Scientific & Clinical

2010 IMF Research Grant Recipients Announced

The recipients of the 2010 IMF Research Grant awards were announced at the gathering of the Foundation's Scientific Advisors, held at the 51st annual meeting of the American Society of Hematology.

For the past 15 years, the IMF's research program has been funding promising clinical investigators from around the world in an effort to improve outcomes for myeloma patients. The 2010 IMF grant award presentations took place during the 51th annual meeting and exposition of the American Society of Hematology (ASH). Susie Novis (president and co-founder of the IMF), Dr. Brian G.M. Durie (chairman and co-founder of the IMF), Dr. Robert A. Kyle (chairman of the IMF Board of Scientific Advisors), and many IMF Scientific Advisors from around the globe were on hand during the research grants award presentation ceremony.

The IMF grants are funded by donations from private individuals. Junior investigators receive funding in the amount of $50,000. Senior investigators are funded at $80,000. Over the years, the IMF research grant program has lead to many publications, enabled investigators to become established in the field of myeloma and made important contributions to understanding the biology of myeloma and developing better therapies. We are certain that the work of the recipients of the 2010 IMF research grants will continue to contribute significantly to the field of myeloma.

2010 Brian D. Novis Senior Research Grants

“ Development of the antihelmintic flubendazole as a novel therapeutic agent for the treatment of multiple myeloma”

Aaron Schimmer, MD, PhD, FRCPC
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Toronto, ON, Canada

This project takes the unique approach of studying drugs approved by the FDA for other diseases to assess if they have unrecognized anti-myeloma activity. Any such drug can have an accelerated approval for myeloma use if significant anti-myeloma activity is demonstrated. Dr. Schimmer and colleagues have already identified that flubendazole, a drug used for intestinal worms, has anti-myeloma activity. The research team aims to advance the clinical development of

flubendazole for myeloma by identifying biomarkers for use during a clinical trial and develop a Phase I clinical trial for this compound in patients with relapsed and refractory myeloma.

2010 Brian D. Novis Junior Research Grants

“ Mesenchymal cell cytotherapy for multiple myeloma”

Xin Li, PhD
Myeloma Institute for Research and Therapy
Winthrop P. Rockefeller Cancer Institute
University of Arkansas for Medical Sciences
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Induction of myeloma bone disease is mediated through increased production of pro-osteoclastogenic and anti-osteoblastogenic factors in myelomatous bones, as well as due to potential abnormal properties of bone marrow mesenchymal stem cells (MSCs). Preliminary in vitro experiments by Dr. Li and colleagues showed that MSCs from normal bone marrow directly inhibit osteoclast formation and stimulate osteoblast differentiation, suggesting that these cells affect bone remodeling and myeloma cell growth via interaction with the host osteoclasts and osteoblasts. These findings have led to formulation of an overall hypothesis that, in contrast to patient MSCs, normal MSCs can help control myeloma directly and indirectly by preventing bone loss and stimulating bone formation. The research project will determine the direct effects of MSCs on osteoclasts and osteoblasts, shed light on molecular mechanism by which MSCs affect osteoclastogenesis and osteoblastogenesis. This can lead to new approaches to the treatment of myeloma bone disease.

“ Characterization and preclinical evaluation of NKT cells in multiple myeloma” *

Eline Menu, PhD
Vrije Universiteit Brussel (VUB)
Brussels, Belgium

One strategy to target multiple myeloma is using a patient's immune system to target the tumor. However, myeloma cells can evade the immune system. Therefore, new drugs are being studied that can activate the immune system and enhance anti myeloma activity. In this project, Dr. Menu and colleagues will use the ST33MM mouse model to test a new activator of NKT (natural killer

T-lymphocytes) cells preclinically. They will first characterize the NKT population in these mice and test their functionality against ST33MM cells and a CD1d transduced ST33MMvt cell line. They will then compare the efficiency of a new analogue in its capacity to activate NKT cells and reduce myeloma burden both in vitro and in vivo. This study will provide a potential new approach for immunotherapy in myeloma.

“ Reolysin: a novel reovirus-based therapy for multiple myeloma” **

Steffan Nawrocki, PhD
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The proteasome inhibitor bortezomib (Velcade®) is an important new drug for the treatment of myeloma. Based on this success, novel combination therapies with bortezomib are being tested for enhanced. The reovirus is a naturally occurring virus that is non-pathogenic and has been reported to preferentially replicate in cancer cells, but not in normal tissue. This observation prompted the development of the reovirus-based anticancer agent Reolysin®, which has already demonstrated promise in early preclinical and clinical studies. However, the mechanism by which Reolysin induces tumor cell death remains unclear. Myeloma cells have remarkably high rates of protein synthesis to produce large amounts of immunoglobulins. Therefore, it has been suggested that these cells may be hypersensitive to endoplasmic reticular (ER) stress. Dr. Nawrocki and colleagues hypothesize that Reolysin preferentially induces the accumulation of viral products in myeloma cells and that this selectively stimulates ER stress-mediated cell death. Since abnormal protein accumulation can trigger cancer cell death, the simultaneous induction of different types of protein buildup (ubiquitin-conjugated and viral) may be a promising anticancer strategy. Moreover, the high protein synthesis rates of myeloma cells (compared with low protein synthesis rates of normal cells) may render them uniquely sensitive to proteotoxicity-mediated cell death. Dr. Nawrocki will investigate this possibility by evaluating the benefit of a bortezomib and Reolysin combination therapeutic strategy. The knowledge gained from this research will be rapidly translated into a clinical trial and has the potential to significantly impact myeloma therapy.

“Bone marrow microenvironment and multiple myeloma chemotherapy optimization”

Ariosto Silva, PhD
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While systemic chemotherapy for myeloma is often initially quite successful, tumor sites that are resistant to therapy invariably remain as minimum residual disease (MRD) even after high-dose treatment. The mechanisms of resistance to chemotherapy include both micro-environmental and cellular factors such as (1) regional hypoxia in bone marrow resulting in decreased drug effectiveness due to absence of intermediate oxygen free radicals, (2) environmentally mediated resistance (EMDR) due to signaling between tumor cells and extracellular matrix (ECM), bone marrow stromal cells (BMS), and endothelial cells (EC), and (3) phenotypic resistance through upregulation of xenobiotic metabolism or DNA repair pathways. Dr. Silva and colleagues will examine these complex systems using an approach characterized as "integrated mathematical oncology" in which mathematical models are combined in an iterative way with in vivo and in vitro experiments. Ultimately, through understanding of the dynamics that govern emergence of chemotherapy resistance in myeloma, this research project will explore alternative treatment strategies based on understanding these dynamics to slow the evolution and growth of resistant phenotypes.

"MMSET and epigenetic control in t(4;14) myelomas" ***

Vyacheslav Yurchenko, PhD
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The overexpression of IgH enhancer/promoter driven genes such as cyclin D1, cyclin D3, or c-maf is likely to contribute to myeloma cell proliferation. Recent findings suggest an important role of histone methyltransferase MMSET (Multiple Myeloma SET domain protein) in malignant progression of myeloma. In about 15% of all myeloma cases, the t(4;14) translocation brings MMSET gene under the control of the μ enhancer followed by increased, as compared to healthy plasma cells, expression of the protein. It is not currently known how the increased expression of MMSET in plasma cells is translated into myeloma development and/or progression. Provided that MMSET acts as a transcriptional co-repressor and histone methyltransferase, Dr. Yurchenko and colleagues propose that the developmental program of normal and neoplastic plasma cells is regulated by this enzyme. Specifically, they hypothesize that deregulation of MMSET in plasma cells contributes to the disease initiation and/or progression. The goal of this research project is to establish the role of MMSET-dependent genetic program in normal plasma cell differentiation and myelomagenesis in mice. To achieve this goal, this project aims to define the role of MMSET in normal plasma and

myeloma cell development and to identify the genetic network directly controlled by MMSET in B cells.

2010 IMF Aki Horinouchi Research Grant

"Novel anti-myeloma therapy by targeting molecular signaling regulated by galectin family proteins" ****

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Because myeloma cells acquire the chemo-resistant phenotype not only by cell intrinsic molecular abnormalities but also by the support of extracellular bone marrow (BM) components, it is essential to development new agents simultaneously targeted for those two divergent but mutually interacting, abnormal molecular signaling networks for myelomagenesis. To this purpose, Dr. Kuroda and colleagues are currently investigating the molecular signaling modulation which is specifically responsible for chemo-resistance of myeloma cells in tumor microenvironment model consisted of BM stromal cells, cytokines, and extracellular matrix. Preliminary data suggest that several members of galectins, a family of animal lectins that show affinity for b-galactosides (such as galectin-3 or galectin9), play important roles for myeloma cell survival, the resistance to cellular insults, cell adhesion, or deregulated cell proliferation in BM microenvironment.

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