

CRISPR

**Definitely possible, not quite ready:
The ability to slice out the gene mutations
that cause MPNs**

It's more than a little ironic that the hottest new biotech tool for gene editing should have been invented several billion years ago, just about the time the Earth cooled down enough to start being fruitful and multiplying.

Microorganisms struggling to survive evolved a vaccination system to ward off invading viruses.

Viruses, those rudimentary troublemakers, are incapable of reproduction outside living cells. To compensate, they swarm all over and into available living forms – in this case, bacteria. Then they use the bacteria's energy to reproduce more viruses until the bacteria is destroyed and the virus is released to invade surrounding bacteria.

The bacteria's defense is to snatch a bit of the virus's miniscule DNA and incorporate it as "spacers" between repetitive sequences of code in its own genome. This all takes place in a portion of the genome called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats).

In response to renewed virus attack, these spacers join up with a killer enzyme called Cas, which is capable of cutting and destroying the viral DNA. (When reading about CRISPR, you'll also see references to the CRISPR/Cas9 system.)

Building on this bacterial weaponry, researchers are developing the technology to insert a CRISPR/Cas9 DNA sequence into a mutated gene. *And kill the mutation.* One researcher even excised a mutated JAK2 kinase in a human stem cell.

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ASH MEETING HIGHLIGHTS

By John Crispino, PhD, Scientific Advisor

Attending the ASH meeting this past December was an exercise in multitasking and endurance. MPN research and reporting continued to stand out as one of the major focuses in the hematological science community. We counted at least 45 posters reporting MPN research results in all corners of our world.

Additionally oral presentations filled up much of the time in the presentation rooms. Your MPNRF representatives met separately with biotech and pharma companies to track the progress of new treatments in the pipeline. We left exhausted, trying to assimilate everything that was presented. More importantly, the feeling of intense research activity in our area leaves a strong takeaway of significant progress.

The most exciting news came just before the meeting with the announcement of FDA approval of Jakafi for polycythemia vera patients. There were promising reports on the anti-fibrotic PRM 151 and the telomerase inhibitor Imetelstat. Generally, there were no major breakthroughs that are likely to affect patient lives in the immediate future. But looking not too far down the road, things are likely to change.

This report briefly summarizes ASH presentations in four areas:

- JAK inhibitor clinical updates
- New mechanisms of action, clinical updates
- Combination studies
- Notable basic science reports

Many of the researchers involved received funding from the MPN Research Foundation. For my full report, please

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MISSION

The primary mission of the MPN Research Foundation is to stimulate original research in pursuit of new treatments — and eventually a cure — for myeloproliferative neoplasms (MPNs). In addition, the MPN Research Foundation promotes collaboration in the scientific community to accelerate research, and serves as a powerful patient advocacy group for patients and their families.

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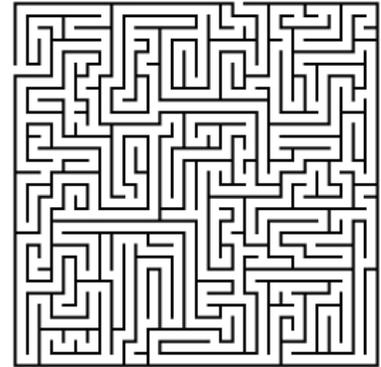
Hugh Rosen, PhD

The Scripps Research Institute

WATCH THIS

By Robert Rosen

20 years ago Craig Venter stunned the scientific world when he mapped the entire human genome. Since then progress has been steady in understanding the role that genetics play in the development of disease. Until now conversion of this knowledge to new treatments has come more slowly than hoped for. Although there have been some notable successes, like Jakifi, the medical community is still searching for a more comprehensive approach to treating disease through genetics.



However, new technologies have suddenly burst upon the scene that have the potential to be as significant as sequencing the human genome. The MPN Foundation is paying close attention.

We're speaking now mainly of advances in immunology, or immune therapies, and the recent exploration of CRISPR/cas9 gene editing. Both technologies are in early stages of development and each potentially has the ability to transform disease.

Enhancing the immune system has long been a dream of many researchers and patients. After all, your body successfully fights infection and other maladies, just using its inherent biological mechanisms. Boosting T cell effectiveness to recognize and fight mutant agents in your body is understandable and appealing and might now be a technique for all kinds of cancers. There is much current literature on this subject.

Gene editing in theory also provides an elegant solution to cancers. Simply find the offensive gene within the tens of thousands in your DNA, snip it out, and voilà, you are cured. Or are you? Again there is enormous energy going into understanding this new technology, which is described elsewhere in this publication.

We don't know how these technologies will ultimately pan out, but we do feel absolutely committed to investigating them for the MPNs. Most recent research has been directed to solid tumors, not hematology and certainly not the MPNs. Our goal at the foundation is to *promote these transformative technologies* for our disease group. Stay tuned as we move down this path.

CRISPR

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The promise now is for accelerated development of targeted therapeutic use of CRISPR technology. And we want MPNs to be one of the first targets. But currently, hematologists are new to gene editing, and genetic engineers likely never heard of MPNs.

Gene Editing: A Potential Revolution in the Treatment of MPNs

The MPNforum (<http://mpnforum.com>) points out that despite significant advances in recent years, there is still no treatment that affects the fundamental gene mutations that cause MPNs.

As stated on the MPNforum, “With the advent of gene editing...we finally have the technology to address the root cause of our disease and not simply abate our symptoms temporarily through drugs that carry their own physical impacts. MPNs start with stem cell mutation and will only end with repair of that mutation....

“The mission now is to bring gene editing to MPN clinical practice. The first step is to secure working partnerships between hematologists and MPN researchers with genetic engineers, biochemists, and related scientists to study gene editing applied to MPN clinical applications.”

That’s why one focus of this year’s MPN Challenge, the annual grant program of the MPN Research Foundation, is to build bridges between the MPN and CRISPR worlds.

We also hope to accelerate the investigation of gene editing technology in MPNs through direct research funding.

Ahead is a long and difficult campaign. But it could well change the whole approach of MPN medicine from managing symptoms to eliminating mutations, and we want to be part of it. As always, we’re counting on your donations to help make it possible for us to succeed.

FEATURED PARTNERS’ CORNER



Zhenya Senyak is a good friend of the MPN Research Foundation and also the driving force behind MPNforum Magazine – a lively online review of international MPN news, science & opinion. It also has far more to say about CRISPR than we could fit into the article to the left.

MPNforum and its companion MPN Quarterly Journal are open source publications entirely managed and staffed by patients and caregivers, with the volunteer participation of scientists, hematologists and healthcare providers. If it’s important to the MPN community, MPNforum covers it.

MPNforum also sponsors the MPNclinic – an on-line resource for patients to have their questions answered by MPN specialists such as Dr. Richard Silver, Dr. Srdan Verstovsek, Dr. Ruben Mesa, Dr. Claire Harrison, Dr. Attilio Orazi, Dr. Ross Levine, Dr. Moshe Talpaz, Dr. Jason Gotlib, Dr. David Steensma, and Dr. Hans Carl Hasselbalch.

If you don’t subscribe, check out the current issue at <http://mpnforum.com>.

WE CAN'T DO IT WITHOUT YOU

Like it or not, MPNs are rare diseases, and they don’t attract widespread publicity. So it’s up to us in the MPN community – patients, family, friends and caregivers – to do everything possible to help develop new treatments and, one day, a cure. And we can do it – if we do it together. Please be generous.

mpnresearchfoundation.org

ADVOCATES AT MANY LEVELS

By Michelle Woehrl

Denial of coverage for SCT. High copay for medicine. Confusion about clinical trials. These are some issues faced by patients today, above and beyond the wait for more effective treatment options. While we wait, we're working with other groups to improve life in small ways for people with PV, ET and MF. Some things we are working on now include:

We've partnered with the Leukemia & Lymphoma Society on **Cap the Copay**, which seeks to reduce the amount people pay for specialty-tier medications. Our efforts are focused in Illinois, but we are primed to expand our efforts as we learn more. Visit capthecopay.org for more info.

We joined the **One Voice Against Cancer** group last year in order to learn more about the policy process and to ensure that where there was an opportunity, we'd be in a position to advance the interests of MPN patients.

The Clinical Trials Transformation Initiative has activated a steering committee to investigate how to re-envision clinical trials so that they work better for patients, tackling issues such as recruitment for trials. In 2015 we became a member and hope to both contribute and learn.

We met our goal of identifying a patient to participate on an **FDA** advisory committee. Patrick Corcoran has stepped up and is ready to serve on behalf of the MPN community.

In 2015 we nominated an MPN patient to sit on a Peer Reviewed Cancer Research Program within the **Department of Defense**. This was prompted by the DOD being granted a total of \$25 million for research funding focused on diseases with a higher prevalence among those who have served in the military – including MPNs.

In addition we're using social media to reach out to a broader network of patients. Initiatives like Rare Disease Day and the #unselfie campaign during Giving Tuesday help patients spread the word themselves about why funding for MPN research is so important. To join the conversation, follow us at [@MPN_RF](https://twitter.com/MPN_RF) on Twitter or on Facebook under **MPN Research Foundation**.

SOMEONE TO TALK TO

Living with PV, ET, or MF can be frustrating and confusing, largely because these conditions are so misunderstood. But you can talk to someone who understands, either online or in person.

For a list of support groups please go to www.mpnresearchfoundation.org/Support-Groups or email rnunez@mpnresearchfoundation.org

You can talk freely with these groups, and expect understanding responses, because membership is restricted to patients, caregivers, families, close friends and physicians.

MPN Research Foundation Update is a periodic newsletter published by the MPN Research Foundation to provide members of the MPN community with information on current research and the Foundation's activities.

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BREAKING NEW GROUND IN 2015

By Barbara Van Husen



After its own meeting, the MPN Research Foundation Board attended an MPN Roundtable last November. These periodic events bring together scientific experts from industry and academia to discuss current issues in MPN science. The discussions also guide our research grant programs. Left to right: Robert Rosen, David Boule, Ed Ogunro, JoAnn Mason, Barbara Van Husen, Bob Cohen, Sam Klepper, Dr. John Crispino, Robert Horwitz, David Ricci and Felisse Sigurdson.

The Foundation, with continued support from the Leukemia & Lymphoma Society, is excited to announce that our 2015 MPN Challenge grant program is underway, with issuance of a Call for Proposals in early February.

This year's grant program will be focused on four new avenues of research that promise significant benefits for MPN patients:

- **Targeting the Malignant JAK2 Clone.** New interdisciplinary approaches suggest that it may be possible to target the mutant JAK2 allele specifically, avoiding some of the complications of current JAK inhibitors. We are currently funding one such project and seek additional researchers to pursue this goal.
- **Application of Immunotherapy Approaches to MPNs.** Recent discoveries in other cancers suggest that using a patient's own immune system to fight their disease holds great promise, but these approaches have not been tested in MPNs. We seek proposals to test immunotherapy in MPNs.
- **Gene Editing as Applied to MPNs.** Exciting developments in gene editing (CRISPR) are

currently being applied to other forms of solid tumor and blood cancers. The applicability of this technology to MPNs is not currently known. We seek joint proposals from gene editors and MPN experts to investigate the applicability of these techniques to MPNs.

- **Additional New Mechanisms of Action.** The Foundation believes that when transformational ideas are applied to other cancers, they should also be evaluated for MPNs. Therefore, we seek proposals for additional new mechanisms of action (over and above those mentioned above) where our funding can help ensure the identification of any benefits which may accrue to MPN patients.

In addition, starting in 2015 we will be awarding two-year grants of \$100,000 per year, to ensure that the innovative ideas of our grantees can be brought as close to translation for patients as possible.

Proposals are due to the Foundation by April 1, 2015.

For additional information on the 2015 MPN Challenge program, visit mpnresearchfoundation.org.

ASH MEETING HIGHLIGHTS

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visit mpnresearchfoundation.org.

JAK Inhibitor Clinical Study Updates

There were several notable clinical advances presented at the meeting, primary related to myelofibrosis. These include the following:

1. Update on pacritinib (CTI Biopharma/ Baxter) and its mechanism of action. What makes this JAK inhibitor unique is that it reduced spleen size and symptoms, but did not decrease the platelet count or hemoglobin levels. Thus, it may be suitable for patients with low platelet counts. The drug is now in Phase 3 development.

2. Update on momelotinib (Gilead). Momelotinib is a JAK1 and JAK2 inhibitor that demonstrated improvement in anemia and splenomegaly in a Phase 1/2 clinical trial. Its ability to improve anemia in PMF patients clearly distinguishes it from the other JAK inhibitors. However, a high percentage of patients developed neuropathy. Therefore, going forward, it will be important to weigh the good (anemia response) with the bad (potential of neuropathy).

New Mechanisms of Action, Clinical Updates

1. Update on the clinical study of imetelstat (Geron) in PMF. Of 33 patients in the pilot study, four reached a complete remission, three a partial response, and several others showed clinical improvement in such areas as splenomegaly and/or peripheral counts. The complete responders displayed a resolution of blood counts, reduction in spleen size and reduced bone marrow fibrosis. Imetelstat therapy was also associated with substantial decreases in CALR mutant allele burden in patients with essential thrombocythemia. With respect to side effects, the drug is associated with myelosuppression and reversible hepatic toxicity. Geron plans to open a Phase 2 trial of imetelstat in primary myelofibrosis in mid-2015.

2. Update on the Phase 1 study of PRM151 (Promedior) in PMF. PRM151 (pentraxin 2) is a naturally occurring protein that prevents or reverses

fibrosis. Early data from a Phase 2 study showed improved bone marrow histology and reduced fibrosis. There were also modest improvements in spleen size, symptoms and peripheral counts. Given the potential of this compound as an anti-fibrotic agent, Promedior is moving ahead with the Phase 2 study in 2015.

Combination Studies

In addition to these novel, single agent trials, there were several reports of clinical studies that combined ruxolitinib with an investigational drug targeting a different pathway.

1. Hedgehog proteins mediate cell signaling and promote growth, especially of cancer cells. They are also suspected of cooperating with activated JAK/STAT signaling in the MPNs. A Phase 1b trial of the combination of a hedgehog inhibitor and ruxolitinib in patients with myelofibrosis showed that the combination led to a reduction in spleen size and that the drugs were generally well tolerated.

2. In addition to STATs, MPN mutations that enhance JAK signaling activate the PI3 kinase pathway. This observation suggests that targeting the two pathways may lead to a stronger anti-tumor effect. A Phase 1b study of the combination of a PI3K inhibitor with ruxolitinib showed a spleen response in over 70% of patients that had not had prior exposure to a JAK inhibitor. In addition, a modest decrease in the allele burden was observed. A future Phase 2 trial will shed light on the efficacy of this combination in PMF.

3. HDACs are cellular proteins that modify other proteins to alter their functions. Relevant to the MPNs, HDAC inhibition has been shown to affect the interaction of JAK2 with a stabilizing protein named HSP90, leading to impaired activity. A Phase 1b trial of the pan HDAC inhibitor panobinostat in combination with ruxolitinib demonstrated a spleen response that was similar to that seen in clinical trials of ruxolitinib. Side effects include GI and hematologic toxicities.

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Notable Basic Science Reports

1. Calreticulin (CALR) mouse model. Mutations in CALR are seen in the majority of ET and PMF patients who lack mutations in JAK2 or MPL. In a CALR animal model, mice that express mutant CALR variants developed an ET-like disease with elevated platelet counts. Moreover, mice that express the type 1 CALR mutant showed progression to reduced platelet counts, anemia and splenomegaly suggesting evolution to myelofibrosis. This model will be extremely useful in determining how calreticulin mutations contribute to the disease and may also lead to novel pathways for therapeutic intervention.

2. Preclinical data on novel JAK2 specific “Type II” inhibitor NVP-CHZ868. To date, all JAK inhibitors in development fall within the so called Type I family. Recently, a new compound named NVP-CHZ868 was identified as a Type II JAK inhibitor. This class of inhibitors binds to the kinase in a manner that is distinct from the first generation drugs and thus is postulated to have a different effect on JAK activity. In pre-clinical experiments, treatment of either the MPL or JAK2 mutant mice led to near complete resolution of the disease with significant reductions in splenomegaly, bone marrow fibrosis and the mutant allele burden. The drug was also active against JAK2 mutant cells that developed a form of resistance to ruxolitinib, suggesting that it may provide an important therapeutic advance. The next step will be to perform a clinical trial in patients.

3. Preclinical studies to evaluate the anti-MPN activity of a thrombopoietin (TPO) antagonist. The presence of TPO is required for myelofibrosis. An inhibitor of TPO signaling reduced growth and induced cell death of MPN cells, and also interfered with the ability of MPN stem cells to engraft in recipient mice. These results indicate that this drug can target the leukemia stem cell population and may provide a novel therapeutic strategy for myelofibrosis

Prognostic Scoring Systems

The current prognostic scoring system for primary myelofibrosis doesn't incorporate cytogenetic and/or molecular data. Two proposed new scoring systems seem to be better at predicting survival than the current IPSS (International prognostic scoring system). These revised protocols may be practice-changing in that they would aid physicians and patients in determining the best course of therapy.

Summary

In summary, the 2014 ASH meeting provided important updates to novel therapies and biologic studies in the MPNs. There have been rapid advances in moving combination studies from the laboratory to the clinic. Moreover, every new biologic discovery brings us closer to designing new and more potent therapies. Finally, it should be noted that the meeting included six full sessions dedicated to the MPNs and that all of these sessions were well attended.

Thus, there continues to be strong interest in the MPNs among scientists, clinicians and industry. In the coming year, watch for a number of Phase 2 and Phase 3 studies of novel agents for treatment of myelofibrosis.

**The MPN Research Foundation
has provided key support for
virtually every major advance in
MPN research since 2000.**

– Andrew Schafer, MD, Director of the
Richard T. Silver, MD Myeloproliferative
Neoplasm Center at Weill Cornell and
Chairman, MPN Research Foundation
Scientific Advisory Board.

TRY THIS AT HOME

How family and friends can make a difference!

by JoAnn Mason



JoAnn Mason, Secretary of the Board of Directors of the MPN Research Foundation (standing), meeting with John Crispino, PhD, Scientific Advisor, Barbara Van Husen, President, and Andrew Schafer, MD, Scientific Advisory Board Chair.

It's been 15 years since our daughter was diagnosed with Polycythemia Vera. We had many questions, few answers and did not know where to turn. It was a very lonely feeling. Then we discovered the MPN Research Foundation.

The MPN Research Foundation has provided key support for virtually every major advance in MPN research since 2000. While we have learned a great deal, we still need answers to many things.

To help the Foundation in these efforts, our family created the Mason Fund. We launched a letter writing campaign appealing to our friends and other families of MPN patients.

With the help of our friends, we are contributing in a meaningful way to improving outcomes for MPN patients around the world. Once again, we send our deepest appreciation to all those who have been so thoughtful and generous. To learn more or make a donation, please visit mpnresearchfoundation.org and click on the Jaclyn Mason Fund in the lower right corner of the page.

AT THE MPN RESEARCH FOUNDATION, EVERY GIFT MATTERS

By Bill Crowley

You have many worthy causes to choose from when you are considering a charitable gift. By giving to the MPN Research Foundation, you are demonstrating a great trust in our ability to continue direct support to critical research to find a cure for MPNs. We take that trust very seriously.

Just as you have a choice in causes to support, you also have a choice in how to give. If you are considering a gift to the MPN Research Foundation and have investments in the stock market, you may want to consider transferring appreciated securities.

The financial markets have seen a much-anticipated upturn. The Dow is now hovering around 18,000.

Using appreciated securities has always been a good way to make a gift. Because a gift is not a sale, you will not have to pay capital gains tax. Gifts of stock generally provide an income tax deduction. It is very easy to make a charitable donation using stock.

If you are interested in using appreciated securities to make a gift, contact me for instructions that you can share with your broker: Bill Crowley at 312 683-7226 or wcrowley@mpnresearchfoundation.org.

While donating appreciated stock can help you with all your charitable giving, we hope you will continue to include the MPN Research Foundation in your charitable plans.

The Foundation cannot provide legal or financial advice. We urge you to meet with your legal or financial advisor.