life data from MPD-Net subscribers and was a co-author of two journal articles on the subject.

SAVE THE DATE FOR ANOTHER NYC PATIENT SYMPOSIUM CO-HOSTED BY MPD FOUNDATION AND THE CR&T FUND

The MPD Foundation will co-host another NYC Patient Symposium with the CR&T (Cancer Research and Treatment) Fund on November 4, 2009 at the New York Athletic Club. Once again, speakers will include experts from the MPD community.

This daylong event will be a great opportunity for patients, family members, physicians and anyone interested in learning up-to-date information about the state of MPDs. We look forward to seeing you there.

SENATOR SPECTER SECURES \$5.5 MILLION FEDERAL GRANT TO RESEARCH PV CLUSTER

In our Fall 2007 newsletter, we reported on the potential link between a significant number of cases of polycythemia vera and environmental contaminants in Schuylkill, Luzerne and Carbon counties in eastern Pennsylvania. With funding from the MPD Foundation, Ronald Hoffman, MD, Professor of Medicine and Director of the Myeloproliferative Disorders Program at Mount Sinai School of Medicine, and colleagues used a molecular diagnostic test (JAK2) to confirm a large number of patients with polycythemia vera within close proximity to known areas of hazardous waste material. Those sources include waste-coal power plants and US Environmental Protection Agency Superfund sites.

Dr. Hoffman's study, published in the February 2009 issue of *Cancer Epidemiology, Biomarkers and Prevention*, found the incidence of polycythemia vera was 4.3 times more likely near hazardous waste material than in the rest of the study area. "The role of the environment in the origin of this blood cancer has not been previously documented," said Hoffman. "This study may prove that diagnosis of this cancer based solely on

clinical criteria may be inaccurate. The frequency of this form of bone marrow cancer could be specifically related to the environment."

U.S. Senator Arlen Specter, R-Pennsylvania, has been working with residents in the three affected counties to get answers. According to the senator's spokeswoman, Kate Kelley, "This study highlights long standing concerns Senator Specter has had regarding the higher than usual incidence of polycythemia vera in the tri-county area. This underscores the need for more resources to further study the problem, including the basic biology of polycythemia vera and related conditions as arising in this cluster."

Senator Specter included a grant of \$5.5 million to study the cancer cluster in the \$410 billion spending bill passed by Congress and signed into law by President Obama on March 11, 2009. On March 12, the Associated Press reported that The Centers for Disease Control and Prevention (CDC) researchers will get \$5 million to conduct risk assessments and lead efforts to improve PV reporting. Drexel University's School of Public Health will receive about \$500,000. In addition, an expert panel convened by the government has proposed a dozen related research projects.

IT'S ABOUT THE SCIENCE

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The Role of the MPD Foundation

As a group we are impatient. When JAK2 inhibiting drugs didn't work immediately there was collective disappointment. But not so fast. Clinical trials have shown that these drugs have the capacity to alleviate dreadful symptoms in MF patients. And better yet, there is now evidence that the drugs might reduce JAK2 burden after all.

The MPD Foundation has multiple missions, including patient education through this newsletter, our website and our participation in sponsoring symposia. We have lobbied the FDA, and we work with over 50 support groups worldwide to increase patient engagement. We are eager to encourage new investigators to commit to our field through our new investigator grants.

But above all is the commitment to science. Good, meaningful scientific investigation will show us the way. The MPD Foundation is proud to have funded much of the science that has reshaped our world, and to have had a meaningful role in the discovery and ongoing investigation of the TET2 mutation.

Finally, there is no one in our world who is not aware of our current economic downturn. Not-for-profit organizations like ours depend on donations, and in our case it is the patients and their families and friends who ultimately fund our work. We understand that this might be a difficult year, but we hope you will continue to keep us in mind as you have done so impressively in the past.

EVENT UPDATES

by Ann Brazeau, VP of Development

MPD Foundation Booth Attracts ASH Convention Attendees

For the first time ever, the MPD Foundation hosted a booth at the ASH (American Society of Hematology) Convention, which took place in San Francisco last December. The Foundation's goal was to engage as many hematologists as possible while at the convention, and we believed a booth would provide the presence necessary to attract attendees. It worked. In two days, over 200 physicians, researchers and educators stopped by for informational packets, patient brochures and a brief conversation about the history and mission of the MPD Foundation.

Besides attending scheduled meetings and numerous sessions, the Foundation held a dinner attended by the Bay Area patient support group coordinators; board member Sam Klepper and his wife Susan; board member Rob Horwitz; Research Alliance investigator Dr. Ayalew Tefferi; Marion and Sam Urcis; Marilyn Canon and several other members of the MPD community.



Left to right: Marilyn Canon, a member of the Bay Area support group, with Sam and Susan Klepper.

Two Fundraising Dinners Shed Light on MPDs

Flourtown, Pennsylvania Country Club Event Raises \$40,000

Jennifer Giorno was recently diagnosed with myelofibrosis. In an effort to raise money for MF research, she hosted a fun-filled dinner in Flourtown, Pennsylvania for over 200 guests.

Through live and silent auctions and the sale of event tickets, Jen raised over \$40,000. David Stokes, a patient living close by and a special friend to the MPD Foundation, also attended. He will be assisting Jen with the formation of a patient support group in their area. You can visit Jen's website at faithhopeandacure.com.

120 Guests Attend Detroit Institute of Arts Fundraiser

Michigan patient support group coordinator Josephine Pompeo hosted a fundraising dinner last November for over 120 guests. Josephine was diagnosed with myelofibrosis two years ago and since then has been actively involved in reaching out to other patients.

The dinner was held at the Detroit Institute of Arts and raised money for MPD research. Speakers included Dr. Muhammad Sharafa from Karmanos Cancer Center and Ann Brazeau, VP of Development from the MPD Foundation.



Left to right: Linda Clarke, Josephine Pompeo, Teresa Palleschi and Cathy Jannette.

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

MPD Foundation

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