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DOCTOR ON CALL: STEVEN P. TREON, M.D., PH.D.



Steven P. Treon, M.D., Ph.D.

Dr. Steven Treon discusses the recent discovery of a mutation present in a large majority of WM patients in his research team's study and its future implications for the diagnosis and treatment of our disease. The IWMF is proud to have provided partial funding for this groundbreaking research.

A team of scientists led by Dr. Steven P. Treon from the Bing Center for Waldenstrom's Macroglobulinemia at the Dana-Farber Cancer Institute and Harvard Medical School announced the identification of a gene mutation that underlies most cases of Waldenstrom's macroglobulinemia. The research, which was presented at the 53rd Annual Meeting of the American Society of Hematology (ASH) on December 12, 2011, described a mutation, occurring in one single DNA molecule out of three billion DNA molecules which make up the genetic code of a cell, as the leading culprit in Waldenstrom's and a target for

new diagnostic tests and drug development for this disease.

The mutation was discovered after the team performed whole genome sequencing of tumor and normal cells from thirty patients with Waldenstrom's macroglobulinemia. By lining up and comparing the DNA sequences of tumor and normal cells, Treon and his colleagues were able to detect the same recurring mutation in the MYD88 gene, a finding present in ninety percent of patients with Waldenstrom's macroglobulinemia who were tested. In most patients the L265P mutation was found in one of the 2 copies of the MYD88 gene, but in some patients with a longstanding history of WM, a reduplication of the segment of chromosome 3 where MYD88 is located resulted in 2 copies of the L265P mutation being present. The clinical significance of having an extra copy of the mutation remains to be determined.

Importantly, Treon and colleagues showed that the mutation, which results in a change in the amino acid *leucine* for *proline* at position 265 in MYD88, helps keep the malignant Waldenstrom's cells alive by activating a signal pathway which leads to activation of NF- κ B, a protein essential for the growth and survival of Waldenstrom's cells. Using either genetically engineered viruses which knock down MYD88 or drugs which shut down the MYD88 signaling pathway, the Treon team was able to induce Waldenstrom's cells to undergo a form of programmed cell death called apoptosis. Treon and colleagues are currently working on development of agents which can be used in the clinic to shut down the MYD88 pathway. "We are fortunate that the MYD88 pathway has been under study for many years by scientists interested in rheumatology diseases. As such, we have a running start with many agents that have been developed to block the MYD88 pathway, and it will not be long before we have these agents in clinical trials for Waldenstrom's patients." Treon estimates that in the next 1-2 years the first clinical trial using agents blocking the MYD88 signaling pathway will become available.

How did whole genome sequencing lead to the discovery of MYD88 L265P mutation in WM patients?

Whole genome sequencing (WGS) is a powerful new technology that enables the reading of each of the 3 billion DNA molecules that make up the 23 paired chromosomes that are found in the nucleus of a human cell. This includes the DNA molecules that make up genes that code for proteins that regulate how a cell functions, as well as the DNA molecules that string together genes, which include regions that regulate how genes function.

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To perform whole genome sequencing, malignant cells (lymphoplasmacytic cells) in the bone marrows of patients with Waldenstrom's macroglobulinemia were isolated. DNA was then isolated from the purified WM lymphoplasmacytic cells and, by using enzymes, shredded into smaller fragments that were subjected to sequencing. The resulting small DNA sequence readouts were aligned with the aid of supercomputers to a "reference genome" made possible by the Human Genome Project. Since hundreds of thousands of differences in DNA molecules (polymorphisms) can exist from one person to another, the patient's own WM cell DNA readouts were compared against their own normal cells. This process, known as paired sequencing, used non-WM blood cells to supply "normal DNA" which was then aligned against "WM cell DNA." Paired analysis for 10 WM patients revealed that the MYD88 L265P mutation was present in all 10 patients. The same mutation was then found in unpaired WM cell DNA from 17 of 20 other WM patients who also underwent whole genome sequencing. The presence of MYD88 L265P was confirmed in all the positive patients using an alternative (Sanger) method of gene sequencing. In addition to the MYD88 L265P mutation, other mutations were also discovered in WM cells although the frequency for these mutations was much lower. Dr. Zachary Hunter from the Bing Center will be presenting the finding of other (non-MYD88 L265P) mutations in WM patients at the Annual Meeting of the American Society of Oncology (ASCO) in June 2012.

What is MYD88?

MYD88 is as an "adaptor" or linker protein which controls signaling through receptors found on the surface of immune cells, including Toll-like receptors and Interleukin-1 and Interleukin-18. Toll-like receptors are important for receiving signals from pathogens like bacteria or viruses, while Interleukin-1 and Interleukin-18 play roles in infections and inflammatory conditions. Following stimulation of these receptors, MYD88 becomes recruited to the activated receptor complex and then complexes with the proteins IRAK1 and IRAK4. The MYD88/IRAK protein complex then stimulates the MAPK and NF- κ B pathways, both of which are known to play important roles in the growth and survival of Waldenstrom's cells.

How does the L265P mutation in MYD88 function?

The L265P mutation, which is present in 90% of Waldenstrom's patients, causes a change in the amino acid leucine for proline. This change causes a shift in the three dimensional character of the MYD88 protein. The mutation is found in a region that is highly conserved in evolution, which means that all mammalian species carry this domain of MYD88 without much difference, implying that it is critical to the function of MYD88. Waldenstrom's cell lines that carry the MYD88 L265P show activation of proteins, including the IRAK proteins, which funnel down to two important pathways

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ASH 2011 HIGHLIGHTS

BY SUE HERMS, ASSOCIATE EDITOR

The 53rd Annual Meeting of the American Society of Hematology (ASH) was held on December 10-13, 2011, in San Diego, California. The ASH meeting attracts hundreds of clinicians and researchers, representatives from pharmaceutical companies and medical technology industries, and members of patient advocacy groups. The IWMF information booth was staffed by Sara McKinnie from our office and volunteer Laurie Rude-Betts. As many of you are well aware, Laurie, whose late husband, Ben Rude, was the second president of the IWMF, continues to be very interested and involved in the work of the IWMF. The IWMF was also represented by Dr. Robert Kyle, IWMF Trustee and Chair of our Scientific Advisory Committee (SAC), and by our current President, Judith May, who attended our SAC annual meeting, traditionally held during the ASH conference.

Sara and Laurie both reported that of the 220 visitors to the IWMF booth, most were at least somewhat knowledgeable about WM or had a WM patient, in contrast to previous years when the majority of visitors who took our literature were not necessarily familiar with WM but were interested to learn about it. Sara also said that several researchers picked up research grant applications and that some international attendees offered to translate our booklets into other languages. Sara speculated that the Internet has raised awareness of WM, as have our partnerships with the National Organization for Rare Disorders, the Lymphoma Coalition, the Leukemia & Lymphoma Society, the Lymphoma Research Foundation, and Myeloma Euronet.

A number of poster and oral presentations at ASH focused on WM. To make it easier to organize and read this very technical literature, I have grouped summaries of the presentations into several broad topics.

WM BIOLOGY

A great deal of “buzz” was generated about several related discoveries presented by Dr. Steven Treon’s group from Dana-Farber Cancer Institute. These discoveries resulted from whole genome sequencing of WM patients, the first time that this has been performed on our patient population. See also Dr. Treon’s Doctor on Call article which begins on page 1 of this issue.

Whole genome sequencing (WGS) is a laboratory process that determines the complete chromosomal DNA sequence of an organism and searches for all genetic alterations in DNA that can affect susceptibility to cancer and other diseases. Heretofore, WGS has been a costly process but is now poised to become an affordable tool for understanding the basic biology of many diseases. Because the amount of data produced can be quite large, genomic data is stored electronically and requires a large amount of computing

power. Whole genome sequencing would have been nearly impossible before the advent of modern computers and other advances in information technology.

Abstracts arising from this whole genome sequencing study are briefly summarized in the following paragraphs:

Hunter et al. from Treon’s group isolated tumor cells from the bone marrow of 30 WM patients for WGS sequencing; for 10 of these patients, sequencing of both tumor and matched normal samples was performed in an effort to determine where significant genetic differences may have occurred between the tumor and normal cells. The most frequent genetic variant occurred in chromosome 3p in the MYD88 (myeloid differentiation primary response) gene, resulting in a change at amino acid position 265 from leucine to proline in 86.7% of WM patients. The variant gene is called MYD88 L265P. Other variant genes and their percentages in WM patients were identified as TAP2 23%, CXCR4 20%, LRP1B 17%, MSLN 13%, ARID1A 10%, HIST1H1E 10%, and RAPGEF3 10%.

Another abstract by Treon et al. reported that the MYD88 L265P variant is found in two WM cell lines (BCWM.1 and MWCL-1) used in pre-clinical research to study WM. In contrast, this variant was not detected in sequencing of 8 multiple myeloma patients, in 12 healthy individuals, or in 7 of 8 patients with IgM-MGUS. In the sole IgM-MGUS patient in whom the variant was detected, subsequent evolution to WM occurred. Further studies suggested that the MYD88 L265P variant enhanced survival of the WM cell lines, and knockdown of MYD88 expression led to loss of NF-kappa B signaling and apoptosis (cell death) of these cells.

[note: ‘knockdown’ refers to manipulated suppression of gene expression]

Cao et al. from Treon’s group also sought to determine whether the MYD88 L265P variant induces microRNA dysregulation in WM patients. MicroRNAs are small RNA fragments that can regulate or silence the expression of certain genes, and several microRNAs have been implicated in the pathogenesis of WM. This study performed microRNA profiling and real-time PCR testing of tumor cells in WM patients, compared them to total B-cells and to memory B-cells from healthy donors, and determined that microRNA-21 and microRNA-155 were significantly more highly expressed in WM tumor cells than in normal memory B-cells. Levels of both microRNAs decreased following knockdown of MYD88 expression in WM cell lines, whereas over-expression of MYD88 L265P led to enhanced microRNA-21 expression.

Yang et al. of Treon’s group delineated the signaling pathways involved with the MYD88 L265P variant and their possible

ASH 2011 Highlights, cont. on page 22



PRESIDENT'S CORNER



Judith May, President

It is with great sadness that I begin my report with mention of the death of Jim Bunton. Jim was the IWMF Treasurer and Vice President for Administration from 2000 to 2009, and during this time he worked steadily to expand the services and develop the infrastructure of the Foundation. With Jim's death we truly suffer the loss of one of the IWMF's foremost supporters. A remembrance is on page 5.

With the coming of spring the IWMF Board has been doing some spring cleaning by reviewing all our activities as a Board and as a Foundation, with an eye toward updating and revising where needed to enhance our efficiency and effectiveness. Much of this work to date involves a close review of the Board's structure and our internal policies. Future reviews will cover the information and services we provide you, including the manner in which they are provided. We seek ways to add value to our services without adding cost, and we are looking to identify the services that, with some adjustment, could cost less, thereby releasing funds to enhance other services. We will seek your input in the near future to help decide such issues. IWMF Board members continue to work

long and hard in committees, in teams, and individually to improve the benefits the Foundation provides for you, our members.

Speaking of hard work, I want to once again bring to your attention our need for more good people to work with us. Most urgently and importantly, we need to fill the position of IWMF Treasurer, vacant for the past year. A more detailed announcement of this position and required qualifications follows below. Those who wish to be considered and who meet the qualifications should e-mail me with resumé attached.

The Board of Trustees also needs the services of an attorney for advice on numerous issues, including copyright laws, privacy laws, and other questions that range from liability insurance to issues regarding an employee handbook. This position could be filled by an incoming member of the Board or by a volunteer reporting to the Board. If you are qualified and interested in an active role with the IWMF Board, please e-mail me with resumé attached at: judithamay@comcast.net.

I am happy to announce that we have a new member on the Board of Trustees. Elena Malunis of New York brings to the Board many essential talents and skills. Elena is a retired IBM executive; for over thirty years she held a number of positions in marketing and management. She also has past experience with not-for-profit boards and community committees. We are very lucky to have Elena join us. You will meet her in person at the Ed Forum.

Speaking of the Ed Forum: don't forget to register and reserve your room for the upcoming IWMF Educational Forum to be held June 1-3 at the Philadelphia Airport Marriott. An easy walk from your arrival gate brings you into this charming hotel. Don't miss this opportunity to hear about Waldenstrom's macroglobulinemia from eleven top physicians and researchers. You will also meet other patients from around the nation who are interested in sharing their journey with you and hearing about yours. I hope to see you there.

Stay well,
Judith

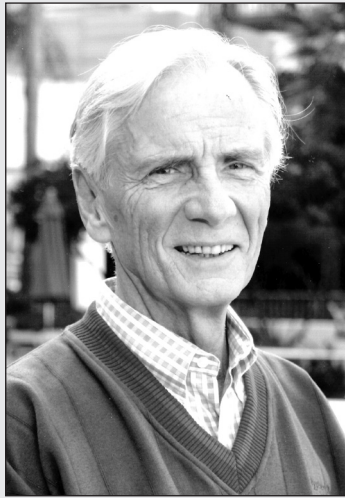
POSITION OF IWMF TREASURER

The IWMF seeks to fill the position of Treasurer on the IWMF Board of Trustees. The Treasurer serves as the financial officer responsible for the management and disbursement of funds. Among the Treasurer's duties are:

- assist in the preparation and monitoring of the budget
- prepare financial statements for Board review
- advise the Board with regard to significant budget variances
- ensure that the Board's financial policies are followed
- oversee the financial aspects of Board decisions
- maintain oversight of all bank accounts and financial transactions
- review the annual audit

Qualified candidates should have an undergraduate degree in business, economics, or finance and have experience in budgeting and financial reporting. A chartered or certified accountant is preferred. If you have the skills, the desire, and the time to do your part in helping the IWMF, please contact IWMF President Judith May at judithamay@comcast.net.





In Remembrance of Jim Bunton

October 27, 1933 - January 4, 2012

It is with heavy hearts that we share with you the news of the passing of Jim Bunton.

Jim actively served as Vice President and Treasurer of the IWMF for over eight years, from 2000 to 2009. Jim was a truly wonderful person who gave so much to the IWMF through his wise counsel and leadership, always considering the needs of patients first. He was a reliable confidant and advisor to former IWMF President Ben Rude and to me as well, during the seven years I've been President. With his years of experience, perspective, and guidance, Jim helped shape our Foundation. He was an outstanding critic in the best sense of the word, as he saw the root of a problem and offered solutions. His enthusiastic contributions were essential to the mission of patient services, scientific medical research, and foundation growth. Jim was also on the Board of the Waldenstrom's Macroglobulinemia Foundation of Canada where he assisted in the formation of the WMFC to reach out to Canadian patients and offer them support, comfort, and hope in living with WM. Our sadness at losing this dear friend is balanced with our gladness at having had him at our side.

Our deepest condolences go to Jim's wife, Barbara, and his two daughters, Patricia and Allison, their husbands, Mark and Patrick, and his much loved grandchildren, Elyse, Jonathan, Katherine, and Benjamin. Born in Belleville and raised in Toronto, Jim was a Scoutmaster and avid cyclist in his youth. He had a long career with Ernst & Young, from which he retired as an executive partner.

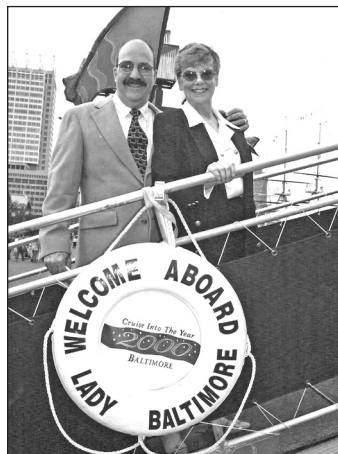
Many organizations have benefited from his leadership and support. Jim served as President of Canadian Goodwill Industries, he was Treasurer for the Royal Canadian Institute for the Advancement of Science, and was awarded the Queen's Golden Jubilee Medal in honor of his service.

Jim's journey with WM was long and courageous. He passed away at home one year after his diagnosis with squamous cell carcinoma, a second cancer that affected his face and throat. Though Jim has left us in the physical sense, he lives on in our hearts and memories. We who knew him are much the richer in the personal sense. For all of us, his legacy is the structure of our Foundation. As guardians of the IWMF mission we will always remember him with deep and heartfelt appreciation.

Judith May, President, for the IWMF Board of Trustees



CAPSTONE GIFT TOPS \$5M GOAL FOR RESEARCH CAMPAIGN



Gregory and Marilyn Fitzwater, residents of the Baltimore area, depart from their homeport in 2000 on the first of many cruises they have enjoyed in retirement.

Five years ago the IWMF announced the Five-in-Five campaign to raise \$5,000,000 in the span of five years for the Research Fund. Many thought we were stretching too far and that our goal was over-ambitious. Now, five years later, with donations from many of you – plus a generous capstone gift from Gregory Fitzwater and Marilyn Zollner-Fitzwater – we have exceeded our ambitious goal! We are grateful to each and every person who participated in this successful campaign.

Special thanks are due to Marilyn and Greg, whose gift provided such a terrific finish, and also to the fundraising team members who shared a vision five years ago – Tony Brown, Dick Weiland, and, posthumously, Dave Lively.

Marilyn was diagnosed in December of 1998. Since that time, she and Greg have donated several hundred dollars every year to the IWMF, including virtually all of their memorial gifts. Their consistent support caught the eye of IWMF senior development officer Dave Benson, who contacted the Fitzwaters when he was in their area and arranged to stop by and thank them in person for their support.

During his visit Dave also spoke of the 2011 matching gift challenge program for the Membership Services Fund. Marilyn and Greg agreed to make a three-year pledge to help meet the match. Dave also asked if they had ever thought about making a gift through their estate for the IWMF. At that point Marilyn informed Dave that they had already made significant provision for the IWMF, a bequest that included their house.

Describing what the IWMF has meant to her, Marilyn said: “In 1998, when I was first diagnosed, I was terrified. I had cancer and I could barely pronounce the name of the disease that I had. There was very little information available and most of it sounded awful. At best, I was told I might have 2-4 years. Then somehow I heard about a man named Arnie Smokler. I started calling Arnie at 7 pm that night and finally reached him at 11 pm. He was very helpful. He explained more about WM and suggested that I ask my oncologist to contact all my other doctors. He also suggested that I keep track of the various medications I received each year. With the help of Arnie, and later the IWMF, I began to see a light at the end of the very dark tunnel I was in. And I

really appreciated being connected to others with the disease. Greg and I have always been very grateful and wanted to do something to really help the IWMF.”

Of the Fitzwaters’ generosity, Dave says, “When Marilyn first said they wanted to leave a significant portion of their estate to the IWMF, I was floored but ecstatic. This kind of extraordinary gift was just what the IWMF needed to wrap up the Five-in-Five campaign. The commitment of people like Marilyn and Greg gives us all hope that someday we will find a cure for WM.”

As a Foundation, we have achieved major advances in understanding WM. Our current research program successes include:

- The on-going development of the first transgenic mouse model of WM by Dr. Siegfried Janz of the University of Iowa, who is in the process of validating his new mouse strain. The availability of mice with disease characteristics of WM will enable researchers to consistently test new therapies before human trials.
- The creation of two new WM cell lines by Dr. Stephen Ansell of the Mayo Clinic in Rochester, MN, and by Dr. Asher Chanan-Khan, who is now at the Mayo Clinic in Jacksonville, FL. These cell lines will enable researchers around the world to test the effectiveness of new drugs and new treatments against a common standard – a



Capstone Gift Tops \$5M Goal, cont. on page 7



standard that stays constant from test to test, from country to country, and over time.

- The establishment of a tissue bank by Dr. Irene Ghobrial of the Dana-Farber Cancer Institute. This will help researchers understand WM cells in various stages of the progression of our disease.
- The identification by Dr. Steven Treon at the Dana-Farber Cancer Institute of a single gene mutation shared by 90% of WM patients. This will enable researchers to target this gene mutation for better treatments and possibly a cure.

These important advances were made possible by the generous donations of individual WMers like Marilyn and Greg and like you.

Of course, we all know that there is still much to do to accomplish the IWFM vision: *Support all affected by Waldenstrom's macroglobulinemia while advancing the search for a cure.*

We hope some of you will be inspired by the generosity of Marilyn and Greg and will consider a generous legacy gift from your estate for the IWFM. Please note the article about the Ben Rude Society on page 5 of the January 2012 issue of the *Torch* for more details or call Dave Benson at 952-837-9980 to discuss a matching gift or an estate gift.

Thank you for your support and best wishes for a happy and healthy 2012.

From the IWFM Fund Raising Team: L. Don Brown, Carl Harrington, Dave Benson, Dick Weiland, and Julie Jakicic.

IWFM UPDATES ITS VISION

During the summer of 2011 the IWFM Board of Trustees conducted a strategic review of our organization and its objectives. We raised the following questions:

- For whom do we provide our services?
- Are we providing the services most needed?
- Are we moving in the optimal long-term direction?
- How will we know if we have succeeded?
- How satisfied are WM patients with the work we are doing on their behalf? Could we do better? If so, in what way?

To provide some of the answers, we decided to survey the membership. This survey, which is to be professionally formulated and conducted electronically, will take place in the second half of 2012. The results will be published.

We also saw a need to express our goals more clearly. As a first step, we adopted a new vision statement: *Support all affected by Waldenstrom's macroglobulinemia while advancing the search for a cure.*

We will take a fresh look at our activities with this new, more inclusive vision in mind. It will drive our objectives more clearly and direct our efforts as we go forward.

Our new objectives in line with this new vision are:

- 1) Include everyone.
Through new outreach efforts we aim to expand our IWFM membership and keep all members – patients, families, friends, medical professionals and others – on our roster as ongoing members.
- 2) Communicate regularly to members.
E-mail is the most cost effective and easiest

method. So those of you who have an e-mail address will be receiving more communications from us by e-mail. Our newly improved website is another easy way for us to make information available in a timely fashion and for you to receive it. Keep watching for future updates and expansions. As we learn new information daily about research findings and treatments we will spread the news to our members.

We will continue our strong efforts to support research to find a cure for WM. Our Scientific Advisory Committee is very excited to see the recent progress towards understanding the origins of WM and how the disease progresses. More research studies are the top priority for the future.

What can you do to help?

Give us a current e-mail address – if you don't use the Internet, we suggest that you might find a relative or friend whose e-mail address you could give to the office so that with their help you are kept informed of the latest information, meetings, presentations, et cetera.

Stay connected to us – We encourage you to check the website regularly, attend a support group meeting, watch the DVDs, and attend our annual Ed Forum.

We know, and you know, how important it is to stay updated on WM so that you are well informed and prepared to participate in the management of your disease. We will be working even harder to make the necessary information available to you.

The IWFM Board of Trustees



IWMF RESEARCH UPDATE

BY TOM MYERS, VICE PRESIDENT FOR RESEARCH

Two projects funded by the IWMF were concluded in the fourth quarter of 2011. The principal investigators were Dr. Steven Treon from Dana-Farber Cancer Institute and Dr. Stephen Ansell from the Mayo Clinic in Rochester.

Dr. Treon's whole genome sequencing (WGS) of 30 WM patients was very notable because it was the first time this process has been used in our disease. WGS is a laboratory process that determines the complete chromosomal DNA sequence of an individual and searches for all genetic alterations in DNA that can affect susceptibility to cancer and other diseases. The result of this project was that 90% of the patients had the same mutation of the gene MYD88. This finding will lead to studies to identify agents that interact with this mutated gene and hopefully result in effective treatments for WM.

Dr. Ansell's project studied the effect of various cytokines (proteins involved in cell signaling) on IgM production and cancer cell growth. The study has traced the pathways by which the cytokines affect one another to stimulate IgM production, and Dr. Ansell's research team believes it has identified the proteins which are at the beginning of the signaling chain. These cytokines, called STAT5a and STAT5b, are the subjects of a new project starting in 2012 and extending into 2014. The project will elucidate the mechanisms by which these cytokines function. In addition, techniques for interrupting the process of IgM production will be explored in an effort to come up with new treatment methods for WM.

Dr. Siegfried Janz from the University of Iowa continues with what appears to be a successful project to develop a transgenic mouse model of WM. A transgenic mouse is genetically altered to develop tumors that behave in a similar manner to those produced by humans and can pass the tumor characteristics to

its offspring. Dr. Janz has crossbred three strains of mice, each having a different characteristic with the potential to contribute to the development of WM, and the resulting new strain has several features of WM, including lymphoplasmacytic tumors in the lymph nodes and spleen and increased IgM production. His project, which ends on July 31, 2012, is continuing to verify that the mice are representative of WM. Strains of this mouse model will be available from a commercial laboratory for researchers around the world. The existence of a WM mouse model will facilitate studies of new treatment agents before they are used in patients.

The project at the Deeley Cancer Centre in Victoria, British Columbia, was also technically concluded at the end of 2011. The project was funded in its entirety by the WM Foundation of Canada and aimed to develop techniques for identifying tumor-specific gene sequences and reactive T-cells from WM patients, leading to possible immune-based (vaccine) therapies for WM. Although several techniques for developing the process were validated, no tumor-specific sequences were identified. Because of the discovery by Dr. Treon's group of the mutated MYD88 gene in WM patients, the Canadian researchers have asked for a no-cost extension of the project. With a known target for a vaccine, they believe they can be successful with their approach.

Finally, the IWMF Board of Trustees has approved the funding of a new project at Dana-Farber Cancer Institute under the direction of Dr. Abdel Kareem Azab. This project postulates that the WM cells in the bone marrow will move out of areas that are hypoxic (with low oxygen levels) and migrate to other areas in the bone marrow and that inhibition of this response will lead to inhibited tumor dissemination.

COMMENTS MADE BY ATTENDEES AT LAST YEAR'S ED FORUM

"Loved finding other patients with my same disease!"

"The doctors were all so good to talk to us individually about our specific questions, it was like having a second opinion!"

"Invaluable for first-timers! Knowing that 50% of those in attendance were like me really helped!"

"Hearing about the treatment successes and research accomplishments was worth the trip – I now have hope!"

"As usual, the Ask the Doctor panel was the highlight of the weekend!"



LIVING WITH WM: SEVENTEEN YEARS AND GOING STRONG

BY MARGUERITE REGAN, PH.D.

Dr. Marguerite Regan, a resident of the Washington D.C. area, was diagnosed with WM in 1995 at the time when Arnold Smokler, the founder of the IWME, had formed the original support group – meetings of a small number of WM patients in his home. Seventeen years later, Dr. Regan recounts the treatments that allowed her to continue her career and shares her practical wisdom with advice for those affected by a diagnosis of WM.



Marguerite Regan and her lucky new dog, Cabby, recently adopted from a shelter.

In January of 1995, I went to my internist with what I thought were gallbladder symptoms. She sent my blood to the lab for testing. At the lab they were unable to read the results. She took another test; the results also turned out to be unreadable. She talked about my case to a hematology colleague who thought he had an answer.

On February 9, 1995, I had a bone marrow biopsy. When I came out of the sedative, the hematologist informed me that I had Waldenström's macroglobulinemia and I should rethink my life plans. At this time, WM had a five-year prognosis. I then went to the Johns Hopkins Hospital in Baltimore for a second opinion. Hopkins had a bone marrow transplant center and the hematologist there suggested I "upload all my risk factors and go for a transplant." At this time, I was on watch-and-wait and bone marrow transplants had a very high mortality rate and their utility for WM was questionable. After a discussion with my hematologist, I decided against the transplant. I also adopted a dog as a life-affirming decision, and he was a good companion during the treatment times.

I was given Arnold Smokler's name as someone who had WM and had researched it. Arnie was getting a support group together, so I attended a couple of those at his home. There were probably 4 to 5 of us in the beginning. Arnie had compiled a wealth of information on WM and it was good to know I was not alone. Later Arnie and his wife moved to Florida, and Sarasota became the center for WM information.

Watch-and-wait ended in 1999, when I was treated with cladribine (2CdA). I was in remission until summer 2004,

when I had four sessions of Rituxan. That remission lasted until May of 2010, when I again had four sessions of Rituxan.

During these past 17 years I have been active with my work (at Envision EMI) as the curriculum director designing simulations for elementary through college students and as the Dean of Academic Affairs involved with accreditation. I traveled to various cities in the United States giving presentations and also abroad to Mexico, Jamaica, and Ireland, enjoying vacations. I plan to travel again this year. While I officially "retired" in January, 2011, I just signed a new consulting contract, good until 2014, for my company and am keeping busy at it.

Now I am faced with being treated once more for WM. I may seek a second opinion for the best combination of drugs, as well as discussing them with my hematologist-oncologist who has treated me for 17 years. Life with WM goes on. I also adopted another dog this month.

The most important lessons I learned during the last 17 years:

- View WM as a treatable illness, not an end game.
- Get a second or third opinion if necessary and find the best doctor to treat you.
- Be an advocate for yourself. Keep your records from diagnosis on.
- Keep your job if you are able to. I worked fulltime during most treatments (at Lombardi Cancer Center of the Georgetown University Medical Center), and it was a welcome diversion.
- Surround yourself with life-affirming people and stay away from naysayers.
- Gather your support group, be they family, friends, colleagues, dogs, cats.
- Divert your focus with creative projects and hobbies.
- Research information but do not over-focus on WM.
- Join a support group but remember that everyone may have different symptoms.
- Maintain your sense of humor, an important asset in dealing with any disease and with healthcare providers.
- Do not focus on "what-ifs" but stay in the present and seize the day.

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@sy-thetis.org



MEDICAL NEWS ROUNDUP

BY SUE HERMS, ASSOCIATE EDITOR

Velcade Approved for Subcutaneous Administration – Millenium Pharmaceuticals announced that the FDA has approved the subcutaneous method of administration for bortezomib (Velcade). The approval was based on results from a randomized Phase III trial in multiple myeloma patients. The study, which had two arms, compared subcutaneous Velcade with intravenous Velcade – patients receiving subcutaneous administration achieved an overall response rate of 43% and a complete response rate of 7%, compared to intravenous administration with an overall response rate of 42% and a complete response rate of 8%. The safety profile was similar for both arms; however, differences were observed in the incidence of peripheral neuropathy (PN). In the subcutaneous arm, 6% of patients experienced PN of grade 3 or higher, compared with 16% in the intravenous arm. In the subcutaneous arm, 38% of patients experienced PN of all grades, compared with 53% of patients in the intravenous arm.

FDA Removes Pre-Treatment Requirement for Zevalin – The U.S. Food & Drug Administration (FDA) removed its pre-treatment requirement for a bioscan prior to therapeutic treatment with Zevalin, which is a radioimmunotherapy that combines a monoclonal antibody with a radioisotope. Zevalin was first approved for the treatment of patients with follicular lymphoma. The removal of the bioscan as part of the treatment regimen has changed the way Zevalin will now be administered. Prior to this ruling, patients received an intravenous infusion of rituximab, followed by a diagnostic dose of Zevalin and a whole body scan at a nuclear imaging center. Over the next several days, two additional whole body images were taken to view the path of the diagnostic dose, and one week later the patient returned for the second infusion of rituximab followed by the therapeutic dose of Zevalin. The removal of the bioscan requirement eliminates the diagnostic dose and imaging scans; now patients being treated with Zevalin will receive two rituximab infusions followed by Zevalin.

New Study Presented on Incidence and Trends of WM in the U.S. – A population-based study of WM patients conducted by MD Anderson Hospital looked into geographic incidence and disease trends in the U.S. Twenty-year data from the SEER (Surveillance, Epidemiology, and End Results) program of the National Cancer Institute were used for this statistical study. Of the 95,797 cases of non-Hodgkin's lymphoma diagnosed between 1988 and 2007 in 9 SEER registries, 1,835 (1.9%) were new cases of WM. Median age at diagnosis was 73 years, and the overall incidence was 0.38 per 100,000 persons per year. The incidence of WM was higher in men than in women and higher in Caucasians than in African Americans or other races. The annual incidence increased with age, and the most significant annual percentage increases were seen in the group aged 70-79 years, in whites,

and in three geographic registry areas – Seattle, Detroit, and Connecticut.

Court Ruling Permits Payment in Western States for Circulating Donor Stem Cells – A federal appeals court ruling could make it easier for patients with blood cancers to find matching donors for allogeneic stem cell transplantation. The Court of Appeals for the Ninth Circuit said that a federal law prohibiting payment for donated organs did not apply to stem cells extracted from circulating blood. The National Organ Transplant Act of 1984 counts bone marrow as an organ for which payment is prohibited but does not ban payments for blood, sperm, or eggs. The statement said that compensation for circulating stem cells would now be permitted in the Western states covered by the Ninth Circuit; however, the ruling still does not apply to stem cells collected directly from bone marrow.

Amgen Planning to Develop Generic Biosimilar Drugs – Amgen, a biotechnology company, is planning to develop generic versions of some best-selling drugs and is teaming up with Watson Pharmaceuticals, a leading generic drug manufacturer. Although Amgen did not specify which drugs it would develop, the most likely candidates are the products sold by Roche and its Genentech subsidiary – Herceptin for breast cancer, Rituxan for lymphomas, and Avastin for various cancers. Because the 2010 law overhauling the U.S. health care system orders the FDA to develop rules for the approval of these types of drugs – called biosimilars – the rules have not yet emerged, so there is still uncertainty about how extensive clinical trials will have to be before the biosimilars can be approved. These drugs might reach the U.S. market around 2018 or 2019 when patents expire; in certain other countries, the drugs could be available sooner.

Navitoclax in Phase I Study for CLL – A joint Australian-U.S. study reported on the use of navitoclax (ABT-263) in chronic lymphocytic leukemia (CLL). The drug inhibits BCL2 and related proteins, and this Phase I study included 29 patients with relapsed or refractory CLL who received daily navitoclax for 14 days or 21 days. Among these patients, 35% achieved a partial response. Median treatment duration was 7 months and median progression-free survival was 25 months. Thrombocytopenia was the major dose-limiting toxicity and was dose-related. A dose of 250 mg/day in a continuous dosing schedule was determined to be optimal for future Phase II studies.

Experimental Treatment Enhances Immune Responses in Cancer Therapies – Idera Pharmaceuticals presented animal model data on its treatment called IMO-4200, designed to stimulate the immune responses mediated through the Toll-like receptors TLR7 and TLR8, which are expressed in human dendritic cells, B-cells, monocytes, and macrophages.

Medical News Roundup, cont. on page 11



This therapy, when administered in combination treatments, enhanced the antitumor effect of ofatumumab, rituximab, and bortezomib, as well as cytotoxic therapies such as fludarabine and bendamustine.

New Proteasome Inhibitor Tested in Multiple Myeloma –

An investigational proteasome inhibitor, known as MLN9708, was well-tolerated by patients and led to a marked reduction in monoclonal protein during the first therapy cycle in a small study of multiple myeloma patients. MLN9708 is a sister drug to bortezomib (Velcade), but it shows greater tissue penetration, is given orally, and appears to cause a lower degree of peripheral neuropathy.

Micromet Expands Development of Blinatumomab –

Micromet announced that it has entered into a Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute (NCI) to expand development of the company's lead product candidate blinatumomab, also called MT103. Blinatumomab is the first of a new class of agents called BiTE antibodies, designed to harness the body's T-cells to kill cancer cells expressing CD19. Under the terms of the agreement, the NCI and Micromet will collaborate on a series of clinical trials to evaluate the safety and efficacy of blinatumomab as first-line treatment for older patients with acute lymphoblastic leukemia or for patients newly diagnosed with acute lymphoblastic leukemia or WM. Micromet is in the process of being acquired by Amgen, a biotechnology company that may be in a better position to speed the development and marketing of BiTE antibodies.

Italian Study Looks at Second Cancers in WM Patients –

A multi-center Italian study looked at the risk of second cancers in 230 patients with WM and compared the incidence with that of an age- and sex-matched control population. The overall risk of second cancer in WM was 1.69 times higher than expected. WM patients were at increased risk from diffuse large B-cell lymphoma, myelodysplastic syndrome/acute myeloid leukemia, and brain cancer. The sample size did not allow for firm conclusions about the effect of therapy on the development of second cancers.

Phase II Trial Compares Obinutuzumab (GA101) to

Rituximab –

A Phase II trial comparing rituximab with the investigational monoclonal antibody obinutuzumab in patients with relapsed non-Hodgkin's lymphoma (NHL) showed a trend toward more responses to the new agent. Obinutuzumab, also called GA101, is a novel anti-CD20 antibody that has been engineered to more effectively interact with the immune system, so that it can induce a stronger reaction of the immune system against the lymphoma cell. The overall response rate for GA101 was 44.6% vs. 33.3% for rituximab, and the complete remission rate in the GA101 arm was 12.2% vs. 5.3% for rituximab. The safety of the two agents was comparable, although patients on GA101 had more temporary reactions to infusion and a higher rate of mild cough. Phase III trials are underway to test GA101 as part of initial therapy for NHL patients.

Carfilzomib Shows Promise for Multiple Myeloma

Patients –

The experimental drug carfilzomib produced very promising response rates when combined with Revlimid (lenalidomide) and low dose dexamethasone in a Phase II study for newly diagnosed multiple myeloma patients. In the study of 53 newly diagnosed patients, 94% experienced a partial response after receiving one cycle of the three-drug combination. After 12 cycles or more, all patients in the study had a very good partial response, defined as 90% reduction of disease. In addition, most patients were able to remain on their original dosing schedule without developing peripheral neuropathy. Carfilzomib is a newer generation proteasome inhibitor.

The author gratefully acknowledges the efforts of Arlene Carsten, Peter DeNardis, Mike Dewhirst, Gareth Evans, John Paasch, Colin Perrott, Howard Prestwich, Wanda Huskins, and Bert Visheau in disseminating news of interest to the IWMF-Talk community. The author can be contacted at suenchas@bellsouth.net for questions or additional information.

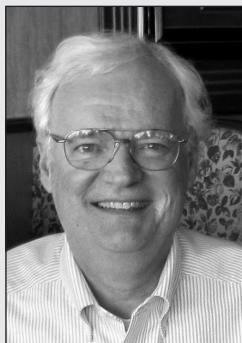
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AMBITION ACHIEVED!



Novelist John McCann

Congratulations are in order to IWMF member and WM patient John McCann who, following diagnosis in 2004 and treatment in 2005, set his sights on undertaking “something he always said he would do,” namely to write “the great American novel.” Seven years later, John has not only completed his opus entitled *Other Than Honorable* but also recently signed a contract for publication later in the year of this murder mystery set in 1983 Philadelphia, “mixed with large doses of politics, organized crime, and romance.”

While time and the critics will tell if John indeed fulfilled his ambition to write *the* great American novel, we can all take cheer at his achievement, for he has set an admirable example of survivorship with WM.

Retired in 2009 after forty years of service in various management and executive positions in the U.S. government, John lives in Buckingham, PA. His diagnosis of WM was the result of exposure to pesticides in Vietnam where, as a conscientious objector, he served as a medic (1970-71). John expresses his gratitude to IWMF member Jerry Fleming, now deceased, for navigating him through the application process with the Department of Veterans Affairs.

Other Than Honorable will be published in hardback by BlackRoseWriting in June with the eBook version to follow shortly.

COOKS' HAPPY HOUR

BY PENNI WISNER

Now arrives the time of year when spring weather beckons us outdoors and we begin – I do, do you? – to think of warm weather foods. Dishes that cool the thirst and perk up the appetite. And I think I may have just the thing to help you celebrate the season during your cook's happy hour.

I'm not sure what to call them: are they “coups” or perhaps “couptails?” Whatever we decide, they are half soup and half cocktail. Instead of making a drink and then a canapé to go with it, why not combine the two? And, when we hear exhortations to “eat more vegetables” and to “follow an anti-inflammatory diet,” we can feel smug: these will be vegetable and fruit combos, full of antioxidants.

You won't need special equipment: just a sharp knife and a food processor or blender. And ice. Plus fun glassware: you can finally put those oversize martini glasses to use. And some glass pitchers to show off the colors of your couptails. But probably the most important tool you need is your imagination.

First up is a gazpacho-Bloody Mary. Take your favorite gazpacho recipe. It's based on tomatoes. Just like a Bloody Mary. How many of you use V-8 juice for your Bloody Mary? Raise your hands high. Good, now call it “gazpacho,” spike it with Worcestershire, horseradish, and vodka, pour it into a tall glass or a fat, double old-fashioned, and garnish the drink with celery sticks or pickled green beans or asparagus. For

a more substantial “swizzle,” skewer several small chunks of fresh mozzarella interspersed with olives or cherry tomatoes on a long skewer. Or thread some small shrimp (or dice larger ones) or lumps of fresh crabmeat on the skewers.

However, since I believe in starting with whole foods, preferably organic, let's begin our gazpacho with ripe tomatoes. Until local tomatoes arrive at the market, use good quality canned tomatoes with no salt added. And, when you make your own soup, you have the luxury of skewing the recipe to your taste. If you keep it Spanish, add cucumber, green pepper, a fresh hot chile (if you have, or someone gave you, a chile-flavored vodka, use it instead of the chile), a small yellow onion or several shallots, a couple garlic cloves, sherry or red wine vinegar, plus herbs such as basil, mint, and flat-leaf parsley. If you want your couptail chunky, pulse all the ingredients in a food processor. If you want it smooth, keep going or, better yet, use a blender. If you want it thick, soak a slice or two of country bread (crusts removed) in the vinegar and some of the vegetable juices until very soft. Then pulse it, or blend it into your soup. If you want to maintain your grip on virtue, use wholegrain bread, but I'd steer clear of those with wheat berries and other grains that won't disappear into the puree. For richness, blend in extra-virgin olive oil to taste. Don't forget to season with salt and pepper.

Cooks' Happy Hour, cont. on page 13



There are, of course, infinite variations. To give it an Asian twist, add a stalk of lemongrass, bashed up and then thinly sliced, plus hot sauce such as sambal olek or sriracha, rice vinegar, lime juice, and herbs such as cilantro, mint, and Thai basil. To keep the Bloody Mary theme, you need a fermented fish product so try a splash of fish sauce.

Spring nights can be cool and maybe you wouldn't mind turning on the oven or even starting a day ahead. In which case you could roast your tomatoes. (You remember roasting, right? Toss with olive oil, season with salt and pepper, and pop in 375°F to 400°F oven.) For that matter you could roast the aromatics right along with them – try celery, onion or even some leek (why not?), and garlic for starters. Or while you are roasting tomatoes, roast some red bell peppers (or open a jar of piquillo peppers from Spain), skin both the tomatoes and the peppers (unless you have a Blendtec or Vitamix which is strong enough to pulverize the skins), and puree them together. Spike with black-pepper vodka, serve hot or cold, and garnish with crunchy celery or fennel.

But we do not live by tomatoes alone. So let's move on to cucumbers. I've just finished a cookbook for Hubert Keller (*Souvenirs*, to be published this fall by Andrews McMeel). In it he gives a recipe for "white gazpacho": a puree of cucumber, green grapes, finely ground almonds, thick yogurt, sherry vinegar, shallot, garlic, and salt and pepper. He garnishes his gazpacho with a skewer of frozen grapes and dots of vanilla oil (vanilla bean seeds scraped into neutral-flavored oil and

left to infuse for several days; shake before using). And he doesn't suggest spiking it but there is no reason (that I can see) why not.

If we start again with cucumbers, puree them with avocado, fresh lime juice, orange juice, a little yogurt or buttermilk, salt and pepper, and then garlic and shallots or scallions (or not), ginger (or not), wasabi or cayenne (or not), plus herbs such as cilantro, mint, dill, basil, and chives. How about a light rum to turn the mix into a couptail? Garnish with long spears of cucumber. You are nearly a saint now. At least as far as your diet is concerned.

Now that you have the idea, take a look at the fresh salsas in the store. Wouldn't many of them lend themselves to couptails? And as warmer weather approaches bringing fruit in abundance, make smoothie couptails. Oh. You prefer coffee in the afternoon? Never fear, we've got you covered. Blend your coffee beans (decaf if you like but preferably dark roast) with ice and sweetened condensed milk. Add sprigs of mint and spike with coffee-flavored tequila. Olé!

Our motto: Eat Well to Stay Well

Coup in hand, we bid 'Olé!' to Penni until the October issue when she's sure to have a store of tips for early autumn healthy happy hours. Ample time for us to try out those piquillo peppers and sambal olek or sriracha! In the meantime, we can always visit Penni at penniwisner.com and see what's cooking.

FROM IWMF-TALK

BY MITCH ORFUSS

One of many things you can say about winter – most of us probably spend a little more time indoors. This could mean more time on the computer than in other seasons, possibly contributing to how busy the TALK discussion was. The base of readers is also growing, adding to the diversity and frequency of opinion. With a population now exceeding 1200 readers and (unfortunately, there are always newbies to our world) growing every day, more people are on TALK than ever, both asking for and giving support to others regarding every aspect of WM imaginable. What follows is a summary of some of the most frequent threads over the winter of 2011-2012.

Stem Cell Transplant

Transplant is a controversial path in WM. There are success stories with the *autologous* variety and experimentation with the *allogeneic* variety. **Liane Cochran-Stafira's** doctors felt it was important to do her transplant early before she'd had too much treatment – so that they would be able to harvest sufficient cells. As it was, Liane had one course of 2CdA,

and that was enough to reduce her tumor load for her harvest. There were enough stem cells for one transplant and also enough for a booster if a future chemo leaves her with a depleted bone marrow.

Colin Perrott said it can be too late to harvest in almost a blink of an eye and that there is no clear demarcation point between "good" and "poor" prospects for ASCT. He does believe the data say that patients with "good" prognosis would do better on conventional treatments. If you knew in advance you would be an outstanding responder to ASCT, then Colin says go ahead with transplant. Since progressive treatment reduces the odds of a successful stem cell harvest, early harvesting is a wise step to create more options for the patient. The published conclusion of one study Colin referenced is that "ASCT is a feasible procedure in young patients with advanced WM. ASCT should not be offered to patients with chemo-resistant disease and to those who received more than three lines of therapy."

From IWMF-Talk, cont. on page 14



Peter DeNardis, sitting on the sidelines of transplant discussions, mused over whether he is too conservative. After each “successful” treatment he receives, Pete is relieved to see his symptoms resolve and questions the wisdom of tempting fate . . . especially with his IgM in the undetectable range and all other blood values normal. Why endure the rigors of a transplant, not to mention the time off from work without pay? Why venture into the land of ASCT? Is this (he further reflected) a false sense of security given his current condition? Or should he wait it out for another relapse and then decide?

Jeff Atlin cited a study reporting that the indolent nature and favorable genetic profile should make WM an ideal disorder for *autologous* stem cell transplant with high, durable response rates. The study concludes that autologous transplant is effective and under-utilized in the management of WM, but *allogeneic* transplant should be used only in the context of a clinical trial or when other chemotherapeutic options have been exhausted.

Leg Cramps

Leg cramps are a common nuisance, and sometimes much worse in terms of quality of life (QOL). **Hank Stupi** writes about the unbearable leg cramps he experienced over his last round of Rituxan x 4. Hank’s post ironically came just two weeks after posting a message about his “Best Rituxan Infusion Ever,” where he discussed how, for the first time in 27 Rituxan infusions, he staved off the shakes by being pre-medicated with Demerol. Hank wanted us to know he wasn’t so lucky during his last two infusions despite the Demerol pre-med. He still got the rigors, but stopped the Rituxan temporarily and took more Demerol. Within 10 minutes the rigors stopped, and he could continue the infusion at 25 mL/hr, slowly creeping back up in 25 mL/hr increments to a max of just 125 mL/hour. All of which makes for a very long day! Extremely problematic for Hank over his last 5 Rituxan infusions were unbearable leg cramps. Hank awoke 5 or 6 times during his infusion with terrible cramps, and, because of the Demerol, he could not stand or put weight on his legs to relieve the pain. Nothing helped save waiting for it to stop on its own.

Jim Streeby responded that he has had experiences like Hank’s, with increasing severity of leg cramps over time, and he believes that only by standing or jumping up and walking, multiple times as necessary each night, can you stop leg cramps. Jim’s family doctor said that athletic people were more likely to be affected. So maybe these cramps aren’t an electrolyte problem but rather a neurological issue?

Chaz in Cleveland described “creeping” cramps last winter and spring during his FCR (fludarabine, Cytosan, and dexamethasone) treatments. The muscles would tighten slowly, causing an interior rotation of the foot, calf, and thigh before the pain would even hit. A yoga student of Chaz’s had the same cramps and suggested taking a teaspoon of prepared

mustard. Chaz started to do it and, surprisingly perhaps, it seemed to work. Of course (he added), hopping down the stairs and into the kitchen to the fridge and then back up the stairs into the bedroom was probably the more active ingredient in that treatment regime! Six months following FCR, Chaz’s cramps were gone.

Betty McPhee added that she also gets terrible leg cramps, which were going on even before she took Rituxan. Betty finds that magnesium helps, as does the quinine found in Schweppes tonic water. Betty believes that keeping hydrated is also important. More recently she has been monitoring her leg cramps after a glass of wine, which almost predicts for her that she will have cramping during the night.

Rituxan

Rituxan is an ever-popular topic, as it was the first big breakthrough in the new area of antibody therapy in the late 1990’s, and it remains an enormously popular, effective treatment. **Greta Cooper** recently completed six cycles of Rituxan plus chemotherapy (FCR) with a complete response (CR) and a reduction of IgM from 7500 mg/dL to 300. Greta’s oncologist is not planning to continue with maintenance Rituxan, just bimonthly checkups. In contrast to this hands-off approach, she noticed that many TALK participants received maintenance Rituxan after first-line treatment, and she wanted to make sure she understood the issues so as not to miss out on potentially beneficial therapy. Greta found contradictory views in recent literature. For example, Dana-Farber Cancer Institute seems to believe that maintenance-R works whereas Mayo Clinic does not recommend it. She asked if anyone can clarify.

Art Mulholland replied that he had just completed bendamustine and Rituxan treatment. His bone marrow involvement decreased from 70% to barely measurable, and his IgM dropped from 2300 mg/dL to 630 and appears to be continuing down. Prior severe fatigue has improved, as has his peripheral neuropathy (PN). On the advice of his oncologist at Rush University Medical Center in Chicago, Art began bimonthly Rituxan maintenance, which will continue for the next two years.

Carl Graf wrote that he had no fewer than 26 treatments between January 2004 and May 2011. Rituxan seemed to work fine but he was warned by his oncologist that he might relapse at some future date when a single agent would no longer work. Then, Carl said, he “hit the wall.” Rituxan didn’t do anything. His hemoglobin wouldn’t improve from 8.2 g/dL, and his IgM wouldn’t come down from the mid-4000’s. After consultation with a WM specialist, Carl started a six-cycle program of Cytosan and Rituxan that ended in November 2011. Even though his CBC readings aren’t the best because of the Cytosan, Carl’s hemoglobin is up to 9.5 g/dL and his IgM is down to 3000 mg/dL after four cycles.



Anita Lawson said that after her unhappy time with Velcade in 2007, she started Rituxan maintenance in early 2008. It was once a week for four weeks, once a month for six months, and then bimonthly for a couple of cycles. At that point her insurance changed, and she couldn't afford the co-pays for bimonthly, so changed it to quarterly from late 2008 until the end of 2010, at which point her IgM had risen and her lymph nodes were more enlarged than usual. So she started on combination bendamustine and Rituxan in January of 2011. She finished with that and is now on "no maintenance," but her three years on Rituxan kept her IgM between 1900 and 2100 mg/dL, until it stopped being effective.

Linda Garding is currently in a Rituxan maintenance program, receiving Rituxan every two months for two years. This is a follow-up after six months of RCP (Rituxan, Cytosan, and prednisone) chemo treatments. So far there have been no negative side effects. After four of these Rituxan-only treatments, her IgM has dropped to 1014 mg/dL and all other blood tests are normal.

Sue Pruce is currently receiving Rituxan maintenance every two months. Sue previously had six rounds of BDR (bendamustine, Rituxan, and dexamethasone) beginning in January 2010 when first diagnosed. However, due to PN and nerve pain, she and her oncologist decided to stop in January 2011 and move to maintenance Rituxan. Her IgM came down from 6410 mg/dL to approximately 2200 at the conclusion of the BDR treatments and with the maintenance regimen is now around 1800. Hemoglobin at diagnosis was 8 g/dL – now holding steady at 12. Sue had 55% bone marrow involvement, which went down to 10%. She has had no problems with the infusions, with the exception of the Benadryl pre-medication, which makes her shaky, as if she could jump out of her own skin. Sue takes Xanax before the infusion and makes sure to have the Benadryl mixed in normal saline and infused slowly before the Rituxan. While her PN has not subsided, she still has hope.

Prednisone and Dexamethasone (Decadron)

Carl Graf asked for help understanding why most of our WM procedures recommend using Decadron, prednisone, and other corticosteroids in conjunction with chemo agents. Carl understands they relieve inflammatory distress, but, if that's not a factor, what are the benefits of using it? Carl mentioned that he became hyper the few times one of them

was used, and so he opted out of it. His hematologist said he could reduce the dose or even eliminate it since it won't reduce the synergistic effect of the chemo agents – in his case, Cytosan and Rituxan.

Eunice Johnson said that when she was first diagnosed in 2004 and resisted having any treatment, she was told by her hematologist-oncologist to at least take the prednisone. Eunice, who had also been diagnosed with autoimmune hemolytic anemia, was told that prednisone would reduce the tendency of her red blood cells to destroy themselves, plus it would have some action against the lymphoma. She did take that "familiar enemy" finally – she had three "pulses" over a two-year period. Her hemoglobin went up to 8-9 g/dL from 5.7, but her IgM continued to trend in the wrong direction. In 2008 Eunice took Decadron on four consecutive days in an attempt to treat the WM without beginning real "chemo." This unfortunately was ineffective. As part of the chemo treatments that followed, Eunice would get a steroid prep with the chemo infusions, then oral prednisone on days 2 through 5, with each of her eight treatments. She believes this was for its anti-cancer effect as well as to reduce allergic reactions and nausea.

Peripheral Neuropathy (PN)

Neuropathy is an all-too-common problem that causes much suffering in our community. **Greta Cooper** asked which treatments work best to reduce PN and referenced the following: Neurontin or Lyrica alone; Neurontin or Lyrica + painkillers (over-the-counter pain relievers, prescription painkillers, pain patches); Neurontin or Lyrica + tricyclic antidepressants (e.g., amitriptyline); Neurontin or Lyrica + duloxetine (e.g. Cymbalta); or painkillers, tricyclic antidepressants, duloxetine, opioids, etc., alone.

Catherine Callahan said she found higher dose Lyrica superior to Neurontin in managing pain. She also takes Cymbalta (for a different purpose) and has seen no side effects with respect to her PN. Catherine adds that, after several years of leg neuropathy, she has had some return of sensation – no apparent cause.

Brett Blakeslee added that his neuropathies were also getting progressively worse, and so he spoke with other TALK readers who recommended plasmapheresis (PP). Brett tried it and it offered relief, though only temporarily. Brett's neurologist

From IWMF-Talk, cont. on page 16

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

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

2. Contact Peter DeNardis at pdenardis@comcast.net and provide your full name



thinks the rebound of the antigens that cause the problem can be stopped or slowed with maintenance Rituxan.

Fay Langer (a cryo patient) said that when she was on PP, the nursing staff told her that veins do better if the patient is properly hydrated, so she started drinking lots of water the day before. Her veins did in fact do better.

And Much More

In addition, TALK over the past few months covered numerous other topics related to WM that we do not have space to summarize here, including such relevant concerns

as joint pain, serum viscosity, Cytoxan, benzene exposure, and bendamustine – to name just a few. No matter what you may want to talk or hear about related to WM, it seems there are experienced, interested, and generous fellow-WM-travelers who will listen and offer their points of view on TALK. Please remember that no one practices medicine on TALK. WM patients differ markedly from one another, and only you and your doctor are sufficiently well informed about your individual variant of WM to make treatment decisions. Best of health to all.

SUPPORT GROUP NEWS

EDITED BY PENNI WISNER

Support Group List and Lifeline

These lists are published in the Torch twice each year and will be printed in the October Torch. The most up to date lists are available at www.iwmf.com

CALIFORNIA

Monterey

In January, sixteen members continued a conversation begun at the previous meeting: the temptation by patients and doctors alike to assume every symptom is Waldenstrom-related. Support group leader **Sandy Skillicorn** reported that when she had trouble with her legs two years ago the neurologist told her the cause was Waldenstrom's and that her condition would never improve. Luckily she was quite wrong on both counts. So the combined wisdom of the group is: 'Don't don't buy it until you are sure they are right.' In fact, Sandy does not tell any new doctors about Waldenstrom's until she thinks it pertinent. The next gathering will be in Carmel on Saturday 15 April from 1-4. Sandy is in Carmel year round now; she used to spend part of the year in Hawaii. Now it's down to just a few weeks a year. She plans to be in Philadelphia in June for the IWMF Ed Forum. If any WMers from the area have not met Sandy, look for her there.

Sacramento and Bay Area

It has been described as the most significant Waldenstrom's discovery since the disease was identified! Dr. Steven Treon and his team at the Dana-Farber Cancer Institute have identified a specific gene mutation common to a large portion of Waldenstrom's macroglobulinemia patients. In March, the group met in Roseville to watch the video-recorded session of Dr. Treon's February 5 announcement in Boston. Everyone there was thrilled by the news and the opportunities for more research and new treatment options that the discovery opens. A circle discussion of personal WM-related issues followed, fueled in part by the potluck finger foods.

COLORADO & WYOMING

On a gorgeous winter day in January – 56 degrees, clear, and

calm – eighteen WM regulars attended the share-and-discuss meeting at the University Park Methodist church near the University of Denver. They shared great breakfast snacks and watched Dr. Steven Treon's presentation from the Minneapolis 2011 Ed Forum DVDs. One of the members is nearing treatment and half of the rest had just finished treatments (mostly bendamustine and Rituxan). Many experiences – good and bad – were shared and many other issues came up as well. Another member discussed his status and expected treatments after being informed that his WM had just transformed to a more aggressive B-cell lymphoma. The group wishes both of these great folks well this year. The next meeting will be a break-out lunch for WMers in the middle of the one-day Leukemia & Lymphoma Society's Blood Cancer Conference in Denver on 14 April. All WMers and their families are encouraged to participate in the full day of educational topics and, above all, to hear Jeffrey V. Matous, M.D., talk about WM and other Non-Hodgkin's lymphomas, treatments, and issues. Dr. Matous specializes in blood cancers, including leukemia, lymphoma, and multiple myeloma. Currently he is the medical director for the Rocky Mountain Blood and Marrow Transplant Program as well as an associate clinical professor of medicine at the University of Colorado Health Sciences Center. The IWMF will have a table of materials at this event. If anyone needs information, please contact group leader **Cindy Furst** at cindyfurst@gmail.com.

FLORIDA

Ft. Lauderdale Area

Back in July, **Phil Lewis** and **Charlie Koch**, the facilitators of the southern Florida group, began planning an ambitious day-long patient educational conference. Held mid January at the Memorial Hospital in Hollywood, FL, the conference was supported by both the IWMF and the LLS and was highly successful. Dr. Steven Treon, one of the conference headliners, spoke about his research breakthrough announced just a month before at the Annual Meeting of the American

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The panel of doctors answered questions at the conclusion of this very busy and informative day. From left to right: Dr. Fred Hochberg, Dr. Steven Treon, and Dr. Mark Stein.

Society of Hematology. Additional speakers included: Dr. Fred Hochberg, associate professor of neurology at Harvard Medical School; North Palm Beach internist and immunologist Dr. Mark Stein; and Hippocrates-certified cancer nutritionist Tracy Hritz, M.S., R.D.. At 9:30 am, the 101 patients and companions began to fill the main auditorium to register and enjoy a complimentary breakfast. Ms. Hritz led the group first in a deep breathing and meditation sequence followed by a detailed slide presentation entitled "Smart Nutrition for Patients." Then Dr. Stein presented a revealing look at the immune system problems of WM patients in his talk "Immunodeficiency Secondary to Lymphoproliferative Disorders and Their Therapy." His presentation sparked many questions from interested patients in the audience. After lunch Dr. Hochberg captivated the audience with his subject, "Waldenstrom's and Nerves; Waldenstrom's and the Brain." Dr. Hochberg has a unique way of communicating with his audience that creates insightful questions and exchanges with patients. Finally, Dr. Treon described his groundbreaking research in his presentation "The Genetic Basis of Waldenstrom's Revealed through Genome Sequencing: Implications for New Treatment Strategies." His passionate and uplifting presentation with detailed slides depicting the MYD88 pathway and the implications for both today and in the future gave the group hope and inspiration. The concluding "Ask the Doctor Panel Q&A" was moderated by Chris Patterson, Administrative Director of the Bing Center at Dana-Farber Cancer Institute. The spirited exchange, highlighted by questions of mutual interest, sparked a commentary from each panelist. A standing ovation, and even some cheers, at the conclusion of the Q&A demonstrated the enthusiasm of all the attendees.

Southwest Florida

The third of March was a big day for WMers in Sarasota when approximately 100 patients and family members gathered at Doctors Hospital to hear a presentation by Dr. Steven Treon on genome sequencing and the exciting news about MYD88. Dr. Treon's willingness to travel frequently and share such important information means a lot to so many.

The opportunity to have questions answered by an expert really makes a difference!

Also in attendance was Dr. Luis Chu, a local physician in Sarasota who treats WM patients and consults on WM cases with Dr. Treon. IWMF founder Arnie Smokler was one of Dr. Chu's patients. The use of the auditorium at Doctors Hospital was arranged thanks to Dr. Chu, while **Herb** and **Marge Kallman** and **Joe** and **Connie Gallo** coordinated the meeting together with **Sara McKinnie** from the IWMF business office. We are grateful to both doctors for generously sharing their weekend and family time.

GEORGIA

Dr. Steven Treon from the Bing Center at Dana-Farber Cancer Institute will present at the Saturday 19 May meeting at 1 pm in Atlanta. All IWMF members, friends, and family from Georgia, Alabama, and South Carolina are invited to attend. It's a terrific opportunity for any and all, especially those not able to travel to Philadelphia to hear Dr. Treon at the IWMF Patient Educational Forum. The Leukemia & Lymphoma Society of Georgia is generously supporting the event and making Dr. Treon's trip possible.

IDAHO

The southeast Idaho support group includes the Jackson Hole, WY, region and parts of Montana as well. It has always been a very small group of five patients and three caregivers. Three patients (all male) passed on in a two-year period. The smaller group, consisting of two female patients and their spouses, plus the widow of one member of the original group, has continued to meet. The emphasis has been on caring, sharing, frequent phone calls, and informal kitchen-table meetings while continuing to try to locate other 'Wallies'. Often the distance is too great for others to come to the meetings. So members keep the telephone lines busy to stay informed, encouraged, and involved – especially by joining IWMF-Talk. Recently, the group broke from tradition and met in a local restaurant to welcome another caregiver, sister of **Janet Corson Stanton**, who was in town for a visit.



From left to right: Marsha Stanger (widow of John Stanger), Sue (sister of Janet Corson Stanton), Janet (survivor), and Barb Britschgi (survivor).



Wisely, the husbands decided it would turn into a hen party, with much laughter and the sharing of funny stories of their ups and downs. Since it is a small town, many guests in the restaurant recognized the gals who felt very à la *Cheers*.

ILLINOIS

Chicago Area and Southeast Wisconsin

Dr. Sherine Elsawa, a Waldenstrom's researcher and assistant professor at Northern Illinois University, will speak at the 21 April meeting to be held at Lutheran General Hospital in Park Ridge starting at 12:30 pm. The annual summer picnic will be hosted by **Sara Thran** during the month of August. Everyone is welcome!

INDIANA

Because winters can be so brutal, the group decided not to even try to meet during the depth of winter. This winter, however, turned out to be mild. To celebrate spring, the group met on the last day of March at the LLS offices in Indianapolis. There was a large turnout to hear Dr. Rafat Abonour, Associate Dean of Clinical Research at Indiana University Medical Center, speak on his area of particular expertise, stem cell transplants. Coffee and breakfast snacks were served and helped fortify members for the spirited question-and-answer period.

NEW YORK

New York City

The New York metro area support group met on an exceptionally cold Sunday in January, smack in the middle of a three-day weekend, so the turnout was perhaps understandably lower than usual. Even so, those who made it enjoyed a spirited discussion. The highlight – perhaps more appropriately the lowlight – was the dramatic story of a member's experience in a drug trial that had been underway

for more than a year. The participant had been doing very well for almost the entire time, and then, mysteriously, he suddenly wound up in the hospital, in alarmingly bad shape, with crashing numbers and serious loss of weight in addition to other unpleasant symptoms. This participant stopped the drug, began to recover from the experience, and arrived at the meeting on the thin side but highly energetic and eager to tell his story, in all its novelistic detail, with a wry sense of humor. This extremely knowledgeable participant was quick to remind the group that his experience was an outlier across the broad range of this particular trial, perhaps (but who knows?) resulting from other “co-morbidity” health conditions. The story was a bracing reminder of the extreme importance of drug trials, the hope for progress they provide, and the significant risks that courageous patients may take when they consent to enter a trial, no matter how promising it is. WM can be a wild ride!

Rochester, Western and Central NY

Valentine's Day turned into a day to celebrate long-term survival at Red Lobster Restaurant. By 1 pm when the eight members (six patients and two spouses) arrived for their lunch meeting, other parties were already in progress. The restaurant meeting, a departure from the usual Gilda's Club rendezvous, was so successful that the group plans a late spring meeting, again at a restaurant, but perhaps dinner instead of lunch. Most of the members have been together since the group formed in 1998 and remain generally healthy. This 14-year history speaks well of their medical care and the advances made in the treatment of WM. A quick head count revealed that five of the WMers are in remission (one since 2002) and another has not yet needed treatment. All remain upbeat and look forward to the next outing.

Northeast NY, Western New England



Group members gathered in September to hear Dr. Sheldon Staunton. From left: Claire Wengraf, Mel Horowitz, Lorraine, Pam Fox-Ferro, Joe Palermo, Dr. Staunton, Doug Jones, Dottie and Ralph Hoyt (front) and Judy and Neil Scharpf (rear).



In September, November, and February we met at the ACS Hope Club in Latham, NY. In September we all enjoyed an excellent speaker, neurologist Dr. Sheldon Staunton. With a sense of humor and a great deal of experience and wisdom, Dr. Staunton spoke informally and answered questions for almost 90 minutes. He volunteered to come back another time and we all agreed to accept his offer. At our November meeting we watched with interest the first four doctors' presentations of the Mayo Clinic Report at the IWMF Forum. More recently, nutrition expert Georgia Decker, past president of ONS (Oncology Nursing Society), spoke with the group and outlined the best nutritional practices for a healthy lifestyle. Her emphasis was on how proper supplements and making healthy food choices can improve our ability to cope with cancer (or any other disease). She unflinchingly answered all of the group's many questions which spanned a large range of issues. Everyone agreed that this was an excellent meeting. The next program will be the annual restaurant outing on Saturday 14 April at 11:30 am, at the Route Seven Diner located at 1090 Troy-Schenectady Road in Latham, NY. Anyone who will be in the Albany area on that date is welcome to join in. Please let **Mel Horowitz**, group facilitator, know (wmcure@yahoo.com) if you plan to attend.

NORTH CAROLINA

Seven WMers along with six caregivers met at the end of January at the Pardee Hospital Education Center in Hendersonville. A guest speaker representing the LLS described the available programs including financial aid that may be accessed by WM patients. A new member, age 55, called into the meeting and described, via speakerphone, his decision-making process as he considers an autologous stem cell transplant. He has explored the option with the Duke University Medical Center where several transplants have been performed. The group asked many questions and plans to keep in touch as he nears his final decision. Another new member and her husband drove four hours from Pinehurst, NC, in order to attend. She has had WM for 21 years and is in treatment quite often. The group found her story quite interesting and helpful. The meeting then opened into a period of sharing among the members and concluded with a luncheon. In addition to the Pinehurst couple, other members arrived from the Winston-Salem, Charlotte, Asheville, and Hendersonville areas. The next meeting has not been scheduled but is likely to be in the early spring.

EASTERN OHIO, WESTERN PENNSYLVANIA, & WEST VIRGINIA

Marcia and Glenn Klepac hosted a pre-holiday potluck and informal meeting. The **Smiks** joined the group for the first time and expanded the eastern Ohio representation. As always, the atmosphere was uplifting with everyone socializing, trying new potluck dishes, and sharing WM stories. The topic of keeping a healthy perspective on WM (living life between WM visits and treatments) stimulated a discussion of members' hobbies and special interests. Of

course, IgM levels and symptoms were also hot topics. Then the mild winter weather offered the rare opportunity for an early February meeting. While enjoying many delicious culinary contributions, members shared the latest challenges and victories in their WM journeys. The tissue bank study and questionnaire by Dana-Farber's Dr. Irene Ghobrial was reviewed. All the members were encouraged to participate in this comprehensive project to examine genetics, medical, lifestyle, and environmental factors related to Waldenstrom's. Dr. Jan Waldenström's 1991 editorial, "To Treat or Not To Treat, This is the Real Question," triggered a discussion of personal reflections on treatment issues: treating on numbers or symptoms, low-dose or standard-dose regimens, and quality of life. The informal group setting provides a supportive environment to debate these tough choices.

OREGON/SOUTHWEST WASHINGTON

On a rare and beautiful sunny January day, Dr. Stephen D. Smith, a new addition to the faculty at the Knight Cancer Center at Oregon Health Sciences University in Portland, spoke at the quarterly meeting. Twenty-three came to enjoy the warmth and friendship of the group and to hear Dr. Smith update the group on the news from the Annual Meeting of the American Society of Hematology. Dr. Smith, a clinician and researcher in blood disorders who has had much experience with Waldenstrom's at the Cleveland Clinic, gave a lively presentation and discussed in detail the possible causes of WM and some of the new understanding emerging from the recent genetic sequencing of WM cells. It was especially interesting that there seem to be some causes of WM that may be genetic while others may be "acquired." Dr. Smith also discussed the current approaches and medications used to control WM, discussing the differing purposes of the drugs: some are intended to create an inhospitable environment for a WM cell (to disrupt the WM cell's "cozy niche"), while others inhibit the growth of certain detrimental cells. He then continued to talk about the future directions of treatment, emphasizing the targeting of the microenvironment of WM in cell development to create the possibility of personalized therapies, new drug combinations, better antibodies, and oral treatments. A lengthy Q&A session with Dr. Smith helped make the information more accessible to the layman audience. Everyone left feeling grateful for the dedicated physicians and researchers working on behalf of WMers and happy to have Dr. Smith in the northwest. The next meeting will be on Saturday 28 April, 12 noon to 2 pm, at the Fairfield Inn & Suites, 6100 Meadows Road, Lake Oswego, OR, just off I-5. Lunch is provided and parking is free.

PENNSYLVANIA

Philadelphia

Right around the holidays, the group got together to watch the DVD of Dr. Steven Treon's talk at the 2011 Ed Forum. All twenty-eight attendees greeted with enthusiasm Dr. Treon's announcement of the identity of the genetic





In spite of the nippy February weather, patients coming from three states met in Memphis and heard from Dr. Thomas Ratliff.

mutation implicated in 90% of WM patients in his whole genome sequencing study. **Carl Harrington** and **Ron Yee** from the IWMF Board attended the meeting and added much to the discussion. Many in the group volunteered to help with the June 2012 Ed Forum taking place this year on our home turf. Heidi, the four-legged mascot, wore a fetching red holiday bow. Her outfit meant even more treats fell her way than usual. The meeting closed with time for chitchat and refreshments.

TENNESSEE

Western Tennessee, Eastern Arkansas, Northern Mississippi

The group met on Saturday 11 February in Memphis on what turned out to be the coldest day of the year thus far. That didn't stop fourteen people, representing patients in all three states, from attending. The Memphis Team is tough! The group discussed the status of their disease and treatment. Dr. Thomas Ratliff, a local oncologist from the Boston Baskin Cancer Foundation, participated in the discussions, adding information, clarifying symptoms, and giving encouragement.

Some of the topics whipping around the room were: pros and cons of Rituxan and Velcade, how WM affects hypertension, when to take diuretics safely, peripheral neuropathy and how it manifests itself, dealing with watch-and-wait, choosing a knowledgeable ophthalmologist, genetic testing, and current research to find treatments tailored to the WM patient. It was emphasized that there is no direct correlation between the level of monoclonal IgM and symptomology. Patients with similar laboratory test results may show markedly different types and degrees of symptoms. During the discussion, it was discovered that nearly two-thirds of the patients in the group seemed to suffer from cancer-related fatigue. Information was given concerning the June IWMF Educational Forum in Philadelphia. Several members of the group continued their discussions over dinner. The members extend their sincere thanks to Dr. Thomas Ratliff for spending a large portion of his Saturday with them and to Dr. Connie Paul of the Memphis Center for Women & Families for once again providing meeting space.

THE INTERNATIONAL SCENE

WM IRELAND SUPPORT GROUP

Sheila Thomson took over from Anne Staples as leader of our small group during the spring of 2011. We held a meeting in Sheila's house on 23 October with four WMers, together with the partners of two. One of the WMers, our first male member, had been recently diagnosed and was very interested to hear our stories, as we were to hear his. We discussed the encouraging news from Dr. Steven Treon in relation to genome sequencing and agreed that we were looking forward to hearing him speak at the Third International Patient Forum sponsored by WMUK in London on 11 March. All four, and possibly more, of us hope to attend.



that regulate cell growth – the MAPK and NF- κ B pathways. Velcade (bortezomib) affects the NF- κ B pathway, so the discovery of the MYD88 L265P mutation now gives us an important clue as to why this drug has been so successful in the treatment of Waldenstrom's patients.

Is there a test for the MYD88 L265P mutation?

Whole genome sequencing requires lots of purified DNA. For many patients with WM, obtaining such amounts is problematic. In addition, whole genome sequencing can take 4-6 months and, at present, can cost \$5,000 per genome (down considerably from \$100,000 just 3 years ago).

An alternative to whole genome sequencing is the use of Sanger sequencing. One limitation of Sanger sequencing is that WM cells have to be purified so as to provide enough DNA for this test; another limitation is that there have to be enough cells in the bone marrow for testing of unselected bone marrow samples. Since most clinical laboratories do not purify cells, we sought to develop a highly sensitive test using a platform called PCR (polymerase chain reaction) to selectively test for the presence of the MYD88 L265P mutation. An abstract detailing the successful use of this PCR test to detect MYD88 L265P in WM patients will be reported by Dr. Lian Xu from our center at the Annual Meeting of ASCO in June 2012. This test is currently being validated in clinical laboratories and potentially can pick up one WM cell in a background of 4,000 normal cells. This test also has the potential to be used as a blood test and to possibly assess residual disease in patients who have undergone treatment. The PCR test for MYD88 L265P should become available for commercial use in the next few months.

Are there diagnostic implications for MYD88 L265P for WM patients?

There are many overlapping disorders that have clinical and pathological features similar to Waldenstrom's macroglobulinemia. These include marginal zone lymphomas (such as splenic, nodal, and MALT lymphomas) as well as IgM multiple myeloma. The MYD88 L265P mutation is either absent or rarely expressed in these entities, allowing the MYD88 L265P mutation to be used as an aid to separate WM from these other entities. In the studies presented by Dr. Lian Xu at the 2011 Annual Meeting of ASH, the MYD88 L265P mutation was absent in almost all patients with IgM monoclonal gammopathy of unknown significance (MGUS), a precursor condition to WM. This finding may either imply that the mutation is altogether absent in IgM MGUS patients or is expressed at a very low level, far lower than the threshold of detection using Sanger sequencing. It is interesting that for one IgM MGUS patient who had the MYD88 L265P mutation, disease progression to WM occurred. A larger series of studies of IgM MGUS patients with long term

follow-up will be required to clarify whether MYD88 L265P is a mutation that transforms IgM MGUS to WM.

Does the MYD88 L265P mutation distinguish those patients with familial versus non-familial forms of WM? Can it be used to identify family members at risk for WM?

Up to 27% of patients have a familial form of WM, defined as having at least one first or second degree relative with WM or another type of lymphoma, myeloma, chronic lymphocytic leukemia or MGUS. The MYD88 L265P mutation was found in WM cells from patients with both familial and non-familial WM and appeared at the same frequency (90%). These results suggest that MYD88 L265P is unlikely to be a predisposition gene for familial forms of WM. A search for predisposition gene(s) for familial WM is currently underway using whole genome sequencing to compare the genomes of patients with and without familial forms of WM.

Does the finding of the L265P mutation in MYD88 have implications for the treatment of Waldenstrom's patients?

The most important implication of the discovery of the MYD88 L265P mutation in WM patients is the prospect of developing novel targeted therapies for WM patients. In studies reported at the 2011 Annual Meeting of ASH, Bing Center scientists Dr. Yangsheng Zhou, Dr. Xia Liu, and Dr. Yang Cao used gene knock-in and knock-down models to show that the MYD88 pathway was essential for keeping WM cells with the MYD88 L265P mutation alive. These studies suggested that drugs blocking the MYD88 pathway could provide a targeted approach for WM therapy. The MYD88 pathway has been under active investigation for many years, primarily because of its importance in rheumatologic (autoimmune) diseases. Inhibitors for both MYD88 and the signaling proteins for MYD88 – IRAK1 and IRAK4 – have already been developed. Bing Center scientist Dr. Guang Yang reported at the 2011 Annual Meeting of ASH that both MYD88 and IRAK1/4 inhibitors induced dramatic cell death of the BCWM.1 and MCWL-1 WM cell lines which carry the MYD88 L265P mutation, as well as primary malignant lymphoplasmacytic cells purified from bone marrows of WM patients. More potent inhibitors of both the MYD88 and IRAK proteins are currently under study by the Bing Center team. It is anticipated that in the next 1-2 years the results from these laboratory studies will identify lead drug candidates for use in clinical trials for WM patients.

Dr. Steven Treon is Director of the Bing Center for Waldenstrom's Macroglobulinemia at the Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston, MA. Dr. Treon currently serves on the Scientific Advisory Committee of the IWMMF and is a regular participant at IWMMF Educational Forums.



impact on the pathogenesis of WM. These pathways included IRAK1, NF-kappa B, and JAK/STAT. Treatment of WM cell lines and primary tumor cells with inhibitors of MYD88 and IRAK1/4 kinase activity resulted in robust apoptosis (cell death), activation of caspase-3, decreased BCL-2 expression, and decreased release of the cytokine Interleukin-6 and of IgM.

There were also other interesting discoveries in the world of WM biology. Zibellini et al. from Italy analyzed the immunoglobulin heavy chain rearrangements in a series of 123 patients with WM, IgM-MGUS, and other IgM-related disorders, with the aim of determining if a limited set of antigens is involved in the transformation of normal B-cells to the B-cells of these monoclonal disorders. The variable region of heavy chains, including IgM, is made up of segments that are joined together and can be grouped into families based on the similarity of their DNA sequencing. A particular heavy chain family called IGHV3 occurred more frequently in WM, IgM-MGUS, and IgM-related disorders than in normal B-cells, while other heavy chain rearrangements (IGHV1 and IGHV4) were significantly under-represented. The study also analyzed the amino acid sequences of heavy chain complementarity-determining region 3 (CDR3) from these same patients and compared them to known subsets of other similar diseases. CDR3 is the highly specific region of an antibody that binds to an antigen. No relationship was seen with known CDR3 sequence clustering of chronic lymphocytic leukemia or splenic marginal zone lymphoma. The study also concluded that, although one IgM-MGUS showed similarities with sequences derived from hepatitis C-related lymphomas, there was little evidence to support the identification of specific antigens involved in the majority of IgM-related disorders, including WM.

In a German study, Grass et al. investigated the role for chronic autoantigenic stimulation in the development of MGUS, multiple myeloma, and WM. This abstract cited previous studies which stated that carriers of hyperphosphorylated paratarg-7 (pP-7) have an 8 to 13 times increased risk to develop IgA- and IgG-MGUS and multiple myeloma, as well as a 6.5 times increased risk to develop IgM-MGUS and WM. This gene is inherited in a dominant fashion, providing an explanation for cases of familial disease. Analysis of the T-cell response against pP-7 indicated a strong and specific CD4+ T-cell response, indicating that these T-cells can stimulate B-cell clones with the same specificity, eventually resulting in the clonal evolution of the B-cell clone. The different prevalence of pP-7 carriers in various ethnic groups (15% of Caucasians, 4.5% of Asians, and 28% of African-Americans) may explain the relative incidence rates of MGUS, multiple myeloma, and WM in these ethnic groups.

A Greek study reported by Lymberi et al. of Dr. Meletios Dimopoulos' group stated that serum monoclonal immunoglobulins of patients with monoclonal gammopathies are known to possess antibody activity against autoantigens, bacterial antigens, and haptens (partial antigens), but their rate

of occurrence is controversial. The aim of this study was to investigate the frequency of monoclonal immunoglobulins that exhibit natural autoantibody activity and to explore possible correlation with the clinical features of disease. Patients with monoclonal IgG, IgA, and IgM were tested – 50 of these were WM and 43 were IgM-MGUS patients. Their sera were studied for reactivity with six autoantigens (actin, carbonic anhydrase, tubulin, myosin, and TNP) and for activity against human polyclonal IgG. Among the monoclonal IgM immunoglobulins, the highest incidence of activity was against actin and carbonic anhydrase, and a high percentage of WM patients were polyreactive (reacted with at least two antigens). There was no significant correlation of immune-related features of symptomatic WM (cold agglutinin disease, thrombocytopenia, cryoglobulinemia) with any of the detected activity profiles. These findings suggest that monoclonal gammopathies with natural autoantibody activity might reflect the expansion of a clone normally producing a natural autoantibody rather than an antibody in response to an antigen stimulus.

Hodge et al. from Dr. Stephen Ansell's group at Mayo Clinic examined the expression of Interleukin-21 (IL-21) and its receptor in WM cells to determine whether it contributes to the biology of WM. IL-21 is a cytokine (cell signaling molecule) involved in the differentiation of B-cells into plasma cells. Eight WM patients and the MWCL-1 cell line were assessed for IL-21 expression; nearly all (7 of 8) expressed IL-21, as did the cell line. Addition of IL-21 to WM tumor cells and to the cell line caused the cells to proliferate by 50% and 37%, respectively, over untreated controls. IL-21 also significantly induced IgM secretion. Additional experiments suggested that IL-21 works primarily through the STAT3 pathway. IL-21 also increased BLIMP-1 and BCL-6 levels whereas PAX5 was significantly decreased. Lastly, IL-21 significantly increased IL-10 secretion from MWCL-1 cells; IL-10 is known to be involved in normal B-cell development but may have synergistic effects with IL-21 in WM cells.

Another abstract by Zhou et al. from Treon's group reported on aberrant expression of several transcription factors and their effect on plasma cell differentiation in WM. Transcription factors are proteins that bind with specific DNA sequences thereby controlling the flow of genetic information from DNA to messenger RNA. Typically, the lymphoplasmacytic cells of WM exhibit deficiencies in their ability to differentiate from mature B-cells to plasma cells. Comparing the bone marrow B-cells of 12 untreated WM patients with 15 age-matched healthy donors, this study showed increased expression of factors Oct-2 and Spi-B and decreased expression of Id2 and Id1 in WM. The data suggest that Oct-2 is involved with regulation of Id2 and Id1 in concert with Spi-B during B-cell differentiation by repressing several factors involved in plasma cell differentiation, including BLIMP1, XBP-1 spliced form, and IRF4, while promoting WM cell survival



through BCL-2 expression.

DIFFERENTIAL DIAGNOSIS AND DISEASE MONITORING

Lymphoplasmacytic lymphoma (which includes WM) and marginal zone lymphoma (MZL) are distinct entities, but the differential diagnosis between the two can be difficult due to overlapping features. Xu et al. from Treon's group examined the importance of the MYD88 L265P variant described above (see **WM BIOLOGY**) in distinguishing between these diseases. This study looked at 51 LPL patients, 49 of whom had WM, and 46 patients with various MZL subtypes. Among LPL patients, the variant was found in malignant cells from 90.1% of cases; by comparison, only 6.5% of MZL patients exhibited the variant and none of 15 healthy donors did. The MZL patients who did exhibit the variant had clinical disease features which overlapped with LPL.

Measurement of serum M-spike is used to determine disease status and response to therapy in WM; however accurate measurement by serum protein electrophoresis (SPEP) can be difficult, as can total IgM measurement by nephelometry. Consequently, there is a need to identify markers that reflect disease burden and correlate with treatment outcomes. A French study by Manier et al. reported on Hevylite, a test that measures IgM kappa and lambda chains separately. Serum samples from 86 WM patients untreated and currently in treatment were measured with Hevylite. Normal ranges were also determined: IgM kappa 0.29-1.82 g/L, IgM lambda 0.17-0.94 g/L, and kappa/lambda ratio 0.95-2.3. The concordance of IgM by Hevylite with M-spike was quite good. The authors concluded that Hevylite has the potential to be a reliable marker for monitoring disease progression and response to therapy.

Rombaoa et al. from Dr. Irene Ghobrial's group at Dana-Farber affirmed that microRNA-155 is elevated in chronic lymphocytic leukemia (CLL) and in WM and investigated it as a potential biomarker for both diseases. Both plasma and serum samples were collected from CLL patients, WM patients, and healthy individuals. A total of 20 CLL plasma samples showed a 100% positive ratio of detectable microRNA-155, while 20 CLL serum samples had only a 50% positive ratio. A total of 96 WM plasma samples had a positive ratio of 74%, while 30 WM serum samples showed a much lower positive ratio of 3%. The 10 plasma and 10 serum samples from healthy individuals were all negative for microRNA-155. The disparity between plasma and serum seen in CLL and WM samples was unexpected. While possible explanations are still under investigation, the disparity may be due to a difference in the level of exosomes (vesicles which are known to carry microRNAs) between plasma and serum. Further investigation is warranted to confirm the status of microRNA-155 as a reliable plasma biomarker for these malignancies.

CLINICAL FEATURES OF DISEASE

A retrospective analysis by Paba-Prada et al. from Dana-Farber reported on the incidence of peripheral neuropathy at diagnosis in WM patients. Of the 182 patients examined from November 2000 to October 2009, 47 (25%) were identified with neuropathic symptoms at the time of initial presentation. The most common symptoms were paresthesias (prickling, tingling, burning) and weakness of the extremities. Most patients with peripheral neuropathy had low risk disease by ISS-WM staging (55%), had a median IgM level of 3095 mg/dL, and a median beta-2 microglobulin level of 2.5 mg/L. In the patients without PN, the median IgM level was 4002 mg/dL and beta-2 microglobulin was 3.5 mg/L. The study identified 2 patients with positive anti-MAG and 1 patient with anti-GM1 antibodies, while 3 patients had evidence of amyloidosis and 2 patients had positive cryoglobulins. Three patients were identified with B12 deficiency, which could have contributed to their neuropathy.

A United Kingdom study from Tute et al. attempted to determine whether there are distinct entities within the spectrum of MZL, LPL, and WM and to correlate these entities with clinical features. Samples from 146 people with MZL, LPL, WM, hairy cell leukemia, reactive lymph nodes, and normal bone marrow were analyzed using flow cytometry with a panel of 39 CD and other markers. Tumor cells in all groups typically expressed CD31, CD39, and CD49d with lack of CD10, CD23, and weaker expression of CD305, CD185 and CD22 compared to normal B-cells. The study identified five clinical entities with significant differences in their phenotypic profiles as follows: (1) clustered with normal mature B-cells, characterized by weaker CD20/CD95 and stronger CD185 expression, shorter survival, anemia and lymphadenopathy, typically requiring therapeutic intervention at diagnosis; (2) clustered with hairy cell leukemia, characterized by CD25 and CD11c expression and a higher degree of extranodal involvement; (3) did not cluster with other B-cell types, characterized by very strong CD79B and surface IgM expression, often with anemia requiring supportive care; (4) characterized by strong CD24 expression, with relatively good clinical course; and (5) clustered with normal bone marrow plasma cells, characterized by weak CD20, CD24, and IgM expression, also with better clinical features.

TREATMENTS – PRE-CLINICAL AND CLINICAL

This topic generated several abstracts about WM – a good sign – indicating the development of more and better treatments for WM and hopefully paving the way for their use by clinicians.

Zhang et al. from Ghobrial's group examined the effect of a novel **LNA (locked nucleic acid)-modified anti-microRNA-155** in WM and CLL. Developing therapeutic agents that specifically target microRNAs has been hampered



by the lack of appropriate delivery of inhibitors into tumor cells. Cell lines and primary tumor cells of both diseases were treated, and cell proliferation was reduced by 30-50%. Efficiency of drug delivery was higher than 90%. In addition, this study identified several microRNA-155 targeted genes, which may help to design individualized clinical trials for WM and CLL patients with elevated levels of microRNA-155 in their tumor cells.

Final results were summarized for a Phase II clinical trial of single agent **panobinostat (LBH589)** in relapsed/refractory WM. Ghobrial et al. enrolled patients from August 2009 to March 2011; of the 36 patients that received treatment, 35 were evaluable for response, and all had received prior rituximab therapy. Minimal response or better was achieved in 49% of patients, and the most common toxicities included anemia, leukopenia, neutropenia, thrombocytopenia, fatigue, and GI symptoms. There were 4 cases of asymptomatic pulmonary infiltrates consistent with idiopathic pneumonia or pneumonitis. The original protocol was based on a starting dose of 30 mg three times a week, but a reduction to 25 mg proved to be better tolerated. Further studies to include this agent in combination with rituximab and/or bortezomib are warranted.

A multicenter pre-clinical study by Tai et al. discussed Bruton's tyrosine kinase (Btk) in multiple myeloma and WM and investigated the effects of **PCI-32765**, a potent oral Btk inhibitor, on MM and WM cancer cells. A higher expression of Btk and its downstream signaling components was demonstrated in WM cells than in normal bone marrow cells, and PCI-32765 inhibited growth and survival in co-culture with bone marrow stromal cells. The authors concluded that the evidence strongly supports clinical trials of PCI-32765 to improve patient outcomes in MM and WM.

The role of **bortezomib** therapy in improving responses in WM patients was investigated by Banwait et al. from Dana-Farber. This retrospective analysis was performed on 182 WM patients enrolled in various clinical trials from November 2000 to October 2009 who were characterized as newly diagnosed/upfront or relapsed according to their disease status at the time of entry into clinical trials. The study compared response rates for bortezomib-containing regimens vs. non-bortezomib therapies and concluded that bortezomib can improve response rates in the relapsed setting, while in the upfront setting, bortezomib had activity similar to other therapeutic agents.

Continuing with outcomes in **bortezomib** therapy, Treon et al. examined the impact of familial predisposition to WM on treatment outcomes and determined that responses were better among patients with familial WM who received a bortezomib vs. non-bortezomib containing regimen. A longer time to disease progression was also observed for familial patients receiving bortezomib, suggesting that certain signaling

pathways are present in familial patients and amenable to select targeting by proteasome inhibitors such as bortezomib.

A multicenter study, presented by Treon et al., discussed the MTOR inhibitor **everolimus, also called RAD001**, as primary therapy for WM patients. Therapy consisted of 10 mg of oral everolimus administered daily, with sequential dose de-escalation every other day permitted for toxicity. Patients were treated until progression or unacceptable toxicity and were encouraged to use an oral dexamethasone solution to prevent oral ulcerations associated with everolimus. Thirty-three patients were evaluable for response; the median time to best response was 3 months, and the overall response rate was 66.7% with a major response rate of 42.4%. However, discordance was noted between serum IgM levels and bone marrow disease response, and this complicated response assessment. Toxicities associated with everolimus included anemia, thrombocytopenia, neutropenia, hyperglycemia, oral ulcerations, pneumonitis, fatigue, rash, and cellulitis. The study concluded that, because of serum IgM discordance to bone marrow disease burden, serial bone marrow assessments are important for response monitoring in WM patients receiving everolimus.

Ghobrial et al. summarized results from a Phase I trial of **everolimus/rituximab and everolimus/bortezomib/rituximab** in relapsed/refractory WM. The study aimed to determine the safety and maximum tolerated dose of these combinations. Subjects who had a response to therapy continued to maintenance therapy with everolimus alone until progression (or a maximum of 24 months). Because of the potential for an IgM flare after rituximab, patients who showed an increase in IgM after rituximab in the first 3 months were not deemed as having progressive disease unless they showed evidence of clinical progression. A total of 23 patients were enrolled; an overall response rate of 53% was attained, with a 33% response rate for the everolimus/rituximab arm and a 62% response rate for the everolimus/bortezomib/rituximab arm. The most common toxicities included neutropenia, leukopenia, anemia, and thrombocytopenia, but, importantly, no severe neuropathy was seen. Based on the safety of this study, a Phase II study of two arms, everolimus/rituximab for low risk patients and everolimus/bortezomib/rituximab for intermediate and high risk patients, is underway.

A multicenter Phase II trial of **ofatumumab** in WM was presented by Furman et al. Ofatumumab is a fully human monoclonal anti-CD20 antibody already approved for refractory CLL and has demonstrated activity in indolent B-cell lymphomas. This trial had two arms: (1) Treatment Group A received 300 mg week 1 and 1000 mg weeks 2-4, and (2) Treatment Group B received 300 mg week 1 and 2000 mg weeks 2-5. Thirty-four of 37 patients completed the study; some were treatment naïve and some had received prior therapy, including rituximab. The overall response rate



was 59% (47% for Treatment Arm A and 68% for Treatment Arm B). Infusion-related events occurred, and 15 patients developed infections. There was a lower incidence of IgM flare with ofatumumab than has been reported with rituximab, and Treatment Arm B was more effective in patients previously exposed to rituximab or with a high baseline IgM (≥ 4.0 g/dL) at treatment onset.

An international multi-center abstract from Dr. Véronique Leblond et al. reported on a Phase III study of **chlorambucil vs. oral fludarabine** as initial therapy for 414 patients with WM and related disorders, including marginal zone lymphoma and other non-WM lymphoplasmacytic lymphoma. The overall response rate was 47.8% in the fludarabine arm vs. 38.6% in the chlorambucil arm, and the median progression free survival and disease free survival were longer in the fludarabine arm. The main toxicity was hematological, including thrombocytopenia and anemia. The overall survival rate at 5 years was 70.3% in the fludarabine arm and 61.4% in the chlorambucil arm. The incidence of second malignancies (solid tumors and hematological malignancies except Richter syndrome) was statistically higher in the chlorambucil arm.

PROGNOSIS AND SURVIVAL

Terpos et al. from Dimopoulos' group in Greece investigated whether CCL3 is an independent prognostic factor for survival in WM. CCL3 is a chemokine that is elevated in multiple myeloma and chronic lymphocytic leukemia (CLL); for CLL it provides such a prognostic survival factor. This study investigated 41 newly-diagnosed symptomatic WM patients who required therapy. Circulating CCL3 was evaluated in all patients and in 40 healthy, age- and gender-matched individuals. Median circulating CCL3 levels were higher in WM patients than in the controls (66 pg/mL vs. 15.4 pg/mL). All WM patients received rituximab-based regimens as first-line therapy, and 67% of them achieved at least a minor response. The study then evaluated the effect of circulating CCL3 on patients' survival, using as a cut-off value the highest CCL3 value of the normal control group. The median survival for WM patients with CCL3 levels ≥ 54 pg/mL was 67 months, while it had not been reached for patients with CCL3 levels < 54 pg/mL. The authors concluded that high circulating levels of CCL3 were associated with a clear trend for inferior survival and that CCL3 is a potential target for developing novel drugs for WM treatment.

A retrospective German study by Hensel et al. compared standard treatment and outcomes of WM patients treated in

private oncology practices to those treated in a university hospital in a region of southern Germany. The study reviewed charts from the last two decades and identified 170 WM patients – 74 from private practices and 96 from the university hospital. Private practice patients tended to be older and had higher initial hemoglobin levels. The most common first-line treatments for private practice patients were chlorambucil, bendamustine, and bendamustine/rituximab; the most common first-line treatments for university hospital patients were pentostatin/cyclophosphamide/rituximab, chlorambucil, and COP (cyclophosphamide/vincristine/prednisone). The time to first treatment was significantly shorter in patients from the university hospital, but median overall survival of all patients was 25 years and did not differ between the two groups. This survival statistic is much better than has been previously reported for WM.

A multi-center study provided by Ailawadhi et al. undertook a large SEER-based analysis to describe outcome disparities in different subgroups of WM patients, with a focus on various ethnicities. SEER is a program of the National Cancer Institute and is a source of statistical cancer information and survival in the U.S. The study's final analysis included 2,840 WM patients diagnosed in 1992 or later. Patients were stratified by gender, age group, and race/ethnicity. Patients were also stratified based on year of diagnosis (before or after 2002) to study the impact of certain novel agents (proteasome inhibitors, immunomodulatory drugs) on WM treatment. The ethnic breakdown was as follows: Caucasian 87%, African-American 4%, Hispanic 5%, Asian 5%, and Native American 0.1%. There was a significant difference in age at diagnosis of WM patients, with African-Americans the youngest (median 61.5 years) and Caucasians the oldest (median 73 years). Survival analysis revealed that for all patients, females had better median overall survival than males (7.3 years vs. 6.2 years). Among the different age cohorts, patients with age ≥ 75 years had a significantly worse median overall survival than those 65-74 years old or 18-64 years old (4.1 years, 7.3 years, and 10+ years, respectively). Patients diagnosed after 2002 had a significantly better median overall survival compared to patients diagnosed before 2002 (7.3 years vs. 6.1 years). Hispanics had the worst median overall survival and Caucasians the best (5 years vs. 6.8 years).

If you have questions about ASH 2011 or would like to have an electronic file of ASH 2011 abstracts on WM, please contact the author at suenchas@bellsouth.net.



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In memory of Esther Freedman:

Bob & Eileen Whitman

In memory of Mary Gallo:

Joe & Connie Gallo

In memory of Jack & Carol Gelber:

Jed Gelber

In memory of my mother

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Your daughter Simona Cimato

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