

## INSIDE THIS ISSUE

Eighth International Workshop ..... 1

President's Corner ..... 5

Getting the Most from My Provider Visit..... 9

Research Update..... 12

Donate and Participate! ..... 13

Fifth International IWMF Doctor-Patient Forum London 2014 ..... 14

My WM Story ..... 15

Medical News Roundup ..... 17

Howard's List for Caregivers..... 19

From IWMF-Talk..... 20

Treasurer's Report..... 22

## EIGHTH INTERNATIONAL WORKSHOP ON WALDENSTROM'S MACROGLOBULINEMIA IWWM8: SUMMARY I

BY GUY SHERWOOD, MD, VICE PRESIDENT FOR RESEARCH



*Dr. Roger Owen, recipient of the Robert A. Kyle Award, receives congratulations from Dr. Kyle during the Opening Ceremony.*

The Eighth International Workshop on Waldenström's Macroglobulinemia (IWWM8) was held August 14-16 in London, United Kingdom. This bi-annual scientific conference, by far the most important scientific event for WM, follows the previous conferences in Newport (2012), Venice (2010), Stockholm (2008), Kos, Greece (2007), Paris (2004), Athens (2002), and Washington DC (2000). More than 250 investigators from 30 countries registered to attend the conference – a new attendance record for these IWWM Workshops. The IWMF was a key

supporter of the 2000 Workshop in Washington and has continued its support for all the successive international Workshops, including IWWM8 in London.

Researchers who have made outstanding contributions in the field of WM were recognized at evening events throughout the conference. At the Opening Ceremony of IWWM8, held during an elegant dinner cruise on the river Thames, Dr. Roger Owen of St. James's Institute of Oncology, Leeds, United Kingdom, was presented with

the Robert A. Kyle Award for his important contributions to the study of Waldenström's macroglobulinemia. At the Closing Ceremony, held in the historic House of Parliament in London, Dr. Morie A. Gertz of the Mayo Clinic, Rochester MN, and Dr. Enrica Morra of the Ospedale Niguarda Ca' Granda, Milan, Italy, received the prestigious Waldenström Award. Both were presented with academic attire and medallions in recognition of their lifetime commitment in both clinical service and research in WM.



*At the Closing Ceremony, Dr. Enrica Morra and Dr. Morie A. Gertz received the Waldenström Award for their outstanding contributions to the field of lymphoma in their research in Waldenström's macroglobulinemia. From left to right, Dr. Pierre Morel, Dr. Gertz, Dr. Eva Kimby, Dr. Giampaolo Merlini, and Dr. Morra. Drs. Morel, Kimby, and Merlini comprised the committee for the selection of this year's awardees.*

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*Eighth International Workshop, cont. from page 1*



*Dr. Steven Treon on board for the dinner cruise on the river Thames the first night of the Workshop.*

Following closely the formula of previous IWMF conferences, the number of lecture sessions, debates, poster presentations, consensus panel discussions, and a special guest lecture by Dr. Shirley D'Sa of the University College London Hospital NHS Trust on "Current Treatment Approaches to WM in the UK" resulted in a very busy and comprehensive Workshop. Congratulations are in order to the Workshop's organizers Dr. Steven Treon, Dr. Shirley D'Sa, Dr. Charalampia Kyriakou, and Dr. Roger Owen for producing such an outstanding program and to Christopher Patterson of the Bing Center for Waldenstrom's Macroglobulinemia, Dana-Farber Cancer Institute, for the advance planning and on-the-spot coordination of program events and evening festivities.

For the first time at these prestigious conferences, the IWMF sponsored a total of 4 Young Investigator Awards. One of these Young Investigator Awards (YIAs) was co-sponsored by the Waldenstrom's Macroglobulinemia Foundation of Canada and yet another by WMUK, the IWMF affiliate in the United Kingdom. The European Waldenström's Macroglobulinemia network (EWMn) also independently supported a fifth YIA.

The lecture sessions, comprised of a number of 15 minute presentations by world renowned clinicians and researchers, included topics about WM such as its genetic basis, cell signaling, origin of the WM cell, diagnosis, predisposition, novel drug development, prognosis and survival, current therapy, treatment considerations, and special topics. Perhaps the most spirited session was the "Great Debates in WM" whereby a series of 4 debates was held on controversial topics in WM treatment. In each instance two expert



*Dr. Shirley D'Sa. One of the key organizers of the Workshop and the Doctor-Patient Forum that followed, Dr. D'Sa has recently been granted funding by the IWMF to establish a WM biobank in the UK.*

*Eighth International Workshop, cont. on page 3*



The IWMF Torch is a publication of:

International Waldenstrom's Macroglobulinemia Foundation

6144 Clark Center Avenue • Sarasota, FL 34238

Telephone 941-927-4963 • Fax 941-927-4467

E-mail: [info@iwmf.com](mailto:info@iwmf.com) • Website: [iwmf.com](http://iwmf.com)

This publication is designed to provide information about the disease Waldenstrom's macroglobulinemia. It is distributed as a member service by the International Waldenstrom's Macroglobulinemia Foundation, Inc., to those who seek information on Waldenstrom's macroglobulinemia with the understanding that the Foundation is not engaged in rendering medical advice or other professional medical services.

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Guy Sherwood, M.D.

#### CONTRIBUTING AUTHOR

Morie A. Gertz, M.D.

#### PHOTOGRAPHERS

Mary Brown, Eleanor Levie,  
Bob Manning, Phil Manning  
Doug Wolf

#### FORMATTING & PRODUCTION

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IWMF is a 501(c)(3) tax exempt non-profit organization Fed ID #54-1784426. Waldenstrom's macroglobulinemia is coded 273.3 in the International Classification of Diseases (ICD) of the World Health Organization.



Dr. Owen and family celebrating on the cruise.

clinicians discussed the pros and cons of hotly contested viewpoints regarding treatment controversies in WM.

In this issue of the *Torch* I will summarize the lecture sessions that dealt primarily with WM pathophysiology (Merriam-Webster's definition: *pathophysiology is the physiology of abnormal states; the functional changes that accompany a particular syndrome or disease*). We will touch on genetics, cell to cell signaling, WM cell origin, characteristics of the WM cell, diagnosis of WM, and finally predisposition to developing WM. In the January issue of the *Torch* we will focus primarily on treatment related issues, including new treatments now on the horizon.

Summarizing intense scientific conferences of this nature in layperson language can be arduous work for the writer, not to mention how difficult it can be at times for the reader to understand some of the terminology and not be overwhelmed by the strange names of biochemical molecules (STAT5 for example). A simple suggestion: do not get too hung up on terminology; rather, try to grasp the overall concepts.

The conference sessions started off bright and early Thursday, August 14, with the first "Genetic Basis for WM" session. As is fitting for this conference, the first speaker was **Zachary Hunter**, a brilliant young researcher from the Bing Center for WM, directed by Dr. Steven P. Treon at the Dana-Farber Cancer Center at Harvard University. Hunter described the ground breaking work of the Bing Center in the decoding of the MYD88 L256P mutation (present in approximately 90% of WM patients; unclear if prognosis is affected), as well as the CXCR4 mutation (present in approximately 30% of WM patients; confers a worse prognosis). Both genetic mutations have important implications, not only for the treatment of WM patients but also for prognosis and risk stratification. The overall picture of genetic mutations in WM is slowly unfolding, and this is definitely a new era in WM research and treatment, one which may lead to tailored, targeted therapies.

**Dr. Marzia Varettoni**, Department of Hematology-Oncology, University of Pavia, Italy, presented an elegant study

demonstrating that IgM-MGUS patients with the above-mentioned MYD88 L256P mutation are at a significant risk of progression to WM. The 5 and 10 year WM progression rates for IgM-MGUS MYD88 L256P patients were 15% and 46%, compared to 2% and 14% in patients with IgM-MGUS and no MYD88 mutation. Dr. Varettoni added that IgM-MGUS patients with high IgM levels were also at increased risk of progression to WM.

**Dr. Xavier Leleu**, well-known alumnus of Dr. Treon's lab at the Bing Center and now a practicing hematologist-oncologist in France, further characterized clinical features of WM patients, both with and without the MYD88 L256P mutation. Dr. Leleu observed that WM patients who did not have the MYD88 mutation tended to be mostly female, to have an enlarged spleen, to have lower tumor cell burden, to be of older age, and to have lower prognosis scores. Dr. Leleu actually challenged the conference attendees with the assertion that possibly IgM-MGUS MYD88 L256P patients are in fact "undiagnosed WM patients" and similarly that WM patients who do not carry the MYD88 L256P mutation may in fact not be WM patients at all but some other variant of non-Hodgkin's lymphoma, similar to, but not, WM. Dr. Leleu predicts "a wave of discoveries" as a result of the identification of the MYD88 L256P mutation and a new era of promising novel treatments and resultant increased life expectancy for WM patients.

**Dr. Bruno Paiva** of the University of Navarra in Pamplona, Spain, further strengthened the connection between IgM-MGUS and WM by using very sensitive and advanced flow cytometry techniques to detect and sort specific B-cell clones in bone marrow samples from WM and IgM-MGUS patients. His studies demonstrated that clonal B-cells from IgM-MGUS patients did indeed demonstrate a molecular profile that overlaps with clonal B-cells from WM patients, strengthening the argument that IgM-MGUS is a precursor to WM. Dr. Pavia also noted that the WM genetic profile is also closest to memory B-cells.

Following a short break and the obligatory coffee refill, the second "Genetic Basis for WM" session began with a very interesting talk from a relative newcomer to the WM scene, **Dr. Keisuke Horikawa**, Department of Immunology, Australian National University, Acton, Australia. Dr. Horikawa characterized the consequences of the MYD88 L265P mutation in WM mouse models. MYD88 L265P caused rapid transient B-cell division in two mouse models. This aberrant B-cell growth was decreased by a TLR9 deficiency (TLR9: Toll-like receptor 9, a protein in the TLR family that plays an important role in pathogen recognition and activation of innate immunity). B-cell proliferation was also rapidly restrained by the induction (increase) of TNFAIP3, an inhibitor of the NF- $\kappa$ B pathway. The MYD88 L265P mutation also down-regulated the surface expression



of the B-cell receptor (BCR) by decreasing CD79B gene expression. BCR expression can be enhanced by inducing the CD79B gene. This complex research essentially describes multiple checkpoints that may be considered when attempting to block the MYD88 mutation from increasing WM B-cell proliferation.

**Dr. Alessandra Trojani** of the Department of Hematology, Niguarda Hospital, Milan, Italy, investigated the bone marrow CD19+ cells of WM and IgM-MGUS in order to attempt to differentiate genes and key molecular pathways between the two closely related disease entities. Dr. Trojani and colleagues were able to identify 66 genes as “robust biomarkers” capable of differentiating between WM and IgM-MGUS. They are currently investigating the role of these identified genes as they pertain to the progression of WM from IgM-MGUS.

**Dr. Stéphanie Poulain** of the Service d’Hématologie-Immunologie-Cytogénétique, CH, Valenciennes, France, used single nucleotide polymorphism (SNP) array studies to better define genetic abnormalities in WM. SNPs (pronounced “snips”) are variations in a specific DNA sequence that occur commonly. As one may suspect, the MYD88 L265P mutation was the most common SNP in WM. Dr. Poulain suggests that the MYD88 L265P mutation may in fact lead to other mutations or CNAs (copy number alterations) that may indeed drive the development of WM from an otherwise healthy precursor cell. The higher the number of CNAs, the more unstable the WM cell and the greater likelihood of progressive disease. Dr. Poulain also reported on CD79B mutations, which as noted above, are important in B-cell receptor expression.

**Dr. Steven Treon** spoke about the clinical implications of the key MYD88 and CXCR4 mutations now found to be so important in WM patients. Dr. Treon and his team at the Bing Center used whole genome sequencing in 175 WM patients. They observed significantly higher bone marrow (BM) disease involvement and serum IgM levels, as well as symptomatic disease requiring therapy, in patients with MYD88 and CXCR4 mutations. Risk of death was not impacted adversely by the presence or absence of a CXCR4 mutation but was surprisingly increased by the absence of the MYD88 L265P mutation. These studies would therefore suggest that mutations in MYD88 and CXCR4 may determine the clinical presentation and impact the overall survival of WM patients. It follows that targeted therapies based on MYD88 and CXCR4 mutational status may provide a personalized treatment approach to WM.

**Dr. Nikhil Munshi**, a colleague of Dr. Treon and Zachary Hunter at the Dana-Farber Cancer Institute, compared the genomic signatures of WM to a disease often felt to be a close relative – multiple myeloma (MM). Fifty-two mutations were noted in MM versus 26 in WM. There were no identifiable specific mutations in the large majority of MM patients while in WM the presence of the MYD88 L265P mutation in 90%

(or is it 100% as suggested by Dr. Leleu?) and the presence of the CXCR4 mutation in 30% of WM patients present quite a striking difference between the two disease entities. Clearly, as Dr. Munshi noted, MM and WM are two different diseases.

The IWWM8 attendees were given a much needed dinner break to digest the genetics lecture session. The conference resumed with the complex and fascinating topic of “Cell Signaling in WM.”

**Dr. Claudio Sette** of the Department of Biomedicine and Prevention, University of Rome, presented an interesting lecture on the development of drugs that can target the MYD88 adaptor protein. This adaptor protein, the focus of much new research at this conference, plays a key role in the innate and adaptive immune response through its interaction with a number of signaling pathways (including TLRs or Toll-like receptors; IRAK1, 2, 4; IL-1). The MYD88 L265P mutation that is common in WM, however, can cause a number of undesirable and unwanted effects. A number of synthetic MYD88 inhibitors have been developed using sophisticated protein engineering techniques – it is truly a “hi-tech” world! Many of these putative drugs will inhibit the proper function of the MYD88 adaptor protein by targeting a specific area(s) of the three dimensional protein, thus rendering it incapable of properly interacting with other proteins such as IRAK4 to form a structure that is called a myddosome.

**Dr. Guang Yang**, a very prolific researcher from Dr. Treon’s team at the Bing Center, expanded on the multiple downstream signaling pathways arising from the mutated MYD88 protein. Not surprisingly, a number of relatively well-known signaling pathways involved in WM, including BCR, BTK (the pathway inhibited by ibrutinib), PI3K/AKT, and NF-κB can be targeted in WM treatment by novel drugs, both alone and in combination.

**Dr. Yang Cao**, also of the Bing Center, discussed how the CXCR4 mutation seen in 30% of WM patients causes resistance to the popular BTK inhibitor ibrutinib when stimulated with a specific chemokine ligand SDF-1α (SDF: stromal cell derived factor). Interestingly, WM cells with the CXCR4 mutation showed variable levels of drug resistance to bendamustine, fludarabine, bortezomib, and idelalisib in the presence of SDF-1α. Consequently, inhibition of CXCR4 could theoretically reduce the WM cell’s resistance to ibrutinib (and other drugs listed above).

**Dr. Stephen Ansell**, well known WM clinician and researcher at the Mayo Clinic, Rochester MN, presented his latest update on his IWWMF funded research into signaling pathways that regulate IgM production in WM. Despite recent advances in the treatment of WM, this disease remains incurable. Therefore strategies are needed to effectively suppress IgM production. Dr. Ansell’s ongoing research focuses on the complex mechanisms resulting in increased serum IgM levels and identifying cell signaling in the bone

*Eighth International Workshop, cont. on page 6*



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## PRESIDENT'S CORNER

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*Elly and Carl Harrington with actor Gerry George impersonating Winston Churchill.*

**“Never give in! Never, never give in!”** Those were the words of Winston Churchill during the darkest days of WWII when bombs were raining down on London. England stood alone in Europe against the Axis powers and a Nazi invasion seemed imminent. The IWWM8 (the Eighth International Workshop on WM) held in London this August featured a Churchill impersonator, who uttered that famous command along with Churchill’s historic promise: “We shall defend our island, whatever the cost may be, we shall fight on the beaches, we shall fight on the landing grounds, we shall fight in the fields and in the streets, we shall fight in the hills; we shall never surrender.” As Edward R. Murrow recalled, “Churchill mobilized the English language and sent it into battle.”

Beyond the thrill of having Churchill himself – well, a wonderful actor – speaking to us at the House of Parliament, IWWM8 was a remarkable conference. Just have a look at Guy Sherwood’s first installment of his detailed report on page 1 of this issue. For three days, more than 250 WM researchers and oncologists from around the globe gathered for presentations from 8am until 5pm and beyond. Everyone remained incredibly engaged despite time zone differences that stretched our mental and physical capabilities. That’s right, more than 250 of the best cancer researchers in the world were fascinated by presentation after presentation on WM. No one left. No one fell asleep. They were totally involved in learning about and solving the riddle that is WM. Among the most amazing facts I discovered, this one stands out: There were more papers published about WM in the last year than were published in the previous ten years combined. This burst in activity was inspired by the discovery of the MYD88 L265P mutation by Dr. Steven Treon and his DFCI team. And the IWMF was a sponsor of this seminal research.

On Sunday, August 17, the same seats occupied by the top WM researchers were occupied by 220 WM patients from the UK and from all around Europe for the Fifth International IWMF Doctor-Patient Forum. I had the pleasure of meeting patients from Germany, France, The Netherlands, Italy, and

Finland. We were all treated to an extraordinary program presenting the highlights of IWWM8 in terms that we could easily understand. Visit the WMUK website to buy a DVD and to learn more about this Forum coordinated by Dr. Shirley D’Sa and Roger Brown of WMUK: [www.wmuk.org.uk/news-and-events/events](http://www.wmuk.org.uk/news-and-events/events)

At both IWWM8 and the Fifth International IWMF Doctor-Patient Forum, the IWMF was represented by yours truly and by Vice President for Research Guy Sherwood, Vice President for Member Services Elena Malunis, and IWMF Office Manager Sara McKinnie.

What’s next for us?

- **The Twentieth IWMF Educational Forum:**

Be sure to put the date on your calendar now. The Twentieth Ed Forum will be held in Dallas, Texas, on May 1-3, 2015, at the Hilton DFW Lakes Executive Conference Center. Since this will be our twentieth Ed Forum, Texas is the only place big enough to hold it! Plan on coming!!

- **We need your help in improving our records.** We’d like to have the e-mail address, date of birth, and date of diagnosis for every WMer (month and year or just the year). If you’re not sure we have that information for you, please e-mail it, mail it, or call it in to Lisa Abbott at [office@iwmf.com](mailto:office@iwmf.com) or IWMF, 6144 Clark Center Ave., Sarasota FL 34238 or (941) 927-4963. This information is needed to help the IWMF Office function more efficiently. As with all of your data, it will remain confidential.

To continue our momentum, the IWMF needs your support and we need it now. Let me remind you all that WM is an orphan disease. We don’t receive government funding or a lot of outside support. We currently have more good research proposals than we can fund. What we are able to do is dependent upon you.

Let’s pretend that I’m as powerful and eloquent as Churchill and that I have convinced you of the urgent need to win the battles on two fronts: the Member Services Fund and the Research Fund. That we are counting on you to give as generously as you can. And that we must mobilize the troops – your friends and family – by asking them to donate now in your honor. Let’s work together to make sure we “Never give in.” Let’s fight together until we find a cure for WM.

Stay well!

Carl



*Gerry George speaking in Parliament.*



marrow microenvironment that supports WM cell growth. BAFF (B-cell activating factor) is increased in the serum and bone marrow of WM patients and acts as a significant driver of increased serum IgM levels. BAFF signaling is activated by a mutation in the BAFF receptor, BAFF-R, and the cytokines IL-6 and IL-21 bolster BAFF-mediated IgM production. IL-6 and IL-21 signaling through the JAK/STAT pathway increases the secretion of IgM, and IL-6 secretion is regulated in part by the chemotactic cytokine CCL5. STAT3, a component of the JAK/STAT pathway, can be targeted by a STAT3 inhibitor, resulting in decreased IL-21-mediated IgM secretion. IL-21 increases the expression of the STAT3 targets BLIMP-1, XBP-1, IL-6 and IL-10 that are involved in B-cell differentiation. Targeting the cytokine-mediated JAK/STAT signaling that promotes IgM production may therefore be a very useful clinical strategy.

Everything has a beginning, and WM malignant cells are no different. **Dr. Linda Pilarski** of the University of Alberta Cross Cancer Institute presented an interesting lecture on the “Origins of WM: Implications from Genetic Analysis.” Dr. Pilarski and her team of able genetic researchers believe that continuous malignant transformation occurs in WM and that one clone, among many, eventually dominates and leads to apparent homogeneity. She notes that in research done in 2006, 20% of WM patients had at least two identifiable clones and one clone was dominant. She identified HAS1 as the gene that she suspects is important in causing genomic instability and progression of WM. Further, Dr. Pilarski labels WM as “a moving target” and states that over time WM can change.

**Dr. Ramon Garcia-Sanz** from the University Hospital of Salamanca, Spain, is a world expert on the immunophenotyping of WM. Immunophenotyping is a technique used to identify the surface proteins expressed by cells (for example, CD-20, the target of rituximab). Dr. Garcia-Sanz notes that the MYD88 L265P mutation is clearly strongly expressed in WM yet essentially absent in most other B-cell lymphomas and that WM cells usually are unable to undergo class switch recombination (that is, to change from producing IgM to producing IgG). The typical immunophenotype of WM B-cells is CD19<sup>+</sup>, CD22<sup>lo</sup>, CD23<sup>-</sup>, CD25<sup>+</sup>, CD27<sup>+</sup>, CD45<sup>+</sup>, CD38<sup>-/+</sup>, SmIgM<sup>+</sup> and is also characterized by the absence of CD5, CD10, CD11c and CD103 expression. This immunophenotype is essentially identical to the memory B-cells present in the blood (memory B-cells make up about 30% of the B-cells in the blood). Dr. Garcia-Sanz cautions, however, that despite the data supporting the memory B-cell as the cell of origin for WM, the possibility still exists that a small fraction of WM cells could have a different origin than that of memory B-cells (a “moving target” as suggested by Dr. Pilarski).

**Dr. M.C. Kyrtsonis** of the University of Athens studied the immunoglobulin heavy chain (IgH) genes in WM and WM precursors. Using clonotypic antibodies (antibodies that react with specific types of cells or those closely related),

Dr. Kyrtsonis suggests that indeed the precursor cell for WM does appear to arise from a memory B-cell. Once again the possibility of WM clonal heterogeneity (WM tumors having two or more types of WM cells from slightly different origins) is raised, and further research is encouraged.

**Dr. Surinder Sahota** from the Tumor Immunogenetics Group, Faculty of Medicine, University of Southampton in the UK, has long been involved in the study of phenotypic and genotypic evidence tracing the cell of origin in WM. The phenotype of a cell is essentially the physical, biochemical, and physiologic makeup of a cell as opposed the genotype, which is the genetic makeup of a particular cell. Dr. Sahota presented an interesting lecture on tracking the origins of WM tumor cells. The bulk of WM cells express the B-cell receptor (BCR) as mature B-cells, and this, he suggests, aids in tumor survival and persistence. Dr. Sahota’s team evaluated a new surface cell marker FcRL5 as a useful tool that may be of interest for tracking WM cells as well as BCR function.

The second day of the IWWM8 conference heralded a change in focus from genetic and laboratory research to more clinically applicable topics of interest. The lecture sessions on the diagnosis of WM were led by **Dr. Roger Owen** of the HMDS Laboratory, St. James’s Institute of Oncology, Leeds, UK. Dr. Owen discussed the implications of the recently identified MYD88 L265P mutation with respect to current diagnostic criteria employed in WM. The bone marrow biopsy remains the main diagnostic tool for the diagnosis of WM and for the evaluation of disease response in WM. The biopsy of the bone marrow aspirate provides a definitive diagnosis of WM and exclusion of other hematological malignancies including IgM myeloma; distinguishes WM from IgM MGUS; identifies specific phenotypes of WM; provides an important appreciation of the cellular heterogeneity seen in WM (proliferative B-cells and IgM-producing lymphoplasmacytic cells), an important factor to consider in the post treatment setting; identifies additional clonal B-cell and plasma cell populations; and, finally, provides an assessment of underlying hematopoiesis (formation of blood cellular components in the bone marrow). Simply put, the bone marrow biopsy/aspirate has definitive advantages over the much anticipated MYD88 L265P mutation assay of peripheral blood WM cells in the assessment of underlying hematopoiesis. The advantage of the bone marrow biopsy is based on the following: not all WM patients have WM cells circulating in the peripheral blood; not all WM patients have the MYD88 L265P mutation; certain antibodies react to WM plasma cells but not to WM B-cells; and, finally, there is the possibility of coexistent WM and DLBCL disease which could complicate a diagnosis made from the peripheral blood assay. Dr. Owen does concede, however, that the MYD88 L265P mutation promises to be a valuable adjunct in the diagnosis of WM along with the unpopular (at least from the WM patient’s point of view) bone marrow biopsy/aspirate.



**Dr. Robert Kyle** of the Mayo Clinic, Rochester, MN (and member of the IWMF Board of Trustees as well as Chair of the IWMF Scientific Advisory Committee), presented a very topical lecture entitled “Where Does IgM MGUS End and WM Begin?” There has been much speculation, and of late increasing evidence, that the seemingly benign condition IgM monoclonal gammopathy of undetermined significance (IgM-MGUS) is a direct precursor of WM. Dr. Kyle defines IgM MGUS as characterized by the presence of an IgM monoclonal protein  $< 3$  g/dL,  $< 10\%$  lymphoplasmacytic infiltration of the bone marrow, and absence of symptomatic anemia, lymphadenopathy, hepatosplenomegaly or hyperviscosity as well as no constitutional symptoms. Approximately 1.5% of IgM-MGUS patients will progress to WM per year. Dr. Kyle subsequently defined smoldering Waldenström’s macroglobulinemia (SWM) as characterized by the presence of a serum M protein  $\geq 3$  g/dL and/or a bone marrow containing  $\geq 10\%$  lymphoplasmacytic infiltration, absence of symptomatic anemia, lymphadenopathy, hepatosplenomegaly and hyperviscosity, and no constitutional symptoms. About 12% of SWM patients will progress to symptomatic WM each year for the first 5 years, and then the risk of progression decreases to approximately 2% per year for the following five years. For the sake of completeness, Dr. Kyle also defined the diagnosis of Waldenström’s macroglobulinemia as requiring the presence of an IgM monoclonal protein (no size limits),  $\geq 10\%$  bone marrow infiltration by lymphoplasmacytic cells which stain with IgM and are CD19 and/or CD20 positive (CD5 and CD23 are generally negative), the possibility of constitutional symptoms consisting of fever, sweats, fatigue and weight loss, the presence of symptomatic hepatosplenomegaly and/or lymphadenopathy, or a reduction in hemoglobin. Hyperviscosity and peripheral neuropathy are also well-recognized symptoms of WM that often require treatment. Dr. Kyle suggested that it now appears that all SWM patients had pre-existing IgM-MGUS, and by extension all WM patients had pre-existing IgM-MGUS. Finally, Dr. Kyle cautions that patients who are diagnosed with WM should only be treated when symptomatic or when significant anemia develops.

**Dr. Lian Xu** of the Bing Center discussed a potential new test that could detect the MYD88 L265P mutation in the peripheral blood and bone marrow of patients with WM and IgM-MGUS. Using the sophisticated laboratory technique of peripheral blood (PB) allele-specific PCR (AS-PCR) examination in selected CD-19 positive cells, Dr. Xu was able to demonstrate that among the positive MYD88 L265P patients identified by bone marrow assay sampling, the MYD88 L265P mutation was detected in their respective peripheral blood CD19-selected samples in 92% of the smoldering WM patients and 100% of the symptomatic WM patients. The detection of the MYD88 L265P mutation in the peripheral blood may provide a convenient and less invasive method to make WM diagnoses. However, he noted

that in previously treated WM patients, the MYD88 L265P mutation was detected in 92% of bone marrow samples but only in 68% of peripheral blood samples. Clearly treatment for WM decreases the amount of circulating WM cells in the peripheral blood as opposed to the WM cells in the bone marrow which are usually readily accessible. This suggests that at this point in time the peripheral blood assay for the MYD88 L265P mutation is limited to newly diagnosed untreated WM patients.

**Dr. Ranjana Advani** of Stanford University reviewed the National Comprehensive Cancer Network (NCCN) 2014 Diagnostic & Treatment Guidelines for WM. These guidelines can be accessed on the NCCN website. The most important changes in the guidelines can be summarized by the inclusion of bendamustine as a regimen potentially toxic to stem cells, as well as the addition of the newer agents everolimus, ibrutinib, and ofatumumab for salvage therapy. Stem cell transplantation was also added as an option for salvage therapy in selected patients.

Many WM patients often wonder what genetic or environmental event predisposed them to developing WM.

**Dr. Ola Landgren** of the Memorial Sloan-Kettering Cancer Center discussed predisposition to MGUS. It is now accepted that monoclonal gammopathy of undetermined significance (MGUS) is associated with a 0.5-1% annual risk of developing multiple myeloma, Waldenström’s macroglobulinemia, and other lymphoproliferative disorders. In WM the MYD88 L265P mutation has been found in up to 90% of patients and the CXCR4 mutation in up to 30% of patients. The search for other select genetic mutations continues. Dr. Landgren suggests that germline mutations – detectable and heritable variations in the lineage of germ cells (reproductive cells that give rise to organisms) – lead to IgM-MGUS. Thereafter, somatic mutations – acquired alterations in DNA, frequently caused by environmental factors that can be passed on to the progeny of the cell in question – lead to the progression from IgM-MGUS to WM.

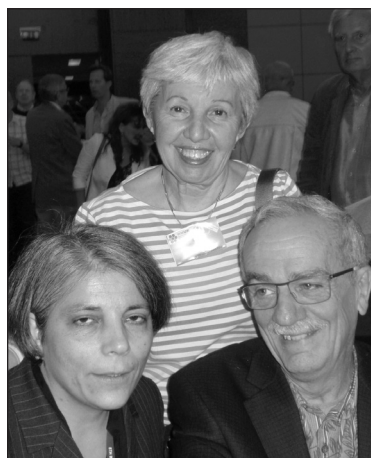
**Dr. Mary McMaster** of the National Cancer Institute, National Institutes of Health, USA, discussed familial predisposition for WM by studying the genes of 32 individuals from 9 families at high risk for WM. Dr. McMaster has observed that the multiple genes involved in immune dysregulation, chronic antigen stimulation, and other select environmental exposures are often seen in individuals and families at high risk for WM. Her research team is currently focusing on 17 specific genes in 2 WM patients and 92 relatives from their families, as well as an additional 272 subjects (95 familial WM, 28 nonfamilial WM, and 149 informative relatives).

**Dr. Helga M. Ögmundsdóttir**, Faculty of Medicine, University of Iceland, Reykjavík, Iceland, continued her fascinating research into eight Icelandic families with high



occurrence rates of monoclonal gammopathies. A particular phenotype was repeatedly observed – that of the hyper-responder (HR). It seems that the HRs in this study are very sensitive to an antigen (poke weed) and manifest enhanced production of immunoglobulins when exposed to the antigen in question. Dr. Ögmundsdóttir also supported Dr. Linda Pilarski's long-held assertion that a mutation or mutations in the Hyaluronan Synthase 1 gene (HAS-1) predisposes people to WM, MM, MGUS, and the hyper-responder phenotype. The HAS-1 mutation(s) affect the centromere and mitotic spindle that are central to the process of cell division by altering the intracellular cytoskeleton.

**Dr. Sigurdur Y. Kristinsson**, Professor of Hematology, University of Iceland, discussed epidemiologic studies suggesting that repetitive immune stimulation and genetic factors play an important role in the development of WM. There would appear to be a 20-fold genetic risk for family relatives of WM patients to develop WM themselves. In individuals and families with a history of autoimmune disorders, the risk of developing WM is considerably increased as well; for example, the increase in risk is 12-fold if there is a history of Sjögren's syndrome and 24-fold if there is a history of autoimmune hemolytic anemia. Dr. Kristinsson also noted that a WM patient's risk for infection, unsurprisingly, increases with time and certainly with each successive treatment a patient receives. Upper respiratory tract and urinary tract infections seem to be the predominant culprits. Interestingly,



*Dr. Charalampia Kyriakou, left, IWMF Vice President for Member Services Elena Malunis, center, with IWMF President, Carl Harrington. Dr. Kyriakou, together with Drs. Treon, Owen, and D'Sa, was responsible for the Workshop's program.*

WM patients also have a 4-fold increased risk of venous thrombus (blood clot) in their first year and a nearly 8-fold increased risk of venous thrombus over a span of 10 years. Thankfully, Dr. Kristinsson finished his lecture with the assertion that the relative survival for WM patients is greatly improving in Iceland in recent years.

In the next issue of the *Torch* we shall review the lectures that deal with the clinical

aspects of WM, including the currently recommended treatment options as well as the existing new drugs that are soon to be in clinical trials and the newer agents being developed. As always I will reserve the last segment of these articles for my impressions of this fantastic and encouraging WM conference. There is hope, much hope on the horizon.

Donate and Participate!

## GOOD-BYE TO SUMMER 2014

As you are reading this *Torch* in November, the summer of 2014 is already a fading memory. We've heard a lot in this issue about the four memorable August days in London when the who's who of WM reported on the most recent research and when the IWMF and WMUK presented the Fifth Doctor-Patient Forum. We should not, however, overlook the fact that IWMF support groups throughout the US are quite active during the summer months hosting guest speakers, formal lectures, restaurant forays, and potluck luncheons, suppers, and picnics. And this summer was no exception.

Here is a photograph of one such event, the sixth annual picnic held by the Chicago area support group at the home of Karl and Kathy Coyners on a beautiful summer's day in St. Charles, IL. As Chicago area support group leader Don Brown noted, "Support groups are not just about education – they also, and perhaps most importantly, foster fellowship and caring across generations."

We will catch up with the more support groups and hear about other events of the summer of 2014 in the January 2015 issue of the *Torch*.



*All ages were represented at the Chicago area support group's picnic in June. It was a beautiful day and a good time was had by all. Support group leader Don Brown is seated in the front row, to the far right. To his left is Kathy Coyners, who welcomed the group members to her home.*



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# GETTING THE MOST FROM MY PROVIDER VISIT

BY MORIE A. GERTZ, MD, MACP

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## Introduction

The treatment of Waldenström macroglobulinemia is indicated only for those patients who have symptoms. If you are an asymptomatic patient placed on a “watch-and-wait” strategy, it is important for your provider to be able to identify whether any relevant symptoms exist. In other words, you as a patient need to be aware of what your provider is looking for so that your appointment time is optimized and leaves an ample period for questions to be satisfactorily addressed. Today, all providers are very busy and their time available to manage a face-to-face visit is limited. As a consequence, having a checklist becomes important in expediting your evaluation.

## First Visit to a General Oncologist

When patients are referred to a medical oncologist in this setting, typically they have already been identified as having a monoclonal IgM protein or they are being sent for evaluation of lymph gland enlargement or anemia. Reporting symptoms is of critical importance to the provider so that he or she understands what drove the evaluation initially. To say, “I have anemia” or “I have peripheral neuropathy” is *not* to state symptoms. Such statements represent diagnoses, and diagnosis is the responsibility of the provider. The responsibility of the patient is to report the symptoms that led to medical evaluation, whether stating, “I have no symptoms; my doctor found a low blood count or a protein abnormality on my annual physical examination,” or “I was feeling run down and tired, was unable to climb stairs, so I went to the doctor,” or “I have numbness and burning in my feet that began eight months ago,” or “I found a lump in my neck or a lump under my arm, which I believe to be a lymph gland.” Such symptomatic reports will allow your provider to immediately focus the evaluation to ensure that you have the greatest satisfaction from this first visit.

On seeing a general oncologist for the first time, you may have outside records from your primary care provider. To bring 200 pages that have been photocopied and are in random order is not particularly beneficial. Most of the office visit will be spent sorting records with very little time spent in face-to-face dialogue about your concerns. In the case of Waldenström, what the doctor will need to see on the first visit will include any protein levels done at any time over the past few years, as well as complete blood counts, since anemia is such a conspicuous problem with this disorder. If you have had regular checkups over a long time, tracking changes in the blood count levels can be extremely useful in trying to reconstruct the tempo of this disease. Therefore, if it is possible for you to sort through and get the specific laboratory tests that relate to protein levels and complete blood counts, the results of any imaging studies such as X-rays or CT scans,

and year-over-year records that outline changes in these parameters, you will be helping your oncologist understand how long the disorder has been present.

By sharing this information, you will be able to give your provider answers to key questions, including: How long has this likely to have been present? How serious is the impact on my body? If treatment is indicated, how urgent is it? To understand some of the relevant testing that your doctor will be looking for in the records is to know the five key parameters for staging of Waldenström macroglobulinemia. These parameters are age, hemoglobin, platelet count, IgM level, and  $\beta 2$  microglobulin. These tests will not only help your physician, but they will also help you since you will know what your disease stage is, should you require therapy.

## Subsequent Visits to the Oncologist – “Watch-and-Wait”

In the situation where observation (“watch-and-wait” as it is often called) has been selected, the primary parameters will be monitoring for increases in the IgM level or declines in the hemoglobin level. The physical exam is adjunctive because it allows the physician to determine if there is lymph gland enlargement or liver/spleen enlargement. The key questions for patients include the following. Has there been increased fatigue? Have you noticed any lumps or bumps anywhere (lymph nodes)? Have there been any infections since I last saw you? If so, how were they treated, and how long did they last? Follow-up office visits for “watch-and-wait” patients generally can be efficiently accomplished in 15 minutes or less by recounting interim symptoms. Always point out if you have had nose bleeding or gum bleeding, or numbness or tingling in your hands or feet. Always bring to your visit a list of all medications that you are currently taking so that this can be reconciled with what the physician has on record. This is particularly important if there has been a change in medication since the last visit; if so, this should be identified clearly in the written list.

## Subsequent Visits to the Oncologist – While on Therapy

For patients on therapy, the two key issues with each visit include understanding treatment efficacy as well as treatment toxicity and side effects. A change in clinical level of fatigue, whether better or worse, becomes important. Whether there were any interim infections related to therapy, reporting of fever or chills related to treatment, the need for any transfusional support since last seen, hospitalizations, numbness or tingling in the hands and feet – all are relevant for your provider to know because a key part of the subsequent visit of a patient on treatment is to determine if adjustment or modification of dosage is appropriate to help manage toxicity. Not all side effects can be measured by your provider using blood tests. Insomnia, mood swings, and

*Getting the Most, cont. on page 10*



agitation are common side effects of certain medications but cannot be measured on any diagnostic tests. The same is true for the development of numbness or tingling in your hands or feet, which can be a toxic and irreversible side effect that must explicitly be mentioned to allow dosing adjustment that prevents permanent effects of therapy.

## Seeing a Waldenström Specialist for the First Time

### When to Get the Second Opinion

In the majority of individuals, Waldenström macroglobulinemia does not require emergency treatment, so there is time to contemplate the next steps. Because there are so many different options available for patients and because patients may be potentially eligible for innovative and less toxic therapies, the ideal time for first contact would be *before therapy has begun*. Once therapy has been initiated, the ability to benefit from new and innovative therapies available at specialty centers is severely limited since many of them are reserved for previously untreated patients. Therefore, it is more preferable by far to get a second opinion *before* treatment rather than after two cycles.

It is important before seeking a second opinion to discuss it frankly with your local oncologist. This conversation will provide a significant degree of insight into the relationship as it goes forward. Given that Waldenström macroglobulinemia is an extremely rare disease and most local providers see it only occasionally, one would expect a warm response to the question of a second opinion. Confrontation or threats should suggest this relationship is not one that will be an ideal in the long-term. A new practitioner might be considered. Likewise, it is the responsibility of the Waldenström specialist to communicate respectfully with referring physicians, to respect their choices when they are reasonable, and not to try to set up a situation of conflict with the patient in the middle.

One of the advantages of early contact with a Waldenström specialist is that it allows development of a long-term relationship, so that if there is a status change, it becomes possible to return for ongoing care and advice with an already-established record.

### Identifying a Waldenström Specialist

There are a number of ways to identify specialists in Waldenström. Most university medical centers have a list of experts who see large numbers of patients with Waldenström. Search engines such as Google Scholar will allow you to identify specialists who have extensively written about

Waldenström macroglobulinemia. If you have a name in mind, a Google search of the physician will certainly identify whether he or she has specific expertise in Waldenström macroglobulinemia.

The International Waldenström's Macroglobulinemia Foundation (IWMF) website is a tremendous asset in identifying a specialist. The IWMF support groups will allow you to connect with individuals who have sought second opinions and identify specialists with expertise. Checking the agenda for the annual patient Educational Forum sponsored by the IWMF will introduce you to WM experts among the speakers invited by the IWMF to discuss aspects of Waldenström, usually based on expertise that has been identified by the Foundation. On its website, the IWMF has a section called "Finding a Doctor," which includes an international directory of doctors and their locations. This list is by no means exhaustive, and there are many outstanding individuals who have not been mentioned, but it is a wonderful starting place.

### What Do I Bring to the Second Opinion

Ideally, you should bring a short summary from your home physician outlining the indications for the referral and the pertinent laboratory studies. If a bone marrow or lymph node biopsy has been performed, carrying by hand or having the slides sent in advance for review is helpful. For pathologic tissue samples, a review of an outside photocopied report is insufficient. My best patients have gone to the trouble of providing a pertinent summary of prior therapy regimens and dates, protein levels, and complete blood counts over time. Even better, they will usually do this in Excel format and hand-carry it for me so that, at a glance, it is possible to see each treatment, the impact on the IgM level, the impact on the blood counts, both good and bad, and some discussion of side effects – this is the ideal situation. When patients are proactive, they get the most out of their second opinion since they can spend their time asking questions relevant to

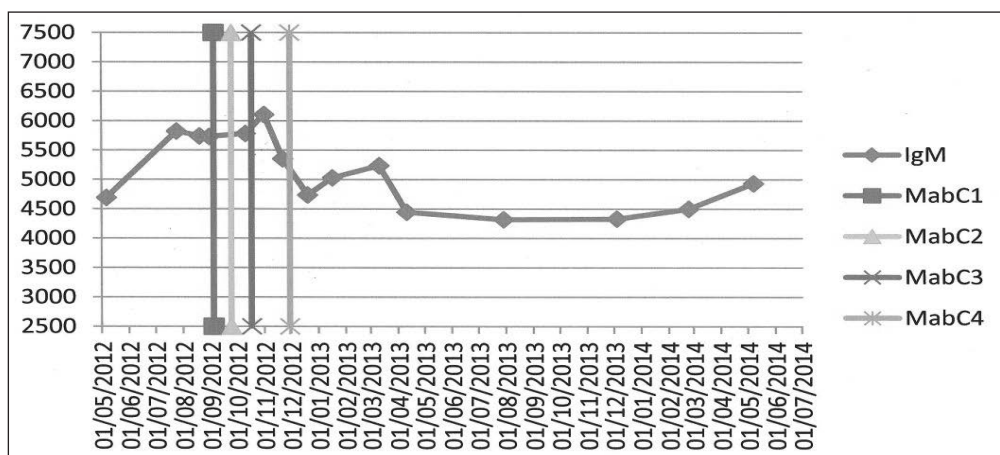


Figure 1



them and receive the most from an expert's advice, rather than spend the time in record review. In Figure 1, my patient shows, over a period of two years, serialized changes in the IgM level as well as the dates of rituximab therapy.

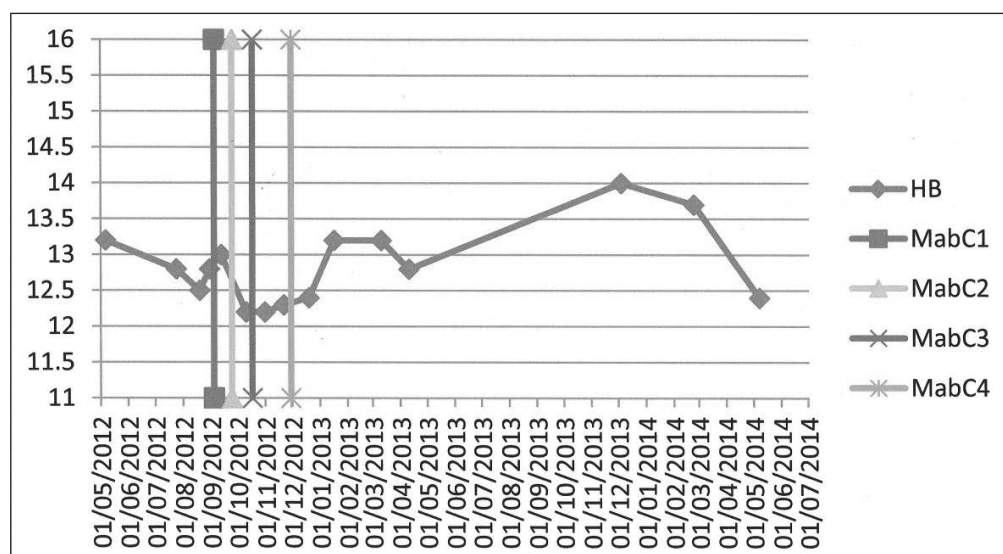


Figure 2

It is very easy, at a glance, to see that this patient had a very nice response to rituximab (Mab in the figure) therapy. The chart can be updated every three months to monitor ongoing response. In Figure 2, the patient has charted his hemoglobin level and demonstrated how the hemoglobin was in decline, fell further with treatment, subsequently recovered and, after a period of two years, is showing modest reductions once again.

Even if a patient lacks the technical ability to produce such sophisticated charts, a simple lined table, showing the changes in IgM and blood counts over time, with treatments in the right margin, can be invaluable. In this way, a long-term relationship can be established and updated periodically.

The doctor who provides the second opinion will want to know the same information as the doctor who first saw you, which includes the following: What were the symptoms? Have you had bleeding, lymph gland enlargement, infections, hospitalizations, numbness or tingling in your hands or feet? It is completely appropriate to ask an expert whether he or she agrees with the therapy that has been initiated.

Whether a second opinion includes additional testing will depend on how complete the outside information is. In some instances, an evaluation has been so thorough that no additional tests are required. In others, there may be some

gaps that require filling to render an appropriate opinion. When research is involved, patients will often be asked to provide specimens, not for their own direct clinical benefit, but to further research in the field.

If the specialist disagrees with the local provider's opinion, a specific letter should be issued with the recommendation so that the patient does not find himself as a mediator between conflicting opinions. Typically, the local doctor will send subsequent follow-up visit information to the expert to be filed in the record for future visits. It may be

necessary to return and see the expert if there is a status change or a need for additional therapy. Most academic centers have the ability to electronically file outside reports from a local doctor so that they can maintain current information during therapy. This, however, is not a substitute for the charts outlined in Figures 1 and 2.

## Conclusion

When it comes to getting the most from your provider visits, keep in mind that if you become your own best advocate you will optimize your visits to both your local oncologist and your WM specialist. Your effort to organize records and to understand the key information set forth in the documents will pay you dividends. You will ensure an optimal consultation with your provider, and some initiative on your part will enable you to better understand your illness and to participate in the decision making process regarding your care.

*Dr. Morie A. Gertz is the Roland Seidler Jr. Professor of the Art of Medicine and Chair, Department of Internal Medicine, at the Mayo Clinic in Rochester, Minnesota. At IWWM8 in London, Dr. Gertz received the prestigious Waldenström Award.*

## 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 *Torch* editor Alice Riginos at [ariginos@me.com](mailto:ariginos@me.com)



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# RESEARCH UPDATE

BY GUY SHERWOOD MD, VICE PRESIDENT FOR RESEARCH

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The past three months have been a very busy time for the IWMF Research Committee. Composed entirely of volunteers from the IWMF community, this energetic committee has not only reviewed progress reports from five of the seven research projects currently sponsored by the IWMF but has also reviewed and accepted two new research project proposals, both of which were subsequently approved for funding by the IWMF Board of Trustees.

## CURRENT IWMF RESEARCH GRANT RECIPIENTS

**Dr. Steven P. Treon** of the Bing Center for WM at the Dana-Farber Cancer Institute, Boston MA. Dr. Treon and his very able team of researchers have made great inroads into the oncogenic signaling of the MYD88 L265P mutation in WM, have identified and validated inhibitors of MYD88-directed signaling in WM, and continue to characterize MYD88 pathway inhibitors *in vivo* and initiate early clinical phase studies in WM patients.

**Dr. Ruben Carrasco**, also of the Dana-Farber Cancer Institute, has undertaken the difficult and complex task of generating a mouse model of the disease that replicates both the clinical and the pathological characteristics of the MYD88 L265P mutation in the mice. These mice will hopefully one day serve to further evaluate the biochemical and functional characterization of transgenic B-cells and define the role of MYD88 L265P mutation in oncogenesis. This important research and development of a WM mouse model is co-sponsored by the Leukemia & Lymphoma Society (LLS) and the Waldenstrom's Macroglobulinemia Foundation of Canada (WMFC), together with the IWMF.

**Dr. Abdel Kareem Azab** of Washington University, St. Louis MO, recently completed his study determining the role of hypoxia (low levels of oxygen concentration, in this case in the bone marrow) in WM cell dissemination *in vivo*. Further, Dr. Azab's research characterized molecular changes regulated by hypoxia in WM cells *in vitro* and helped determine the role of a signaling pathway called Hypoxia Inducible Factor (HIF) in the WM cell's response to hypoxia, as well as the effect of HIF inhibitors on the progression of WM *in vitro* and *in vivo*.

**Dr. Stephen Ansell** of the Mayo Clinic, Rochester MD, continues his complex research into the expression and activation of important cytokines (specifically the signaling molecules STAT5A and STAT5B) in WM cell lines and patient-derived tumor cells. Currently Dr. Ansell's focus is on determining the individual influence of these cytokines on downstream targets in WM and evaluating the effects of specific STAT5 inhibition on the biology of the WM tumor cells.

**Dr. Irene Ghobrial** of the Dana-Farber Cancer Institute continues her efforts to develop a tissue bank of WM specimens linked to clinical characteristics of patients in different stages of the disease. Characterization of the genetics and proteomics of WM cells during disease progression will lead to developing biomarkers that evaluate the activity of therapeutic agents in clinical trials for WM patients.

**Dr. Sherine ElSawa** of Northern Illinois University, DeKalb, IL, has recently submitted her first progress report on her research of a novel signaling pathway that regulates the crosstalk between malignant cells and the tumor microenvironment, thus increasing the understanding of the signaling pathways in the tumor microenvironment that contribute to the progression of WM. Ultimately this research aims to facilitate the development of new targeted therapies for WM patients.

**Dr. Aldo M. Roccaro** of the Dana-Farber Cancer Institute has also recently submitted his first progress report on his new research project. His research focuses on mutations in the CXCR4 gene with the intent to identify novel common pathways of disease progression that may lead to dissemination of WM cells to distant organs and increased WM cell growth, ultimately resulting in disease progression. Demonstrating genomic aberrations of the CXCR4 mutation will be crucial for identifying new effective targeted WM treatments.

## RESEARCH GRANTS RECENTLY APPROVED

Two new exciting proposals recently received the approval of the IWMF Board of Trustees.

**Dr. Brad Nelson** and **Dr. Julie Nielsen** of the British Columbia Cancer Agency, Deeley Research Centre, Victoria BC, Canada, were awarded a two year research grant for the project "Mutant MYD88: A target for adoptive T-cell therapy of WM."

T-cells can be genetically modified to express receptors that redirect them to kill tumor cells, thereby eliminating the need to remove and isolate tumor-reactive T-cells from individual patients. Adoptive T-cell therapy involves expanding tumor-reactive T-cells *in vitro* and infusing them into the circulatory system of individual patients with the expectation that these reactive T-cells will recognize and destroy tumor cells. Effectively, this procedure delivers very high numbers of tumor-reactive T cells without requiring the patient to mount an active immune response.

Building on their discovery of a T-cell receptor that specifically recognizes mutant MYD88, the researchers propose to develop a novel, highly targeted treatment for WM involving genetically modified T-cells. This project is co-sponsored by the IWMF and the Waldenstrom's Macroglobulinemia Foundation of Canada (WMFC).

**Dr. Shirley D'Sa** of University College London Cancer Institute and University College London Hospital has received a grant for yet another new and co-sponsored project, this time involving the IWMF and the Waldenstrom Macroglobulinemia United Kingdom (WMUK) patient group. Entitled "The UCLH WM Biobank: from biology to treatment," the project has been granted funding for two years to set up a biobank (tissue bank) and clinical data repository for WM within the University College London Cancer Institute and University College London Hospital. The biobank and

*Research Update, cont. on page 13*



the data repository are expected to provide an essential resource for a series of research projects and to act as a springboard for national and international collaborative work through access to high quality processing and recording of samples, through the establishment of a longitudinal clinical data collection and a clinical data information registry, and through the creation of an environment of openness aimed at promoting clinical progress through genetic research.

### Donate and Participate!

Research efforts supported by the IWMF through donations from members to the Research Fund are paying off in great dividends for the WM community. At the recent Eighth

International Workshop in Waldenstrom's Macroglobulinemia in London (see pages 1-8 of this issue), the IWMF was frequently cited by world experts in WM research for the crucial support received for their past and ongoing research activities. Treatments for WM are always five or ten years away from new advances in research, but one can certainly feel very encouraged by the pace of WM research these days. More and more targeted effective WM treatments are on the horizon and more and more WM patients are participating in clinical trials. There is no question that WM will soon become a very treatable disease. A cure is no longer an unrealistic dream. It is now an almost palpable reality.

## DONATE AND PARTICIPATE!

As you read this final issue of the *Torch* for 2014, have you noticed how frequently mention is made of the accelerated pace of current research on WM? We are rapidly learning more and more about this puzzling disease.

As new research reveals more about the genetic basis of WM, about the origin of the WM cell, about the signaling pathways that lead to increased IgM in the blood, so our expectations rise for new and more targeted treatments and for a cure.

Vice President for Research Guy Sherwood has contributed two important articles to this issue which illustrate the pace and scope of research today. Guy's front page article summarizes the presentations given by the leading WM researchers and clinicians invited to speak at IWW8, the Eighth International Workshop on Waldenstrom's Macroglobulinemia held this past August in London. This summary (and it's only Part I; Part II will follow in the January 2015 *Torch*) demonstrates that in major centers around the world research dedicated to WM is surging forward in a remarkable number of directions but with a unified aim: more effective and less invasive drugs and treatments, ultimately a cure.

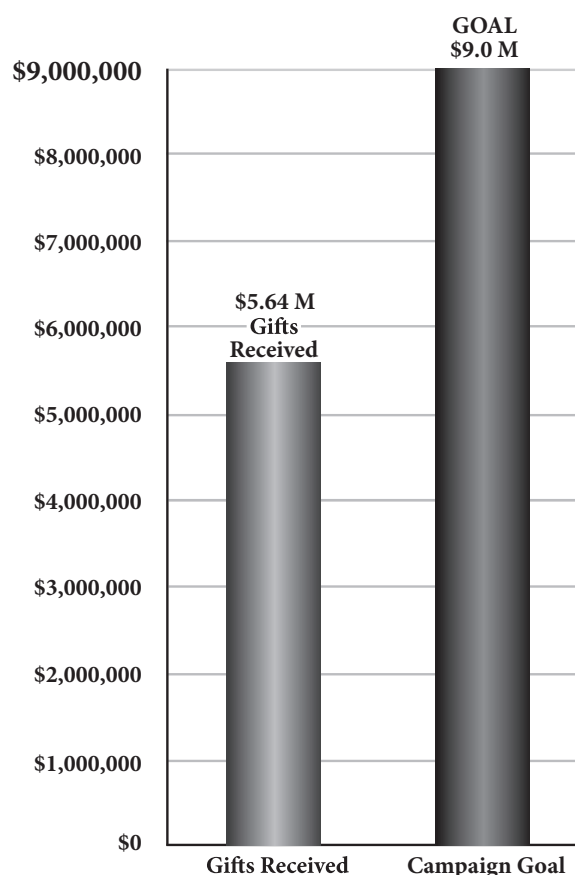
Guy's second article, Research Update (see the facing page), reports on the projects that the IWMF is funding through your contributions to the Research Fund. No less than seven research projects are well underway while two more have just been granted support.

Take a close look at the nine projects receiving your support. The IWMF is funding research in major centers and universities in the US, Canada, and now the United Kingdom, illustrating the impressive role that the IWMF is playing in the worldwide effort to conquer WM.

Think carefully about the words of your Vice President for Research in the final paragraph of Research Update. As Guy emphatically states, the important role played by the IWMF in the effort against WM is made possible only by your contributions to the Research Fund.

As a small foundation, we have accomplished much in our support of WM research. We can, however, do more if we increase the amount available for research through the Research Fund. The Research Committee has a backup of

### Imagine a Cure Campaign Progress Report as of August 31, 2014



*The total amount for Gifts Received includes all gifts to the Member Services and Research Funds, pledges made over a five year period, and planned legacy gifts.*

applications for a number of worthy projects for which there are insufficient funds at present.

Please consider the IWMF Research Fund when making your year-end contributions. Let's keep up the surge!



# FIFTH INTERNATIONAL IWMF DOCTOR-PATIENT FORUM LONDON 2014

BY ROGER BROWN, WMUK



*Guy Sherwood at the Doctor-Patient Forum. The bell was put into action to call participants back to the auditorium. Guy and Roger Brown were responsible for organizing this successful IWMF-WMUK event.*

Two hundred and twenty patients, doctors, and carers gathered in London in August for the largest ever WM Doctor Patient Forum outside the USA, co-hosted by the IWMF and WMUK.

Attendees from fourteen countries listened to the latest in treatment and research from doctors who had contributed to the IWWM8 meeting in the previous days. A world class speaker programme organised by Shirley D'Sa included Meletios Dimopoulos on upfront treatment, Stephen Ansell on relapse, Robert Kyle on

symptoms, Zachary Hunter on key genetic information about WM, Sandra Kanan on personal survival strategies, Michael Lunn on neuropathy, and Steven Treon with a masterly state of the art summary of the latest research presented at IWWM8. In addition to the main sessions, WMUK had its popular 'Ask the Doctor Lite' sessions – one to one 'speed dating' for doctors and patients in the breaks – and there were displays of forty Patient Tales from the UK and Europe, plus stands from WMUK, IWMF and other support organisations.

The IWMF had two presentations, one from IWMF President Carl Harrington stressing partnership collaboration and another by Guy Sherwood showcasing current and new grant funding of research projects, including the announcement of a grant towards the UK biobank (tissue bank) project at University College Hospital London.



*Roger Brown of WMUK and well-known BBC broadcaster Charlotte Green confer at the Doctor-Patient Forum. Charlotte is leading the WMUK campaign to fund a UK WM clinical data registry.*

During the day the campaign to fund a UK WM clinical data registry, led by WMUK patron, broadcaster Charlotte Green, met with great success, and Roger Brown was able to announce that the total was over £27,000, enough for doctors to start building the online registry immediately, and that fund raising had started to match the IWMF grant for the UK biobank.

If there was one clear overall message that delegates came away with, it was one of optimism and steady improvement in treatment results, tempered by the daunting potential cost of novel treatments, and, at least in the UK, the long time lags to bring them into general use.

The two disc Forum DVD with all presentations is available for purchase at [www.wmuk.org.uk](http://www.wmuk.org.uk), and there are still a few of the specially created WM mugs with a word cloud of the 212 most popular words associated with WM. There is also a more extensive gallery of photographs on the site.

WMUK will be running a doctor-patient forum in Birmingham on 11 April 2015, and details will be posted on the WMUK website.

## Assistance to Set Up WM Patient Groups in Europe

If your country in Europe does not have a WM patient support organization and you would like to start contacts between WM patients and/or carers, you can make use of the following web-site: [www.waldenstrom.info](http://www.waldenstrom.info)

A webpage is now available for each country in Europe. This country page can also be reached via [www.ewmnetwork.eu](http://www.ewmnetwork.eu)

Information relevant to your own country can be posted on the page in your language. Sharing such information may eventually lead to the formation of a WM patient support group which would be affiliated with the IWMF.

For more information: [webmaster@waldenstrom.info](mailto:webmaster@waldenstrom.info)

Marlies Oom  
Secretary EWMnetwork



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# MY WM STORY

BY JENNIFER HOEGERMAN

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*Jennifer Hoegerman's life is, by every measure, an active one filled with parental and professional commitments, volunteerism of a challenging sort, an enthusiasm for the outdoor life whether sailing, canoeing, or riding her beloved Arabian horses, and a love of nature. Jennifer is also a nineteen-year survivor of Waldenstrom's macroglobulinemia. A "younger WMer," Jennifer was diagnosed when her children were young and before the era of Rituxan, a time when the strategy of watch and wait was not an option so frequently followed as it is today. Jennifer's account of survivorship is not a report of one effective treatment that has held WM in abeyance for so long. Her account records how she faced the increasing challenges of WM as the years went by. It is also the account of how she successfully led her "real life" by combining modern medicine and alternative therapies down to the present when ibrutinib has provided new energy and enthusiasm. We may also appreciate the role played by the IWMF in Jennifer's story when she refers to information acquired from IWMF-Talk and the fifteen Ed Forums she has attended, including Tampa in 2014.*

I will never forget the emotions – mostly disbelief and fear – that arose when I arrived at the cancer center. The word *cancer* literally stopped me in my tracks at the door. I had not yet been diagnosed, but the feeling was surreal. My life, with all its various roles, flashed before me: wife, mother of five-year old Tiare and seven-year old Henry, nurse, volunteer firefighter, equestrienne – a life of so much goodness and fulfillment with so much yet to do.

An abnormally elevated erythrocyte sedimentation rate (ESR) led to my arrival at the cancer center; otherwise I'm sure it would have been years before I was diagnosed with Waldenstrom's macroglobulinemia as I had none of the symptoms commonly preceding this diagnosis. In 1994 my physician father-in-law ordered blood work for my husband and myself because he did not trust our vegetarian diet of twenty years' standing. The only abnormality found then was my high ESR, which simply indicates the presence of inflammation. I was told that my ESR probably reflected a minor viral process and that I should repeat the test in a month. A year passed before I retested, and the result then was an even higher ESR. This time I followed up with subsequent testing through the emergency department where I work as a registered nurse and through my regular doctor. Finally I was referred to a hematologist-oncologist for further workup (little did I know that this would include the dreaded bone marrow biopsy!).

When the diagnosis came back as Waldenstrom's macroglobulinemia, the treatment recommended was fludarabine. At that time a cautious period of watch and wait for an asymptomatic patient was not the recommended

approach and Rituxan was not yet available. Current prognosis was three to five years. Intuitively I felt I should not turn to immediate chemotherapy since I felt fine and had no symptoms. I made an agreement with my oncologist: to remain under close observation and report any changes.

One source of encouragement was my Australian shepherd, Belle, who had a type of autoimmune hemolytic anemia and was miserable on prednisone. One day her eyes said "No more." So we discontinued the drug and consulted a homeopathic nutritionist veterinarian. On his program Belle lived an additional and happy two and a half years. The day Belle died we took a walk on the beach and found a crosspiece of bone washed up in the surf. It displayed a cross section of marrow, and I snatched it up as a gift from either Belle or the sea. This talisman assumed a place in my meditation room, representing a healthy bone marrow ("the garden" as Dr. Gertz would describe it). To my regular activities of meditation, exercise, good nutrition, acupuncture, and horseback riding this imagery practice was also added.

All was well until the 2003 IWMF Educational Forum in Reston, Virginia. Neurologist Todd Levine was present to study WM patients with peripheral neuropathy. I volunteered for Dr. Levine's blood work and nerve conduction studies and, when my conduction study was repeated, I sensed something was amiss. I opened my eyes to find the entire group of researchers standing around me. One said, "Well, we're finished here, where is your wheelchair?" They had recorded no nerve conduction up my legs (to me, signifying that those numb toes I'd had for years actually meant something). Dr.

Levine and his group all seemed surprised when I walked away on my own power.

Following this experience at the Reston Ed Forum, it was clear that my watch and wait was over and that treatment was needed. At this turning point another "message from beyond" came while riding Maple, my Arabian mare. We were alone on the trail, and I said to her, "Maple, you can be my legs if I can't walk one day." She came to an abrupt halt and – I'm not



*Jennifer with Rosie,  
her magnificent Arabian.*

imagining this – somehow communicated that she would *not* be my wheelchair, that I needed to do whatever was necessary to preserve my mobility.

*My WM Story, cont. on page 16*



My first treatment was Rituxan, twenty-six infusions over the next five years, mostly solo, plus a six-month course of dexamethasone and chlorambucil. The Rituxan was rough – fevers, rigors, aches, and low blood pressure – and twenty-four hour stays in the hospital for slow infusions. With the passage of these five years Rituxan seemed at best to keep my IgM stable at around 1900 and my red blood counts just below normal. In the meantime I saw several WM experts in consultation, including Dr. Steven Treon at the Dana-Farber Cancer Institute, Dr. Ranjana Advani at Stanford University, and Dr. Levine in private practice in Phoenix.

By the spring of 2011 my test values were deteriorating month by month, and I was feeling the fatigue and “ill-being” associated with active WM. The recommendation from a second consult at Stanford didn’t seem right: “You’re working, you’re walking – no treatment needed now,” I was told. Shortly thereafter I attended the 2011 Ed Forum where bendamustine was all the talk. I took notes and more notes and questioned Dr. Stephanie Gregory regarding her reservations about this drug. A month later as I was doing dishes one evening I started to see a cloud of white moths and grabbed at them, while my husband claimed to see nothing. The next day at work in the ER I suddenly began to see spiders; this episode resulted in a same-day visit to a retinal specialist who confirmed sausaging and hemorrhaging of the retina. Within a week I began the first round of bendamustine. Four cycles reduced IgM from over 4,000 to my “normal” range in the 1900’s. This therapy was repeated in 2012, and by 2013 more treatment was again indicated. I expected more bendamustine, but this time Michael Lutrell came to the rescue with a posting on IWWMF-Talk regarding a clinical trial of ibrutinib at Stanford. Once again the stars lined up and I was selected as a participant.

I’ve now been a year on ibrutinib and am still amazed that within the first few weeks of taking it my life changed dramatically. I was transformed from feeling like a wilted plant into an energized and extremely active whirlwind! In fact, my husband began to dread coming home to our five acres after work when he faced the piles of trimming and yard work debris that needed to be loaded onto the tractor – all projects I’d not had the energy to tackle for years.

We WMers usually introduce ourselves to one another stating date of diagnosis, treatments received, and IgM level, but that is not all there is to say about any one of us. Do not think that the last nineteen years have solely involved treatments and preoccupation with WM. The initial nine years were spent in watch and wait, then ongoing Rituxan treatments for five years, and finally the past five years of bendamustine and now ibrutinib. All the while my life has been filled with joy and has unfolded quite normally. When I was diagnosed, our children attended a Waldorf school that required much parental participation. Because of their very young ages they seemed to incorporate Waldenstrom’s as a fact of our lives. It was probably far more upsetting to them to hear fire



*Jennifer and Robin Hoegerman hit the trail in Costa Rica.*

department calls and ER stories recounted at the dinner table! We remained active as a family – visiting Hawaii nearly every year, camping, canoeing, canoe-camping, and my husband and I trail riding on the horses. I even had to stand by as husband and both kids became dirt bike racers. I’ve been able to attend many nurturing meditation retreats, one lasting seven weeks. The last few summers have included two weeks spent camping on an isolated and deserted Baja beach with my childhood friend, our families, and our dogs, carrying in all our food and water. During plasmapheresis as recommended by Dr. Treon I elected to have a huge catheter placed in my chest so as to be able to actively trail ride. I continue nursing, the last twenty-nine years spent in the emergency department of a regional trauma center. We’ve buried two horses and currently have four more. Two years ago I took a fall off the younger Arab and had a total hip replacement (thankfully before starting ibrutinib with its associated platelet problems). Even setting out for the most recent Ed Forum in May was an adventure, as we came by way of three weeks in Costa Rica and two in Puerto Rico before reaching Tampa for the conference.



*Jennifer and husband Robin on the coast of Costa Rica, May 2014  
Next stop: Tampa and the IWWMF Ed Forum!*



The road since diagnosis has truly been a journey. I wonder if I'd feel so rich in soul if I hadn't travelled this route. It's been both interesting and challenging, but ultimately very rewarding. Dr. Marek Bozdech has been a wonderful oncologist and partner in the process, so willing to confer with Dr. Treon and Dr. Advani. Being a patient myself has made me a much better nurse in the face of my own patients' discomfort and pain. I'm thankful for the Tibetan Buddhist lamas whose message concerns suffering, impermanence, and compassion. They've shown me that suffering is experienced when resisting one's present situation or wishing

it was different. Some say if you're going to have cancer, a slow-growing lymphoma is the best diagnosis to receive. The silver lining in all this seems to be having the time and opportunity to reflect, to look at one's life and decide what is really important. Through attending the last fifteen Ed Forums I've realized that we WMers are not alone as we walk this path. Together we travel from feeling bewilderment and disbelief toward knowledge and confidence, and hopefully we come to discover both numerous blessings and a profound sense of gratitude.

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## MEDICAL NEWS ROUNDUP

BY SUE HERMS, IWWMF TRUSTEE

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**Phase III Trial Opens for Ibrutinib and Rituximab in Previously Treated WM Patients** – A randomized Phase III trial for ibrutinib (Imbruvica) and rituximab is opening for previously treated WM patients. This trial will have three arms: arm A will consist of combination ibrutinib and rituximab, arm B will consist of combination placebo and rituximab, and arm C will consist of ibrutinib only. The estimated enrollment will be 180 patients, and the trial is registered as NCT02165397 on the *clinicaltrials.gov* website.

**Phase II Results Reported for Ibrutinib and Rituximab in CLL** – Meanwhile, the journal *Lancet Oncology* reported results for a Phase II trial of ibrutinib (Imbruvica) plus rituximab for 40 high-risk chronic lymphocytic leukemia patients at the MD Anderson Cancer Center. Patients received 28-day cycles of once-daily ibrutinib at 420 mg, together with rituximab every week during cycle 1 and then once per cycle until cycle 6. Following cycle 6, dosing consisted only of continuous daily ibrutinib until disease progression or until toxicities precluded further treatment. The primary endpoint was progression-free survival (PFS), and 78% of patients achieved 18-month PFS. Toxicity was mild to moderate, primarily including diarrhea, bleeding events, nausea or vomiting, fatigue, and infections.

**Phase II Trial for Oral Proteasome Inhibitor Is Enrolling Relapsed MM and WM Patients** – A Phase II clinical trial for the use of oprozomib (ONX 0912) in relapsed multiple myeloma (MM) and WM plans to enroll 66 patients in the WM arm of the study. Oprozomib is an oral second generation proteasome inhibitor, in the same class as bortezomib (Velcade). This study is currently enrolling only in the 2/7 schedule where patients take oprozomib 2 days in a row every week until disease progression or unacceptable toxicity. This trial is registered as NCT01416428 on the *clinicaltrials.gov* website.

**New BTK Inhibitor Begins Phase Ib Study for Relapsed/Refractory WM** – Acerta Pharma BV has opened a Phase Ib study of ACP 196 for relapsed/refractory WM patients. ACP 196 is another BTK inhibitor in the same class as

ibrutinib (Imbruvica). The clinical trial identifier on the *clinicaltrials.gov* website is NCT02180724. The estimated enrollment is 32 patients.

**Study from India Correlates MYD88 Status with Treatment Response and Prognosis in WM** – A study from Tata Memorial Hospital in Mumbai, India, analyzed 32 cases of lymphoplasmacytic lymphoma/WM over 7 years for the presence of the MYD88 L265P mutation and its correlation with the International Prognostic Scoring System for WM (IPSSWM) and with treatment response. This study found that 27 of the 32 cases (84.3%) harbored the mutation. WM patients with unmutated MYD88 presented with a lower number of tumor cells, older age, and a lower IPSSWM score compared to patients with the mutation. On evaluation of treatment response in 23 of the patients, 44.4% of mutated MYD88 had progressive disease whereas no patient in the unmutated group had changed baseline status.

**Study Looks at Risk Factors for LPL/WM** – The InterLymph Non-Hodgkin's Lymphoma Subtypes Project analyzed medical history, lifestyle, family history and occupational risk factors for lymphoplasmacytic lymphoma (LPL)/WM. InterLymph is the International Lymphoma Epidemiology Consortium, which pooled data from 11 population-based studies from North America, Europe, and Australia for a total of 374 LPL/WM cases and 23,096 controls. In this study, LPL/WM risk was associated with a history of Sjögren's syndrome, systemic lupus erythematosus, hay fever, positive hepatitis C serology, hematologic malignancy in a first-degree relative, adult weight, duration of cigarette smoking, and occupation as a medical doctor. This analysis confirmed associations with immune conditions and a family history of hematologic malignancy and identified new associations.

**New Analysis by DFCI Looks at Survival Trends in WM** – Dana-Farber Cancer Institute looked at survival trends in WM by analyzing the U.S. Surveillance, Epidemiology and End Results (SEER) database in a letter that appeared in the

*Medical News Roundup, cont. on page 18*



journal *Blood*. The study's objective was to investigate trends in survival rates of WM patients and included those diagnosed between 1980 and 2010 but excluded patients younger than 20, patients in whom WM was not the first malignancy, and patients diagnosed by autopsy. The resulting cohort was composed of 6,231 WM patients. Relative survival was the endpoint of interest. Patients diagnosed during 2001-2010 had a higher 5-year survival rate (78% vs. 67%) and 10-year survival rate (66% vs. 49%) than patients diagnosed during 1980-2000.

**MYD88 Mutation May Aid in the Diagnosis of Extramedullary LPL/WM** – The presence of the MYD88 L265P mutation in extramedullary (outside the bone marrow) tissues may be an aid to the diagnosis of LPL/WM. Typically, the differential diagnosis of lymphoplasmacytic lymphoma (LPL)/WM in these tissues can be challenging and must be distinguished from other small B-cell cancers with plasmacytic differentiation, including nodal marginal zone lymphoma, splenic marginal zone lymphoma, and chronic lymphocytic leukemia/small lymphocytic lymphoma. This joint study, reported by the Cleveland Clinic, the University of Virginia, and the University of Pittsburgh, performed a morphologic review of 87 previously diagnosed cases and evaluated them for the presence of the mutation. Almost all cases associated with the mutation were consistent with LPL/WM rather than with other types of small B-cell cancers, suggesting that the presence of the mutation may assist in establishing the diagnosis of LPL/WM in extramedullary tissues.

**Presence of MYD88 Mutation May Be Useful in Diagnosing Bing Neel Syndrome** – A French study published in the *British Journal of Haematology* suggests that the presence of the MYD88 L265P mutation in cerebrospinal fluid may be useful in diagnosing Bing Neel syndrome (BNS), which is a rare neurological complication associated with WM. BNS is a direct involvement of the central nervous system by the lymphoplasmacytic cells of WM, and its diagnosis can be challenging because of the variety of clinical presentations associated with difficult histological techniques. In all cases of BNS studied by these researchers, the mutation was identified by quantitative PCR (polymerase chain reaction) and Sanger gene sequencing. No mutations of CXCR4, CD79A and CD79B were identified. The researchers suggest that not only could identification of the mutation be a useful diagnostic tool for BNS, but also that monitoring the quantitative expression of the mutation following chemotherapy could be a useful way to monitor treatment response.

**CaRD Therapy Evaluated in Phase II Trial of Symptomatic WM Patients** – The Bing Center at Dana-Farber Cancer Institute evaluated the use of carfilzomib in combination with rituximab and dexamethasone (CaRD therapy) in symptomatic WM patients who had not previously used bortezomib and rituximab. This Phase II study resulted in an overall response rate of 87.1%, and responses were not impacted by MYD88 or CXCR4 mutational status. Toxicities included reversible neutropenia (reduced neutrophils), asymptomatic increases

in the pancreatic enzyme lipase, and cardiomyopathy (heart muscle disease) in one patient with multiple risk factors. Carfilzomib is a neuropathy-sparing proteasome inhibitor in the same class as bortezomib (Velcade).

**Phase III Trial Evaluates Ibrutinib vs. Ofatumumab in CLL** – A multicenter Phase III study evaluated the efficacy of ibrutinib (Imbruvica) vs. ofatumumab (Arzerra) in 391 previously treated chronic lymphocytic leukemia patients. At a median follow-up of 9.4 months, ibrutinib significantly improved progression-free survival. At 12 months follow-up, the overall survival rate was 90% in the ibrutinib arm vs. 81% in the ofatumumab arm. The most frequent non-hematologic adverse events were diarrhea, fatigue, fever, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. This trial was reported in the *New England Journal of Medicine*.

**ABT-199 Studied in Several Trials for CLL** – Updated results were released on the investigational BCL-2 inhibitor ABT-199 in a Phase I clinical trial of relapsed or refractory chronic lymphocytic leukemia (CLL). The overall response rate was 77%, with 23% of patients achieving complete response. Complications from tumor-lysis syndrome had temporarily halted this and other ABT-199 trials, but use of a modified dosing scheme and aggressive prophylaxis for tumor lysis syndrome appeared to have reduced this risk. A 400 mg once-daily dose has been identified for Phase II dosing. The most common adverse events were diarrhea, neutropenia, and nausea. Another Phase Ib trial with combination ABT-199 and rituximab for relapsed or refractory CLL reported an overall response rate of 84%, including 36% complete responses. Studies with combinations of ABT-199 and other therapies such as bendamustine, obinutuzumab (Gazyva), and ibrutinib (Imbruvica) are being evaluated or contemplated.

**TG Therapeutics Releases Preliminary Results for Novel Combination Therapy for CLL and NHL** – TG Therapeutics, Inc., announced preliminary results from its ongoing Phase I study of TG-1101 (ublrituximab) in combination with TGR-1202 in patients with advanced chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma (NHL). TG-1101 is an engineered anti-CD20 monoclonal antibody, and TGR-1202 is an oral PI3K delta inhibitor. The combination was well tolerated in the 21 evaluable patients, with infusion reactions on day 1 being the most frequently reported adverse event. Other adverse events included neutropenia, nausea, and diarrhea. Only a few patients were evaluable for effectiveness this early in the study: 4 of 5 CLL patients achieved a partial response and 1 had stable disease; of 10 heavily pre-treated NHL patients, 9 of 10 achieved stable disease or better.

**TG Therapeutics Begins Phase I Trial with Triple Combination Treatment for B-Cell Malignancies** – TG Therapeutics, Inc., also announced that it is beginning a triple treatment study combining TG-1101, TGR-1202, and



ibrutinib (Imbruvica) in patients with chronic lymphocytic leukemia and other B-cell malignancies. The trial is being led by MD Anderson Cancer Center and the University of Nebraska and will be run as a Phase I study with fixed doses of TG-1101 and ibrutinib and dose escalation of TGR-1202.

**Idelalisib (Zydelig) Approved by FDA as Relapse Therapy for Several B-Cell Malignancies** – The U.S. Food and Drug Administration has approved idelalisib (Zydelig) in combination with rituximab to treat patients with relapsed chronic lymphocytic leukemia. It has also approved Zydelig for relapsed follicular lymphoma and relapsed small lymphocytic lymphoma in patients who have received at least two prior therapies. Zydelig carries a Boxed Warning alerting patients and healthcare professionals of liver toxicity, diarrhea and colitis, lung inflammation, and intestinal perforation. Common side effects include diarrhea, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash.

**FDA Approves Obinutuzumab (Gazyva) in Combination with Chlorambucil for CLL** – The U.S. Food and Drug Administration has approved obinutuzumab (Gazyva) in combination with chlorambucil for the treatment of previously untreated chronic lymphocytic leukemia patients. The most common adverse reactions reported

were infusion reactions, neutropenia (reduced neutrophils), thrombocytopenia (reduced platelets), anemia, fever, cough, and musculoskeletal disorders.

**Study Looks at Maintenance vs. Retreatment Rituximab in Follicular Lymphoma** – The Eastern Cooperative Oncology Group reported study results for a comparison of maintenance rituximab vs. retreatment rituximab in 289 follicular lymphoma patients with low tumor burden. Treatment initially consisted of four doses of rituximab, with responding patients randomly assigned to either retreatment as needed or to maintenance dosing once every three months until treatment failure. With a median follow-up of 4.5 years, there was no significant difference between the groups in time-to-treatment failure or in health-related quality of life. The authors concluded that the retreatment strategy uses less rituximab while providing disease control comparable to that achieved with maintenance.

*The author gratefully acknowledges the efforts of Peter DeNardis, Charles Schafer, John Paasch, Wanda Huskins, and others in disseminating news of interest to the IWMF-Talk community. The author can be contacted at [suenchas@bellsouth.net](mailto:suenchas@bellsouth.net) for questions or additional information.*

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## HOWARD'S LIST FOR CAREGIVERS

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Recently on IWMF-Talk a pertinent question was posed for the caregivers among us by long-time list participant Howard Prestwich, a practicing attorney, who for fourteen years has taken the responsibility for care of his wife, a WM patient.

“What,” asked Howard, “do you have in your grab bag? In that bag, package, pak, kit, or bundle containing those things you might need for a medical emergency or when traveling with the WM person you care for?”

It's a good question, and Howard provided a thoughtful answer as well. Here is Howard's List of items he has stored in his bag and at hand if an emergency arises.

A copy of insurance cards with names, numbers, etc.

A spreadsheet of blood test results with dates on the left up and down axis, most recent date on top.

Copies of most recent blood work.

Names, addresses, phones, e-mails, and faxes of the doctors and medical facilities involved in previous care.

Same as above for family and friends. You might include names from the WM family of those who could be called for help.

A phone, or a credit or calling card so you can use a public phone.

A list of current medications including dosages.

Also a list of drugs the patient might have had bad reactions from.

Several recent medical articles on WM in case the medical personnel are unaware of the condition or what the treatment options are. You might include some from the IWMF as they are very good.

A copy of IWMF-Talk passwords and logons so you can ask the talk list for help from a strange Internet logon.

Make sure you can access your e-mail from a strange location.

Copy of medical power of attorney with a HIPPA compliant medical release.

Howard's final word: “For some of these I have multiple copies. It is a good idea to store them in the iCloud.”

It would certainly be difficult to grab all these lists and printouts while heading out the door in response to an emergency. Thanks, Howard, for your valuable suggestions.

And, really, the wisdom of advance preparation for an emergency should be evident to all of us – patients and caregivers alike.



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# FROM IWmf-TALK

BY JACOB WEINTRAUB, MD

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Despite summer vacations and other outdoor activities, the discussions and postings on IWmf-Talk continue unabated. There were several reviews of the Educational Forum in Tampa, articles about old and new treatments, and discussions about clinical issues, second opinions, and lab testing. Ibrutinib/Imbruvica continues to be a frequent topic, with many people in treatment who are reporting their progress and others just starting treatment who are asking about results, side effects, and cost.

## HUMAN INTEREST ITEMS

Summaries of major medical news and research appear in the Medical News Roundup column in each *Torch* issue. Many posts on IWmf-Talk also include links to news releases and medical articles. However, there are frequently posts and links to items of human interest. These include patient experiences with cancer, the role of caretaker to cancer patients, fundraising events, and movies and TV shows about cancer patients.

**IWmf-Talk Manager and IWmf Trustee Peter (Pete) DeNardis** posted several of these latter items. One was about a US TV show called “Chasing Life.” This show has a main character who was recently diagnosed with cancer and is struggling to adjust. Pete included quotes from some scenes and compared several of the main characters to IWmf “veterans” he has encountered – caring people willing to help and offer advice. Video clips of “Chasing Life” can be viewed at [www.youtube.com/watch?v=v2-PhwXTkfY](http://www.youtube.com/watch?v=v2-PhwXTkfY)

Pete shared an article entitled “Our unrealistic views of death, through a doctor’s eyes.” This was in the *Washington Post* and describes how many members of the public overestimate modern medicine’s power to prolong life, a misconception fueled by the dramatic increase in the American life span over the last century. To see this article, go to [www.washingtonpost.com/opinions/our-unrealistic-views-of-death-through-a-doctors-eyes/2012/01/31/gIQAeaHpJR\\_story.html](http://www.washingtonpost.com/opinions/our-unrealistic-views-of-death-through-a-doctors-eyes/2012/01/31/gIQAeaHpJR_story.html)

An additional link was to an article in *U.S. News & World Report* entitled “10 Lessons from Empowered Patients.” Pete mentioned that many of us already practice the items being discussed in these lessons but still felt it worth sharing. The lessons come from 10 patients with different medical conditions, not all of them cancer. One patient was Trisha

Torrey, a patient advocate and the author of “Every Patient’s Advocate.” Several other patients in this article write blogs or are active on online information sites. This article can be found at [news.yahoo.com/10-lessons-empowered-patients-210141274.html](http://news.yahoo.com/10-lessons-empowered-patients-210141274.html)

**Wanda H** posted an article that likens the child in us to how we cope with our cancer. If a child spends its early years in a stable and loving environment, he or she will have the inner strength to cope with tragedy, disease, and eventually death. The article was by James Salwitz, MD. He describes the range of adjustments that patients make to chronic illnesses, including understanding, denial, and laughter. Many use other modalities to help them cope, such as family support, art, discovery, and dreams. His conclusion is that if an early supportive environment for children is the best way to help them cope with the extremes of life, we should give them a smile, hug and kiss, when they are pure, frail and very young. This blog appears at [sunriserounds.com/ coping-childs-eye/](http://sunriserounds.com/ coping-childs-eye/)

**Cynthia N** posted a link to an article about fasting before chemotherapy. Reported at the University of Southern California, this article covered a study during which cycles of “prolonged fasting” not only protected against immune system damage but also induced immune system regeneration, shifting stem cells from a dormant state to a state of self-renewal. This prompted some discussion about whether anyone on IWmf-Talk had tried this before a chemo cycle, and no one had. This very thought-provoking report can be found at <http://news.usc.edu/63669/fasting-triggers-stem-cell-regeneration-of-damaged-old-immune-system/>.

**Wanda H** also posted a link to an online journal article entitled “Living with Cancer: Parting Gifts.” This was written by Susan Gubar and is about cancer support groups and the types of relationships that can be formed. There is an exceptional story about one close relationship between the author and a woman at the end of her life. This article appears at [well.blogs.nytimes.com/2014/07/10/living-with-cancer-parting-gifts/?\\_php=true&\\_type=blogs&\\_r=0](http://well.blogs.nytimes.com/2014/07/10/living-with-cancer-parting-gifts/?_php=true&_type=blogs&_r=0) Susan Gubar also has written the book *Memoir of a DeBulked Woman* about her own experience with ovarian cancer. **Tina** posted that she is currently reading this book and recommended it to anyone who enjoys a thoughtful,

*From IWmf-Talk, cont. on page 21*

## HOW TO JOIN IWmf-TALK

Here are two ways to join:

1. Send a blank e-mail to: [iwmf-talk-subscribe-request@lists.psu.edu](mailto:iwmf-talk-subscribe-request@lists.psu.edu)

Make sure to enter the word “subscribe” as your subject, and do not sign or put anything in the message area (make sure you do not have any signature information in there). Also, do not put a “period” after “edu” or it will reject. Once approved you can post by sending e-mail to [iwmf-talk@lists.psu.edu](mailto:iwmf-talk@lists.psu.edu)

2. Contact Peter DeNardis at [pdenardis@comcast.net](mailto:pdenardis@comcast.net) and provide your full name



passionate mind “expressing herself with compassion and literary deliciousness.”

## FATIGUE

Fatigue is a common area of discussion on IWmf-Talk. Many of us report fatigue in varying degrees and circumstances.

**Christopher C** suggested there are possibly as many reasons for fatigue as there are people with WM. He feels the body is dealing with treatment even after its cessation. There is also the disease burden that we all deal with, not to mention the psychological factors that are inherent in coping with an illness such as WM, a chronic condition that can be treated but almost never cured. However, he also suggested that we all make sure there isn't some other underlying condition affecting our energy level.

**Ken C** recommended maintaining a regimen of light exercise. He participates in a supervised program at his local cancer center that helps participants not to overdo it.

Several people reported various degrees of improvement in their fatigue levels after treatment. However, some people reported return of fatigue at some time following the improvement.

There also was some discussion about use of stimulant medications to combat fatigue. **Pat G** reported having received a prescription from her doctor, but she will take only small doses to minimize other side effects.

## FLU VACCINE

As we approach flu season, there was the recurring annual discussion about whether we should receive the flu vaccine.

**Linda H** reported that she received the new “high dose” flu vaccine last year during her treatment. She was told that the vaccine is less effective during treatment but still better than nothing. She did not report any significant adverse reaction to the higher dose shot.

**Dr. Jacob Weintraub** strongly advised everyone to obtain the flu shot, which is a killed virus vaccine. The nasal spray Flu Mist is live attenuated virus and is contraindicated in people with a compromised immune system, such as WM patients. Almost all the flu shots this year will be tetravalent, which is supposed to be better than the trivalent vaccine used previously. He also noted that there is no consensus about the new “high dose” vaccine. There have not yet been any studies about increased efficacy or increased occurrence of side effects.

## INSECT BITES

Through the summer, there was discussion about the various reactions to insect bites experienced by a number of us.

**Lowell G** reported that, although his WM is under control with no treatments for over 14 months, he was having multiple intense swollen prolonged reactions after insect bites. He had heard that patients with chronic lymphocytic leukemia may have exaggerated reactions to insect bites but questioned if others with WM have had the same reactions.

**Gerri M** added that mosquitoes never bothered her until she was diagnosed with WM. Now she seems to be attractive to them, her bites become angry red and swollen and stay like that for days. She is trying some commercially available mosquito traps to see if they will help reduce the mosquito population.

**Dr. Guy Sherwood** agreed with Gerri about the intensity of his reaction to mosquito bites. He gets welts, itching, and fluid-filled blisters. One of his oncologists told him that this is typical for lymphoma patients. Apparently this question was raised at an Educational Forum “Ask the Doctor” session, but the discussion was very limited.

**Dr. Tom Hoffmann** suggested that Schnitzler's syndrome is an IgM-mediated disease sometimes seen in WM. He thought that perhaps a subclinical type of Schnitzler's could be a part of the bug bite “mystery.”

## SIDE EFFECTS

There are ongoing reports of side effects and potential side effects from various treatments.

**Carl G** asked for input about low blood pressure with bendamustine treatment. He had just completed his second cycle of bendamustine. He also received Decadron and Zofran. Two days after treatment he felt a bit tired and noticed a significant lowering of his blood pressure, about 20 mm Hg below normal.

**Lou B** also reported being treated with bendamustine plus Rituxan, followed the next day by a significant drop in his blood pressure and a trip to the local emergency room. He was found to be dehydrated, was admitted to the hospital, and received IV fluids for rehydration. Subsequent courses of treatment have not resulted in similar events.

After others reported lower blood pressures, **Dr. Tom Hoffmann** posted the possibility of other significant medical conditions that could result in low blood pressure. Autonomic dysfunction, orthostatic hypotension, or a rhythm disturbance could cause these symptoms. He recommended further medical workup to be sure there isn't another treatable medical condition involved.

Side effects from Velcade were also discussed. **Fay L** reported the neuropathy that others have experienced, but she also has bone pain and itching. She added that she has had a significant positive response to treatment.

**Sue P** also reported bone pain and neuropathy. She had GI side effects and overwhelming fatigue but also had a very significant positive response. Sue advised getting anti-nausea meds before treatment since this was a problem for her.

The discussions will continue on IWmf-Talk. With a multitude of topics presented and many levels of interest, medical knowledge and experience, there is always something to be learned from the general discussion or from personal requests for help, advice, and information. Everyone is welcome to join and participate.



# TREASURER'S REPORT AS OF AUGUST 31, 2014

BY CYNTHIA RUHL, IWMF TREASURER AND SECRETARY

The finances of the IWMF are accounted for through two separate funds. The Research Fund is used solely to fund research grants that the Research Committee has reviewed and recommended. The Member Services Fund provides for all of our membership services, including the Educational Forum, the website, and the *Torch*. Both funds are critically important to the work of the IWMF.

The following is a summary of the financial results for the first eight months of 2014. The amounts are rounded to the nearest thousand and have not yet been audited. However, I wanted to share with you where the IWMF stands financially for 2014 through August.

We hope you will continue to support the IWMF throughout the rest of the year. The Research Committee recommended two new grants, which were approved at the August Board of Trustees meeting. Member Services has a large expense this year, primarily because our website, *iwmf.com*, is in the process of being updated.

	Research	Member Services	Total
Revenue	\$ 301,000	\$ 345,000	\$ 646,000
Expenditures	\$ 374,000	\$ 479,000	\$ 853,000
Net Revenue	\$ -73,000	\$ -134,000	\$ -207,000

Cash reserves at the end of August 2014 for the Research Fund are \$701,768 and for the Member Services Fund \$163,024.

The financial audit for 2013 has been completed and posted on *iwmf.com*. As a Board member, I can assure you that the Board of Trustees does its very best to make sure that every dollar is wisely spent on serving you, our members, and keeping important research moving forward. Thank you for your continued support.

If you have any questions, please feel free to contact me: [csruhl@hrmcpas.com](mailto:csruhl@hrmcpas.com)

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**20th IWMF Educational Forum**  
**May 1-3, 2015**  
**Dallas, Texas**

The 2015 Ed Forum will be held at the  
Hilton DFW Lakes Executive Conference Center.

Look for details in the next *Torch*.

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