MPN FOCUS

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia Newsletter

May 2014

It Takes a Team by Karen Stern

I was diagnosed with high-risk Myelofibrosis (MF) in April 2012. My first reaction was total immobility. I was frozen in time. My mother was diagnosed with this disease 20 years ago and she died three months after the diagnosis. I was 69. It was a scary time, not knowing how much time I had, not knowing how quickly the disease would progress. Fortunately, I have an excellent primary care physician, Dr. Neal Sklaver. He is calm and smart, an excellent diagnostician and an excellent communicator. He is the one who first suspected I had blood cancer and he referred me to Dr. Minal Barve, a local hematologist/oncologist. I liked Dr. Barve from the first time I met her because she was able to manage the seven family members who joined me in her examining room big enough for three. She answered everyone's questions; she was straightforward and honest. Her instinct was to "watch and wait" but when she realized that I would not be comfortable until I spoke with a doctor who specializes in MPN's, she supported my decision to look for a specialist and advised me to go to MD Anderson. I have come to appreciate how important that step was for me – finding an oncologist whose ego did not get in the way of my treatment. I felt confident that there was an MPN specialist in Dallas, Texas where I lived. Houston is 240 miles from Dallas. Dallas has a fabulous medical community.

I interviewed a couple of doctors in the Dallas area who have outstanding credentials, looking for an MPN specialist, but it didn't take me long to realize that the hundreds of patients that were being seen at MD Anderson in Houston for MF far exceeded the hand-full who might have been seen by a local doctor in Dallas. It was at this point that I realized how important it was for me to be my own advocate and to build a team to help me manage this disease. I chose to stay with Dr. Barve as my local hematologist. The office procedures at her office are patient centered. The staff is well trained and I always feel special when I am there. Her nurse, Nikki Zannakos has been my advocate from the first day I met her. Dr. Barve is an excellent physician, a good listener and she communicates well. The third member of my medical team became Dr. Srdan Verstovsek (Dr. V) at MD Anderson.

Each member of my team plays a unique role. Dr. Sklaver examines me quarterly and monitors my overall health. He communicates regularly with Dr. Barve. For example, when I had nosebleeds, Dr. V referred me to Dr. Sklaver, Dr. Sklaver referred me to an Ear, Nose Throat specialist, and a blood vessel was cauterized. My appointments with Dr. V are quarterly. He and his PA, Lindsey Lyle, examine me, evaluate my treatment plan, and answer my questions and concerns. I have monthly blood draws at Dr. Barve's office and see her every 6 or 8 weeks. She encourages me to exercise and eat healthy, and she monitors my blood work. We all take direction from Dr. V. He recommends medication and dosages. We listen to him. Dr. Barve's nurse, Nikki Zannakos, is available every time I have a blood draw. She prints out the CBC while I wait and discusses the test results with me. My husband goes with me to all the visits with Dr. Barve and Dr. V; my friends and family are there to give me love and support. My support group validates what I am experiencing and provides suggestions for dealing with issues that arise with this disease.

> "Dr. V and his team are patient centered. They spend the time with me that I need and I also try not to take advantage of their availability."

I am doing well on the treatment plan that Dr. V developed for me. I haven't needed a transfusion in a year and I feel fortunate that I have a fairly good quality of life. To effectively manage MF, I learned the importance of the following:

1. Advocating for myself – I bring prepared questions to Dr. V at each appointment; I am honest about how I feel; I have built a team that works with me and for me; I continually educate myself about latest treatment options. Being an advocate for myself reduces the stress in my life because I know that I will get my questions answered. I watch the Patient Power videos and attend the MPN Education Foundation conferences. I attended the MD Anderson MPN conference held last November. There is so much that I don't understand about the disease, about the terminology, about the future; however, what I have learned is empowering and I will continue learning and advocating for myself.

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• • • • • **It Takes a Team,** continued from page 1

2. Finding a primary care physician who is an excellent diagnostician, a good listener and available when I need him. Dr. Sklaver refers me to specialists when I am dealing with a questionable symptom. Sometimes he knows the answer, sometimes he says that I should talk to Dr. V or Dr. Barve, sometimes he refers me to another specialist. He is thorough and is always available when I need him, and I have never taken advantage of his availability.

3. Finding a local hematologist who is a team player and will work with my primary care physician and my specialist; one who is a good communicator and a good listener; one who doesn't have a big ego; and one whose office is patient centered. For me the search for a local hematologist was challenging. I wanted someone locally who could check my blood work regularly and would know if there was a "red flag" or a problem that needed to be addressed right away. I wanted someone who would respond to me and whose office procedures were patient friendly. I wanted to talk to a human being and not communicate through an inner office online e-mail option. I wanted someone who would listen to Dr. V and work with him. I wanted someone who was not defensive and who cared more about my treatment then her ego. Dr. Barve met these criteria.

4. Finding a specialist who treats hundreds of patients who have my disease; one who is an outstanding physician, is aware of clinical trials; has expertise and experience; is an excellent communicator; and is patient centered. I feel fortunate to be a patient at MD Anderson. It is a huge intimidating complex, and patients are there under the worst of circumstances; however, my experience has been warm and nurturing. They have a system in place and the system works. On my first trip, one of their caregivers accompanied me all over the hospital for various tests. Now I visit the hospital on a quarterly basis for a blood draw and doctor visit. Dr. V and his team are patient centered. They spend the time with me that I need and I also try not to take advantage of their availability.

5. Talking to my spouse and letting him know what my needs are; being kind to those who help me; being honest about how I feel; asking for help when I need it. I feel very guilty that I got sick and need help from my spouse. I know this is not what either of us wanted. At first he hovered over me not wanting me to do anything and then we talked and agreed that I would do what I could do and ask for help if I couldn't do something. He can tell if the fatigue is getting me down, he can tell if I'm feeling generally crummy and sometimes he does step in and tell me to go lie down. He has assumed many of the tasks that I did before I was sick. He also handles many of the stressful insurance, financial, and documentation issues that complicate my life. I appreciate his support and the way that he cares about me and I feel very fortunate.

6. Finding a support group on line and in person; people who understand my disease and my options. I learn a great deal from the MPN listserve – oftentimes the focus is on ET or PV, which I do not have, but the consistent advice to trust your gut feeling, see a specialist, and follow up with a doctor if you don't feel good is relevant for me as well. I look forward to spending time with the Texas Support Group members. They have become my friends and I worry about each of them as if they were family. We struggle together if someone isn't feeling good. We support each other.

> "They have become my friends and I worry about each of them as if they were family. We struggle together if someone isn't feeling good. We support each other."

7. Reaching out to friends and family, telling them what I need, accepting their help and mostly their hugs. I cannot deal with cancer alone. I have been surprised since my diagnosis that individuals who I thought would be there for me have disappeared and those who I barely knew before the diagnosis have become close friends. People react differently when they learn that someone they know is sick. I think oftentimes they don't know what to say or do. However, I am very fortunate that I am surrounded by friends and family who are there for me, and I do ask for what I want by calling them to go to lunch or dinner or to come over. I don't like being alone, and my friends and family support me.

8. Being positive and being grateful for each day is a blessing. The diagnosis and my age caused me to realize that I may not have years and years left to do the things I always wanted to do. I decided to take action and do the things that were on my "bucket list". One of my friends who is an artist bought me all of the equipment I needed to paint, and painting has helped me deal with some of my inner demons. I have many hobbies and although I retired right before my diagnosis, I have started a consulting business that enables me to help others on a part time basis and that feels really good. MF is causing me to stop and smell the roses; to love wholeheartedly; to appreciate life's many gifts.

Forum Brings Together Patients and Physicians

Living Well with Myeloproliferative Neoplasms: Understanding What New Options Mean for You

On November 23, 2013 more than 175 MPN patients and caregivers attended a live forum held at MD Anderson Cancer Center. The meeting featured an expert panel that included Dr. Ruben Mesa from Mayo Clinic in Phoenix, AZ, Dr. Srdan Verstovsek (via Skype), Dr. Jorge Cortes, from the Leukemia Department at MD Anderson, Dr. Carmelita Escalante, Director of the Fatigue Clinic at MD Anderson, Lindsey Lyle, a physician assistant in the Department of Leukemia, and Clemencia Lara, MSW, MBA, LMSW, as clinical social worker at MD Anderson.

The meeting was presented in a town meeting format, with much of the time reserved for attendees to ask questions of the experts. The physicians shared the latest news in MPN research and treatment and also provided helpful strategies for coping with disease symptoms and treatment side effects. They also provided advice on communicating with your medical team. In addition, three patient advocates, Mike Harris, Rhonda Williams, and Barbara Miller also joined the discussion to tell their stories and share their advice for living well with an MPN.

Save the Date!

The first meeting was such a success that Patient Power is again partnering with Dr. Verstovsek and MD Anderson to host a second meeting to be held on **Saturday, November 1, 2014** at MD Anderson. Registration will be free for patients, their family members and caregivers.

For more information on Patient Power and for updates and additional information on the next meeting please visit **www.patientpower.info.**

MPN Clinical Trials

Listed below are all open clinical trials enrolling patients with MPNs as of May 2014. For more information on these clinical trials, call the information line toll-free at **1-800-392-1611** or the Leukemia New Patient Referral Line at **713-85-LEUKEMIA**

Evaluation of Ruxolitinib and Azacytidine Combination as a Therapy for Patients with Myelofibrosis and Myelodysplastic Syndrome/ Myeloproliferative Neoplasm

2012-0737 (clinicaltrials.gov NCT No: NCT01787487)

Principal Investigator: Naval Daver
Treatment Agent: Ruxolitinib and azacytidine

Study Description: This goal of this Phase 2 research study is to learn if the combination of ruxolitinib and azacytidine can help to control disease in patients with MF and myelodysplastic syndrome (MDS)/MPN. Ruxolitinib is designed to block some of the proteins in the blood that may cause MF symptoms. Azacytidine is a drug that has been used to treat MDS. Combination of these agents, which have different targets, may improve the overall effectiveness of each drug. Ruxolitinib is a pill that will be taken twice per day for the first 3 months, after which time low-dose azacytidine will be added. Azacytidine will be given intravenously daily for the first 5 days of each 28-day cycle. This trial is accepting patients with MF or MDS/MPN.

A Phase-2, Prospective, Open-Label Study to Determine the Safety and Efficacy of Sotatercept (ACE-011) in Subjects with Myeloproliferative Neoplasm-Associated Myelofibrosis and Anemia

2012-0534 (clinicaltrials.gov NCT No: NCT01712308)

Principal Investigator: Srdan Verstovsek
Treatment Agent: Sotatercept (ACE-011)

Study Description: Sotatercept (ACE-011) is a biological therapeutic (a treatment that uses your immune system to fight disease) that blocks signaling by activin A. Studies suggest that sotatercept may increase the growth and development of red blood cells by blocking activin signaling. The goal of this clinical research study is to learn if sotatercept can help to control MPN-associated MF and anemia. The safety of this drug will also be studied. Patients will be given subcutaneous injections once every 3 weeks in continuous 21-day cycles for at least 6 months. This study is accepting patients with primary or secondary MF and significant anemia.

A Phase 1/2, Open-label, Dose-escalation, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Orally Administered NS-018 in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

2011-0090 (clinicaltrials.gov NCT No: NCT01423851)

Principal Investigator: Srdan Verstovsek
Treatment Agent: NS-018

Study Description: The goal of this clinical research study is to find the highest tolerable dose of NS-018 that can be given to patients with MF. The safety and efficacy of this drug will also be studied. NS-018 is a drug that blocks the JAK2 protein, which is involved in the growth and survival of cancer cells. NS-018 is a pill that will be taken once or twice a day. Study visits will be once per week during the first month, once per month during cycles 2-4, and then every 3 months thereafter. This study is accepting patients who have primary or secondary MF.

A Phase 3, Randomized, Double-Blind Active-Controlled Study Evaluating Momelotinib vs. Ruxolitinib in Subjects with Primary Myelofibrosis or Post-Polycythemia Vera/Post-Essential Thrombocythemia Myelofibrosis

2013-0741 (clinicaltrials.gov NCT No: NCT01969838)

Principal Investigator: Srdan Verstovsek
Treatment Agent: Momelotinib or Ruxolitinib

Study Description: The goal of this study is to compare the effectiveness of momelotinib to ruxolitinib when given to patients with primary myelofibrosis (PMF) or post-polycythemia vera/essential thrombocythemia MF. The safety of these drugs will also be studied. Momelotinib is a drug that is designed to block JAK2 like ruxolitinib, which may help control the signs and symptoms of MF. Patients will be randomized to receive either momelotinib orally once daily plus placebo twice daily (to match ruxolitinib) or ruxolitinib orally twice daily plus placebo once daily (to match momelotinib). Study visits will be every 2 weeks until week 24. This study is accepting patients with advanced MF who have not previously been treated with a JAK inhibitor and have platelets above 50,000/uL.

A phase 2, open-label, randomized study to evaluate the safety and efficacy of momelotinib in subjects with polycythemia vera or essential thrombocythemia

2013-0977 (clinicaltrials.gov NCT No: NCT01998828)

Principal Investigator: Srdan Verstovsek
Treatment Agent: Momelotinib

Study Description: The goal of this study is to determine the safety and efficacy of momelotinib in subjects with PV or ET. Momelotinib is a drug that is designed to block JAK2 like ruxolitinib, which may help control the signs and symptoms of MF. Patients with will receive either 100 or 200 mg of momelotinib orally twice daily. Study visits every 2 weeks during the first 8 weeks and then monthly up to week 24. This study is accepting patients with PV or ET who require treatment and have not yet received treatment with a JAK inhibitor.

Study of Oral Pacritinib vs Best Available Therapy in Patients with Myelofibrosis

2013-1001

Principal Investigator: Srdan Verstovsek
Treatment Agent: Pacritinib or Best available therapy

Study Description: The goal of this study is to compare the efficacy of pacritinib with that of best available therapy. Pacritinib is an oral tyrosine kinase activity, which inhibits the activity of JAK2 like ruxolitinib, which may help control the signs and symptoms of MF. Patients will be randomized to receive 1) pacritinib 400 mg once daily or 2) pacritinib 200 mg twice daily or 3) best available therapy (which may include ruxolitinib). Study visits will be every week for the first month and then once per month up to week 24. Patients with advanced MF are eligible for this study. This study will soon be open at MD Anderson

A Phase 2 Study of Anagrelide Controlled Release in Subjects with Myeloproliferative Neoplasms

2014-0354

Principal Investigator: Srdan Verstovsek

Treatment Agent: Anagrelide controlled release

Study Description: The purpose of this study is to determine the safety and efficacy of anagrelide controlled release (CR) patients with MPN-related elevated platelet counts (thrombocytosis). Anagrelide is a drug that lowers platelet count in patients with MPNs. Anagrelide CR is a formulation that is designed to reduce the incidence of side effects seen with the original immediate release formula. Patients will initially receive 0.5 mg anagrelide orally twice per day and the dose will be titrated once per week to find the lowest dose that can lower platelet counts to between 150,000/uL and 400,000/uL. Patients with an MPN and platelet counts ≥ 600,000/uL are eligible to enroll. This study will soon be open at MD Anderson.

Open Label Phase 2 Single-Agent Study of LCL-161 in Patients with PMF, post-PV or post-ET MF

2013-0612 (clinicaltrials.gov NCT No: NCT02098161)

Principal Investigator: Naveen Pemmaraju

Treatment Agent: LCL-161

Study Description: The goal of this study is to determine the safety and efficacy of LCL-161 in patients with MF. LCL-161 is an inhibitor of proteins in the cell called inhibitors of apoptosis proteins (IAPs), which are involved in signaling pathways that control cell survival. Inhibiting these proteins may improve MF. Patients will receive 1500 mg LCL-161 orally once per week. Patients with intermediate-1, intermediate-2, or high-risk MF requiring treatment will be eligible to enroll. This study will soon be open at MD Anderson.

A Phase 2, Open-Label, Prospective Study of PRM-151 in Subjects with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis

2013-0051 (clinicaltrials.gov NCT No: NCT01981850)

Principal Investigator: Srdan Verstovsek

Treatment Agent: PRM-151

Study Description: Study Description: The goal of this clinical research study is to learn if PRM-151 can help to control MF. Two different dosing schedules will be compared. The safety of this drug will also be studied. PRM-151 is designed to be active at places in the body where there is tissue damage, which may help to control tissue scarring (such as bone marrow fibrosis). Some participants will also receive ruxolitinib. Ruxolitinib is designed to block some of the proteins in the blood that may cause MF symptoms. PRM-151 will be given intravenously for at least 6 months. This study is accepting patients with primary or secondary MF.

A study of brentuximab vedotin (SGN-35) in CD30-positive mastocytosis +/- an associated hematological clonal non-mast cell lineage disease

2012-0734

Principal Investigator: Srdan Verstovsek

Treatment Agent: Brentuximab vedotin

Study Description: The purpose of this study is to determine if the drug brentuximab vedotin (Adcetris) can help control systemic mastocytosis. Brentuximab vedotin is a biological therapeutic designed to bind to a certain protein (CD30) on cancer cells. This may kill the cancer cells. Patients will receive brentuximab vedotin intravenously once every 21 days for up to 8 cycles. This study is currently accepting patients with advanced systemic mastocytosis with or without an associated hematological clonal non-mast cell lineage disease.

Fort Worth MPN Patient Support Group Meeting, April 27, 2014

Front row: Vicky Teherani, Pat Lium, Mona Wyatt.

Second row: Larry Kramer, Florence Kramer, Wendy Sue, Marilyn Fulbright, Karen Stern, Barbara Minella.

Third Row: Cyrus Teherani, Patricia Yarborough, Charles Wyatt, Tom Minella - not pictured: photographer, Mike Stern

Support for Patients in Texas

The North Texas, Dallas-Fort Worth support group is organized by patient Karen Stern and meets quarterly. The South Texas, Houston support group is organized by patient Charlie Nielsen.

To find out more information or join either of these groups, please contact us either by e-mail or through our Facebook page:

- North Texas, Dallas/Ft. Worth – **Karen-Stern@sbcglobal.net**
- South Texas, Houston – **CharlieNielsen@aol.com**
- Facebook: **https://www.facebook.com/groups/MPNSupportTX/**

Beyond the JAK2^{V617F} Mutation: Role of Other Mutations in Myeloproliferative Neoplasms

By Srdan Verstovsek, MD, PhD and Kate Newberry, PhD

Mutations in Cancer

Cancers are thought to arise as a result of mutations that cause uncontrolled cell division, which allows cells to grow out of control and out-compete normal cells. Some mutations are inherited from your parents and are present at birth in the "germ cells" (sperm and eggs), while other mutations develop in other cell types over a person's lifetime (somatic mutations). The majority of cancers are caused by somatic mutations. Sometimes the acquisition of a single gene mutation is enough to induce the development of cancer. For example, chronic myelogenous leukemia has been found to be caused by a genetic change that results in a fusion protein called BCR-ABL that is always turned on, resulting in abnormal cell division. Targeting this abnormal protein with drugs that can switch it off (Gleevec) has led to disease remission in most patients. However, in general, cancers are more complex and arise only after the accumulation of several mutations.

Advances in our ability to sequence the genetic code (genome sequencing) in recent years have resulted in an explosion of information regarding genetic mutations in cancer cells. The JAK2^{V617F} mutation discovered in 2005 was the first mutation found to be involved in the biology of myeloproliferative neoplasms (MPNs). Approximately 95% of patients with polycythemia vera (PV) and 50%-60% of patients with essential thrombocythemia (ET) or primary myelofibrosis (PMF) have the JAK2^{V617F} mutation. However, it was not clear how one mutation could lead to three different diseases. Therefore, scientists focused their efforts on identifying other mutations that led to the development of MPNs. In the years since the discovery of the JAK2^{V617F} mutation, numerous studies have identified other mutations in MPNs that are found at varying frequencies. These mutations can be grouped according to their effects on one of three biological functions that are crucial for maintaining normal cell growth: 1) cytokine signaling, 2) epigenetic regulation and 3) splicing. We will explain what this means and discuss the relevance of these three functions to MPNs.

1.) Cytokine signaling

The development and production of blood cells is mainly controlled by proteins that we call cytokines and growth factors, which bind to receptors (structures that protrude from the cell surface) on blood and bone marrow cells and turn on JAK-STAT signaling pathway. JAK and STAT are the first in a cascade of proteins inside the cell that turn each other on, eventually leading to cell growth. This is why we call it a signaling pathway. Normally, the body maintains balance by turning the JAK-STAT pathway on and off as needed. However, the JAK2^{V617F} mutation causes the JAK2 protein to be stuck in the "on" position, which means that signaling through the JAK-STAT pathway is always on (Figure 1). While the JAK2^{V617F} mutation is not found in all patients with MPNs, increased levels of JAK-STAT signaling have been seen in all MPN patients, suggesting that there are other mutations that keep the JAK-STAT pathway turned on. Another mutation in the JAK2 gene (called the JAK2 exon 12 mutation) has been found 2-5% of PV patients without the JAK2^{V617F} mutation. Therefore, nearly 100% of patients with PV have a mutation in JAK2. For patients with ET and MF, the genetic cause appears to be more complicated. Five to ten percent of ET and MF patients without the JAK2^{V617F} mutation have a mutation in the MPL gene, which encodes a receptor called the thrombopoietin receptor. The thrombopoietin receptor also turns on the JAK-STAT pathway and is responsible for the development of platelets. Very recently, mutations in a gene called CALR were identified in approximately 25% of patients with ET and MF. Importantly, the mutations are only found in patients who do not have JAK2 or MPL mutations. While the CALR protein appears to have several functions, its main role is to help proteins fold into the proper structure after they are made inside the cell. In cells that have the CALR mutation, the JAK-STAT signaling pathway is turned on, but the role of CALR in that process is still unknown. When taken together, we now have very good evidence that mutations that turn on the JAK-STAT signaling pathway account for approximately 90% of patients with MF and ET, which supports the idea that dysfunction of JAK-STAT signaling is a major contributor to the development of MPNs. Other mutations in genes that normally turn off the JAK-STAT pathway inside the cell are found in the remaining, fewer than 10% of MPN patients.

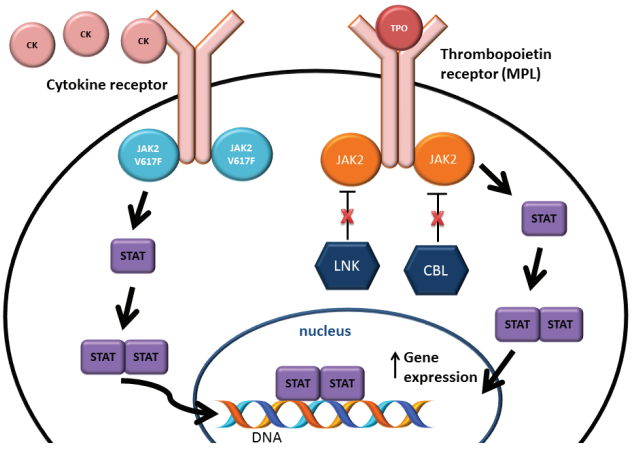

Figure 1. Mutations in several proteins in the JAK-STAT pathway lead to unchecked activation of the pathway and uncontrolled cell growth. Under normal conditions, cytokines (CK) such as thrombopoietin (TPO) bind to cytokine receptors, activating JAK2 and the JAK-STAT pathway. MPL is the gene that encodes the TPO receptor, and mutations in MPL keep the JAK-STAT pathway turned on. The JAK2V617F protein is always on, also leading to overactive JAK-STAT signaling. In addition to mutations in JAK2, some patients have mutations in genes such as CBL and LNK that normally turn off JAK-STAT signaling (shown as blue hexagons). All of these mutations have the same effect: they result in the JAK-STAT pathway being stuck in the "on" position. The larger, thicker arrows represent this hyperactive signaling.

Epigenetic regulation of genetic code

Other mutations found in some patients with MPNs are in genes that are involved in controlling whether genes are turned on or off. These proteins are called "epigenetic" regulators. Epigenetics refers to the ability of cells to control which genes are turned on and off. All of the DNA within a given cell is wrapped around proteins called histones, which are further coiled and condensed to form chromosomes (Figure 2). This packaging of DNA is crucial for regulating which genes are turned on an off. For example, DNA can have certain chemical tags attached (methylation), which leads to tighter coiling of the DNA around the histone proteins. This tightly coiled DNA is inaccessible to the machinery which transcribes the information stored in the DNA into RNA and proteins, effectively keeping the gene turned off. Other marks on the histones themselves can act to release the DNA and allow the genes to be turned on (transcribed to RNA and then to proteins). Furthermore, there are several proteins called "epigenetic modifiers" that are involved in attaching and removing the chemical tags on DNA and histones. These epigenetic modifiers regulate the process of turning genes on and off. As you might imagine, any disruption in the function of these proteins can lead to unchecked gene expression and potentially cancer. Mutations in epigenetic modifiers have been found in up to 20% of patients with MPNs. However, their exact role in the development of MPNs is not clear, as these mutations have also been found in other myeloid cancers, such as myelodysplastic syndrome and acute myeloid leukemia (AML). These types of mutations are present in MPN patients in addition to the previously described mutations in cytokine signaling and may help explain why patients with the $JAK2^{V617F}$ mutation end up having different diseases, e.g., ET vs. PV vs. MF. Importantly, mutations in epigenetic modifiers are found more often in MPN patients whose disease has progressed to AML, suggesting that they may also be involved in disease progression or perhaps a more aggressive disease. As you can imagine, the complexity of genetic and epigenetic interactions is a hot topic of research.

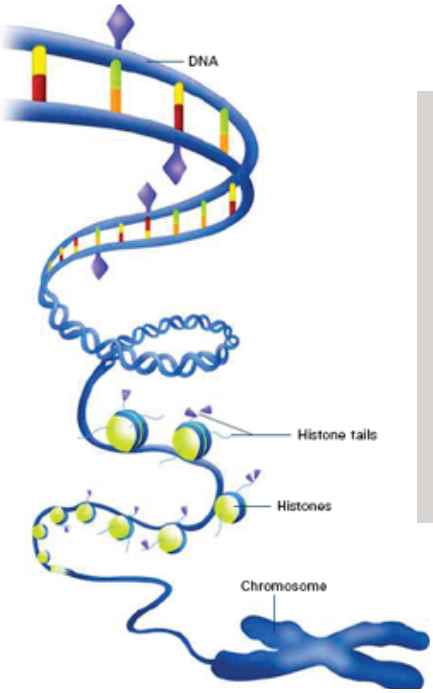

Figure 2. Diagram of how chromosomes are assembled. The yellow spheres are histones and the purple diamonds and triangles represent the chemical marks attached to DNA and histones by epigenetic modifiers. These marks determine whether genes are turned on or off.

Reproduced from *The New Genetics*, published by the National Institute of General Medical Sciences.

Splicing

The third group of mutations found in MPNs affect a cellular process known as "alternative splicing," which controls part of the process through which information encoded by the DNA is translated into a protein. The journey from gene (DNA) to protein (the molecule the carries out the gene's function) does not occur in two steps as originally thought (DNA→RNA→protein), but rather involves some intermediate steps to remove parts of the DNA that is not needed to make the protein. All human genes are made up of "introns" and "exons." Introns are DNA segments that are not necessary to make the protein, while exons are the DNA segments that contain the instructions necessary for making the protein. Splicing is the process by which the introns are removed and the exons are sewn back together (Figure 3). Each cell contains a large multiprotein machine called the spliceosome that recognizes the introns, cuts them out of the messenger RNA and "splices" the exons back together. For many genes, the exons can be put back together in different patterns, which can result in proteins with different functions (called alternative splicing). Alternative splicing is a tightly regulated process, which ensures that the correct proteins are produced in the correct place and at the right time. However, mutations in the splicing machinery can lead to cellular defects that promote or induce cancer. Like the mutations in epigenetic modifiers, mutations in the splicing machinery have been found in several myeloid cancers, and their exact role in MPNs is not yet known. These types of mutations are also present in MPN patients in addition to the previously described mutations in cytokine signaling and bring another level of complexity to our understanding of the biology of MPNs. This is to say that patients may have mutations of all 3 types described in this article. Future studies will need to focus on understanding the process of splicing and how mutations in the spliceosome machinery can promote MPNs and other cancers.

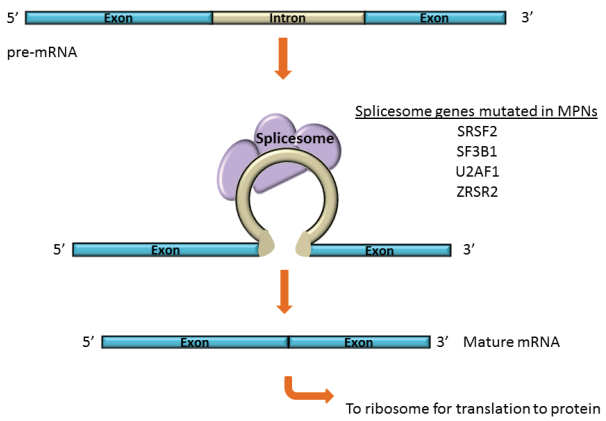

Figure 3. The splicing process. A large protein complex called the spliceosome assembles on the DNA, recognizes and removes the introns, and puts the exons back together. Mutations in several of the proteins that are part of the spliceosome have been found in patients with MF.

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MPN FOCUS
The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia Newsletter

MPN Focus is a periodic newsletter published by The Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia at MD Anderson Cancer Center to provide members of the MPN community with information on current research and treatments.

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Letter from the Director

Since the first issue of our newsletter was published, we are advancing in our efforts to educate patients and their families on MPNs. The patient support groups in Texas have been active, meeting every few months to share advice, support and camaraderie. And, the forum we hosted with Patient Power for patients and their families in November was a great success. We are already planning the second event to be held on November 1, 2014, so mark your calendars!

In addition to our educational efforts, we are progressing in our research efforts. We have opened some new clinical studies for patients with MPNs and are currently accepting patients. Great strides are also being made in research to understand the cause of MPNs. We are optimistic that new findings will ultimately lead to the development of new and better treatments.

Dr. Srdan Verstovsek, Professor of Medicine in the Department of Leukemia at MD Anderson, serves as Director of the Hanns A. Pielenz Clinical Research Center for Myeloproliferative Neoplasia. Dr. Verstovsek is an internationally recognized physician scientist dedicated to understanding the biology of and developing new therapies for MPNs.

Beyond the JAK2^{V617F} Mutation continued from page 7

Summary
Much has been learned about the role of mutations in MPNs in the decade since the discovery of the JAK2^{V617F} mutation. The known mutations in cytokine signaling account for approximately 90% of patients with MPNs, are in general exclusive of each other (a patient usually has either the JAK2^{V617F} mutation, MPL mutation, or CALR mutation), and help explain why hyperactive JAK-STAT signaling is the unifying abnormality in all MPNs. This also explains why JAK inhibitors are effective in all patients with MF, regardless of whether the patient has the JAK^{V617F} mutation. JAK inhibitors simply inhibit the hyperactive JAK-STAT pathway and therefore benefit all patients. The result of such inhibition is the significant improvement in patient symptoms, weight, ability to walk, and reduction in enlarged spleen and liver. However, reducing JAK-STAT signaling and cytokine levels does not lead to the eradication of the disease. While patients treated with JAK inhibitors may live longer with better control of the signs and symptoms of MF, there are other genes and/or processes involved in the development and progression of MPNs that are targets for the development of new therapies. Future studies will likely identify additional new mutations that may be responsible for different parts of the disease process, helping us to understand the biological complexity of MPNs and ultimately develop better curative treatments.

To Schedule an Appointment

Call **1-85-LEUKEMIA** (toll-free) or **713-563-2000**

Leukemia Department at MD Anderson

The Leukemia Department at MD Anderson is the largest leukemia program in the world, with a large team of world-renowned and highly experienced physicians focused on the treatment of Leukemia. We currently have more than 150 active clinical trials for leukemia, many of which are not available elsewhere. To find out more information please visit our website at **www.mdanderson.org/leukemiacenter**

Leukemia Insights: Leukemia Insights is a quarterly newsletter for physicians and other health professionals. Insights has the latest leukemia news, research and results from ongoing clinical trials, and available leukemia programs at MD Anderson. **http://www.mdanderson.org/publications/leukemia-insights/index.html**

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