



Dear Reader,

The beginning of a new year is always exciting. It's a fresh start a clean slate — anything is possible. More than ever, I hear myeloma experts and researchers say that they believe we are on the brink of making myeloma a chronic disease. Can cure be far behind? We are making huge strides in many areas: research, quality of life, awareness about myeloma, advocacy, and reaching out to lend a hand to those in need. We're proud of the fact that the IMF has been able to reach so many people around the world, giving them hope, empowering them through knowledge, and letting them know they are not alone.

The past year was a very busy one for the IMF and we were able to accomplish a great deal. We didn't do it alone. We're grateful to so many people who share our vision and who have enabled us to achieve our goals. We formed partnerships and collaborated with many people and I'd like to share with you what we've been able to do in 2002:

- held 5 Patient & Family Seminars, including the first ever "Interactive" P & F Seminar
- held the first ever "Challenging Cases for Multiple Myeloma"
- held the 3rd Annual Support Group Leader Retreat
- held the 2nd Scientific Advisors Retreat
- personally visited with 20 support groups
- NCI-trained hotline coordinators Nancy Baxter & Debbie Birns joined our team
- developed and produced the Myeloma Matrix
- developed and produced "Myeloma At The Movies"
- established a Patient Advisory Council
- began two new research initiatives — Bank On A Cure™ (BOAC) and the International Prognostic Index (IPI)
- funded 6 junior grants and 2 senior grants

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Ribbon of Hope — Making a World of Difference IMF 12TH ANNIVERSARY GALA



IMF President Susie Novis with Gala honorees Daniel E. Smith, the Honorable Geraldine Ferraro, and Tom Bay

By The Unknown Patient

As The Unknown Patient and his Unknown spouse dragged their luggage onto the shuttle to Washington DC, there was much to celebrate. His battle with myeloma was approaching its thirteenth year and for reasons far from Unknown, he was still going strong and feeling well. And, the Unknown couple was headed south for the IMF's 12th Anniversary Ribbon Of Hope Gala.

Landing in DC, the Unknown couple headed for our hotel. For some reason, the elevator bank was filled with rather large security guards in ill-fitting suits. Stepping

into the elevator, we found ourselves riding up with Rolling Stone Keith Richards — that explains the security.

The Unknown couple met IMF board member Rich Saletan and his lovely wife Susan for a late lunch in the hotel lobby. We were joined by IMF President Susie Novis and IMF board member Michael Katz and his lovely wife Susan (every woman in this article seems to be named Susan.) While crunching on his Caesar salad, your unknown author was stunned to see none other than Mick Jagger, looking none the worse for decades

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The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure.

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The information presented in *Myeloma Today* is not intended to take the place of medical care or the advice of a physician. Your doctor should always be consulted regarding diagnosis and treatment.

COVER STORY – continued



Suzanne and Rich Saletand with Susie Novis and Lindsay Luke

of wear, trying to make a quiet exit out the back door. Springing into action, Susie Novis grabbed a napkin and dodged two bodyguards to get to the elder Stone. "Mick, Mick," she said, "we're holding a benefit here tonight, won't you please sign this? Come on, Mick, it's to help cancer patients!" Susie returned to her quesadilla with a new item for the silent auction, a napkin autographed by Mick Jagger.



Robin Leach with IMF Director Don Woodward and Chairman of the Board Dr. Brian G.M. Durie

Not too much later, the Unknown couple put on their evening duds and made their way to the IMF Gala, which opened with a reception and silent auction. This was a great opportunity to introduce the Unknown spouse to folks who were good friends and prominent members of the myeloma community but Unknown to her.

The Unknown couple had an interesting discussion with Dr. Bill Bensinger of the Fred Hutchinson Cancer Research Center, one of the world's leading experts on myeloma transplants. Also present was IMF board member, Dr. Edith Mitchell, a Philadelphia-based oncologist who is a general in the U.S. Army. Dr. Mitchell also chairs the Eastern Cooperative Oncology Group's Underserved Committee. The Unknown couple was also pleased to see the evening's master of ceremonies, Robin

Leach, of *Lifestyles of the Rich and Famous*. Robin lost friend Brian Troup to myeloma and has been donating his services to the IMF in his memory for the past three years.

During the reception, Dinner Co-Chair Benson Klein presented the Quality of Care award to Deborah Doss, a multiple myeloma clinical research nurse at the Dana-Farber Cancer Institute in Boston. Benson has experienced first-hand the outstanding service and care Deborah provides to myeloma patients and their families.

Between drinks and tête-à-têtes, the Unknown patient managed to place bids



Deborah Doss with Quality of Care award

on a number of silent auction items, including some jewelry for the spouse and a script from one of his favorite episodes of "Everybody Loves Raymond." Soon, the doors into the ballroom opened and the guests entered and were seated to the sounds of the band singing "We Are Family."

Master of Ceremonies Robin Leach welcomed everyone and introduced IMF founders Brian Durie and Susie Novis. Brian and Susie spoke about the IMF's mission, improving the quality of life of myeloma patients while working towards a cure, and remembering fellow IMF founder Brian Novis. They introduced this year's dinner chairs, Carol and Benson Klein, who spoke about their personal battle with myeloma and how important the IMF is to myeloma



Dinner Co-Chairs Carol and Benson Klein with IMF Event Producer Suzanne Battaglia

patients and caregivers worldwide. The Kleins announced IMF Ribbon of Hope awards to Senators Kay Bailey Hutchison and Barbara Mikulski for their passionate commitment to increasing the level of federal funding for cancer research.



Honoree Tom Bay with family and friends and IMF Director Chuck Newman and wife Sharon

Next up was Michael Katz to present the IMF Courage Awards. The first award was presented to Tom Bay, a motivational speaker who helps people dealing with cancer put their lives back together. When Tom was diagnosed with myeloma, he stepped forward to help other patients, becoming active in the IMF and speaking at IMF Patient & Family seminars.

A second IMF Courage award was presented to the Honorable Geraldine Ferraro. Ms. Ferraro made national headlines when she stepped forward to talk about



Master of Ceremonies Robin Leach and the Honorable Geraldine Ferraro

her personal battle with myeloma. She was instrumental in securing support for the Hematological Cancer Research and Investment Act of 2002. And, she has put a face on multiple myeloma. Presenter Michael Katz said it well, "Tonight, we salute Gerri the human being, Gerri the patient, and Gerri the survivor, for having the compassion and the courage to come forward for the benefit of all myeloma patients." Geraldine Ferraro spoke passionately, offering words of encouragement to fellow patients and caregivers. She also emphasized

the importance of the IMF's work, recalling the phrases "You are not alone. The IMF is here to help you."

The next honoree was Dan Smith, the founder of One Voice Against Cancer (OVAC), a coalition of over forty cancer advocacy organizations, including the IMF. It's easy to ignore forty self-interested organizations each arguing for a bigger piece of the cancer research pie. OVAC brings these organizations together to send a clear message to Congress and to the White House: "We need to make the cancer research pie bigger. We need to fund the cancer research programs that will end the suffering, programs that will stop cancer from shattering



Dan Smith with wife Lorraine Voles and IMF Advocacy Consultant Greg Brozeit

lives." Most recently, Dan was instrumental in arranging a senate appropriations committee hearing on cancer research funding at which IMF president Susie Novis testified as a representative of OVAC. Dan has made a difference for all cancer patients and we were thrilled to be able to present him with the IMF Ribbon Of Hope Award.

The live auction was held during dinner and was lots of fun. Robin Leach and auctioneer David Fox did a spectacular job of working the crowd to get folks to bid.



Auctioneer David S. Fox keeps the bidding lively



Oh, to be a puppy!

Your Unknown author passed on the Mick Jagger napkin, which attracted quite a bit of traffic, and ultimately sold for \$1,700. But the highlight of the auction was clearly the entrance of the chocolate Labrador puppy, donated by a patient's family that is in the breeding business. The puppy was very young, very mellow, and very cute! John Zacarro looked over at his wife Geraldine and said "I'm going to buy the puppy for our daughter." A bidding war of sorts ensued, but John was successful, and the puppy spent the rest of the evening comfortably nestled



Bruce Williams of Genta Incorporated shows off the prized Mick Jagger autograph as a colleague sports the Rolling Stones tour baseball cap.

in Geraldine Ferraro's lap, holding court as hoards of folks came over to get a closer look and pet the puppy.

After dinner, there was a large throng of IMF supporters on the dance floor having a blast until the wee hours. There was much to celebrate. We had a great time, raised a lot of money for the IMF and paid tribute to some very deserving people. The Unknown Patient thanks everyone who helped make the gala a huge success! 🐾

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DID YOU KNOW?

IMMUNIZATIONS IN MYELOMA PATIENTS

By Claire Pomeroy, M.D.

Martin M. Oken, M.D.

Vaccination can help reduce the risk of some infections in individuals with multiple myeloma. Patients should receive the vaccines that the CDC's Advisory Committee on Immunization Practices and the American Academy of Family Physicians have recommended for immunocompromised adults. Tetanus-diphtheria vaccine should be current, influenza vaccine should be administered annually, and pneumococcal vaccine should be provided. Revaccination with pneumococcal vaccine is recommended after 5 years. **Live vaccines should not be administered.**

Myeloma patients who undergo stem cell/bone marrow transplantation may experience a decrease in antibody titers to vaccine-preventable diseases such as tetanus, polio, and encapsulated organisms during the first 4 years after transplantation. Therefore, revaccination of transplant recipients is routinely recommended.

At the present time, vaccine recommendations for recipients of allogeneic and autologous transplants are the same (see CDC guidelines and European Group for Blood and Marrow Transplantation guidelines). Current guidelines suggest tetanus-diphtheria, H. Influenza, and hepatitis B vaccine at 12, 14, and 24 months after stem cell transplant. The hepatitis B vaccine may be omitted in adult patients with no risk factors for this virus. Influenza vaccination should be given **before** the transplant and then annually starting 6 months after the transplant. Pneumococcal vaccine should be given 12 and 24 months after transplant. Measles, mumps, and rubella is a live vaccine and should be avoided for at least 24 months and should only be given if the patient is thought to be immunocompetent.

Physicians caring for patients with multiple myeloma can get further information about vaccine recommendations by calling the National Immunization Hotline at (800) 232-2522 or by accessing the CDC website at www.cdc.gov/nip.

Note: Myeloma patients must keep in mind two concepts when reaching a decision about vaccination.

1. **Reduced benefit** – All myeloma patients have reduced immunity and ability to respond to and therefore benefit from any vaccination.
2. **Increased risk** – The reduced immunity also means that live vaccinations must be avoided (including smallpox), and that other risks must be balanced against realistic benefits. This usually means that hepatitis, polio, and possibly other vaccinations are not required or recommended. Each patient must discuss pros and cons with his/her personal physician.

THE GIFT OF GOOD NUTRITION

By Kim Dalzell, PhD, RD, LD

Almost everyone values the gift of health. By making small dietary changes you can reap rewards all year round. Here are some practical dietary changes that you can make to help you ease into a healthier 2003:

- **Think red and green** — You can find cancer fighting chemicals in every kind of plant. A study by the National Cancer Institute found that regular consumption of cruciferous vegetables like broccoli and cabbage may reduce the risk of cancer. In a hurry? Try 100% fruit juice or organic fruit leathers. Both are delicious and nutritious!
- **Feast on fiber** — Increase fiber intake by consuming at least three servings of whole grains per day. The *International Journal of Cancer* published a study in 1998 reporting that high intakes of fiber consistently reduced the risk of several neoplasms. Remember that brown is not necessarily better. Select breads by weight: those that are heavy and dense usually contain more fiber. Want to bulk up for breakfast? Kashi for Good Friends offers 13 grams of dietary fiber per serving.
- **Mooove over, beef** — Switch to ground turkey and save 3 grams of saturated fat per 3.5 ounce serving or get really serious and try a soy burger. Boca Burger is a popular alternative that contains more than 6 grams of soy protein. Just add ketchup, close your eyes (if you must), and take a bite! The old saying "try it, you'll like it" applies here.
- **Pick a better bread spread** — Most margarines contain a tub full of polyunsaturated and trans-fatty acids, which may damage healthy cells. Try a 50:50 blend of butter to margarine or reduce the amount of trans-fatty acids in your margarine by changing from stick to tub form. Or try Smart Balance, Spectrum, and Brummel & Brown's margarines. They all qualify as trans-free bread spreads.
- **Say good-bye to Ol' Smoky** — Most processed meats like sausages, ham, and bacon contain sodium nitrates and nitrites. These compounds may damage gastrointestinal tissue. Not all processed meats contain nitrates, so check the labels carefully. Hillshire Farms, for example, offers nitrate-free products.

Note: There are no well-studied "silver bullets" to "boost" immunity. The immune system has to remain in a balanced state for whatever it has to fight off. The bottom line is simply to be diligent about getting enough nutrients so that a single or multiple deficiency of certain nutrients does not compromise immune status. There is very little scientific information out there to say anything more specific.

ASK THE EXPERT: Thalidomide and the ImiDs



Steve Schey, M.D.
Head of Service - Clinical Haematology
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London, England

By Steve Schey, M.D.

The first case of myeloma was reported in the medical literature in 1844. She was admitted to St Thomas' Hospital in London where she was treated with orange peel infusions, rhubarb pills, and morphine. However, it took over 100 years before the first effective chemotherapy drug became available and any impact was seen on the outcome of this disease. In the latter half of the last century, better supportive therapy and the availability of haemopoietic stem cell support allowed more intensive chemotherapy treatment with yet better survival. As we enter the new millennium, there has been an unprecedented increase in our knowledge of the basic biology of the disease, and this has allowed the development of novel agents to treat myeloma which work through entirely different pathways from chemotherapy agents. We therefore have the opportunity to treat patients with resistant disease or to use these agents in combination to greater effect.

Thalidomide was the first of these novel agents to be found effective in myeloma when it was used in a group of heavily pre-treated patients, many of whom had already undergone 1 or 2 previous stem cell transplants and relapsed with their disease. Approximately a third of the patients responded, demonstrating that this agent was significantly better than any other chemotherapy drug given as a single agent. The UK Myeloma Forum has also used thalidomide in the relapsed setting and found that most patients are able to tolerate a dose of 300 mg daily by mouth, although some patients responded to as little as 100 mg on alternate days. 49% of patients

achieved a greater than 25% response rate with durable responses. The main side effects seen were pins and needles in the fingers (24%), drowsiness (15%), constipation (7%), and dry skin (6%). All of these side effects were minor and were managed with simple medication and by taking the drug at night. Eleven patients had their medication stopped because of side effects. A number of other studies have also confirmed the effectiveness of thalidomide in the relapsed setting. A randomised study is due to commence of thalidomide in combination with dexamethasone for patients presenting with previously untreated disease to evaluate its effect in this setting.

In an attempt to improve the effectiveness of thalidomide whilst reducing the side-effects of the drug, the Celgene Corporation examined a large number of modified molecules or analogues of thalidomide. These fell into 2 groups characterised by 1) the activity they demonstrated on chemicals that normally are involved in the immune and inflammatory response, and 2) the cells of the immune system that recognise and destroy foreign and tumour cells. Two compounds have now been used in patients with myeloma, namely Revimid (CC-5013) and Actimid (CC-4047). We have recently used Actimid in a phase I relapsed/refractory study designed to identify the optimal dose of the drug when given orally on a daily basis. The average age of the patients entered into the study was 66 years. Patients had received a median of 3 previous courses of chemotherapy (range 1-6), 21% had relapsed following a stem cell transplant, and 29% had failed thalidomide. Five patients reported minimal skin changes (grade 1) and 3 had grade 1 neuropathy; of these patients none required a change of dose and all side effects resolved on continued treatment with Actimid. In addition, 8 patients reported gastrointestinal effects, namely diarrhea, constipation, and nausea, all of which were mild and settled spontaneously or with simple medication and did not necessitate any change in Actimid therapy.

Eight patients with responsive disease, five with stable disease, and one with progressive disease, developed grade 3 or 4 neutropenia. All except 3 patients recovered spontaneously within 4 weeks of stopping drug without the need for cytokine therapy and there were no infectious complications. The 3 patients who failed to recover within 4 weeks were withdrawn from study. The others were allowed to recommence Actimid at a reduced dose. All the

neutropenias occurred in the first 3 weeks of entering the study, bar one patient who developed neutropenia whilst taking 1 mg daily at 10 months post entry.

Four patients who developed neutropenia developed thrombocytopenia. One patient with progressive disease taking 5mg daily of Actimid developed grade 3 thrombocytopenia. One patient on 2 mg daily with unresponsive disease developed grade 4 neutropenia and grade 3 thrombocytopenia. A further two patients with responding disease, one taking 5 mg, and one taking 10 mg developed grade 3 and 4 neutropenia and grade 2 and 3 thrombocytopenia. Both were discontinued because of neutropenia but recommenced Actimid at reduced dose.

Although this study was not designed to evaluate quality of life, it is of interest that patients expressed the opinion that they felt subjectively better on treatment ahead of any objective response in the paraprotein, with less systemic complaints than on entry to study. This we would speculate is due to the potent anti-TNF alpha activity of the drug that has been shown *in vitro* to be a feature of this class of compounds.

The response rates in this study were very encouraging. One patient had a complete response confirmed on bone marrow aspirate and trephine, and 2 further patients had a very good response with a >95% reduction in paraprotein levels. 66% of patients had a greater than 25% reduction in paraprotein at a median of 4.5 months of treatment (range 1-14 months).

Dose-limiting toxicity therefore occurred in this study at doses greater than 1mg given on a daily basis. Neutropenia was the main dose-limiting toxicity occurring at 2-3 weeks, but resolved spontaneously without the need for haemopoietic support. Other common side effects associated with thalidomide treatment were seen less frequently and were easily managed without the need to discontinue Actimid. The high response rate in this group of heavily pre-treated patients is very encouraging but further work needs to be done to develop better treatment schedules and to elucidate the mechanisms whereby the myelotoxic effects of this agent are produced in the marrow.

Similar results have been reported in phase I/II studies of Revimid and it is hoped that a phase III trial of the agent will begin in the United States and Europe during the next 3-6 months. A further phase I/II trial of Actimid is anticipated to

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(l-r) Dr. Gareth Morgan, Ashley Barit, Dr. Philip Greipp, Dr. Federico Caligaris-Cappio, Benson Klein, Dr. Kewal Asosingh, Carol Klein, Dr. Takashi Sonoki, Dr. Jesus San Miguel, Dr. Sun J. Choi, Dr. Brian Van Ness

The IMF Brian D. Novis Research Grant Award presentations took place on Saturday, December 7th, 2002 in Philadelphia, PA during the 44th annual meeting and exposition of the American Society of Hematology. In attendance were many members of the IMF Scientific Advisory Board, IMF Directors, staffers, and supporters whose efforts helped make the grants possible.

IMF President Susie Novis opened the reception with a warm welcome, and provided background information on the IMF research program that dates back to 1995. Dr. Robert A. Kyle, Chairman of the IMF Scientific Advisory Board, and Dr. Brian G.M. Durie, Chairman of the Board, were on hand to present the awards. Individual donors were introduced to the researchers whose projects they are funding. The grant recipients spoke of the objectives of their research projects.

This issue of *Myeloma Today* features research abstracts of several Junior Grant recipients. Others will be profiled in the upcoming issue of the newsletter.



Susie Novis with Senior Grant Recipients Drs. Brian Van Ness and Gareth Morgan

DR. KEWAL ASOSINGH
Tumor-host interactions during MM disease progression; functional roles of CD45 subsets
Vrije Universiteit Brussel (VUB)
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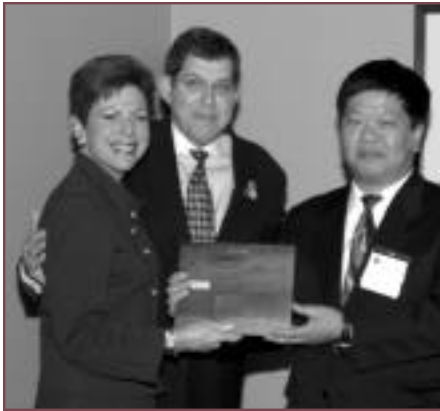
For the development of new, more effective strategies in the treatment of cancer, understanding of the biological heterogeneity in the tumor population is an important goal. Only specific subsets within the parental tumor have the necessary receptors for motility, invasiveness, and tumor spread. In different tumor stages remodeling of the extracellular matrix occurs, by exchange of proteinases and cytokines between stromal cells and cancer cells. This modified microenvironment stimulates invasion and promotes survival and proliferation of the cancer cells. Only specific cancer cell populations are able to induce the production of survival/growth factors and proteolytic enzymes by local stromal cells and have the capacity to induce angiogenesis, which is pivotal for progressive tumor growth. In multiple myeloma (MM) research, understanding of the heterogeneity, in general, and understanding of the specific roles of CD45 subsets, in particular, is still in its infancy. CD45 is a transmembrane tyrosin phosphatase. While immature plasma cells are CD45 positive, fully matured plasma cells lose all CD45 expression. Myeloma patients have a heterogeneous CD45 expression pattern and very recently CD45 appeared to be a predictor of therapeutical response. In our previous work the *in vivo* bone marrow homing, differentiation and proliferation of CD45 subsets in the 5T experimental mouse model (11, 12) were investigated. In the current project the roles

of CD45⁺ and CD45⁻ 5TMM cells during myeloma disease progression will be analyzed. Experiments with mice injected with the heterogeneous 5T2MM cell population indicated major alteration in the CD45 subset composition during disease progression. In the early stage of the disease (few weeks after intravenous injection) the majority of the MM cells had an immature, invasive and apoptosis resistant phenotype (CD45⁺CD138⁺IL6-R⁺). In contrast, end stage MM cells had a mature, less-invasive and apoptosis sensitive phenotype (CD45⁻CD138⁺IL6-R⁻). In between there was a gradual progression in the subset composition towards the endstage phenotype. The early-, intermediate- and endstage myeloma cells will be investigated for functional differences. Invasion, apoptosis and proliferation will be analyzed. Bone marrow samples collected at different time points (with one-week time interval) will be examined for the presence of angiogenesis and osteolysis by microvessel density quantification and micro CT, respectively. Correlations with the presence of CD45 subsets will be analyzed. The observed alterations in the subset composition suggest alterations in tumor-host interactions during the disease progression.



Senior Grant Recipients Drs. Jesus San Miguel and Philip Greipp with IMF Chairman of the Board Dr. Brian Durie

Alterations in gene expression profile of BM stromal cells and MM cells during disease progression will be identified by differential gene expression analysis (cDNA micro array) at different time points (early tumor stage, middle and endstage). In particular, differential expression of genes involved in apoptosis, invasion, proliferation, angiogenesis and osteolytic bone disease and in the signaling cascades of these processes will be analyzed. The differential expression will be confirmed by Real Time-PCR and at protein level by flow cytometry, Western blot or immunohistochemistry. The overexpressed/down-regulated proteins will be tested for their functional involvement.



Carol and Benson Klein with Dr. Sun J. Choi

DR. CHAO-LAN YU
Suppressor of Cytokine Signaling (SOCS):
Its Regulation and Potential Implication as
a Therapeutic Agent in Multiple Myeloma
 Vanderbilt University School of Medicine
 Nashville, Tennessee

Interleukin-6 (IL-6) is the major growth and survival factor in human multiple myeloma (MM) cells. Through the signaling receptor subunit gp130, IL-6 activates the receptor-associated JAK family protein tyrosine kinases and, subsequently, the downstream signal transducer and activator of transcription 3 (STAT3). STAT proteins are latent cytoplasmic transcription factors that regulate the expression of specific cellular genes. Consistent with the critical role of STAT3 in IL-6 signaling, constitutive STAT3 activation has been reported both in human myeloma cell lines and in bone marrow cells from MM patients. Aberrant STAT3 activation may contribute to the malignant progression of MM by the induction of antiapoptotic proteins Bcl-2 and Bcl-x_L. Furthermore, STAT3 activation is also linked to cell cycle progression by the induction of cyclinD1. However, the molecular mechanisms of constitutive STAT3 activation in MM cells still remain largely unclear.

STAT3 can be down-regulated through negative feedback control following cytokine-induced activation. The suppressor of cytokine signaling (SOCS) family members are key players in this process. SOCS proteins are induced by cytokines to prevent further activation of the JAK-STAT pathway. Among eight SOCS family members, both SOCS-1 and SOCS-3 have been shown to be induced by IL-6 and to inhibit subsequent IL-6 signaling. SOCS-1 and



Chao-Lan Yu, Ph.D.

SOCS-3 inhibit JAK kinase activity either by direct association with JAK kinases or by simultaneous interactions with JAK and the receptor. We have preliminary data indicating that the absence of SOCS gene expression correlates with constitutive STAT activation in leukemic T cells. **Therefore, we would like to hypothesize that defect of negative feedback control through SOCS-1 and SOCS-3 proteins may contribute to constitutive STAT3 activation and resistance to apoptosis in MM cells.** This hypothesis will be tested in a well-characterized human myeloma cell line, U266, through the following specific aims:

1. To determine if the negative feedback control involving SOCS-1 and SOCS-3 proteins is intact in MM cells. The observation that exogenous IL-6 could induce further STAT3 activation in U266 myeloma cells suggested that JAK kinases are not effectively inhibited by SOCS-1 and SOCS-3. It is possible that, in U266 myeloma cells, IL-6 autocrine loop cannot induce SOCS-1 and SOCS-3 expression to a level high enough to inhibit JAK kinases. We will first compare the expression levels of SOCS-1 and SOCS-3 in U266 myeloma cells with varying degrees of

STAT3 activity. This can be achieved by treating U266 cells with a high dose of exogenous IL-6 or AG490, a JAK-specific inhibitor. A constant low or undetectable SOCS expression regardless of endogenous STAT3 activity will suggest an intrinsic defect in SOCS expression in U266 myeloma cells. On the other hand, if SOCS expression correlates with STAT3 activity in U266 myeloma cells, we will determine its ability to associate with and inhibit JAK kinases. Our expectation is that functional expression of SOCS-1 and/or SOCS-3 will be defective in U266 myeloma cells.

2. To evaluate the effects of ectopic expression of SOCS-1 and SOCS-3 on survival and growth of MM cells. We will transiently transfect U266 cells with an enhanced green fluorescent protein (EGFP) expression construct encoding SOCS-1, SOCS-3, or the empty vector. EGFP-expressing cells will be isolated by FACS sorting and then subjected to biochemical assays to confirm the expression of SOCS proteins and inhibition of STAT3 activity. Northern blot analysis will follow determine

if SOCS proteins reduce the expression of *bcl-2* and *bcl-x_L*, two known antiapoptotic genes. To determine if SOCS proteins promote Fas-mediated apoptosis, transfected U266 cells will be stimulated with Fas ligand or Fas agonistic antibody CH-11, and then examined by Annexin V-PE staining and FACS analysis. We predict that exogenous expression of SOCS-1 and/or SOCS-3 in U266 myeloma cells will result in lower STAT3 activity, reduced levels of *bcl-2* and *bcl-x_L* transcripts, and increase in Fas-mediated apoptosis. In addition, we will perform

cell cycle analysis and examine cyclinD1 expression on transfected U266 myeloma cells. We hypothesize that forced SOCS-1 and/or SOCS-3 expression may also induce cell cycle arrest by inhibiting cyclinD1 expression.

SOCS proteins have been shown to inhibit proliferation signals induced by a number of oncoproteins. Consistent with the role of SOCS as tumor suppressor, higher incidence of malignancies have been reported both in humans and in mice with defective SOCS expression. Furthermore, SOCS proteins have also been shown to be more effective than dominant-negative STAT proteins in the treatment of certain immune disorders. Results from this proposed research project, therefore, should provide additional insights into the molecular mechanisms that contribute to the pathogenesis of MM and may suggest novel strategies for potential treatment of MM.



Chao-Lan Yu, Ph.D.



Dr. Brian Durie with the Barit family and supporters

DR. LEE ANN GARRETT -SINHA
Identification of the Role of Ets-1 in
Regulating Plasma Cell Numbers
 University of Buffalo
 State University of New York
 Buffalo, New York

Please see page 10

RESEARCH PROGRESS REPORT: Dr. Ivan Van Riet

2002 Brian Novis Research Grant recipient studies homing mechanisms involved in the biology of multiple myeloma



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1. INTRODUCTION AND AIMS OF THE PROJECT

A striking feature of myeloma cells concerns their tendency to reside in the bone marrow compartment during the main course of the disease evolution. The microenvironment provides the appropriate signals for growth and survival of the tumor cells. Since small amounts of myeloma cells are also detectable in the peripheral blood, it can be assumed that these cells directly contribute to disease spreading. The detection of these circulating cells implicates that they must be equipped with the appropriate surface molecules that mediate binding to endothelium, responsiveness to chemokines, transendothelial migration and extravasation. It can be assumed that the migration of myeloma cells to the bone marrow is a multistep process as described for normal lymphocytes. The main objective of this research project is to identify molecular mechanisms involved in the homing of myeloma cells. More specifically we aimed to determine: 1) what explains the selective presence of myeloma cells in the bone marrow, 2) which chemotactic signals mediate the migration of myeloma cells and 3) how myeloma cells transmigrate through bone marrow endothelium.

2. RESULTS

1999 & 2000 Brian Novis Research Grants (Initial Research Project)

1) To answer the question whether the restricted localization of myeloma cells in the bone marrow is the result of selective migration towards bone marrow or/and selective survival in the bone marrow, we

performed a study in the *in vivo* 5T2-mouse MM model. Briefly, the *in vivo* homing kinetics of 5T2 cells 18 hours after injection were assessed in different organs by tracing radiolabeled cells, by immunostaining of isolated cells and PCR analysis. 5T2 cells were found in bone marrow, spleen and liver with all other organs being negative. Adhesion assays of 5T2MM cells to different types of endothelial cells demonstrated a selective adhesion of 5T2MM cells to bone marrow and liver and not to lung endothelial cells. Therefore we concluded that the specific *in vivo* localization of the 5T2MM cells is a result of the combination of a selective entry/adhesion of the 5T2MM cells in the bone marrow, spleen and liver, and a selective survival and growth of these tumor cells in the bone marrow and spleen but not in the liver (published in *British Journal of Cancer*, 2000, 82, 953-959) (1). In addition, we could demonstrate in the same model that adhesion to bone marrow endothelial cells and homing to bone marrow of the myeloma cells involves the CD44v10 molecule (published in *Cancer Research*, 2001, 61, 2862-2865) (2).

2) The migration of lymphocytes and tumor cells through endothelium is believed to be mediated by chemotactic signals provided by the microenvironment. We demonstrated that laminin-1 (LN), a major component of the basement membrane acts as an important chemo-attractant for myeloma cells. This molecule was found to stimulate the *in vitro* migration of 3 human myeloma cell lines (MM5.1, U266 and MMS.1), as well as murine 5T2MM cells and primary myeloma cells immunomagnetically isolated from patient bone marrow samples. Moreover, we found that human myeloma cell lines and murine 5T2MM cells express the 67 kD laminin receptor (67LR). CD38^{bright+} plasma cells in fresh myeloma bone marrow samples showed weaker 67LR expression, but expression increased after direct exposure to a bone marrow endothelial cell line (4LHBM). 67LR has been shown to mediate the actions of LN through binding to CDPGYIGSR, a nine amino acid sequence from the B1 chain of LN. Myeloma cell migration was partially blocked by peptide 11, a synthetic nonapeptide derived from this amino sequence and not by a scrambled (control) peptide. Also a blocking antiserum against 67LR reduced LN-induced migration. Co-injection of peptide 11 with 5T2MM cells in the murine *in vivo* model of

MM resulted in a decreased homing of 5T2MM cells to the bone marrow compartment. We conclude that 67LR on the surface of myeloma cells is involved in the laminin-1 induced migration of myeloma cells and that this mechanism might be important during the extravasation of circulating myeloma cells. (published in *British Journal of Cancer*, 2001, 85, 1387-1395) (3)

3) In order to identify additional receptors for chemotactic molecules that can trigger the bone marrow homing of myeloma cells, we started to analyze the functional expression of chemokine-receptors. We could demonstrate by RT-PCR the expression of the chemokine receptor CCR2 in several human myeloma cell lines. FACS analysis revealed CCR2 expression at the surface of all myeloma cell lines and primary myeloma cells, immunomagnetically isolated from bone marrow samples. In addition, we found that the monocyte chemotactic proteins (MCP's) MCP-1, MCP-2 and MCP-3, three chemokines acting as prominent ligands for CCR2, are produced by bone marrow stromal cells. By *in vitro* migration assays we could demonstrate that myeloma cell lines as well as freshly isolated myeloma cells migrate to MCP-1, to MCP-3 and to a lesser extent to MCP-2. A blocking antibody against CCR2 as well as a combination of antibodies against MCP-1, MCP-2 and MCP-3 significantly reduced the migration of human myeloma cells to conditioned medium of cultured stromal bone marrow cells. These results suggest a potential contribution of CCR2 and the MCP's to the bone marrow homing of human myeloma cells (oral presentation during the 2000 ASH meeting, San Francisco) (4), (manuscript submitted) (5).

4) As part of this project, we also analyzed the functional role of the motility-related protein-1 (MRP-1/CD9) in myeloma cell migration. Previously, we found by representational difference analysis that MRP-1 transcripts are expressed by the stroma-dependent myeloma cell line MM5.1 and not by the stroma-dependent variant MM5.2. Accordingly, most myeloma cell lines that grow stroma-independently were found to be MRP-1 negative. By analyzing *in vitro* migration through Transwell filters and Matrigel (basement membrane extract), MM5.2 cells were found to be more motile and invasive than MM5.1 cells. (*Acta Oncologica*, 2000, 39, 771-776) (6). To

test the functional role of MRP-1 in this different migration behavior, we tried to establish MRP-1 expressing transfectants of CD9 negative myeloma cell lines (MM5.2 and MMs-1). These variants were produced by transfection with MRP-1 cDNA (vector provided by Dr. Adachi, Osaka, Japan). However, when the transfectants were compared with the wild type cells no differences in *in vitro* migration properties could be found. Therefore we could not provide any evidence that the higher motility of MM5.2 cells relates to a differential expression of MCP-1. Interestingly, we found a significantly lower CD9 expression on plasma cells of patients with aggressive myeloma as compared to patients with non-aggressive disease. The recent finding that enhanced CD9 expression on myeloma cells correlates with enhanced susceptibility to cytolysis by IL-2 activated T cells and NK cells, indicates that the observed heterogeneous expression of MCP-1 in myeloma cells relates more to differences in immune-control rather than changes in the migration or motility behavior of the tumor cells. (Manuscript in preparation).

2002 Brian Novis Research Grant (January-August)

1) *Functional role of the metalloproteinases MMP-2 and MMP-9 in the transendothelial invasion of human myeloma cells.* With this part of our work we wanted to determine whether myeloma cells are invasive and at which level the transendothelial invasion of human myeloma cells is mediated by the metalloproteinases (MMP's), MMP-2 and MMP-9. Both MMP's have been described to be expressed by cancer cells but their specific role in the extravasation process of myeloma cells is unknown. Using RT-PCR and zymography, we found that MM cell lines and primary MM cells do not express MMP-2 whereas MMP-9 was expressed in all tested patient samples and 3/8 MM cell lines (8226, LP-1 and MMs1). Furthermore we could demonstrate that MM cells are capable of transendothelial invasion and this process was inhibited in the presence of neutralising MMP-9 antibodies. In addition we demonstrated that human MM cells are more invasive in the presence of endothelial cells as compared to migration through the basement membrane without endothelial cells. We also showed that this endothelial cell-induced stimulation correlates with the up-regulation of MMP-9 in tumor cells, induced by endothelial cells. Final experiments suggest that hepatocyte growth factor (HGF), produced by the endothelial cells, is involved in this up-regulation. These *in vitro* experiments demon-

strate that human myeloma cells are capable of transendothelial invasion and that the protease MMP-9 plays an important role in this process (oral presentation during the 2002 ASH meeting, Philadelphia) (7).

2) *Functional role of the adhesion molecules CD44, VLA-4 and CD38 in the adhesion to and the migration through bone marrow endothelium*

In first instance we showed that human myeloma cell lines (Karpas, LP-1 and 8226) are able to adhere *in vitro* to bone marrow endothelial cells, but this adhesion is not specific because they can also bind to other endothelial cell types (lung and umbilical cord). In addition we demonstrated that human myeloma cell lines as well as primary tumor cells isolated from patient samples, can migrate through transwell filters coated with bone marrow endothelial cells. In order to identify which *adhesion molecules* are involved in this binding- and migration step, we evaluated the expression of several receptors that are known to mediate interactions of endothelial cells with normal lymphocytes. It was found that human myeloma cell lines express at least three adhesion molecules (i.e. VLA-4, CD44 and CD38) of which the corresponding ligands are expressed by bone marrow endothelium (resp. VCAM-1, hyaluronic acid and CD31). By blocking with VLA-4-, CD38- and CD44- specific antibodies we found that both VLA-4 and CD38 partially (up to 55%) mediate adhesion of myeloma cell lines (Karpas, 8226 and LP-1) to bone marrow endothelial cells while the transendothelial migration was partially inhibited by CD44. These data have to be confirmed with primary isolated myeloma cells.

3) *Functional role of additional chemokine receptors in the transendothelial migration of human myeloma cells.*

In a previous part of this project (Brian D. Novis Research Grant 2000) we demonstrated that human myeloma cells express the chemokine-receptor CCR2. Moreover we found that this receptor is involved in the migration to the bone marrow micro-environment by interaction with MCP-1, MCP-2 and MCP-3. By ribonuclease protection assay (RPA) and/or Multiplex-PCR, we found that human myeloma cell lines express also transcripts for CCR1, CCR4, CCR8 and CXCR4. In the last part of this project we started to investigate whether these receptors are functionally expressed by myeloma cells and co-act with CCR2 to enhance the selectivity of the tumor cell homing. FACS analysis revealed that human myeloma cell lines show surface expression of CCR1, CCR2 and CXCR4.

We could not detect surface expression of CCR4 and CCR8. CCR1, CCR2 and CXCR4 were found to be heterogeneously expressed on plasma cells in a series of MM bone marrow samples. Currently we are investigating whether this expression correlates with the clinical evolution. In addition we are analysing at which level co-neutralisation of the main ligand-chemokines, MCP-1 (2 and 3), MIP-1 and SDF-1 can enhance the inhibition of myeloma cell migration towards bone marrow conditioned medium.

3. PRESENTATION OF RESEARCH DATA RELATED TO THIS PROJECT

1. Selective initial *in vivo* homing pattern of 5T2 multiple myeloma cells in the C57BL/KalwRij mouse. K. Vanderkerken, C. De Greef, K. Asosingh, M. De Veerman, **I. Van Riet**, M. Kobayashi, B. Smedsrod and B. Van Camp. *Brit. J. Cancer*, 82, 953-959, 2000.
2. A unique pathway in the homing of murine myeloma cells : CD44v10 mediates binding to bone marrow endothelium. K. Asosingh, U. Günthert, H. De Raeve, **I. Van Riet**, B. Van Camp and K. Vanderkerken. *Cancer Research*, 2001, 61, 2862-2865.
3. Laminin-1 induced migration of multiple myeloma cells involves the high affinity 67kD laminin receptor. I. Vande Broek, K. Vanderkerken, C. De Greef, K. Asosingh, N. Straetmans, B. Van Camp and **I. Van Riet**. *Brit. J. Cancer*, 85, 1387-1395, 2001.
4. The chemokine receptor CCR-2 is expressed by human multiple myeloma cells and mediates chemotaxis to monocyte chemotactic proteins MCP-1, 2 and 3. I. Vande Broek, K. Vanderkerken, N. Straetmans, B. Van Camp and **I. Van Riet**. *Blood*, 2000, 96, 473a.
5. The chemokine receptor CCR2 is expressed by human multiple myeloma cells and mediates cell migration to the monocyte chemotactic proteins MCP-1, -2 and -3. I. Vande Broek, K. Asosingh, K. Vanderkerken, N. Straetmans, B. Van Camp and **I. Van Riet**. Submitted, 2002
6. Homing of the myeloma cell clone K. Vanderkerken, B. Van Camp, C. De Greef, I. Vande Broek, K. Asosingh, B. Van Camp and **I. Van Riet**. *Acta Oncologica*, 39, 771-776, 2000
7. Hepatocyte growth factor stimulates the transendothelial invasion of human multiple myeloma cells through upregulation of matrix metalloproteinase-9. I. Vande Broek, V. Allegaert, K. Asosingh, L. Hellebaut, X. Leleu, T. Facon, K. Vanderkerken, B. Van Camp and **I. Van Riet**. Oral presentation during 2002 ASH meeting, December 2002, Philadelphia, PA. 🌸

DEAR READER – continued

- the IMF's OMNI program reached 61 multiple myeloma support groups
- increased the number of support groups to 57 in the U.S. and 30 international
- testified before the Senate Sub-Committee
- increased our membership to over 100,000!

The IMF is only able to do what we do because people like you believe in and support our programs and services and share our belief that we can and do make a difference.

On behalf of all of us at the IMF a very heartfelt thank you and we look forward working together with you in this new year. We know that together we do improve the quality of life for myeloma patients while we work toward prevention and a cure.

Susie Novis
President

THALIDOMIDE AND THE IMiD – continued

develop a schedule for using this drug in the relapsed setting and to further evaluate the neutropenia. A phase III trial of thalidomide and dexamethasone versus dexamethasone and a placebo is planned in *de novo* disease. Many obstacles lay ahead of us before this disease can be declared curable, but the development of these and other novel agents over the last few years has offered, for the first time in a generation, the opportunity to treat this condition in patients previously thought to be resistant or refractory to conventional treatment. These novel drugs may also provide strategies for improving outcome significantly by combining them with chemotherapy agents or other novel agents to overcome resistance and induce improved outcomes. We live in exciting times and have come a long way from orange peel infusion and rhubarb pills, but more work needs to be done. 🍷

2003 GRANTS – continued

Plasma cells normally function to produce antigen-specific antibodies and thus help control infections. As such they are a critical part of the immune system. Indeed, people who lack plasma cells due to the genetic disease, X-linked agammaglobulinemia (XLA) are subject to severe recurrent bacterial infections. On the other hand, unregulated plasma cell growth can lead to the development of certain tumors (plasmacytomas and multiple myelomas). Thus, it is critically important for an organism to strictly control the production and the loss of

plasma cells to ensure that sufficient cells are available to fight infection, but that excess cells are eliminated.

The processes of cellular differentiation, proliferation, and apoptosis require specific proteins that promote each cell's fate. Transcription factors regulate the expression of the various proteins necessary for each of these different cellular outcomes. Ample evidence implicates members of the Ets family of transcription factors in the regulation of B cell development, expansion, maturation, and death. Ets proteins regulate the expression of membrane receptors that promote cellular differentiation and proliferation such as the interleukin (IL)-7 receptor, the granulocyte/macrophage colony stimulating factor (GM-CSF) and the B cell receptor (BCR) (11,13-18). Ets proteins also regulate the expression of anti-apoptotic proteins such as Bcl-X_L and c-rel as well as pro-apoptotic proteins such as Fas and caspase-3. Therefore, Ets proteins regulate diverse pathways that can lead to cell survival, cell proliferation, or cell death.

Interestingly, up-regulation of Ets-1 protein is detected in a sub-set of tumors. In addition to the receptor genes, pro- and anti-apoptotic genes discussed above, Ets-1 is also known to regulate the expression of certain metalloproteinase genes. Expression of proteinases is required for tumor cells to degrade surrounding extracellular matrix, invade nearby tissues, and metastasize to distant sites. Over-expression of Ets-1 in tumors generally correlates with their increased invasiveness and metastatic potential and with a poorer prognosis for the patient. In addition, expression of Ets-1 in vascular endothelial cells is important during the process of angiogenesis. Since tumor growth requires new blood vessels, the role of Ets-1 in angiogenesis has important implications for cancer growth.

Gene-targeted mice lacking Ets-1 exhibit a ten-fold increase in the numbers of plasma cells in the spleen. The deregulated production of plasma cells found in these animals is reminiscent of unregulated plasma cell growth found in plasmacytomas and multiple myelomas. Thus, Ets-1^{-/-} animals provide an animal model to study factors affecting the equilibrium between plasma cell formation and deletion. The investigations we propose in this application will address how Ets-1 regulates the differentiation of plasma cells, their proliferation and/or their survival. We believe that our studies will have direct bearing on understanding, and perhaps treating, diseases caused by uncontrolled plasma cell growth. 🍷

IMF CALENDAR

January 24-25, 2003
IMF Patient & Family Seminar
Los Angeles, CA

March 5-7, 2003
National Dialogue on Cancer
Public-Private Partnership Meeting
Washington, DC

March 21-22, 2003
IMF Patient & Family Seminar
Little Rock, AR

April 7-8, 2003
OVAC Advocacy Days
Washington, DC

April 9-13, 2003
SWOG Group Meeting
San Diego, CA

April 25-26, 2003
IMF Patient & Family Seminar
Berkeley, CA

May 1-3, 2003
ONS Annual Meeting
Denver, CO

May 17, 2003
4th Annual JC Invitational Golf Tournament
XXX, MN

May 23-27, 2003
IX International Myeloma Workshop
Salamanca, Spain

May 31 - June 1, 2003
ASCO Annual Meeting
Chicago, IL

June 5-7, 2003
ECOG Group Meeting
New Orleans, LA

June 15, 2003
"Hair Cares" MM Fundraiser
Glen Mills, PA

June 27-29, 2003
IMF Support Group Leaders' Retreat
Durham, NC

June 30, 2003
Bob Canter Golf Tournament
TBA

August 2003
IMF Patient & Family Seminar
Tucson, AZ

October 1-5, 2003
SWOG Group Meeting
Seattle, WA

September 2003
IMF Patient & Family Seminar
Philadelphia, PA

November 7-8, 2003
IMF Patient & Family Seminar
Dallas, TX

November 15-17, 2003
ECOG Group Meeting
Miami, FL

December 5-9, 2003
ASH Annual Meeting
San Diego, CA

For more information, please check the IMF website at www.myeloma.org or call the IMF at (800) 452-CURE.

News & Notes



Justine V. Springberg, Olivia Springberg (age 2), and Mark Unatin

RAFFLE RAISES FUNDS FOR RESEARCH

The IMF received a boost with fundraising this fall from *The Mark Unatin Raffle for Research: Finding a Cure for Myeloma*. Participants from 10 states contributed close to \$22,000 to this event in honor of first-time fundraiser Justine Springberg's father, Mark Unatin of Pittsburgh, PA. Twenty-four prizes were awarded to lucky ticket holders at an event outside of Washington,

D.C. The coveted grand prize was a spa package at a resort in Pennsylvania.

Watching her dad derive strength from the kindness and support of friends and family motivated Justine to spearhead the event. Donors were touched and inspired by the spirit and energy of the gathering and were thankful that they were given a chance to help a friend in need. Justine reports that several participants have offered their assistance in expanding the raffle next year.

Mark was diagnosed with multiple myeloma last fall and has recently achieved a remission following an autologous stem cell transplant. He is extremely excited about the success of the fundraiser and, of course, very proud of his daughter.

OUR PHONES ARE RINGING

It has been almost a year since the IMF expanded its Hotline coverage with the addition of NCI-trained cancer information specialists Nancy Baxter and Debbie Birns. As a result, our phonelines have never been busier! Many thanks to all who have made donations allocated to supporting this invaluable resource for patients and their families.

MYELOMA MATRIX

The IMF is committed to providing a total overview of the "future" as well as the current state of myeloma treatments. The Myeloma Matrix provides updated information about drugs beginning with pre-clinical developments and tracks drugs as they proceed through Phases I - III of clinical trials, drugs that have been FDA approved, and information on trials that are being conducted by NCI-sponsored cooperative groups as well as other myeloma study groups. Call (800) 452-2873 for your printed copy or view the Myeloma Matrix online by visiting www.myeloma.org.

HELPING HAND RESOURCE GUIDE

A Helping Hand, a resource guide for people with cancer, is now available in a fourth edition. This guide details cancer-related assistance available regionally and nationally from organizations that offer a wide variety of services, support, and information. Call (800) 813-4673 for a printed copy (shipping and handling charges apply) or view online at www.cancerca.org.

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