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MPD GENE MUTATION DISCOVERED!

**After years of searching,
a major breakthrough.**

The first news came out on March 17, 2005: A team of researchers at the Cambridge Institute for Medical Research, UK, led by Dr. Tony Green, announced that they had discovered a single point mutation in the JAK2 gene that appeared in 97% of polycythemia vera patients they studied, in 57% of essential thrombocythemia patients and in 50% of patients with idiopathic myelofibrosis. The mutation was not detected in any of the control patients.

Only days later, on March 24, a team at Brigham and Women's Hospital in Boston, led by Dr. Gary Gilliland, reported almost identical findings.

Many readers of this newsletter may have participated in the Boston study. Dr. Gilliland's team recruited more than 600 volunteers in a matter of weeks by posting a request at MPDInfo.org and on the MPD-Net listserv.

Anatomy of the discovery

JAK2 actually isn't a gene. It's an enzyme called a tyrosine kinase, which acts as a molecular signaling pathway – essentially, an on-off switch – that triggers the generation of hematopoietic (blood) cells. The researchers believe that the mutation causes the switch to remain in an “on” position, thus causing the uncontrolled cell proliferation for which the myeloproliferative disorders are named. Tyrosine

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As we go to press, the MPD Foundation is engaged in conversation with some of the leading hematological clinicians and researchers about forming a collaborative effort to develop a drug based on the JAK2 discovery. Working together will enable each group to expedite that part of the program where it has the most expertise, and the collaboration could accelerate the process while creating important efficiencies. We intend to undertake a major fundraising campaign to support this important effort, and will let you know as soon as we have more information.

A TRANSPLANT OPTION FOR OLDER MMM PATIENTS

MPD Consortium team reports that transplants using reduced-intensity conditioning have a high rate of complete responses and long-term survival.

*By Ron Hoffman, MD
University of Illinois at Chicago
Member, MPD Foundation Board of
Medical Advisors*

Allogeneic hematopoietic stem cell transplantation (transplantation using the cells of a matched related or unrelated donor) is the only curative treatment for myelofibrosis with myeloid metaplasia (MMM). However, transplants are associated with a high mortality rate and complications, especially in older patients or those with advanced disease.

Preparation for traditional transplants involves total myeloablation, the destruction of the patient's immune system through total body irradiation and/or chemotherapy. The process is highly toxic and leads to transplant-related mortality in 27% to 48% of patients, with increasingly greater risks for older and higher-risk patients.

We recently reviewed the histories of 21 patients, all with poor prognoses, who underwent a slightly different regimen: one involving reduced-intensity conditioning, or RIC. Some have misleadingly described these as mini-transplants; in fact there is nothing "mini" about them. They are serious procedures and may have serious side effects, including death. However, they do offer a reasonable chance of complete recovery to older MMM patients who might not be able to tolerate a myeloablative transplant.

What we learned

Engraftment was achieved in all except one of the patients. Seven of the 21 patients developed acute GVHD (graft versus host disease) and 13 of 18 evaluable patients developed chronic GVHD. However, extensive chronic GVHD was observed in only eight patients.

Eighteen patients were alive 12 to 122 months (median, 31 months) after transplantation. Of the three deaths, one was due to acute GVHD and cytomegalovirus disease, one to bacterial pneumonia and one to relapse. Overall survival was 85% and event-free survival was 81%, despite a median patient age of 54 years and the presence in all patients of intermediate or high-risk disease.

Seventeen patients (81%) are in remission. After 12 months, marrow fibrosis was grades 0 to 2 in all of the evaluable patients. In four cases, a serial analysis of the volume density of reticulin fibers in the bone marrow was performed at 1, 3, 6 and 12 months after transplantation, demonstrating the progressive resolution of marrow fibrosis.

A more than 80% reduction in the degree of splenomegaly occurred in the majority of the patients.

The use of RIC regimens in allogeneic transplantation for myelofibrosis patients with poor prognosis results in a high rate of remission with low transplant-related mortality. The results of this study strongly suggest that for these patients allotransplantation conditioned with reduced-intensity rather than a fully myeloablative regimen produces a better probability of long-term survival.

The paper, "Allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in intermediate- or high-risk patients with myelofibrosis with myeloid metaplasia," by Damiano Rondelli et al, will appear in *Blood*, Volume 105, Number 10, 15 May 2005. The paper had not been posted online as we went to press, but it will appear as a Blood First Edition Paper at

<http://www.bloodjournal.org/papbyrecent.shtml>

DISCOVERY OF THE MPD GENE:

How You Can Help Researchers Learn More

Dr. Gilliland and his colleagues have participated in a remarkable breakthrough in isolating the probable genetic cause of MPDs. But they are still looking for volunteers to help them learn more.

To participate in their ongoing study, you must be

- Living in the United States
- Diagnosed with PV, ET or MF (AMM, MMM)
- Not a stem cell or bone marrow transplant recipient
- Willing to send in a blood sample and mucous DNA sample

The study organizers will send you complete instructions and a prepaid return FedEx package with everything you need to obtain the samples and send them back safely. Most doctors are willing to draw the extra blood as part of taking a normal blood sample during a regular office visit.

If you are interested in participating in the study, please send an email to Dr. Martha Wadleigh at:

MWadleigh@partners.org

Please include the following information in the text:

Diagnosis (ET, PV, MF/AMM/MMM)

Also, please indicate your interest in

- Completing a survey.
- Signing a release of medical records for research purposes.
- Donating a blood sample and mouth swab for research purposes.
- Finally, be sure to include your name and mailing address.

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kinases have been implicated in many cancers, including CML.

JAK2 is also known as Janus protein tyrosine kinase. You can find plenty of references by looking up either one on Google, although most of the studies cited are earlier ones unrelated to myeloproliferative disorders.

What this means to MPD patients

It's big news! This is truly a major discovery that gives all MPD patients a great deal to be thankful for. Dr. Gilliland's team has identified at least one drug that inhibits the uncontrolled cell proliferation caused by the JAK2 mutation. That strongly suggests that JAK2 can be targeted by new drugs developed specifically for MPD patients. That would mean better control of our counts, fewer side effects and healthier, longer lives.

However, researchers have a way to go before they can develop such a drug and demonstrate that it is both safe and effective in humans. Meanwhile, there may be opportunities to participate in clinical trials of any emerging treatment; Dr. Gilliland has announced that his team is still recruiting patients for the Boston trial (see box, left). And since not all MPD patients have the JAK2 mutation, the team continues to search for other mutations that may be implicated in causing MPDs.

More information

The British study, "Identification of the Val617Phe JAK2 mutation lays the foundation for new approaches to the diagnosis, classification, and treatment of myeloproliferative disorders," by E. Joanna Baxter et al, appears in *The Lancet*, Volume 365, Number 9464, 19 March 2005. The full text is available at www.thelancet.com for a fee of \$30.

Articles reporting the study results are available at

<http://www.medicalnewstoday.com/medicalnews.php?newsid=21467>

http://www.ivanhoe.com/channels/p_channelstory.cfm?storyid=10807

<http://washingtontimes.com/upi-breaking/20050317-105747-8880r.htm>

The Boston Study, "Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis," by Ross L. Levine et al, appears in *Cancer Cell*, Vol 7, Issue 4, 24 March 2005. Both an abstract and the full text are available free at cancercell.org.

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Photos courtesy San Francisco Marathon

HELP WANTED

By Jo Ann Mannino

If you live in the Bay Area, please join me raising funds for the MPD Foundation in connection with the San Francisco Marathon on July 31, 2005. There are several distances for participation – a 5k, ? marathon and a progressive marathon (run/walk the 26.2 mile marathon distance over several days or weeks) in addition to the marathon. Those of you who attended the Scottsdale conference know that exercise can be an important part of your MPD treatment, so please consider joining me!! Please see the site for details:

<http://www.runsfm.com/index.html>.

Please email me if you are interested:

jomannino@aol.com.



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<http://www.cancerell.org/content/article/abstract?uid=PIIS1535610805000942>

News stories announcing the discovery appear at

http://www.bio-itworld.com/news/032405_report7908.html

http://www.eurekalert.org/pub_releases/2005-03/hhmi-to1032405.php

<http://www.medicalnewstoday.com/medicalnews.php?newsid=21777>

All of the articles mistakenly classify MPDs as leukemias. Don't worry. The study doesn't say that. It's just that the job of reporters is to attract readers, and more people are likely to read an article with "leukemia" in the headline than one featuring "myeloproliferative disorders."

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

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