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INSIDE THIS ISSUE

A GLANCE AT THE TUMOR MICROENVIRONMENT IN WALDENSTROM MACROGLOBULINEMIA

By Shahrzad Jalali, PhD

Dr. Shahrzad Jalali

Editor's note: Dr. Shahrzad Jalali has been a research associate in the Division of Hematology at Mayo Clinic Rochester since 2015. She received her PhD in biochemistry and medical genetics from the University of Manitoba, Canada, and obtained her postdoctoral trainings from Princess Margaret Cancer Centre and Hospital for Sick Children, University of Toronto, where she studied malignant brain tumors. She currently works as a research associate within the lymphoma group at Mayo Clinic, and her research is focused on B-cell lymphomas, with a primary focus on Waldenstrom macroglobulinemia (WM). Dr. Jalali is investigating the contribution of the bone marrow microenvironment in WM pathogenesis. She was the recipient of an IWMF-LLS Strategic Research Roadmap grant in 2017, as well as an IWMF Young Investigator Award in 2016 and 2018. The results of her work in WM have appeared as peer-reviewed articles in the past five years, and her contribution to the field is ongoing.

The human immune system is composed of a wide variety of cell types, including B-cells, T-cells, mast cells, neutrophils, macrophages, and monocytes. While the functions of all these cell types are necessary to maintain the equilibrium of the immune system, B-cells are central to humoral immunity, which is the part of the immune system that combats invading pathogens by producing and secreting antigen-specific immunoglobulins (Ig), also called antibodies.

B-cells originate from immature cells called multipotent hematopoietic stem cells and common lymphoid progenitor cells in the bone marrow and undergo the steps of maturation to express immunoglobulins of different classes (IgM and IgD) on their cell surface; then they leave the bone marrow to enter secondary or peripheral lymphoid tissues, such as the lymph nodes and spleen. In the peripheral tissues, B-cells complete their development and eventually become specialized plasma cells that secrete large amounts of the same type of antibodies found on their cell surfaces (Figure 1). During this process, B-cells that recognize self-antigens are removed, a process called negative selection, in order to protect one's own body tissues from the effects of B-cell-specific autoimmune responses.

Understanding the detailed molecular events that control the differentiation of normal B-cells has been instrumental in helping to identify the origin of Waldenstrom macroglobulinemia (WM), which is a low-grade B-cell lymphoma. The pathogenesis of WM is due to the infiltration and growth of malignant B-cells, primarily referred as lymphoplasmacytic lymphoma cells, within the bone marrow where they live, proliferate, and secrete large amounts of immunoglobulin class M (IgM), thereby disrupting the equilibrium of the bone marrow.

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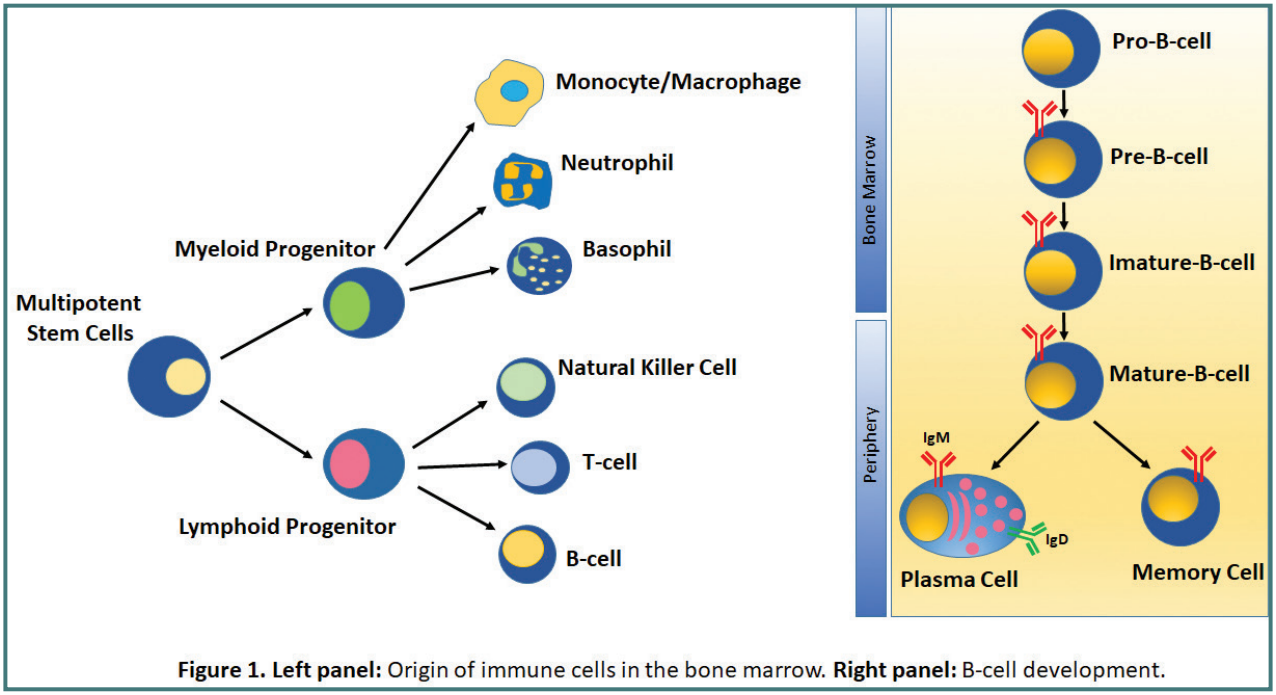

Figure 1. Left panel: Origin of immune cells in the bone marrow. **Right panel:** B-cell development.

Recent studies have shown that the malignant B-cells of WM are unable to go through the process called class switch recombination, during which proliferating B-cells switch the expression of one class of immunoglobulins to another when encountering foreign antigens. An example would be switching from IgM class to IgG or IgA class.

The bone marrow niche

As a main location for the infiltration and proliferation of malignant B-cells, the bone marrow microenvironment plays a key role in the pathogenesis of WM. The architecture of the bone marrow is composed of both cellular and non-cellular compartments. The cellular compartments of the bone marrow contain blood cells and their precursors (such as B-cells, T-cells, neutrophils, monocytes, and red blood cells), as well as non-blood cells (including cells that produce fat, bone, and blood vessel tissues). The non-cellular components of the bone marrow involve extracellular matrix, cytokines, chemokines, growth factors, and metabolites. Indeed, there is a complex, yet harmonized, array of interactions between cellular and non-cellular components of the bone marrow that not only controls continued existence of the hematopoietic stem and progenitor cells, but also determines their ability to generate different blood cells under normal and healthy conditions. Here we highlight some of the findings related to the mechanism by which WM cells home to the bone marrow as well as the contribution of both cellular and non-cellular factors of the bone marrow in WM pathogenesis.

Homing of WM cells into the bone marrow

Scientists have investigated the mechanism by which the WM cells home, or migrate, to the bone marrow microenvironment. They have shown that there is a protein factor, called chemokine stromal derived factor-1 (SDF-1), which is highly expressed in the bone marrow of WM patients. The receptor for this factor, called CXCR4, is found on the surface of WM cells. The interaction between SDF-1 and CXCR4 mediates migration of the WM cells out of the blood vessels. Indeed, approximately 30% of WM patients have elevated levels of CXCR4 molecules on the surface of their WM cells, due to its altered genetic structure. This increased CXCR4 expression, together with an increase in SDF-1 level, could increase the CXCR4/SDF-1 interaction and the homing of WM cells in the bone marrow. Increased survival of WM cells also impacts their migration and homing in the bone marrow.

The role of non-cellular/soluble factors of the bone marrow in WM

Cytokines and chemokines are among the non-cellular soluble factors of the bone marrow and act as messenger molecules that bind to their receptors on cell surfaces and regulate signaling cascades within the cells. Cytokines regulate differentiation of B-cells into plasma cells and facilitate plasma cell equilibrium and immunoglobulin secretion in the bone marrow. For instance, interleukin-21 (IL-21) is a cytokine known to regulate normal B-cell function and B-cell differentiation into immunoglobulin-producing plasma cells. B-cell activating factor (BAFF), also called B-lymphocyte stimulator (BLyS), is another cytokine that binds to its receptor on B-cells (BAFF-R) and causes B-cell proliferation. Moreover, interleukin-6 (IL-6) is a cytokine that induces B-cell differentiation and

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immunoglobulin production as well as promotes plasma cell survival. While cytokines are required to maintain normal B-cell function, any disturbance in their level and function could result in malignant cell growth. It has been shown that the cytokine and chemokine composition of the bone marrow in WM patients is different from the bone marrow in the normal population. For instance, levels of IL-21 and IL-6 are elevated in the serum of WM patients. Elevated levels of IL-21 and IL-6 increase proliferation and IgM secretion by WM cells. BAFF/BLyS is also upregulated in the serum and bone marrow of WM patients and potently causes cell proliferation and immunoglobulin secretion by WM cells.

Metabolites comprise another category of soluble molecules that are altered in WM. It is well-known that the metabolism of cancer cells is different from normal cells, due to their high rate of growth. In fact, cancer cells not only metabolize nutrients at a faster rate, but also alter or bypass the conventional way of consuming nutrients in order to satisfy their increased energy demand. Such an alteration could accumulate intermediary products, which often interfere with the physiological behavior of the cells and generate a favorable environment for cancer growth and progression. In a recent study, we investigated changes in the metabolites and proteins found in the bone marrow and serum of the WM patients to identify the molecules and biomarkers that could potentially contribute to WM pathogenesis. These findings have shown that proteins and metabolites related to the glutathione pathway have significantly been increased in WM compared to normal samples. Glutathione is a well-known anti-oxidant molecule that quenches/neutralizes the harmful effects of reactive oxygen species, protecting cells from stress-induced cell damage or death. While this effect of glutathione could be beneficial for the proper function of normal and immune cells, malignant B-cells in WM take advantage of this mechanism to protect themselves against any damage introduced by increased oxidative stress.

Additional evidence also highlights the importance of changes in lipid metabolism in WM, particularly when transition from the pre-malignant condition of monoclonal gammopathy of undetermined significance (MGUS) to symptomatic WM is a subject of investigation. Lipids are essential molecules that regulate a wide variety of biological processes including energy production, and they comprise the structural and functional properties of cellular membranes, gene activation, and modulation of signaling pathways. Lipids include a diverse group of compounds, such as fatty acids, glycerolipids, glycerophospholipids, sphingolipids, and sterol lipids. Comparison of total serum lipid content between MGUS and WM has indicated that many lipids, including fatty acids, are significantly reduced in WM compared to MGUS serum samples. This

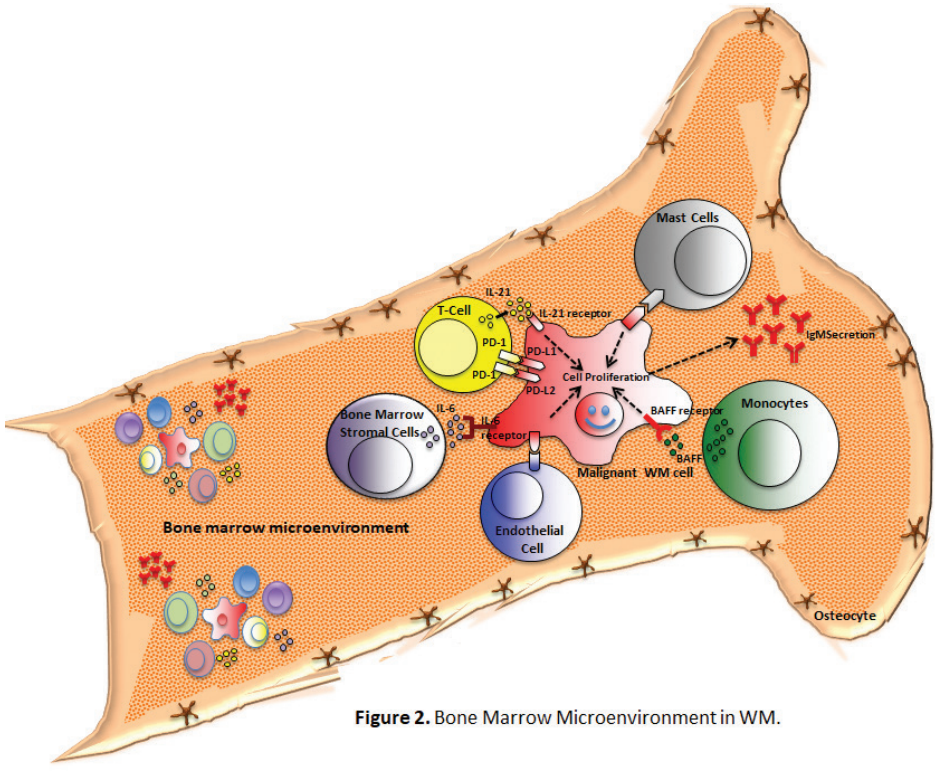

Figure 2. Bone Marrow Microenvironment in WM.

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could indicate that the balance between lipid synthesis and consumption by cancerous B-cells is indeed disturbed in WM.

Further experimental approaches have shown that tumor cells absorb lipids at a higher rate and shuttle them to be peroxidized. During peroxidation, lipids are broken down when free oxygen radicals "steal" electrons from cell membranes, resulting in cell damage. While peroxidation of the lipids can damage and kill cells, the malignant cells in WM are very proliferative, indicating that they use a counteracting mechanism in order to overcome cell death. In fact, glutathione peroxidase activity is higher in WM, and it can neutralize the destructive effect of lipid peroxidation, explaining why WM malignant cells are resistant to cell death despite increased lipid peroxidation. In addition, WM patients also have significantly reduced levels of vitamin D and its precursors in their serum. The anti-proliferative effect of Vitamin D is well-established in the context of several cancers, and its reduced level in WM patients implies that WM cells have elevated proliferation ability.

The role of bone marrow cells in WM

In general, one of the main reasons for cancer growth is that tumor cells escape from being recognized and attacked by the body's immune cells or immune system. A recent study has aimed to identify the cells that result in immune evasion in WM. As described earlier, several molecules which belong to the cytokine and chemokine family of proteins (CCL5, G-CSF, IL-6 and IL-21) are elevated in WM. These molecules have the capacity to engage a heterogeneous population of immature myeloid cells to the bone marrow microenvironment. These cells, called myeloid-derived suppressor cells (MDSCs), are able to suppress effective immune function and thereby promote tumor cell proliferation and growth. It has been shown that the number of MDSCs are increased in the bone marrow of WM patients and, in patients who have responded to treatment, the number of MDSCs is reduced to a level that is comparable to normal individuals.

A few recent studies have reported the role of mast cells, T-cells, monocytes, and endothelial cells in WM. An increased number of mast cells in the bone marrow is one of the characteristics of WM, and mast cells induce the proliferation of malignant cells. T-cells are also shown to contribute to WM. The expression of immune suppressive molecules on the surface of T-cells gives rise to an exhausted and inactive T-cell status in several cancers, including lymphomas. Immune suppressive molecules, such as PD-1, are expressed on the surface of T-cells, interact with binding molecules on the tumor cells and prevent the activation and anti-tumor properties of T-cells, a process called T-cell exhaustion. Increased expression of PD-1 and its binding molecules are shown in the WM bone marrow, highlighting how T-cell exhaustion could impede the effector anti-tumor and cytotoxic function of T-cells in WM (Figure 2).

Summary

While our understanding of the role of the bone marrow microenvironment in WM has evolved in recent years, many unknown facts remain to be answered. Here, we reviewed some of the available data regarding the significance of bone marrow components in supporting WM cells and explained the ways in which soluble factors such as cytokines, metabolites, and cells could impact malignant cell growth, proliferation, and immunoglobulin production. WM cells are in close contact with both immune and non-immune cells within the bone marrow, including bone marrow stroma cells, mast cells, T-cells, monocytes, macrophages, and endothelial cells. These cells support malignant growth and IgM secretion by WM cells.

Additionally, cytokines and chemokines of the bone marrow environment such as IL-6, IL-21, and BAFF/BLyS are key to increased proliferation and IgM secretion by WM cells. Metabolites, including glutathione, lipids, and vitamin D are also among the contributing factors in WM disease pathogenesis. A comprehensive understanding of the role of the bone marrow microenvironment in WM could help us design efficient treatment strategies to target malignant cells within their complex network of interactions in their environment.

TODAY, TOMORROW, AND BEYOND

By Newton Guerin, IWMF President and CEO

Newton Guerin

One thing we know to be true is that the only constant is change. Change is all around us. Like all successful endeavors, changes are always taking place throughout the IWMF.

Our stability through all these changes demands clarity in what we are trying to do. It is also dependent upon everyone knowing how their activities contribute to the overall plan. Every day, IWMF volunteers and staff rely on our Vision, Mission, and Compelling Intentions to provide guidance and direction and help tell our story of where we want to go and how we plan to get there.

During its November meeting, the IWMF Board of Trustees took several key actions that will continue to move the IWMF forward. Knowing the importance of sharing a common vision that provides organization-wide focus and direction, they relied on the IWMF's Compelling Intentions as a framework for their discussion. Doing so helped ensure that we continue to focus on top priorities during this time of transition. Our vision of "A world without WM" is simple and compelling and is shared by volunteer and staff leaders throughout the organization.

First, the Board reviewed and approved funding an additional $432,000 to renew Dr. Stephen Ansell's legacy research project. Since 1999, the IWMF has invested over $18 million in 51 research projects throughout the world. We are approaching more potential scientific breakthroughs, and research momentum is critical. Scientific advances have put us on the brink of a world without WM. The IWMF Board of Trustees has increased the goal of the "Imagine a Cure: A world without WM" campaign to raise an additional $25 million in the next five years. This level of support for WM research will allow for more advanced research and multi-institution projects, which will bring us even closer to a cure. IWMF-funded research projects have made a significant difference toward effectively treating WM and prolonging lives. We know that scientific advances, funded through the generosity of our donors, have tripled the longevity of people diagnosed with WM.

The Board reviewed plans for other high priority activities including:

Global Collaborative Initiative (GCI)

The IWMF will take the lead in convening a Global Collaborative Initiative Summit (GCIS) to bring together like-minded organizations including: IWMF international affiliates, the Leukemia & Lymphoma Society, the Lymphoma Research Foundation, the Lymphoma Coalition, the National Comprehensive Cancer Network, the American Cancer Society, Stand Up To Cancer, and Patient Power to leverage our collective impact on research, education, and support. They will work together to identify and implement strategies to minimize duplicative efforts and resources and enhance the relevance of the WM community worldwide.

New website: *www.iwmf.com*

Our newly redesigned IWMF website went live on November 30. Our new website was designed to:

- Support our vision of "A world without WM," along with our mission to "Support and educate everyone affected by WM while advancing the search for a cure" with a balanced set of messages, including the need for financial contributions to fulfill that mission.
- Provide easy access to content, including information about WM, IWMF publications, videos and podcasts, and search capability for web page content (and soon PDF content as well).
- Provide easy access to the services and support the IWMF provides, such as Stories of Hope, support groups and international affiliates, one-on-one support/LIFELINE, WM Physician Directory, IWMF Connect group discussion, and other online discussion forums.
- Provide easy access to information and registration for IWMF events and meetings, including the annual Ed Forum.
- Clearly communicate that "Our mission-focused programs rely on the generosity of IWMF donors, both current and future. We are very good stewards of donor dollars. We have a very compelling and urgent mission that is deserving of support."
- Provide easy access to IWMF-funded research and results in terms which are understandable by a lay person.

Support Groups

Even in these very difficult times, our support groups continue to find ways to keep their members connected. We currently have 38 groups across the US. Our support group leaders (SGLs) are now better trained and equipped to stay

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connected with their members as well as to each other. We're working to ensure that each group has two or three leaders in place. In addition to our "traditional" support group meetings, we are now identifying and conducting topic-specific meetings via Zoom.

International Affiliates

As we transition from Elena Malunis to Paul Kitchen as chair of the International Committee, our global presence continues to grow. We now have 22 affiliates, including four new ones in 2020: Chile, Israel, Portugal, and South Africa. Almost 300 international registrants, representing 26 countries, took part in our Virtual Ed Forum in August.

Educational Forum

We experienced our first Virtual Ed Forum in August. If you were unable to join us, click on this link to access the presentations, along with all other IWMF videos: *https://iwmf.com/videos-presentations/*. Also, because our time was limited during this two-day Virtual Ed Forum, we supplemented our program with a Global Educational Webinar Series.

Plans are now underway for the 2021 Ed Forum to return to a live event to be held October 29-31, 2021, at the Hilton St. Louis at the Ballpark. This event will include a virtual component as well for those who can't travel. More details will be available soon!

Walk for Waldenstrom's

As our signature event, the 2020 "Virtual" Walk for Waldenstrom's has been our most successful ever. It provided our participants a great way to raise money while creating awareness about WM and its impact on the lives of patients and caregivers. In addition, it attracted many new donors and volunteers.

Leaders in Transition

During 2020, we recruited four outstanding individuals, Glenn Cantor, Paul Kitchen, Carl Lisman, and Meg Mangin, to join the Board. We also thanked outgoing Board Members, Barry Nelson, Carl Harrington, and Elena Malunis, for all they have done for the IWMF and especially their Board service over the years! Our organization is extremely fortunate to have such outstanding leadership. Barry, Carl, and Elena have all played an important role in the IWMF's efforts to improve the lives of people living with WM.

As our Board meeting wrapped up, Carl Harrington encouraged the organization to shake things up a bit and get its creativity flowing to launch a new "Accelerate the Cure" campaign that goes beyond our existing Strategic Research Roadmap projects. To succeed, this will require an organization-wide effort involving all stakeholders, including Board members, patients, caregivers, pharma partners, donors, and our Scientific Advisory Committee (SAC). The first step is to ask the question, "What could we do that would really accelerate our search for a cure?" Carl went on to say, "I hope this inspires you to invent something big and audacious that does accelerate the cure. That is what the IWMF is here for. Think not of constraints and why we cannot, but think instead of how we can! I know you can do this!"

As Carl Harrington steps down from our top volunteer leadership position as Board chair and Pete DeNardis takes on that role, the IWMF is experiencing a leadership transition. We are up to that challenge and with Pete at the helm, our future is very bright!

IWMF LEADERSHIP PASSES THE TORCH

By Peter DeNardis, Chair of the Board of Trustees

"The art of progress is to preserve order amid change and to preserve change amid order." – Alfred North Whitehead

For the IWMF, a new year brings change and a continued effort to focus on supporting and educating everyone affected by Waldenstrom macroglobulinemia while advancing the search for a cure. In the coming months, you can still expect to see changes in the form of expansions in IWMF support, education, and research initiatives that will impact WMers around the world. None of this would be possible without the generosity of donors, a highly functioning CEO and office staff, and the selfless devotion of volunteers, support group leaders, and Board members.

For my part, as the new chair of the Board of Trustees, I'd like to relay recent changes that have taken place with regard to the Board itself. On behalf of WM patients and caregivers around the world, I'd like to extend heartfelt gratitude to two Board members who have stepped down at the end of 2020, Elena Malunis and Barry Nelson.

Among Elena's many volunteer activities on the Board, perhaps her most notable accomplishment has been to ensure the capital I in IWMF. Her efforts led to the successful installation of 22 international affiliates that provide services to WMers (when she joined the Board, just a handful of countries provided services), while supporting them with initiatives for translating IWMF publications into several languages. Barry Nelson, for his part, has been the technology wizard behind the scenes for the IWMF website. He implemented significant enhancements to better organize content on the site and made it much easier to search for publications and video presentations by author, topic, and region. Both Elena and Barry are caregivers who have gone above and beyond—tending to their spouses with WM, while also volunteering to help the IWMF and other patients and caregivers.

I'd like to also take the time to mention that, as 2021 begins, we have four new Trustees (who are also WM patients): Carl Lisman and Paul Kitchen, who both joined in August 2020, and Glenn Cantor and Meg Mangin, who both joined in November 2020.

Carl Lisman brings a strong background in finance and banking and is a retired executive vice president for PNC Bank, after a 38-year career in multiple lines of business with the bank. Carl also serves as trustee at the University of Scranton, Philadelphia Futures, and United Way of Wyoming Valley.

Paul Kitchen is currently the Board chair of the Waldenstrom's Macroglobulinemia Foundation of Canada (WMFC) and will help ensure that the IWMF remains focused on providing services relevant for the global WM community. Paul's background is in education, and he served as head of a prestigious Canadian independent coed boarding school for many years, after having taught math and science there.

Chairs of the Board, past and present: Carl Harrington and Pete DeNardis

Meg Mangin is a registered nurse, with previous experience in the areas of coronary/intensive care and home care. In 2009, she co-founded a 501(c)(3) charity, Chronic Illness Recovery (CIR), to provide information about resolving symptoms of autoimmune and other chronic inflammatory diseases. She is currently the executive director and primary nurse consultant on the CIR website, and many of you may already recognize her via her presence on the IWMF's Facebook Support Group and on IWMF Connect, providing guidance and information in response to questions posed by members.

Glenn Cantor is a veterinary toxicologic pathologist with extensive experience bringing cancer projects from early drug discovery research to development, most recently at Bristol Myers Squibb. Prior to that, he was a faculty member at Washington State University, where his research focused on an animal model of slow-growing B-cell lymphomas. (That role pre-dates his own diagnosis with WM!)

Please join me in thanking Elena Malunis and Barry Nelson for their service to the WM community and in welcoming Carl, Paul, Meg, and Glenn to the Board of Trustees!

Naturally, special mention must be made of retired Board Chair Carl Harrington, who brought significant change and progress to the IWMF during his tenure in that role and has left me with tremendously large shoes to fill. And our thanks also go to his caregiver—his wife, Eleanor Levie—who was at every Ed Forum and an integral part of making sure it was successful. She worked with Carl on behalf of the IWMF, and of course, allowed us to benefit from his time and devotion to helping WMers.

Over the decades since Arnie Smokler started a support group for WM in 1994, the IWMF has seen and implemented significant changes to continually improve the way it provides the latest information regarding WM symptoms, treatment,

IWMF Leadership, cont. on page 9

and support to WMers worldwide. The pandemic that started in 2020 brought about many challenges, but the hard-working staff and volunteers rose to those challenges and implemented changes that led to continued successful progress.

Upon diagnosis in 2003, I reached out to the small band of discussion list members on IWMF-TALK (now renamed IWMF Connect), and received invaluable guidance and advice that helped me navigate past the scary initial diagnosis of 5-7 years left to live. Their support and the example set by Board members and volunteers at the time led me to follow their lead and pay it forward by becoming more involved myself with the IWMF. Carl Harrington and each of the Board presidents before him (Judith May, Ben Rude, Arnie Smokler) have led the organization with different approaches and styles, yet each propelled the organization forward, focusing on their individual strengths and goals.

I consider myself fortunate to have been a part of the global WM community for a long enough period of time to have witnessed amazing progress during each of their tenures. As the new chair of the Board of Trustees, I look forward to the opportunity to pursue progress and change in order to continue to provide much needed support and services to everyone, and to continue to focus on the search for a cure.

My primary goal is simple—work together with IWMF President Newton Guerin, the amazing staff in place at the IWMF office, my dedicated and committed fellow Board members, affiliate leaders around the world, support group leaders, and volunteers—all contributing their time and their individual talents for the same cause: "Support and educate everyone affected by WM while advancing the search for a cure." Toward that end, I will capitalize upon opportunities to provide better and stronger communications on a global scale, to provide more support where support is needed, and to take advantage of opportunities to further enhance the Strategic Research Roadmap and the Robert Kyle Career Development Awards so that they lead to significantly better treatments for WM and a cure.

And so, I'd like to leave you with this notion—for most folks, the thought of a cure may be considered a long shot, but so was the thought of landing a man on the moon back in 1961, when US President John F. Kennedy announced that goal. It took eight years to do it, but it happened! Wouldn't it be amazing to see a cure for WM in eight years?

For me personally, as a veteran WMer for almost two decades now, I would love to see all IWMF members and volunteers working toward the goal of a cure within a similar span of time. As chair of the IWMF Board, my "lofty goal" is to work toward a cure, and my "rational goal" is to work toward the day when WM is just a chronic illness that can be managed for DECADES with minimal, if any, side effects from treatment.

All of us together—patients, caregivers, office staff, support group leaders, volunteers, Board members, donors, family, and friends—can achieve so much more if we continue to work together toward the common goals of focusing on support, education, and research for the global WM community, while advancing the search for a cure.

Best of health to all!

TORCH TOON by Linda Pochmerski

THE 2020 ED FORUM WAS A VIRTUAL EVENT WITH GREAT WM TOPICS, ASK THE DOCTOR SESSIONS, A WALK FOR WM, AND THE ASSOCIATED ACTIVITIES AND CAMARADERIE WELL-KNOWN TO WMERS WHEN THEY GET TOGETHER.

IWMF-FUNDED RESEARCH: PROGRESS REPORT

By Glenn Cantor, IWMF Trustee and Science Editor

Editor's Note: In an ongoing series, the Torch *will update the WM community on progress by IWMF-funded researchers. Dr. Sherine Elsawa was awarded an IWMF grant in 2018.*

Dr. Sherine Elsawa

Dr. Sherine Elsawa, University of New Hampshire, Durham, New Hampshire, USA

Epigenetic regulation of WM biology

Summary:

- Understanding key ways in which WM cells differ from normal cells could lead to new drug targets.
- In WM cells, mutated MYD88 (called MYD88 L265P) leads to an increase in two proteins called MLL1 and menin. These proteins change the WM cells' DNA and cause increased secretion of IL-6 and IgM.
- Increased IL-6 in the bone marrow environment stimulates additional growth of WM cells.
- Identification of MLL1 and menin as key regulators may lead to new targeted drug discoveries.

The WM community is well aware of the significant work identifying the MYD88 mutation called L265P, which is found in WM cells from over 90% of WM patients. This mutation causes MYD88 to be excessively active, resulting in proliferation and increased survival of WM cells. After the MYD88 mutation was discovered, substantial research effort was devoted to understanding exactly how the abnormal MYD88 protein conveyed signals to the WM cells' genes. One result of this research effort showed that excessively activated MYD88 in turn caused too much activation of a signaling protein called BTK, which led to the discovery that ibrutinib, a BTK inhibitor, could help control the disease.

But what other MYD88-driven signals are involved? If researchers understand the signaling pathways better, can they develop other drugs for WM? Dr. Elsawa and her laboratory at University of New Hampshire have taken an interesting approach. They started with the observation that MYD88-activated WM cells secrete several proteins into the bone marrow fluid that surrounds the cells. These proteins, including ones called IL-6 and CCL2, are called cytokines and, when in excess, further stimulate the growth of WM cells.

How does activated MYD88 cause WM cells to make too much IL-6 and CCL2? And if Dr. Elsawa discovers how that happens, can that provide a new opportunity to intercept the process with novel targeted drugs to control WM?

Answering these questions has led to a fascinating series of discoveries. It was already known that when WM cells express the mutated form of MYD88 (MYD88 L265P), they are abnormally activated and jump into high gear. A key finding was that when the abnormal activation occurs, WM cells express higher levels of two proteins, called MLL1 (mixed-lineage leukemia-1) and menin. These two proteins, which are located inside cells, bind with each other and form a complex with six other proteins. The resulting protein complex (called MLL1 histone methytransferase) binds to distinct, specific places on DNA. Once the protein complex which includes MLL1 and menin attaches to DNA, it changes the way DNA acts.

Dr. Elsawa and her group then dove into figuring out what the MLL1 and menin complex did, once it was bound to DNA. The amount of DNA in each cell of the body is huge. If it were strung out end-to-end, it would be about 40 inches long. To fit inside a cell, it is wound up tightly. One of the features of DNA winding is that it regularly encircles small spheres called nucleosomes. When a DNA strand is tightly wrapped around a nucleosome, it is tucked away and inaccessible. In that closed position, the DNA cannot be expressed and is silent.

That is where MLL1 and menin come in. Once MLL1 and menin bind to specific locations on DNA, they change a nearby protein, called histone 3, which controls how tightly DNA is wound around a nearby nucleosome. The nearby presence of MLL1 and menin results in the attachment of three small chemical signals, called methyls, to a specific location on histone 3. Once the three methyls are attached to histone 3 (called tri-methylation, abbreviated as H3K4me3), DNA unwinds from the nearby nucleosome and becomes open and accessible. Once the DNA is accessible, regulatory proteins (such as transcription factors) can bind to the DNA, and the gene can start to be expressed.

Dr. Elsawa's group has identified specific places where MLL1 and menin bind to DNA in WM cells. They show that the result of MLL1 and menin binding, with subsequent tri-methylation of histone 3, is an increase in the cytokines IL-6 and CCL2. This makes WM worse. The increased IL-6 in the bone marrow environment interacts with the IL-6 receptor on WM cells, and sets up a cycle

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Dr. Sherine Elsawa's research group unmasks for a quick photo. Dr. Elsawa is third from the right.

of additional growth and proliferation of the WM cells. Increased IL-6 signaling even causes more MYD88 signaling. Not only that, but another result of MLL1 and menin binding to DNA is that it causes the WM cells to make more IgM. Both aspects of WM disease—too many WM cells in the bone marrow and too much IgM in the blood—are enhanced.

What will happen if MLL1 or menin can be reduced? Dr. Elsawa's group tested this using genetic techniques to "knock down" the expression of MLL1 in WM cell lines. When they reduced MLL1, the cells secreted less IL-6, CCL2, and IgM. To confirm the results, they also tested a prototype drug to inhibit the MLL1 complex. Likewise, it also reduced IL-6, CCL2, and IgM.

Will this discovery lead to a new drug? It certainly suggests the possibility that if a targeted drug could decrease the level of MLL1 or menin, or change the way in which MLL1 and menin bind DNA, then the drug could break the cycle and stop the secretion of excessive IL-6, CCL2, and IgM. In turn, this might slow down the growth of WM cells. Of course, it will be essential to ensure that a new drug would not have unintended toxic consequences to the rest of the body. Dr. Elsawa's work is a first step, and we will see where it leads.

IWMF-FUNDED RESEARCH: NEW 2020 GRANTS

By Glenn Cantor, IWMF Trustee and Science Editor

Editor's note: In 2020, the IWMF selected and funded two research grant proposals. This article describes one of the proposals, which is co-funded by the Waldenstrom's Macroglobulinemia Foundation of Canada. The second research grant proposal, by Dr. Ruben Carrasco at the Dana-Farber Cancer Institute in Boston, is entitled "MYD88 L265P signaling-associated multiplex characterization of the bone marrow environment in WM patients for clinical application." We will summarize that proposal in the next issue of the Torch.

Dr. Zachary Hunter, Dana-Farber Cancer Institute, Harvard University, Boston, Massachusetts, USA

Multi-omic analysis of DNA, RNA, and epigenomic networks for prognostication and novel target identification of WM

Summary:

Dr. Hunter's group at Dana-Farber Cancer Institute will integrate many different molecular tests to look at WM in a more comprehensive way, using samples from a large number of WM patients.

The group will use newly developed artificial intelligence computer methods to uncover how the molecular changes interact in networks, within WM cells, and between WM cells and nearby normal cells.

Analysis of interactive molecular changes will hopefully aid in selecting personalized drug combinations for each WM patient.

Dr. Hunter's ground-breaking work is well known and has transformed our understanding and management of WM, including the discovery of the MYD88 L265P mutation carried by over 90% of WM patients and CXCR4 mutations in 30-40% of WM patients. This work was done by whole genome sequencing, in which Dr. Hunter and his colleagues in Dr. Steven Treon's lab at Dana-Farber Cancer Institute analyzed DNA sequences in WM cells from numerous patients. This detailed genetic information led to the development of ibrutinib as one of the mainstays of WM treatment and now has resulted in clinical trials with CXCR4 inhibitors in WM patients with relevant CXCR4 mutations.

However, DNA sequences do not tell the whole story. Genes, encoded by DNA, must be transcribed into RNA strands, which are then translated to proteins. At each step of the way, there are many key regulatory processes, and if any of these regulators go awry, cancers—including WM—can ensue.

Using powerful new computer techniques, Dr. Treon's and Dr. Hunter's group, in close collaboration with several other state-of-the art laboratories at Harvard, will analyze a massive

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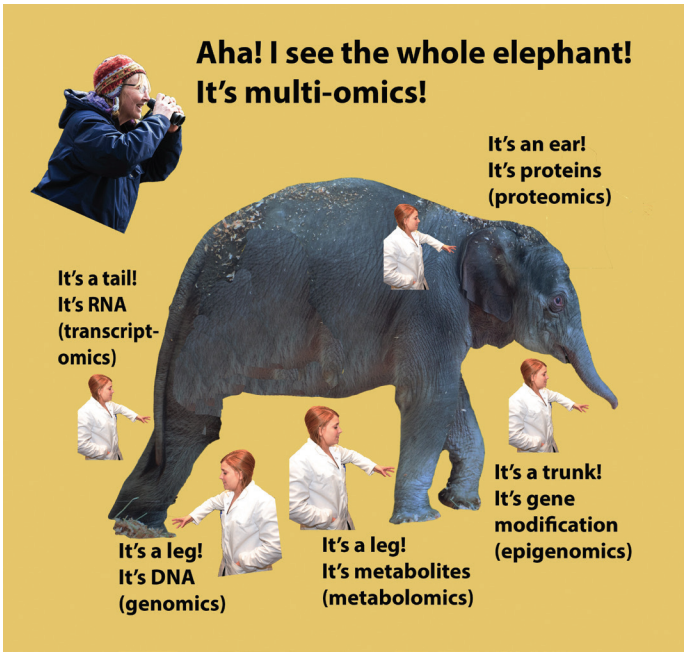
variety of these regulatory processes and their endpoints in WM patients, looking for new patterns that might uncover novel targets for treatment.

Scientists used to pick a small number of genes, epigenetic changes, messenger RNA transcripts, or proteins which they thought were important and study them. An increasingly popular alternative approach is to look at all of these molecules in an unbiased way. This broad, unbiased approach is called "omics." For example, the study of all the genes and their sequences is called "genomics," while the study of all proteins is called "proteomics."

Dr. Hunter's work will analyze WM cells at multiple levels ("multi-omics"). There is "genomics," the sequencing of DNA that make up our genes. But DNA sequence doesn't tell scientists everything. Under tight regulation from small molecules that attach to DNA, cells fold their DNA into complicated patterns, like tightly wound skeins of wool, and only certain parts of the DNA stick out and are available. The study of the small attached molecules that regulate genes, including exactly where they are attached and which genes they regulate, is called "epigenomics." Genes are expressed (or "transcribed") into messages, called messenger RNA (mRNA), and analysis of all the mRNAs in the body is called "transcriptomics." Then, the mRNAs are translated into proteins, and the analysis of all the proteins is called



"proteomics." In turn, the proteins interact and signal to each other, in what is called "interactomics."

Epigenetic changes, DNA, RNA, and proteins do not exist as a general mixture in the body; they are expressed differently in specific cells. WM cells interact with nearby normal cells in what is called the tumor microenvironment. Some of the normal cells enhance the growth of WM and make it worse, other normal cells may help to control WM and keep the disease under control, and still other normal cells have nothing to do with WM. Dr. Hunter's group will use newer technologies to analyze epigenetic changes, DNA, RNA, and proteins on a single-cell basis, performed on a large number of cells, including WM cells and normal cells, from each patient. Each specific cell type will be identified, so that they can understand which type of cell expresses which type of molecular properties.

It is not enough, though, to exhaustively catalog all of these molecules into gigantic lists. The real question is how do they interact. To better understand this, Dr. Hunter's group will analyze networks, which describe how changes in one component influence other components.

To build robust networks, where the results are not just due to one-off chance glitches, it is necessary to analyze many cells from many WM patients. The Dana-Farber group is well-poised to do this since they see so many WM patients. For this project, they will use cells that they already collected from 300 WM patients before their first treatment. On top of that, they will incorporate some of the newest advances in computer technology, including artificial intelligence, to make sense of the massive amount of data. Importantly, they will be able to correlate the molecular results with clinical features and long-term follow-up data from each of the 300 patients.

We already know that WM cells have a number of mutations and other changes, although there are undoubtedly more yet to be discovered. Once we learn how these changes interact with each other in a network, treatment can be planned in a better way. For example, if a new drug inhibits one protein in a network, will the rest of the network compensate, such that the new drug doesn't work very well? Is it necessary to inhibit two or more proteins at the same time, with two different drugs? If so, which drugs, in which patients?

An increasing number of drugs are in use for WM, and more are on the way. It is hoped that this large-scale approach will yield new insights into WM, including why there are differences among WM patients and how to use these differences to personalize the best treatment for each patient.

For more information, Dr. Zachary Hunter's September 9, 2020, IWMF webinar is available at: *https://iwmf.com/iwmf-global-educational-webinar-series/*

AN IMPORTANT NEW CAREER DEVELOPMENT PROGRAM FOR YOUNG INVESTIGATORS

By Carl Harrington, IWMF President Emeritus

In October, the IWMF took a big step toward achieving our vision of a "A world without WM." We announced the Robert A. Kyle Career Development Program, a critical new program designed to bring new researchers with fresh perspectives into our search for a cure. Let me tell you about this award, the man it honors, and why it is so important.

The Robert A. Kyle Career Development Award

In recent years, we have made substantial progress in understanding WM and how to treat it. WM patients used to have four treatment options. Now we have over 40, and they yield longer, deeper remissions with fewer side effects. In addition, life expectancy has increased from 3-5 years to 16-20 years. But we won't stop there…we're not stopping until we find a cure.

In December 2019, the IWMF Strategic Advisory Committee (SAC), made up of the leading WM researchers and clinicians in the world, recommended that we create a program to support the next generation of WM researchers and name it in honor of Dr. Robert Kyle of the Mayo Clinic. And that's exactly what we've done!

Under this new yearly program, the IWMF will award $75,000 a year for two years, for a total of $150,000, to one or more young investigators. These grants will focus on making progress in the five key domains of the IWMF Strategic Research Roadmap:

- Genomics and Epigenomics
- Signaling
- Immunology/Immunotherapy
- Bone Marrow/Tumor Microenvironment
- IgM Monoclonal Gammopathy of Undetermined Significance (MGUS)

We have already issued a global RFP (Request for Proposals). Proposals are due in mid-January 2021. They will be evaluated by a panel of distinguished researchers, including members of the IWMF SAC, under the same guidelines that we use for the Roadmap projects. The winner (or winners, if we have enough funding for more than one) will be announced at the 2021 IWMF Educational Forum. Dr. Kyle will present the award himself. Our goal in creating this program is to ensure that the best minds in research continue to focus on our rare disease.

Dr. Robert Kyle, the man and the legend

Most of you are very familiar with Dr. Robert (Bob) Kyle. He is a legend in the field of WM and actually knew and worked with Dr. Jan Waldenström, who discovered our disease. Bob joined the IWMF Board of Trustees in 2004 and served on the Board through July 2019. By my calculations, that means he attended over 60 IWMF Board meetings and spent over a third of a year just sitting in those meetings!

When Bob stepped down from the IWMF Board, he said "Although I have been on several boards relating to multiple myeloma and amyloidosis, I have never seen one in which the patients were so heavily involved. In fact, the WM patients did everything. I used to tell friends and colleagues that when I walked into a Board meeting, I was the only person in the room who did not have WM! It is an amazing organization."

And Bob Kyle is an amazing man, one the IWMF is proud to honor.

Read more about him in the cover article in the April 2018 *IWMF Torch* at *http://iwmf.wpengine.com/wp-content/uploads/2020/10/Torch_April2018.pdf*

Why this award is so important

When young researchers are beginning their careers, it is important that they select a field of study to concentrate in and begin to find financial resources to support themselves. The new IWMF Robert A. Kyle Career Development Award will allow some of the best and brightest minds in the world to select WM as their area of concentration. Our plan is to select one or more winners each year.

The number of awards we are able to make will depend upon the quality of the applications and the amount of funding we have. Please consider a donation to the IWMF. You can help us make more than a single award each year and expand the number of IWMF Strategic Research Roadmap projects we are able to fund. You'll be joining Dr. Kyle, young researchers across the globe, and the entire WM community to achieve our vision of "A world without WM."

NAVIGATING MY LIFE WITH WALDENSTROM'S

By Jack Sprankle

I was an airline captain for 30 years, flying domestic and international flights on Boeing 757s and 767s. Captains are required to have an FAA first class medical from an aviation medical examiner every six months. I had passed every medical exam and never was ill during my career except for a few common colds. This all changed in 2010 with an emergency back surgery that abruptly ended my career. I was devastated.

The lumbar discectomy had left me with a permanent loss of feeling and constant pain along the right sciatic nerve, neurological weakness, loss of bladder control, and limited mobility. This was followed by double inguinal hernia surgery, resulting in numbness in my lower abdomen. Then along came Waldenstrom's in 2016 and most recently, prostate cancer and a prostatectomy. This was all within a ten-year period. When it rains, it pours! However, I have been able to navigate through all of this by being knowledgeable about each medical issue and maintaining a "wings level" positive attitude.

There is more to flying an airliner then simply climbing aboard and taking off. The preparation for a flight is extensive, not only for the flight crew but also for many others involved prior to departure. My first officer and I would check the weather for the departure and destination airports and along our route for thunderstorms, winds aloft, and turbulence. We reviewed the flight plan for our navigational route, altitude to be flown, and the amount of fuel required. We proceeded to the aircraft for a preflight walk-around inspection, reviewed the maintenance logbook, and programmed the flight computers. The captain needs to know, and is required to know, all the information available to have a safe and successful flight.

I have transferred this "need to know" to navigate my WM. A routine eye exam found hemorrhaging in the back of my eyes. Subsequent lab results had me scheduling with an oncologist, where I was initially misdiagnosed. After a bone marrow biopsy, it was determined I had a rare cancer with a very long name, Waldenstrom's macroglobulinemia. I scoured the internet for information to understand my disease. The IWMF website provided a wealth of information. My initial oncologist was unfamiliar with WM, and after a few visits I realized I actually knew more than he did. I located a directory of doctors specializing in WM on the IWMF website. I contacted The Ohio State University, The James Cancer Hospital, for an appointment with Dr. Beth Christian. Prior to that first visit, I learned all I could about WM. I began a journal to document my journey, a spreadsheet to track my lab work, and I had file folders full of information. I had pages of questions to ask Dr. Christian during our first visit. I was determined to be knowledgeable about WM and be involved in this journey.

My IgM was approaching 6,000 with high viscosity and very low platelets. Fortunately, fatigue was my only symptom. I had only a fair response with my first treatment of bortezomib, dexamethasone, and rituximab (BDR). I did not benefit from the rituximab maintenance after treatment, so it was stopped. Watch-and-wait was short-lived. My IgM neared 6,000 again in 2018, and now my PSA (prostate-specific antigen) numbers were elevated. Numerous urology labs and testing indicated I had prostate cancer. I researched the internet on prostate cancer and treatments. Radiation or a prostatectomy (surgical removal of all or part of the prostate) were my best choices, and my urologist agreed.

Now a dilemma arose. Dr. Christian and I had discussed a stem cell transplant as a possibility at some point along my journey. My next WM treatment was to be rituximab, bendamustine, and dexamethasone (RBD). However, I had read an article explaining how bendamustine can damage stem cells. In addition, I needed to decide on radiation or prostatectomy. I couldn't have treatment for both cancers at the same time. Based on what I learned, I suggested to both doctors to wait on the prostate treatment, as that is a slow-growing cancer, and to harvest my stem cells now and store them to avoid any cell damage before treating with the bendamustine regimen. All were in agreement with the plan. During the summer of 2019, we proceeded with the stem cell harvesting. I then completed the six cycles of bendamustine combination therapy, resulting in a very good response and lowering my IgM to 535.

We allowed my body to recover for a few months before battling the prostate cancer. I elected to have a prostatectomy. Once again, I researched the procedure, watched videos

Jack and Victoria Sprankle

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of the surgery, and located the best qualified doctor. The robotic surgery was successfully completed in 2020, with the cancer becoming undetectable. What a big relief! Now to enjoy my WM watch-and-wait.

A captain also needs a good copilot to share in the various duties and provide support throughout the flight. I could not have navigated any of my medical issues without my wife, Victoria, as my copilot. She has been a wonderful caregiver, providing support and comfort. I call her my "helicopter wife" as she hovers over me to ensure I am cared for. We met 48 years ago in high school. I had just received my private pilot's license at age 17 when I took her flying on our first date. She has been a wonderful copilot in my life ever since.

Jack Sprankle in flight simulator

Continued training throughout a pilot's career is required by the FAA. Every six months, a captain must complete hours of recurrent training on aircraft systems and fly a simulator to review procedures and emergencies. As pilots, we are always learning new information. Likewise, I continue to learn more about WM and new medications, clinical trials, and research discoveries.

I am enjoying life with my family while relaxing at home during this pandemic. I have no desire to travel by getting on an airplane, staying in a hotel, and eating restaurant food (that's what I did for a living for over 30 years). I have many hobbies to keep me occupied. Victoria says my main hobby is to see how many hobbies I can have at one time.

I now have time to volunteer and give back to various groups and organizations. I am a LIFELINE volunteer on stem cell collection with the IWMF, I am a writer for my college alumni association, and I mentor student pilots on their aviation career paths. I hope to become more involved in our community once the pandemic is over.

I continue to learn and be knowledgeable about WM and my other medical issues in order to be an advocate for my health and to help navigate my journey.

MEDICAL NEWS ROUNDUP

BY SUE HERMS, IWMF RESEARCH COMMITTEE MEMBER

Updated Consensus Treatment Recommendations from 10th International Workshop on WM Released – Consensus treatment recommendations for WM were updated as a result of the 10th International Workshop on WM held November 2018 in New York City. According to these recommendations, alkylating agents (bendamustine, cyclophosphamide) and proteasome inhibitors (bortezomib, carfilzomib, ixazomib), both in combination with rituximab, as well as BTK inhibitors (ibrutinib), alone or in combination with rituximab, are preferred first-line therapy options for symptomatic patients with WM. In previously treated WM patients who had an initial durable response, reuse of a previous regimen or another primary therapy regimen are acceptable options. Novel BTK inhibitors (acalabrutinib, zanubrutinib, tirabrutinib) and the BCL-2 antagonist venetoclax appear safe and active, and represent emerging options for treatment. The treatment recommendations can be viewed at: *https://iwmf.wpengine.com/wp-content/uploads/2020/11/IWWM_2018_tx_rec.pdf*

Bei-Gene's New Drug Submission for Zanubrutinib Treatment for WM Accepted by Health Canada – BeiGene, Ltd. announced that its New Drug Submission for zanubrutinib (Brukinsa) for the treatment of WM patients has been accepted by Health Canada and granted priority review status. The drug's efficacy and safety data will be evaluated and a risk/benefit analysis performed by the Health Products and Food Branch of Health Canada. Clinical trial data from the Phase 3 ASPEN study that evaluated zanubrutinib vs. ibrutinib in both treatment-naïve and relapsed/refractory WM will be part of the review. In that study, zanubrutinib demonstrated more frequent very good partial responses and advantages in safety and tolerability compared to ibrutinib.

Results Available for Long-Term Follow-up of Phase 2 Ixazomib Combination Trial in WM – Long-term follow-up of a Phase 2 clinical trial evaluating the combination of the oral proteasome inhibitor ixazomib (Ninlaro), dexamethasone, and rituximab (Rituxan) in 26

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treatment-naïve WM patients was reported in the journal *Blood Advances*. This combination, designated IDR, was administered over 12 cycles: six monthly induction cycles followed by six every-2-month maintenance cycles. The MYD88 L265P mutation was detected in all 26 patients, while CXCR4 mutations were detected in 15. The median progression-free survival was 40 months, the median duration of response was 38 months, and the median time-to-next treatment was 40 months. CXCR4 mutations did not impact these statistics. The overall, major, and very good partial response rates were 96%, 77%, and 19%, respectively. The rate of very good partial responses was higher in patients without CXCR4 mutations (36%) than in patients with CXCR4 mutations (7%). The safety profile was considered excellent, although some patients experienced adverse events that included infections, high blood glucose levels, and infusion reactions.

Phase 2 Study Results Published for Daratumumab in Previously Treated WM Patients – Results from a multicenter Phase 2 study of single agent daratumumab (Darzalex) in 13 previously treated WM patients were published in the journal *Blood Advances*. Daratumumab is an anti-CD38 monoclonal antibody used to treat multiple myeloma and systemic light-chain amyloidosis; CD38 is a marker of plasmacytic differentiation and is expressed in a subset of WM cells. The study protocol called for daratumumab to be administered intravenously once weekly for eight doses, then once every two weeks for eight doses, and finally once every four weeks for 12 doses—a total of 28 doses over 18 months. The median number of cycles received was two, and only two patients completed the planned number of cycles. The overall response rate was 23%. Daratumumab was stopped prematurely in 11 patients because of disease progression or lack of response, and the study was eventually terminated. Despite the lower than expected responses in WM, the authors suggest that daratumumab might have a role in combination with other agents, such as anti-CD20 monoclonal antibodies. A clinical trial combining ibrutinib (Imbruvica) with daratumumab is ongoing.

Ibrutinib Has Positive Impacts on Circulating Immune Cells in CLL – An article in the journal *Leukemia Research* discussed the effect of ibrutinib (Imbruvica) on the landscape of circulating immune cell populations throughout the first year of treatment in previously untreated and relapsed/refractory chronic lymphocytic leukemia (CLL). The study, conducted as part of the RESONATE and RESONATE-2 clinical trials, compared 105 patients to untreated age-matched healthy donors. Ibrutinib significantly decreased pathologically high circulating B-cells, regulatory T-cells, effector/memory CD4+ and CD8+ T-cells (including exhausted and chronically activated T-cells), natural killer cells, and myeloid-derived suppressor cells, while preserving naïve T-cells and natural killer cells and increasing circulating monocytes. Ibrutinib also significantly restored normal T-cell function.

Study Reports Effectiveness of Shingrix Vaccination in CLL and LPL Patients on BTK Inhibitor Therapy – The University of Rochester Medical Center in New York analyzed short-term results of Shingrix vaccination to prevent shingles in patients with chronic lymphocytic leukemia (CLL) and lymphoplasmacytic lymphoma (LPL) on BTK inhibitor therapy. Shingles is caused by reactivation of the varicella zoster virus in someone who has had chicken pox and is characterized by a painful rash and sometimes serious neurological and other complications. The condition is more common with age and in people who are immunocompromised, including those with blood cancers. For this pilot study, published in the journal *Leukemia*, 32 patients at least 50 years old and on BTK inhibitor therapy for at least three months were enrolled, 22 with CLL and 10 with LPL. The only other permitted therapy was rituximab (Rituxan), which had to be completed more than one year before vaccination. Following the standard two doses of Shingrix vaccine, participants were assessed for an immune response, determined by at least a four-fold increase in IgG antibody titers specific to varicella zoster and at least a two-fold increase in activated CD4+ T-cells. Sufficient antibody responses were detected in 24 patients (75%), and sufficient T-cell responses in 25 patients (78%). In the patients with an antibody response, 87.5% also achieved a T-cell response. For the eight patients without an antibody response, only 50% had a T-cell response. Four patients did not meet criteria for either type of response; these were all CLL patients who were treated initially with combination rituximab and ibrutinib therapy and had been on ibrutinib for a relatively longer period. In previous Shingrix vaccine studies, healthy subjects achieved an antibody response rate of 98% and a T-cell response rate of 93%, while patients with blood cancers but not on BTK inhibitor therapy achieved an antibody response rate of 65% and a T-cell response rate of 84%.

New Phase 2 Trial Available for Combination Ibrutinib and Venetoclax for Previously Untreated WM – Dana-Farber Cancer Institute has opened a Phase 2 clinical trial for the combination of ibrutinib (Imbruvica) and venetoclax (Venclexta) in previously untreated WM patients who have mutated MYD88. During each monthly cycle, participants will take ibrutinib once daily; prior to the first dose of venetoclax and for two weeks thereafter, prophylaxis to prevent tumor lysis syndrome will be administered. Daily venetoclax dosing will be ramped up during cycle two, with one arm of the study using a three-dose ramp up and the other arm using a two-dose ramp up. Patients will be treated for two years, with four years of follow-up. The primary outcome measure will be the very good partial response rate (a greater

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than 90% reduction in serum IgM level from baseline). The study anticipates enrollment of 50 participants, and the identification number on *www.clinicaltrials.gov* is NCT04273139.

US FDA Grants Orphan Drug Designation for Treatment of Anti-MAG Neuropathy – The US Food and Drug Administration (FDA) has granted Orphan Drug designation to PN-1007 for the treatment of anti-myelin-associated glycoprotein (MAG) neuropathy, a type of peripheral nerve disorder seen in patients with WM and IgM MGUS. In anti-MAG neuropathy, monoclonal IgM antibodies are directed against part of the myelin sheath of peripheral nerves; PN-1007 mimics the binding site used by the IgM antibodies, thereby preventing the antibodies from binding to myelin. The manufacturer, Polyneuron Pharmaceuticals, is expected to begin a Phase 1/2a clinical trial of the drug later this year. The FDA designation is meant to encourage the development of orphan drugs for the prevention, diagnosis, and treatment of rare diseases or conditions by allowing the US government to provide incentives and policy support.

Long-Term Data Reported for Fixed-Duration Therapy of Venetoclax and Rituximab in CLL – Two-year fixed-duration venetoclax (Venclexta) plus rituximab (Rituxan) produced sustained progression-free survival in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), according to long-term data published in the *Journal of Clinical Oncology*. The four-year follow-up from the Phase 3 MURANO trial evaluated the so-called VenR combination, compared to bendamustine plus rituximab (BR). In the trial, 194 patients were assigned to the VenR arm, and 195 to the BR arm. At the end of follow-up, progression-free survival was 57.3% for VenR vs. 4.6% for BR, and overall survival was 85.3% for VenR vs. 66.8% for BR.

Anti-CD47 Antibodies in Combination with Rituximab Provide New Mechanism for NHL Therapy – At the Society for Immunotherapy of Cancer 35th Anniversary Annual Meeting in November, one of the presentations reviewed progress on antibodies to block CD47. CD47 is a surface protein overexpressed on many cancer cells that prevents macrophages from ingesting them (the "Don't Eat Me" signal). After blocking CD47, macrophage ingestion and killing of tumor cells increases. Magrolimab, an anti-CD47 antibody, has been used in combination with rituximab (Rituxan) in clinical trials for non-Hodgkin's lymphoma (NHL), including diffuse large B-cell lymphoma, follicular lymphoma (FL), and marginal zone lymphoma (MZL). In a Phase 2 trial, the overall response rate for the indolent lymphomas FL and MZL was 61%, and the complete response rate was 24%. One adverse event of anti-CD47 antibodies is transient anemia, since aged red blood cells also use CD47 to avoid being eaten by macrophages. However, red blood cell parameters returned to normal with time in most patients. Other drugs to block CD47 are in early development.

Italian Study Evaluates Mortality and Predictive Factors for Overall Survival in Blood Cancer Patients Hospitalized with COVID-19 – A retrospective Italian study published in the journal *Lancet Haematology* evaluated the mortality and potential predictive factors associated with overall survival in 536 patients with blood cancers who required hospital care for COVID-19. Of this number, 451 were admitted for inpatient care, and 85 received outpatient care. After a median follow-up of 20 days, 98% of inpatients were either discharged or had died, with 18% requiring admission to the intensive care unit. Patients with severe and critical COVID-19 were older, had more comorbidities, and a more recent diagnosis of blood cancer than patients with mild COVID-19. At data cutoff, 37% had died. Compared to survivors, deceased patients had lower hemoglobin values, lower platelet counts, and higher serum lactate dehydrogenase. In addition, blood cancer types associated with higher mortality included acute myeloid leukemia, non-Hodgkin's lymphomas, and plasma cell cancers. Current preliminary data did not suggest a clear protective effect of treatment with ibrutinib in patients with chronic lymphocytic leukemia.

The following are summaries of selected abstracts about clinical trial results and prognosis and survival trends specific to WM that were presented at the recent ASH Annual Meeting held virtually on December 5-8, 2020. Additional discussion of selected abstracts pertaining to basic research will be included in the April 2021 issue of the Torch*. The abstracts are online at* https://ash.confex.com/ash/2020/webprogram/start.html*. To read a specific abstract, type part or all of its title into the Search box; for a general search of all abstracts pertaining to or including WM, type "waldenstrom" into the Search box.*

LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study (Abstract 117) – The BRUIN multicenter international trial studied the non-covalent BTK inhibitor LOXO-305 for its safety and efficacy in patients with previously treated B-cell malignancies, including WM. The drug was designed to reversibly (non-covalently) bind to BTK, preserve activity in the presence of acquired resistance to other BTK inhibitor therapies like ibrutinib (Imbruvica), and avoid off-target effects that have complicated the development of other BTK inhibitors. In this study, LOXO-305 was dosed orally at seven different dosing levels to 186 patients, 17 of whom had WM. Of the WM patients, 71% had received prior BTK inhibitor therapy. The only adverse events seen in 10% or more of all

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patients were fatigue and diarrhea. Among the 15 evaluable WM patients, the overall response rate was 60%, including the subset with prior BTK inhibitor therapy. Dosing of 200 mg once daily was selected for future studies.

Five-Year Follow-Up of Ibrutinib Plus Rituximab Vs. Placebo Plus Rituximab for Waldenstrom's Macroglobulinemia: Final Analysis from the Randomized Phase 3 iNNOVATE™ Study (Abstract 336) – This multicenter international study analyzed data after 50 months of median follow-up of 150 treatment-naïve and previously treated WM patients, 75 of whom were treated with ibrutinib (Imbruvica) plus rituximab (Rituxan) and 75 with rituximab plus placebo. Median progression-free survival was not reached with the IR combination vs. 20.3 months with R. The major response rate was 76% with IR vs. 31% with R, and high response rates were observed with IR, regardless of whether patients had prior treatment and across MYD88 and CXCR4 genotypes. A greater proportion of patients receiving IR had sustained hemoglobin improvement (77% vs. 43%). Median overall survival was not reached in either arm. Median time-to-next treatment was not reached with IR vs. 18 months with R. Overall, the safety profile of IR was consistent with previous reports, with the most common moderate to severe adverse events being atrial fibrillation in 16% of patients, hypertension (high blood pressure) in 15%, neutropenia (low neutrophil count) in 13%, and anemia in 12%.

Bortezomib in Combination with Dexamethasone, Rituximab and Cyclophosphamide (B-DRC) As First-Line Treatment of Waldenstrom's Macroglobulinemia: Results of a Prospectively Randomized Multicenter European Phase II Trial (Abstract 337) – European researchers compared the efficacy and toxicity of adding bortezomib (Velcade) to DRC therapy vs. DRC alone in treatment-naïve WM patients. DRC is a widely recommended chemoimmunotherapy in international WM treatment guidelines and consists of dexamethasone, rituximab (Rituxan), and cyclophosphamide (Cytoxan). In this study, there were six monthly cycles: cyclophosphamide and dexamethasone were taken orally, while bortezomib was administered subcutaneously on days 1, 8, and 15 and rituximab was administered subcutaneously after one intravenous cycle. Median follow-up was 27.5 months. Of 202 patients evaluable, estimated progression-free survival at 24 months was 80.6% for B-DRC vs. 72.8% for DRC. Median overall survival was not reached in either treatment arm. At the end of treatment, B-DRC induced major responses in 79.1% vs. 68.9% for DRC, and complete responses or very good partial responses in 18.7% vs. 11.1% for DRC. Compared to baseline, IgM decreased by 79% and 73% and hemoglobin increased by 28% and 32% in the B-DRC and DRC arms, respectively. Responses and progression-free survival were independent of mutational status in both arms. The most common moderate to severe adverse events included neutropenia (low neutrophil count), anemia, and thrombocytopenia (low platelet count). Peripheral sensory neuropathy occurred in 18 patients treated with B-DRC and in three patients treated with DRC.

Waldenström Macroglobulinemia in the Very Elderly (≥ 75 years): Clinical Characteristics and Outcomes (Abstract 1141) – This Mayo Clinic retrospective study looked at the impact of advanced age at diagnosis on the clinical features and outcomes of patients with active WM. Of 949 consecutive patients with active WM evaluated at Mayo Clinic Rochester between January 1996-December 2018, 177 were 75 years of age or older at time of diagnosis. In general, these older patients had lower IgM and serum albumin levels and higher serum LDH (lactate dehydrogenase) and serum beta-2 microglobulin levels than the group of patients younger than 75. A higher proportion of older patients had coexisting light chain amyloidosis at diagnosis. In the elderly group, the most frequently used front-line therapy was solo rituximab (Rituxan), followed by rituximab-alkylating agent combinations. At time of last follow-up, 89 of the 177 elderly patients were deceased, with 58% of deaths attributable to WM (as determined by progressive disease, Richter's transformation, light chain amyloidosis, infections associated with WM, or toxicities related to anti-WM therapy). The median overall survival of the older patients after diagnosis was 5.9 years compared to 8.3 years for an age-, sex-, and calendar-year matched group derived from the general US population.

Effective Treatment of Cold Agglutinin Disease/Cold Agglutinin Syndrome with Ibrutinib: An International Case Series (Abstract 1678) – In cold agglutinin-mediated autoimmune hemolytic anemia, anti-red blood cell autoantibodies lead to destruction of red blood cells at low temperatures. This condition can occur with B-cell malignancies such as WM. There is no approved treatment, although rituximab (Rituxan) is the most accepted first-line treatment, with an overall response rate of 50% and median duration of response less than one year. This international retrospective study looked at using the BTK inhibitor ibrutinib (Imbruvica) in ten patients who were followed from April 2014-June 2020. After initiation of ibrutinib, all patients showed an improvement in hemoglobin, resulting in one partial response and nine complete responses. Data collection is still ongoing, and updates will follow.

High-Dose Methotrexate Based Therapy for the Treatment of Bing Neel Syndrome (Abstract 2061) – Researchers from the United Kingdom discussed the use of high-dose methotrexate (HDM) as front-line treatment for patients with Bing Neel syndrome, a very rare cause of neurological complications in WM patients occurring when WM cells directly infiltrate the central nervous system (brain and spinal cord). Regimens with high-dose

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methotrexate have been used to treat Bing Neel, but there are concerns regarding their use, largely due to toxicity. Between 2011 and 2020, 27 patients were treated with various HDM regimens. Complete responses were achieved in six patients, partial responses in seven, and no response in eight. Progressive disease on therapy occurred in four cases, and two patients died before response could be assessed. At a median follow-up of 19.4 months, seven patients had died. The researchers observed higher rates of treatment-related mortality and only modest response rates from the combination of methotrexate with cytarabine, thiotepa, and rituximab (Rituxan) vs. other HDM regimens and suggested than the omission of thiotepa appeared to allow the optimal dosing of methotrexate and cytarabine without negatively impacting outcomes.

Long-Term Follow-up of Ibrutinib Treatment for Rituximab-Refractory Waldenström's Macroglobulinemia: Final Analysis of the Open-Label Substudy of the Phase 3 iNNOVATE™ Trial (Abstract 2937) – This analysis was based on a substudy of the iNNOVATE clinical trial; the substudy evaluated the use of single agent ibrutinib (Imbruvica) in 31 WM patients who failed to achieve at least a minor response to, or who relapsed less than 12 months after, their last rituximab (Rituxan)-containing therapy. The median follow-up for this study was 58 months. The overall response rate was 87%, with improvements in IgM and hemoglobin generally rapid and sustained, and responses were consistent across the genotypes of the study participants. The median duration of ibrutinib treatment was 41 months, with progressive disease the most common reason for discontinuing treatment. At the time of study closure, 14 patients remained on treatment. Overall, 97% of patients experienced an adverse event, most commonly diarrhea and fever. Serious adverse events included neutropenia (low neutrophil count), hypertension (high blood pressure), and anemia. Ibrutinib dosage was reduced in 16% of patients, and two patients discontinued treatment because of an adverse event. No patients experienced major hemorrhage or atrial fibrillation.

Neuropathy with IgM Gammopathy: Incidence, Characteristics and Management, a Rory Morrison WMUK Registry Analysis (Abstract 2948) – Peripheral neuropathies associated with IgM monoclonal protein are seen in patients with IgM MGUS (monoclonal gammopathy of undetermined significance) and WM. Anti-myelin-associated glycoprotein (MAG) antibodies are identified in about 50% of such cases, but other neuropathies with other IgM targets have been identified, along with light chain amyloidosis (deposit of amyloid protein in nerves) and vasculitis due to cryoglobulinemia (inflammation of the blood vessels that can restrict blood flow to nerves). The Rory Morrison WMUK Registry in the United Kingdom was searched for all patients with peripheral neuropathy (PN), and clinical data were obtained for 153 such patients, of whom 64.7% had underlying WM and 35.3% had IgM MGUS. These 153 patients were diagnosed with the following: anti-MAG IgM in 54.6%, non-MAG IgM in 34.5%, light chain amyloidosis in 4.3%, cryoglobulinemia in 3.7%, and anti-ganglioside in 2%. At diagnosis of WM with PN, the bone marrow burden, monoclonal protein, beta-2 microglobulin, and rate of CXCR4 mutations were all significantly lower than in those who had WM without PN. PN was the sole treatment indication in 79% of cases, and front-line treatment incorporated rituximab (Rituxan) in 81.5% of those patients. Clinical response was seen in 75.6%, with improvement in 28.9% and stabilization in 46.7%, and was significantly more likely to occur with rituximab-containing therapy, non-amyloid related PN, and attainment of at least a 50% reduction in IgM. Progression of PN occurred in 20.5%, necessitating retreatment at a median of 4.3 years after front-line therapy.

Bendamustine Plus Rituximab for the Treatment of Waldenström Macroglobulinaemia: Patient Outcomes and Impact of Bendamustine Dosing (Abstract 2958) – This multicenter retrospective study included consecutive WM patients treated with bendamustine and rituximab (Rituxan) in the front-line and relapsed settings across 17 sites in four countries. Data from September 2010-May 2020 were collected for 250 patients, 139 of whom were front-line and 111 of whom were relapsed. At a median follow-up of 37 months after treatment, disease progression occurred in 18% of front-line and 43.2% of relapsed patients. Major response rates differed significantly between the front-line and relapsed groups, at 91.4% and 73.9% respectively, as did the combined complete and very good partial response rates, at 47.4% and 24.3% respectively. Front-line patients received higher total bendamustine doses than relapsed patients, and total dose was independently predictive of progression-free survival. Older relapsed patients tolerated lower total bendamustine doses. In both settings, attaining complete or very good partial responses resulted in superior progression-free survival and overall survival. The researchers concluded their discussion with recommended bendamustine dosing to achieve optimum benefit: at front-line, six cycles of bendamustine at 90 mg/m2 on days one and two, while in the relapsed setting, four cycles of bendamustine at 90 mg/m2 on days one and two. For relapsed WM, a starting dose of 70 mg/m2 on days one and two was also sufficient, provided that 5-6 cycles were administered.

Phase 2 Trial of Ixazomib, Cyclophosphamide and Dexamethasone for Treatment of Previously Untreated Light Chain Amyloidosis (Abstract 3246) – This Mayo Clinic trial evaluated the use of the oral proteasome inhibitor ixazomib (Ninlaro) in combination with cyclophosphamide (Cytoxan) and dexamethasone for the treatment of 35 treatment-naïve patients with light chain amyloidosis, a rare

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condition that can occur with WM. Light chain amyloidosis is caused by the presence of abnormal antibody light chains that are deposited as amyloid protein in various tissues and organs, forming fibrils that may injure these body parts or interfere with their normal functioning. The study protocol consisted of twelve 28-day treatment cycles, followed by ixazomib maintenance until progression or intolerance to therapy. Organ involvement included heart in 65.7% of patients, kidney in 54.3%, and nervous system in 14.3%. At data cutoff, eight patients still remained on study. The overall hematologic response was 57%, and confirmed organ responses were so far observed in 14%. The median progression-free survival and overall survival had not been reached. A significant adverse event was observed in 41% of patients. The researchers concluded that, while organ response was observed, longer follow-up would be needed for accurate assessment, given the delay in organ responses to this condition.

The author gratefully acknowledges the efforts of Glenn Cantor, Grete Cooper, Peter DeNardis, Julianne Flora-Tostado, Tom Hoffmann, Pavel Illner, Meg Mangin, Colin Perrott, Howard Prestwich, Richard Savoy, Charles Schafer, Ron Ternoway, and others in disseminating research news of interest to the WM community. The author can be contacted at suenchas@bellsouth.net *for questions or additional information.*

HOW YOU CAN GET INVOLVED IN WM RESEARCH

By Glenn Cantor, IWMF Trustee and Science Editor, and Irene Ghobrial, MD, Dana-Farber Cancer Institute

What causes WM in the first place? Are there ways of predicting and perhaps delaying the onset of WM? What about my family—are they at risk of developing WM? Does WM increase the risk of contracting COVID-19, even in asymptomatic, watch-and-wait patients?

Dr. Irene Ghobrial from the Dana-Farber Cancer Institute presented an IWMF Global Educational Webinar on October 14, 2020, about her research on early progression to WM. She highlighted the need for more WMers to participate in her studies. It's an easy and painless way for you or your family to personally contribute to scientific advances in WM. If you are seeing your doctor and he or she wants a routine blood (or bone marrow) sample, the lab draws a little extra that you send to Dr. Ghobrial's lab. You also agree to share your medical records. That's it—no injections with investigational drugs or anything risky.

PCROWD (*www.enroll.pcrowd.org*) is a tissue and clinical data bank research study open to anyone 18 years of age and older who has been diagnosed with a plasma cell dyscrasia (including, but not limited to, smoldering WM, MGUS, and smoldering multiple myeloma). Participants are asked to share samples a few times a year when they are collected as part of routine follow-up care, allowing for tracking of changes that may occur in their samples and medical record. Dr. Ghobrial's lab provides a blood collection kit and free FedEx mailing supplies.

The PROMISE Study (*www.enroll.promisestudy.org*) is the first study to screen for these precursor conditions using a free supplied blood kit sent to participants' homes. Individuals between the ages of 40 and 75 who self-identify as being Black/African American are considered at higher than average risk of developing multiple myeloma in their lifetime and are eligible to enroll in the PROMISE Study. In addition, those with a first-degree relative (sibling, child, parent) who has been diagnosed with WM, multiple myeloma, MGUS, and smoldering multiple myeloma are eligible. If tested positive after visiting a Quest Diagnostics site for a blood draw, participants are also asked to share samples a few times a year as part of routine care. WMers are encouraged to contact family members to see if they would like to participate. Since WM can run in some families, this is a good way that family members can find out if they are developing WM or a precursor condition. For both PROMISE and PCROWD, collected data will help predict and ultimately prevent these types of conditions from progressing.

WMer Glenn Cantor, a participant in the PCROWD study, with his blood collection kit

All participants enrolled in PCROWD and PROMISE are eligible for IMPACT—an affiliate study that will analyze blood samples for up to one year to study the relationship between COVID-19 exposure and the immune system. All participants enrolled in IMPACT will receive a free antibody test to determine if they have been exposed to the virus causing COVID-19. This study will help researchers understand how the risk for blood cancer impacts response to COVID-19 infection and potential future vaccinations. Learn more at *www.theimpactstudy.org*.

All studies mentioned are led by Dr. Ghobrial through the Center for Prevention of Progression at Dana-Farber and are welcoming new participants. For more information, see an article by Dr. Ghobrial in the January 2020 issue of the *Torch* at *https://iwmf.wpengine.com/wp-content/uploads/2020/10/Torch_January2020.pdf* or look at the links provided above.

Imagine a cure: A world without WM

Make our vision a reality
DONATE TODAY!

Help us support and educate everyone affected by Waldenstrom's macroglobulinemia (WM) while advancing the search for a cure. Together, we will reach our new campaign goal of $50,000,000.

Your gift makes a tremendous difference to our global WM community. **Please, give generously.**

WHAT KIND OF LEGACY WILL YOU LEAVE?

"A person's life is measured by the effort made for the benefit of others."
BEN RUDE, IWMF PRESIDENT 2000-2005

The Ben Rude Heritage Society recognizes those who have made provisions for a future gift to the IWMF, such as a bequest, listing the IWMF as a beneficiary for a life insurance policy or qualified planned asset (such as a 401k or IRA), or a life income agreement, such as a Charitable Remainder Trust. Legacy gifts represent an important component of the IWMF's financial future. Since the establishment of the Ben Rude Heritage Society in 2008, a number of bequests have been received, and the gifts of these generous donors have allowed the organization to expand programs and research commitments significantly over the years. Members of the Ben Rude Heritage Society are dedicated to supporting research, education, and support for countless patients and caregivers, at home and around the globe. There is no minimum requirement to join the Ben Rude Heritage Society—some members have included provisions ranging from $1,000-$1,000,000—but every single gift makes a difference to the future of the IWMF and to those who benefit from the IWMF's research and support.

There are many ways to support the IWMF through a planned gift, but a bequest is perhaps the easiest and most tangible way to leave a lasting impact.

With the help of an advisor, you can include language in your will or trust specifying a gift to be made to the IWMF as part of your estate plan. A bequest may be made in several ways:

- Gift of a dollar amount
- Gift of a percentage of your estate
- Gift of a specific asset
- Gift of the residue of your estate

One benefit of joining the Ben Rude Heritage Society by making a charitable bequest is that it enables you to further the work of the IWMF long after you are gone. Better yet, a charitable bequest can help you save estate taxes by providing your estate with a charitable deduction for the value of the gift. With careful planning, your family can also avoid paying income taxes on the assets they receive from your estate. For more information on estate gifts or to join the Ben Rude Heritage Society, contact Director of Development and Communications Jeremy Dictor at 941-927-4963 or *JDictor@IWMF.com.*

RESEARCH PARTNERS

For a commitment of $50,000 per year for a minimum of two years, or a lump sum of $100,000 or more, you can become a research partner supporting a specific IWMF research project approved by the IWMF's Scientific Advisory and Research Committees. Research Partners will have an opportunity to be kept informed of the progress of the research project and will be formally acknowledged by the investigators in their report of the project as well as in any resulting publications. Generally 10 to 12 research projects are underway with new projects under consideration each year.

The David and Janet Bingham Research Fund of the IWMF supports the following current research project:
Targeting MYD88 Signaling in WM

The Elting Family Research Fund of the IWMF supports the following current research projects:
Towards a Rational Targeted Therapy for WM by Kinome-Centered Loss-of-Adhesion and Synthetic Lethality Screens

Direct Targeting the MYD88 L265P Driver Mutation in WM

Targeting MYD88 Signaling in WM

Multiomic Analysis of DNA, RNA and Epigenomic Networks for Prognostication and Novel Target Identification in WM

MYD88L265P Signaling-Associated Multiplex Characterization of the Bone Marrow Microenvironment in WM Patients for Clinical Application

The K. Edward Jacobi Research Fund of the IWMF supports the current IWMF research

The Ed and Toni Saboe Research Fund of the IWMF supports the current IWMF research

The Carolyn Morris Research Fund of the IWMF supports current IWMF research

The Yang Family Research Fund of the IWMF
Targeting MYD88 Signaling in WM

The Lynn M. Fischer Research Fund of the IWMF supports the following current research projects:
Factors Regulating Immunoglobulin-Producing B-Cells in Patients with WM

Multiomic Analysis of DNA, RNA and Epigenomic Networks for Prognostication and Novel Target Identification in WM

MYD88L265P Signaling-Associated Multiplex Characterization of the Bone Marrow Microenvironment in WM Patients for Clinical Application

The Robert and Nadeline White Family Research Fund of the IWMF supports the following current research project:
Targeting MYD88 Signaling in WM

NAMED GIFT FUNDS

For a commitment of $10,000 per year for five years, or a lump sum of $50,000 or more, you can establish a named fund at the IWMF in your own name or in the name of someone you wish to honor. This fund may support Member Services or Research or a combination of the two.

Baker Family Research Fund of the IWMF	Gary Green Research Fund of the IWMF	Gail Murdough Member Services and Research Fund of the IWMF
Yoshiko Button Member Services Fund of the IWMF	Dr. Robert Kyle Research Fund of the IWMF	Sesnowitz Family Research Fund of the IWMF
Friedlander-Scherer Family Research Fund of the IWMF	Lynn Martin and Carrie Wells Research Fund of the IWMF	Donald and Alison Weiss and Family Research Fund of the IWMF
Dr. Morie A. Gertz Research Fund of the IWMF	Dennis and Gail Mathisen Research Fund of the IWMF	Donald and Kathryn Wolgemuth Research Fund of the IWMF

If you have discretionary giving power and would like to help move our research program forward in a special way, we invite you to join those listed above. For more information about Research Partners and Named Gift Fund opportunities and potential gifting options that might make that possible, please contact Director of Development and Communications Jeremy Dictor at *JDictor@iwmf.com* or 941-927-4963.

Ben Rude Heritage Society Roster

* Deceased ◊ Founding Member

ANONYMOUS (4)

JEAN-MARC AUDIBERT*

MARTIN BAER*

C. EDWIN BAKER*

JACK BAKER

JANET BAUSSER*

DAVID M. BENSON

BEVERLY J. BLOSS

VIVIAN AND ROBERT BOAS ◊

ELSA AND GARY BRADLEY

ARLOU BRAHM*

WILLIAM O. AND ELLEN KANER BRESNICK ◊

RUTH L. BROWN*

L. DON AND MARY BROWN

PETER CARR

GERALD PRESTON CLANCEY*

CHRISTINA CONLEY*

MRS. IVY COOPER*◊

ROBERT* AND ANNE COULBOURN*

FRANCIE AND MICHAEL COWEN

NORMAN W. CRANDALL JR.

TONY DYE*

FREDERICK A. EBELING*

JEAN ELLIS*

RAYMOND* AND BETTE FISHMAN*

MARLYN FRIEDLANDER AND GILBERT SCHERER

CINDY L. FURST*

JEB GELBER

NEWTON GUERIN

LESLIE C. GUTHRIE, JR.*

CARL HARRINGTON

RALPH AND JANE HENDRICKSON

JAN HERGESHEIMER

SUZANNE L. HERMS

ARLENE HINCHCLIFFE

ELINOR HOWENSTINE*

WANDA L. HUSKINS AND JEFFREY A. PRUPIS

DR. EUNICE JOHNSON*

STANLEY KAUFMAN*

SHAN ELIZABETH KEARY

NANCY KERR*

THOMAS KEYS*

EVELYN KLIEN*

GLENN AND MARCIA KLEPAC

GEORGE KNIPELBERG*

CHARLES KOCH

DR. ROBERT A. AND CHARLENE M. KYLE

MICHAEL E. LUTTRELL

LENNY MARTIN

JUDITH ANN MAY

KATHARINE E. MCCLEARY AND K. EDWARD JACOBI*

KATHLEEN L. MINER

ANNE AND PETER MITRO ◊

ELEANOR MOORE*

MAYNARD MORRIS

SAM AND GAIL MURDOUGH

GUIDO AND IDA NEIROTTI*

BARRY NELSON

LINDA NELSON

BRANDT NORQUIST*

JAMES AND BETTE ORTOLEVA

HOWARD F. PRASS*

ALAN PRESTELL*

MARGUERITE C. REGAN, PHD*

PAUL AND JANICE RIPPAS

ROGER AND BARBARA ROBINETTE

MARGARET ROCKELMAN*

JOEL ROSENBLIT

LAURIE RUDE-BETTS ◊

CYNTHIA RUHL

ELMO R.* AND DOLORES E. SCHMID*

MICHAEL AND CAROL SESNOWITZ

ALLAN SHAW*

DR. GUY R. SHERWOOD

ELLEN SMITH

RAY SOBOROWICZ*

KEN AND LINDA SOLOW

CORDELIA AND PETER STEARNS

JUDITH LEE STERLING AND LESLIE CHARLES WILSON

JOHN AND DIANE TIPLADY

RUBEN TROSS*◊

MATHILDE JOHANNA VAN GOGH*

TAMARA VINCENT

DR. JACOB WEINTRAUB

VIRGINIA A. WILLIAMS*

PENNI WISNER

JAMES P YEAGER*

GREGORY FITZWATER AND MARILYN ZOLLNER-FITZWATER

RALPH ZUCKERMAN*

AUSTRALIAN MICHAEL VAN EWIJK RIDES 702 KM FOR A FUNDRAISER

By Annette Aburdene

Kicking off on September 24 in Balranald, New South Wales, WM patient Michael Van Ewijk completed a 702 km (437 miles) solo bike ride on October 2. His trip took him from Balranald through the Riverina region of South Western NSW to Wagga Wagga. The decision to ride 700 km represented his turning 70 in April of this year. "We wanted to do the fundraiser earlier but put it off because of the (bush)fires and COVID-19," as the *Regional Guardian* newspaper quoted him in its September 18 issue.

Michael completed 702 km in nine days, riding for seven days interspersed with two rest days. Stops on the way were Moulamein, Deniliquin, Jerilderie, Boree Creek, Narrandera, and Griffith. He used a cycling app to map out his route, which took him on back roads but also on busy highways with trucks and cars whizzing past at 100 kph (62 mph). While the Riverina is relatively flat, Michael reported that the most difficult part of the ride was the wind. A tailwind helped on the first two days; however, the remaining days were a mixture of crosswinds and headwinds. Despite this, he still managed to average a speed over 25 kph (16 mph) for the whole trip. Michael had trained for most of the year by doing 100 km back-to-back riding sessions on weekends.

Elizabeth and Michael in Balranald at the start

The ride would not have been possible without his partner, Elizabeth Muntz, driving behind in the support vehicle with a large sign on the back to warn cars and trucks there was a cyclist ahead.

For Michael, the best part of the ride was the AUD $11,061 he raised for the Australian Leukaemia Foundation's support of the IWMF-LLS Strategic Research Roadmap Initiative. Donations were made through Every Day Hero, which took a small percentage, leaving more than $10,000 for WM research.

Michael was able to maintain his 50-year passion for cycling following a WM diagnosis in May of 2005. "My journey with WM has been a bit of a roller coaster ride. I was having problems with anaemia in 2003, but my GP could not find what was causing it. I was finally diagnosed in May 2005. I was on watch and wait until 2011, when my first treatment was CDR (cyclophosphamide, dexamethasone, and rituximab), which gave me a partial remission for 12 months. Fludarabine was next. Partway into my second infusion, I went into anaphylactic shock and the treatment was stopped.

The finish in Wagga Wagga

"Fortunately, I was able to get into a trial for ibrutinib in 2014 under Prof. Judith Trotman at Concord Hospital. I haven't looked back." Michael was the first Australian patient to be given ibrutinib. "Life's good for Michael thanks to 'a pill for life,'" the Leukaemia Foundation of Australia reported on its website in 2019.

Since his diagnosis, Michael has done a number of long-distance rides to raise funds for charity, beginning with the 95 km "MS Ride" from Sydney to Wollongong in 2007, followed by the 105 km "Tour Down Under" in Adelaide in 2009, the 580 km "Smiling for Smiddy" ride with his son Flyn in Brisbane in 2014, and the Lymphoma Australia's 300 km "Parliament House Canberra to the Opera House Sydney" ride in 2015.

Michael was born in the Netherlands, immigrating to Australia at a young age. Now retired, he started his working life as a high school art teacher, in Lithgow, NSW, later teaching at Ulladulla High School in NSW, before leaving teaching in 1997. He has since worked as a freelance photographer.

The best takeaway from Michael's story? His being able to complete a 702 km bike ride is a testament to the fact that it is possible to have a healthy life while living with Waldenstrom's.


Riding past a canola field near Narrandera

Remembering Cindy Lou Furst

Cindy Furst

Cindy Lou Furst, former IWMF Trustee and a leader of the Colorado/Wyoming IWMF Support Group, will long be remembered in the WM community. She passed away on September 20, 2020, of complications from Waldenstrom's macroglobulinemia.

Cindy grew up in Missouri, but when she went to Colorado for the summer in 1971, she decided to transfer to the University of Colorado at Boulder, and graduated from there in 1972. She loved Colorado, its air, its mountains, and its active lifestyle. She remained in Colorado the rest of her life.

Cindy worked in HR and marketing for much of her career, mainly at Hewlett Packard in Loveland. She married Hoyle Curtis, and they had a son, Christopher. Even though they divorced over a decade later, Cindy and Hoyle remained close friends and co-parents to provide support and companionship for each other through the rest of her life. They became caregivers for each other during both of their long cancer battles.

In 2004 Cindy was diagnosed with Waldenstrom's, and she became an active volunteer with the IWMF, helping others advocate for their medical needs. Staying healthy and active became a critical part of her life, plus helping those less fortunate than herself. She became a Trustee of the IWMF in 2008, and focused on working with support groups across the country and helping organize IWMF Educational Forums.

Pete DeNardis, current chair of the IWMF Board, says he and Cindy joined the Board at the same time. Right from the start, he says, "you got a sense of her drive and purpose, as she did her best to improve the IWMF's support group network, and was among the first to encourage the Board to think more strategically and focus on both short-term and long-term goals. Even when she personally was having WM-related health issues, she remained committed to her Board duties, to portraying a positive attitude, and to providing support and comfort to fellow WMers. I thoroughly enjoyed working with her, and will miss her calm, yet spirited, guidance."

Cindy Furst and Dr. Jeffrey Matous at the 2013 Rocky Mountain Blood Cancer Conference

Sue Herms interacted with Cindy in the planning of several Ed Forums. She remembers that "Cindy volunteered for a couple of years to be a breakout session moderator, primarily on bendamustine treatment. She was an excellent, dynamic speaker and had a warm and engaging personality. I know that WM patients who attended her breakout sessions found her to be very helpful and supportive."

Cindy also became a leader of her local support group in Colorado and was a friend of Dr. Jeffrey Matous of the Colorado Blood Cancer Institute, who is well known as a WM specialist. As well as working with Dr. Matous on local programs, such as at the LLS-sponsored Rocky Mountain Blood Cancer Conference, Cindy was planning to co-present a program with Dr. Matous for the Support Group Leaders Workshop at the 2020 Seattle Ed Forum, which was cancelled because of the pandemic.

Dr. Matous remembers Cindy: "All of us in the WM community in Colorado are feeling the loss of Cindy. She was not only a courageous WM survivor for so many years, she was the face of the IWMF in the whole Rocky Mountain region. She selflessly supported so many other WMers, doing whatever was asked and beyond."

Carl Harrington says that "Cindy Furst was one of my favorite people. She was always upbeat, energetic, quick with a smile, and dedicated to helping every single person diagnosed with WM. And she was a magician with a microphone in her hand—empathetic, compelling, entertaining, and inspiring!"

We are all grateful for volunteers like Cindy who give of their time and energy to support and educate everyone with WM.

SUPPORT GROUP NEWS

EDITED BY CHRIS STAY

2020 Support Group Statistics
Support Groups: 38
Meetings: 72
People attending meetings: 1,345

PLEASE NOTE

Contact information for all support groups is available at *www.iwmf.com/get-support/us-and-international-support-groups*.

Details of support group meetings and other upcoming events are posted on *www.iwmf.com* under **NEWS & EVENTS**. Please check there to confirm details of future events.

CALIFORNIA

Los Angeles, Orange & San Diego Counties

The Los Angeles, Orange and San Diego Counties Support Group enjoyed a positive, low-key Zoom meeting last fall, with ten members joining in. The meeting touched on several subjects. We had a chance to introduce a new member to someone else who had had similar experiences. A second new member with concerns about ocular Bing Neel was given resource information. Everyone seemed to enjoy responding when the latter asked for stories of what we each like about our local MDs. The rest of the meeting included catching up with each other and sharing resources.

Julianne Flora-Tostado reporting

ILLINOIS

Chicago Area/SE Wisconsin

This group had its annual fall meeting November 7 with 30 people in attendance, representing 18 families. The meeting included a presentation by Dr. Shuo Ma, associate professor of medicine at Northwestern University. Questions related to WM treatment options and treating COVID-19 in Waldenstrom's patients were discussed. (Points made were: zinc and vitamin C may be helpful against COVID but strong data supporting this is lacking; vitamin D is good for the immune system especially in Chicago, which lacks sunlight, but high doses should be avoided; remdesivir, convalescent plasma, steroids, and blood thinners were discussed as ICU options.)

The group is looking forward to its spring meeting, and members are hopeful that, by April, meetings can be face-to-face rather than virtual.

Don Brown reporting

MINNESOTA & WESTERN WISCONSIN

The Minnesota and Western Wisconsin Support Group recently welcomed new Co-Leader Kate Beverley. She says "I retired five years ago after 45 years of working in various areas as a registered nurse and case manager. I have also worked as a parish nurse for seven years and find that volunteering is very rewarding." Beverley found the IWMF on the internet after becoming a patient. She has used both the IWMF and NORD (National Organization of Rare Disorders) as resources.

The Minnesota & Western Wisconsin Support Group welcomes Kate Beverley as a new co-leader.

Beverley and her husband Dave have five children and 11 grandchildren. Since the onset of COVID has made interacting with support group members challenging, she says, "I feel it is very important for us to stay connected for support and friendships that have evolved in our group."

OREGON & SOUTHWEST WASHINGTON

The guest speaker at the September 13 virtual meeting was Dr. Jeffrey Menashe, oncologist/hematologist from the Compass Oncology practice in Portland, OR. After a brief review of Waldenstrom's, the meeting opened to questions from the 20 participants. Dr. Menashe was asked what factors he looks for when treating a WM patient and determining the course of treatment. Hemoglobin, platelet count, sweats, fatigue, circulation issues, and cryoglobulinemia were critical indicators. He excelled at providing straightforward, clear answers that laypeople could readily comprehend. Everyone appreciated the openness with which Dr. Menashe spoke.

The November 14 virtual meeting was a caring/coping/sharing meeting. One member retired in August and made a solo Rocky Mountain hiking and camping trip. After his adventure, he road-tripped eastward to visit family in Ohio whom he had not seen in months. Armed with Clorox wipes for the motel stays and eating freeze-dried food to avoid restaurants, he found traveling by car across the US, mostly on side roads, to be an absorbing and educational journey.

Support Group News, cont. on page 27

Other members stressed the heartbreak of separation from family, inability to visit grandchildren, and difficulty of checking on elderly relatives who may be alone. Traveling by plane is not a viable option for WMers in this time of isolation. One member has occupied her time with cooking, camping, and volunteering. She had just cooked up a yummy pot of mushroom soup and shared the recipe with the group. Others are recuperating from surgery and chemo treatment or working from home. This is just a sampling of the virtual chat session.

Members discussed issues of fatigue that had no logical source. Research Committee Member Glenn Cantor mentioned that elevation of some cytokines can cause fatigue, but that testing for cytokines is beyond the standard blood test. The group was encouraged to watch the educational webinars and other programs available from the IWMF—the content is always informative.

Cindy Jordan reporting

PENNSYLVANIA

Eastern Pennsylvania, Southern New Jersey

Thirty WMers attended a Zoom meeting October 18. An experienced support group member suggested the topic, "How do we choose to share news of our WM diagnosis with family, friends, community, and colleagues—or not share news?" At the same meeting, the group also welcomed Leukemia & Lymphoma Society (LLS) Patient & Community Outreach Manager Megan Smith, who discussed local services by LLS. She left the group with a plethora of links and resources, ranging from free one-on-one nutrition counseling, to the Co-Pay Assistance program now open to WMers, to an invitation to speak one-on-one with an information specialist at LLS at 800-955-4572.

The group hosted a national meeting for 60 attendees on November 8. Christina Bach presented "Navigating Your Health Insurance Coverage: Prepare for Open Enrollment!" She is a clinical oncology-certified social worker, a medical/social work ethicist, and a national leader in the field of financial toxicity and navigation in the cancer world.

Christina helped attendees understand their options during the open enrollment period for Medicare and the Affordable Care Act (ACA), answered questions about the potential impact of the Supreme Court's hearing the case that could potentially overturn the ACA, and addressed how to maximize coverage and obtain financial assistance. She explored tools available to help understand coverage and potential out-of-pocket expenses, as well as how to talk to healthcare providers about financial and insurance concerns. Christina's slides are available on the IWMF website at *https://iwmf.com/wp-content/uploads/2020/10/Insurance_and_Financial_Essentials-Bach.pdf*

Lisa Wise reporting

SOUTH CAROLINA

This group's first Zoom meeting was November 14, with eight members present (and two who unfortunately experienced technical difficulties and were unable to connect). Since it had been a year since the last meeting, it was good to reconnect and update each other on our WM journeys and how we have each been managing through the pandemic. There was also discussion about dealing with multiple specialists at once and the difficulties of sorting out what symptoms were due to WM diagnosis, a new diagnosis, or a side effect of medication. The pros and cons of virtual appointments as well as changes in medical care brought on by COVID-19 were also shared.

The group decided to meet again in January. Although all agreed that they miss meeting in person, they appreciated not having to drive long distances across the state. The group hopes to expand and increase Zoom meeting attendance during 2021.

Jane Loud, Roger and Barb Robinette reporting

TEXAS

Dallas & Northern Texas

The new co-leader in Dallas & Northern Texas is Tony Darata.

The Dallas and Northern Texas group's new co-leader is Tony Darata. He and his wife have been married for more than 27 years. He retired when he was 59 from a Fortune 500 company, partly because of the constant fatigue he was feeling. His mother was in ill health, and he was working full time while driving back and forth to Kansas City, MO, to help his sister care for his mother. Now it's his wife's turn with her mother. Tony says, "Most likely my wife will be going down the same caregiving road with her mother. I'll be there to do what I can."

He says, "The IWMF is literally my one-stop shop for WM health-related issues as well as assuring my psychological well-being by understanding and listening to others. Member stories on the talk list [IWMF Connect] enable me not to 'live in a vacuum'."

Houston

The Houston group had a Zoom meeting October 3. Four couples joined the two leaders for an update on everyone's health and condition, how they were each handling COVID, and a few fun jokes. The funniest story was from a member who said that he drinks wine every afternoon to make sure

Support Group News, cont. on page 28

Support Group News, cont. from page 27

that his taste buds are still working, since a lack of taste is a symptom of COVID. He repeats this COVID test daily! All of these WMers are mindful of not exposing themselves to COVID, are eating well balanced meals, and enjoy Zooming and connecting with friends and family members.

At press time, the next Zoom meeting was scheduled for December 12. Everyone was encouraged to dress up for the holidays, share holiday decorations in brief home tours, and bring holiday memories to share.

Dr. Barbara and John Manousso reporting

VIRGINIA

Richmond

Paul Attanasio is the new leader for the Richmond Support Group. He has been married 43 years, with two sons and a granddaughter. He retired in 2016 after 43 years at GE Power, working the final 31 years as a manufacturing engineer. Paul and his wife have volunteered at Caritas Furniture Bank in Richmond the past four years and are involved with the Central Virginia Cursillo (Weekend Retreat) Coordinating Committee. Paul is also part of the CERT (Community Emergency Response Team) team in Chesterfield County.

Paul Attanasio is the new support group leader for Richmond, Virginia.

Paul explains how he got involved with the IWMF: "I was looking for more information on WM and found the IWMF. I was looking at the large amount of printed information and videos. I was extremely impressed. Then I knew I had to join!" As to why he decided to be a support group leader, Paul says, "I went through two rounds of Rituxan last year after losing 35 lbs. and (being) very fatigued. I felt normal and regained my weight after the second round. I was very blessed, and I knew I needed to give back to other WM patients!"

INTERNATIONAL SCENE

EDITED BY ANNETTE ABURDENE

AUSTRALIA

Australia, like the rest of the world, is adapting to the reality of living with COVID-19. Our news on activities and developments in the Australian Waldenström's community covers funding for WM research, impact of COVID-19 on support group meetings, and Australian Blood Cancer Action Plan.

IWMF-LLS Strategic Research Roadmap

WMozzies have responded to the enthusiastic IWMF invitation to provide funding for the IWMF-LLS Strategic Research Roadmap. We are proud to be part of the international support from the Waldenstrom's Macroglobulinemia Foundation of Canada (WMFC), the Leukaemia Foundation of Australia, and Waldenström France. We are strongly committed to the long-term vision of "A world without WM." WMozzies joined with the Leukaemia Foundation of Australia in a fundraising campaign to raise AUD $150,000 (US $100,000). Three months into the campaign over one-third of the two-year goal has already been raised. The generous support of WMozzies Peter Carr, a member of the IWMF Ben Rude Heritage Society, is greatly valued. As a funding partner, Peter matched equally, dollar for dollar, all other donations.

Impact of COVID-19 on support group meetings

No face-to-face support group meetings have been held for six months due to the Australian government COVID-19 restrictions. WMozzies are still exploring Zoom opportunities for local support group meetings. Participation in IWMF and affiliate Zoom meetings by WMozzies is proving very worthwhile. Notwithstanding the time zone challenges, Zoom has enabled all interested WM Australians to have online access to the latest international WM news from the WM world's best. Noteworthy are the IWMF Virtual Educational Forum, together with presentations by Dr. Richard Furman speaking at the Upper New York State Support Group, Dr. Shirley D'Sa for WMUK, Dr. Zachary Hunter at an Atlantic Support Group Zoom meeting, and a Toronto Support Group meeting with Dr. Steven Treon.

Australian National Strategic Action Plan for Blood Cancer

WMozzies have been an active member of the Partnerships for Change to achieve the goal of zero lives lost to blood cancer. The National Strategic Action Plan for Blood

International Scene, cont. on page 29

International Scene, cont. from page 28

DO YOU KNOW?

If you are looking for a second opinion about your WM, the IWMF has a Directory of WM Physicians on the IWMF website. This is a worldwide list, and in recent months, the following international physicians and researchers who are very knowledgeable about WM have been added. All the physicians in the Physicians Directory have agreed to be included for consultation to patients, as well as other physicians. Please click the link for the complete list:
https://iwmf.com/directory-of-wm-physicians/

Dr. David Brittain
Alberts Cellular Therapy (ACT),
Dr. Brittain and Partners, Medical Suite M34, Netcare Pretoria East Hospital, Moreleta Park, Pretoria, South Africa

Dr. Moshe Gatt
Hadassah Hebrew University Medical Center, Jerusalem, Israel

Dr. Alexander Grachev
National Research Center for Hematology
Moscow, Russian Federation

Dr. Artur Jurczyszyn
Jagiellonian University Department of Hematology, 31-501 Kraków, Kopernika 17 Street, Poland

Dr. Efstathios Kastritis
Department of Clinical Therapeutics, Plasma Cell Dyscrasia Unit, National and Kapodistrian University of Athens, Athens 11528, Greece

Dr. Miguel Pavlovsky
FUNDALEU (Leukemia Foundation), Buenos Aires.
Argentina

Dr. Lugui Qiu
Blood Diseases Hospital and Institute of Hematology
Chinese Academy of Medical Sciences and Peking Union Medical College
Tiainjin, China

Dr. Iuliana (Julia) Vaxman
Rabin Medical Center
Petah-Tikvah, Israel

Cancer has been developed with support from the Federal Government and led by Leukaemia Foundation and Professor John Seymour (IWMF Physician Directory Australian WM specialist) with support by all leaders in Australia's blood cancer community. WMozzies recognise the value of this community-led National Action Plan and look forward to working with other members of the blood cancer community on its implementation.
The shared vision is:

- Zero lives lost to blood cancer by 2035, underpinned by zero preventable deaths from blood cancer, regardless of geography or background, underpinned by equitable access to quality, safe, best practice treatment, and care for all Australians.
- Patients and their families are empowered to make choices for their wellbeing. Patients and their families know what questions to ask at every stage of their cancer journey.
- Patient autonomy and choice are valued and supported.

Through collaboration with patients and leaders in the blood cancer community, the National Action Plan identifies four major priorities to improve outcomes for people living with blood cancer and their families:

- Empower patients and their families.
- Achieve best practices.
- Accelerate research.
- Enable access to novel and specialised therapies.

Andrew Warden, WMozzies, reporting

CANADA

The WMFC continues to hold Zoom support group meetings across Canada. Please visit our website for dates and times at *www.wmfc.ca*. Dr. Steven Treon spoke at our national Zoom meeting on October 21 about WM in the time of COVID-19. His presentation was recorded and is available on our website.

Several Canadian support group leaders attended the IWMF Support Group Leader Training Session on October 28. An important take-away was that support groups are often the *first* contact WM patients have with the WMFC.

The WMFC brochure is now available in French. Special thanks to volunteers Paul Cadrin, Montreal Support Group co-leader, for the French translation and to Chris Baginski for the graphic design work.

Our new WMFC website should be up and running early in the New Year. Please visit us to see what's up!

Betty McPhee, WMFC, reporting

International Scene, cont. on page 30

International Scene, cont. from page 29

CHINA

The breakout of COVID-19 has significantly affected people's daily lives worldwide. Even though the situation has been eased since May in China, most cities reopened after being in lockdown for months. Keeping social distance was still strongly recommended. People remain conscious of cross-region travelling and try to avoid public gatherings, especially for those with weak immune systems. Traditional on-site academic conferences, forums, and meetings encountered challenges. However, virtual meeting systems offered a great opportunity for communication between doctors and patients. In China, doctors and hematologists used online platforms to interact with their counterparts and patients.

On World Lymphoma Day, September 15, 2020, China's Blood Disease Hospital and Institute of Hematology (*www.chinablood.com.cn*) launched an event via Zoom for lymphoma disease treatment lectures and interaction with patients. This event also included one section of online consultation with lymphoma patients and a panel discussion between hematologists and patient support group representatives. Roger Yao, WM China, from Shanghai, and Juanjuan, from Beijing, were invited to attend this virtual discussion with four hematologists, Prof. Qiu Lugui and Prof. Zhou Dehui from Tianjin, Prof. Li Jianyong and Prof. Xu Wei from Nanjin. During this discussion, questions of common concern from lymphoma patients were raised and answered while audiences joined the Q&A through the internet. The event attracted more than 5,000 patients and caregivers.

Roger Yao, WM China, reporting

INDIA

Inspired by the IWMF and its very successful virtual Educational Forum, WM India held its first virtual support group meeting on November 8, 2020. It was an opportunity for many of us to meet each other for the first time, as members from across the country participated online.

We were fortunate to have a diverse group of members join us, from newly diagnosed patients to members undergoing treatment and those in remission. As we shared our stories of overcoming Waldenstrom's, it was fascinating to note the variety of treatments offered to our members and their different paths to recovery. WM is rarer in India than it is in the United States, with a handful of specialists in the country. It was especially encouraging to note how best practices and newer therapies discovered and developed by researchers abroad were being effectively prescribed by medical practitioners in India. While previously, treatment with drugs such as bendamustine was relatively common, today two of our members reported being prescribed rituximab and ibrutinib respectively, with both responding positively to treatment.

Coronavirus lockdown and restrictions were gradually phased out by July in most parts of India. Its residual effect has been to steer patients and caregivers towards telemedicine, with only the most critical consultations and treatments taking place in person. The pace of adoption has been staggering, and anecdotally, treatment options are also being tailored to keep patients away from hospitals to prevent any risk of contracting coronavirus. A member currently undergoing treatment described how his doctor suggested he take ibrutinib, as this could be administered orally—and at home! A point of note—and what may come as a surprise to readers—is that the generic form of ibrutinib manufactured in India costs a tenth of what it would in the United States.

Although it took coronavirus for us to pilot our first online meeting, we were delighted by how well it went. We believe that what we learned can help other support groups successfully conduct their own virtual meetings and are more than happy to share our technical insights. First, we suggest a platform such as Google Meet, as it is free to use, with no time limits. Its interface is simple, and members can join by just clicking on their meeting URL. Second, request members to test their meeting links a day in advance and familiarize themselves with the meeting software. If your members face any technical challenges, then you have enough time to resolve those issues. Third, on the day of the meeting, request that they join a few minutes in advance, to verify that their microphones and webcams are set properly. And finally, ask those not speaking to mute their microphones during the meeting, as it does help everyone else. We hope these steps help in a small way to make your virtual meetings flow seamlessly.

Saurabh Seroo, WM India, reporting

UNITED KINGDOM

As we approach the end of the year and the festive season, COVID restrictions have tightened, with Northern Ireland, Wales, and England all going into "circuit-breakers," to curb the rise in COVID cases and hospital admissions. England's November lockdown is scheduled to end on 2 December 2020.

Although these lockdowns are less restrictive than those in the spring, it has still been a worrying time for many affected by WM. Whereas in the spring, people deemed extremely vulnerable were told to shield, this advice has not been issued this time around. This caused some confusion and anxiety for these people, and of course their household members. Guidelines for each nation have been issued with regard to people in the extremely vulnerable groups—including many with WM—and we at WMUK have been updating our own information to help patients, their families, and friends negotiate this difficult time. The

International Scene, cont. on page 31

critical piece of advice is to stay home as much as possible and keep contact with anyone outside of your household to an absolute minimum.

With this in mind, WMUK has made our summer webinar held in conjunction with Lymphoma Action available on our website, so that people can get advice and information from experts, especially about how to care for their health and mental wellbeing during this time. We also continue to update our website and social media information with the latest guidance.

Ibrutinib available to Scottish patients

In the last issue of the *Torch*, we reported that WMUK was participating in the Scottish Medicines Consortium's (SMC) assessment of ibrutinib in combination with rituximab for WM patients. We are pleased to report that in early October, the SMC approved the treatment (with restrictions). The charity attended the final meeting to highlight key points in our evidence, whilst patient trustees provided personal insights and experiences of living with WM. We are thrilled about the SMC's decision, which ensures that patients in Scotland have access to a treatment that could improve their quality of life. Ibrutinib is currently licensed for adults with WM who are not able to have chemoimmunotherapy, or who have had at least one previous course of treatment.

WM and the flu vaccine

Amongst the increase in COVID rates, it is easy to forget that we have now entered flu season. Therefore, in early autumn we reiterated the importance of WM patients and their households to get the flu vaccine to protect them from seasonal influenza. Extra precautions are being taken at pharmacies and doctors' surgeries to ensure it is safe for people to get their vaccine.

20 challenges for 20 days

WMUK's collaboration with 19 other rare and less common cancer charities comes to an end in December. Fundraisers have come together for the 20 causes to raise over £70K for the charities to help ease the impact of COVID-19. Many charities in the UK have been hit hard by the cancellation of fundraising events and other effects of the global pandemic, resulting in significant drops in income when the need for their services is increasing. Fundraisers for WMUK included Ed, who did football keepie-uppies (can't let the ball hit the ground) in his back garden for 20 days and raised £1,800. In total, he completed 37,000 keepie-uppies! Andrea also took on the challenge, completing a different challenge every day—for example learning to say hello in twenty languages and hula hooping for twenty minutes.

Ed raised £1,800 for WMUK as part of the 20 challenges for 20 days for UK charities.

A huge thank you to all our fundraisers and donors who continue to support WMUK through this difficult time, ensuring we can continue our services, our support, and research.

New chief executive

We were sad to say goodbye to our chief executive, Lindsey Bennister, in November. Lindsey joined WMUK as its first member of staff in 2018 and has given a huge amount of time and energy to build the charity and improve the lives of people affected by WM. A big thank you, Lindsey, on behalf of the WM community in the UK, and we wish you the best of luck in your new position. We are currently recruiting for a new chief executive to lead the charity in an exciting time in its development. More information can be found by contacting us: *info@wmuk.org.uk*

Kat Tucker, fundraising and communications manager, WMUK, reporting

Have Your Say

The *Torch* welcomes letters, articles, or suggestions for articles. If you have something you'd like to share with your fellow WMers, please contact *IWMF Torch* editor Shirley Ganse at *shirleyganse@hotmail.com*

FROM IWMF CONNECT: WINTER 2021

BY JACOB WEINTRAUB, MD

Though the winter brings cold weather, discussion on IWMF Connect continues, sometimes heatedly. Support, encouragement, personal experiences, and links to human interest stories and clinical studies are always present. We said good bye to some members, and wished our "list mom" a fond farewell as he moved on to bigger and better things (though he is not really gone completely from our group). You are all invited to join IWMF Connect to participate or just "lurk" and absorb all the different experiences and observations and opinions.

PERSONAL INTEREST

As noted above, our long-time **IWMF Connect Manager Peter DeNardis** has moved to the position of chairman of the Board of the IWMF. His skill at keeping discussions relevant and civil has been exceptional. We welcome his successor, Dr. Julianne Flora-Tostado.

As always, there were a number of links to items not directly related to our WM, but which were very relevant to feelings and experiences that resonate with the WM community and involve other aspects of life that are unique to our community.

As usual, Peter posted links to very relevant personal interest and informational articles.

One article, from the *Washington Post*, is titled "Talking about my cancer either drew people to me or repelled them far away." Many of us have had similar experiences. Peter noted that fortunately, we at least have resources like Connect and other services provided by the IWMF to help us: "We're all in this together—one big happy WaldenFamily!"

https://www.washingtonpost.com/health/talking-about-my-cancer-either-drew-people-to-me-or-repelled-them-far-away/2020/07/02/41829b24-afe0-11ea-8f56-63f38c990077_story.html

Another link was posted after "The Dude" actor Jeff Bridges announced that he has lymphoma. While we don't know more details about what type of lymphoma he has, Pete noted an article titled "What older adults need to know about lymphoma," which specifically mentions WM, something we don't always find in articles about lymphoma.

https://www.ajc.com/life/health/what-older-adults-need-to-know-about-lymphoma/77QKNQ6CWZBIROMCKBSLQ6UIFE/

Finally, Peter posted a link to an article about "How People with Cancer Can Benefit from Online Therapy," especially mental health therapy. This is especially relevant in these days of a pandemic and the search for new ways to provide medical care:

https://www.cancer.net/blog/2020-10/how-people-with-cancer-can-benefit-online-therapy

IWMF Connect Manager Julianne Flora-Tostado added a link to an essay about cancer growth patterns that are "beautiful in a botanical metaphor." It is an impressive essay with comparison of cancer to crested cacti, which have a unique sculptural beauty but have cancer-like growths.

https://aeon.co/essays/crested-cacti-show-medicine-the-possibility-of-adapting-to-cancer

Julianne also posted a summary of a talk by two UCLA social workers about cancer in a time of uncertainty. This was a Leukemia & Lymphoma Society-sponsored presentation, which included comments that, for many of us, lifestyles have not changed because we already had started wearing masks in public, washing our hands frequently, and avoiding crowds. Not being able to bring in family or visitors for visits or long sessions in infusion chairs have been a challenge. Many people with significant anxiety tend to avoid coming to clinic and now receive services by telehealth. Some of these telehealth specialists are therapists who try to help people address their anxiety. They encourage patients to take control of what they can to help combat the helplessness we sometimes feel as patients, such as learning to say "no" when feeling overwhelmed. Trying to find fun things to do can be a challenge, but they are extra rewarding after a transfusion or other infusion. Even listening to one's favorite music can be rewarding. This is a very nice summary to be viewed in the IWMF Connect archives.

Other topics discussed included nosebleeds, stem cell transplants, itching, multiple links to general interest studies, articles about newer and older treatments, and webinars and presentations to IWMF support group meetings.

NOSEBLEEDS AND MEDICATIONS

This is a subject that recurs as ibrutinib (Imbruvica) becomes more widely used. Some people using newer BTK inhibitors are reporting similar problems at times.

Pete S posted a question about nosebleeds. He takes zanubrutinib and has had nosebleeds in the past due to a vascular issue in his nasal mucosa. Recently he had a much more serious bleed that lasted almost half an hour. He asked about others having nosebleeds and what they have done to alleviate the problem.

Kathy W answered that she had to have one of those vascular sites in her nose cauterized even before her WM diagnosis. That stopped the bleeding.

Ken Z has had laser cauterization for nosebleeds, which he thinks is better than chemical. He goes to a special center for hereditary hemorrhagic telangiectasia, a condition that results in frequent nosebleeds.

From IWMF Connect, cont. on page 33

Cheryl S uses Neo-Synephrine for nosebleeds. She suggested Peter could be checked for von Willebrand disease, a clotting disorder, if the nosebleeds continue frequently.

Ron T added that BTK inhibitors inhibit platelet function regardless of a person's platelet count. Generally, guidelines for ibrutinib indicate holding the med before and after almost any surgery.

A related discussion was started by a question from **Lela H.** She said her husband takes 280 mg of ibrutinib daily and hurt his back. She asked about pain meds but knows he cannot take ibuprofen. She asked about topical meds, including Salonpas.

Jan W replied that Salonpas contains a nonsteroidal anti-inflammatory drug (NSAID), which is what ibuprofen is. She suggested that Lela talk with husband's oncologist.

Richard S suggested taking acetaminophen, which does not cause bleeding.

IWMF Trustee Dr. Tom Hoffmann added that it is common knowledge that BTK inhibitors like ibrutinib and NSAIDs can both cause bleeding, so it is best not to be taking two drugs with that potential.

STEM CELL TRANSPLANTS

David S has had WM for 19 years and has had numerous treatments over the years. He is now facing a possible stem cell transplant. Dr. Richard Furman at Weill Cornell has recommended an allogeneic stem cell transplant (from a donor). David's brother is a match. David knows about the potential risks, especially in this era of coronavirus, but also knows there is at least a slim chance of cure with an allo transplant. He asked for any thoughts from the members. He is 65 years old.

Mitch O responded with mixed results for his wife, who had two allo transplants done more than eight years apart. They are very exhausting procedures. Her first one went very well. She was 54 years old and able to go back to work within four months. She did well for eight years but then needed a second allo transplant. Although she seemed to be doing well, she developed graft vs. host disease, and she never recovered from that.

Sue Herms, of the IWMF Research Committee, posted that her husband had an allo transplant for myelodysplasia, which is cancer of the bone marrow stem cells. He was refractory to other treatment. His transplant, with stem cells from an unrelated donor, was in 2018. He recovered nicely after mild graft vs. host disease and a C. *diff* infection but unfortunately developed another, unrelated cancer, likely because of his history of heavy smoking. However, for most of the prior 12 to 15 months, he had achieved a good quality of life from the transplant, walking every day and playing golf again.

Paul L asked if David had considered CAR-T treatment. Paul noted that at Seattle Cancer Care Alliance, a well-known transplant center, Dr. David Maloney has been saying that many patients in the past who would have been candidates for an allo transplant are having similar success with CAR-T therapy.

Marcia K added that she has personally thought about CAR-T cell therapy. There have been improvements in reducing the cytokine storm issue with this therapy, and she feels it will become an outpatient procedure soon. The medical advisor for the CLL Society had CAR-T treatment a few years ago and is doing well.

ITCHING

This subject arises periodically, both in relation to specific treatments and to our WM, even when not being treated.

Hava posted a question. She was diagnosed with WM three years ago. Severe itching led to the diagnosis, but she has not had treatment yet. Her biggest distress is around the continuing itching, which is on her arms, legs, and back. Her doctors think it is related to her WM but haven't offered any helpful solutions. She asked if anyone else experiences itching, and how do they deal with it?

Martha L posted that she gets itching on her feet. She uses a cream called Fucidin, which helps.

Joan T said the she gets itching too. Her doctor prescribes an antihistamine, and she takes it every night. When one stops working, her doctor changes to another antihistamine for renewed control.

Stephen T posted that he was diagnosed with WM in 2009 after having had a year of severe itching. The remedy was an antihistamine tablet, fexofenadine hydrochloride, brand name Allegra. He took one daily, and after a week the itching was reduced to a bearable level but never went away. He continued to have itching until he was treated for his WM, but it lasted for another two years before finally resolving.

Meg M answered that increased bone marroaw mast cells are commonly found with lymphoplasmacytic cells in patients with WM. Mast cells cause an increased release of histamine which can lead to itching. That is why antihistamine drugs may work. She added a link to an article with itching management strategies:

http://chemocare.com/chemotherapy/side-effects/itching.aspx

FAREWELL

Recently we learned of the passing of two members of the WM community and regular contributors to IWMF Connect. Christopher Court's son wrote with the news about his father. He thanked the members of IWMF Connect for the support that his father received over the years. The messages and advice, both practical and emotional, were greatly appreciated. Many tributes and offers of condolence were posted.

From IWMF Connect, cont. on page 34

From IWMF Connect, cont. from page 33

Anita L noted that Christopher enriched the lives of many of us with his thoughtful and encouraging posts. His family should take comfort in knowing that so many were helped by him. Peter DeNardis added his own perspective: "Christopher always had insightful comments based on his own personal experiences with WM, and what he'd learned about it over the years. We are all better for having known him and having shared experiences with him."

We also learned of the passing of former IWMF Board Trustee Cindy Furst. **Martha K** posted that Cindy was a tireless co-leader of the Denver WM Support Group for many years. She was always welcoming and helpful to all members. Peter DeNardis again commented: "She was always a kind, caring person who also cared deeply about helping others with their WM journey. She touched many lives and was of great help to fellow WMers she encountered."

So, again, this is just a small sample of what is posted online in IWMF Connect. Everyone is welcome to join and participate or just read the posts and benefit from the support and information. If anyone has any questions or wishes to see more on a particular topic, please contact me at *jmw003@aol.com*, and I will try to include those discussions in a future column. I wish you all continued good health.

BETWEEN SEPTEMBER 1, 2020, AND NOVEMBER 30, 2020, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN HONOR OF:

Anwar Al-Kunani
Edward Goldberg

James Hopping and Steve Bernstein
Edward Goldberg

Christie Andrews
Kirk Thomas

Shanthi Aribindi
Edward Goldberg

Jeffrey and Debra Bakal
Edward Goldberg

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