IWMF-LLS STRATEGIC RESEARCH ROADMAP INITIATIVE

Request for Proposals

The International Waldenstrom's Macroglobulinemia Foundation (IWMF) and the Leukemia & Lymphoma Society (LLS) are proud to announce the IWMF-LLS STRATEGIC RESEARCH ROADMAP INITIATIVE - a Request for Proposals (RFP) to help further knowledge in four key domains of Waldenstrom's macroglobulinemia (WM) research:

- Genomics and Epigenomics:

Mutations in signal pathways that drive cancer provide an opportunity to develop targeted therapies to treat the disease. This is highly relevant to WM, since approximately 95% and 30% of WM patients have mutations in MYD88 and CXCR4, respectively. Moreover, since MYD88 activates interleukin-1 receptor-associated kinase and Bruton's tyrosine kinase (BTK), this helps to explain why WM patients have a major response to the BTK-targeted agent known as ibrutinib (approved for

WM by the FDA in January 2015). Nevertheless, cures have not been achieved with ibrutinib, WM patients with mutations in both genes respond only moderately to ibrutinib, and patients with wild-type MYD88 and CXCR4 have no major responses to ibrutinb. Patients with wild-type MYD88 disease show differences in clinical presentation, including lower serum IGM and bone marrow disease burden, CD27+ expressing disease, and lymphocytosis, versus mutated MYD88 patients. The genetic basis for wild-type MYD88 disease remains unknown.

These data indicate that further genetic analyses, coupled with functional studies to understand the effects of mutations in WM, need to be explored further to 1) understand the basis of resistance to existing agents, 2) provide a mechanistic understanding that may justify combination of therapies, and 3) lead to the development of new therapeutics to specifically control or cure the disease.

Recently it has become clear that epigenetic regulators are also critically important in lymphomas and myelomas. However, relatively little is known about the epigenome in WM. Mutations or copy number losses affecting major chromatin remodeling proteins exist for WM, though their impact on specific gene dysregulation remains unclear. A comprehensive dissection of the epigenome of WM cells genotyped by MYD88 and CXCR4 mutation status will provide critical insights into cellular signaling and pathways for potential therapeutic exploitation.

- Signaling:

Much of the knowledge for the signaling apparatus of MYD88 has been generated for wild-type MYD88. Knowledge of mutated Myddosome assembly and molecules involved in downstream signaling could help advance novel therapeutics. The creation of 3D-crystal structures of the mutated Myddosome, MYD88/IRAK complex, and MYD88/BTK complex can provide critical information for medicinal chemistry campaigns aimed at disrupting Myddosome assembly and signaling. Studies aimed at identifying signal pathways associated with mutated MYD88 beyond BTK and IRAK, as well as identification of other pivotal scaffold and kinase nodal points in MYD88 signaling, are needed for advancing medical chemistry campaigns.

The functional consequences of CXCR4 WHIM mutations are poorly understood. Both AKT and ERK are hyperactivated in response to the CXCR4 ligand CXCL12. Nevertheless, little else is known about the nature of CXCR4 mutations. Detailed signaling studies aimed at clarifying CXCR4 WHIM dysregulated signaling, including G-

protein receptor transactivation, beta-arrestin and GRK recruitment, and impact on downstream growth and survival signaling may help advance our understanding of the relevant biology and therapeutic exploitation in WM.

- Immunology/Immunotherapy:

Research to understand the biology of the immune response, in particular the anti-tumor immune response in WM, is vitally important, and clinical approaches to optimize the immune response need to be tested. Continued research characterizing the immune microenvironment in WM and an understanding of immune cell trafficking are needed. Specific knowledge gaps include understanding T effector cell exhaustion, determining the effect of immune checkpoint inhibitors, and defining the role of other immune cells, including NK cells and mast cells. Studies to identify high-risk WM patients who would most benefit from immune therapies, such as CAR T-cell therapy or immune checkpoint therapy, are needed.

- Bone Marrow/Tumor Microenvironment:

The role of the bone marrow and tumor microenvironment in supporting malignant cell growth and promoting resistance to therapy in WM requires additional focused research. Studies are required to better characterize the components of the tumor/bone marrow microenvironment in WM. A better understanding of the contribution of the microenvironment to disease progression (such as progression from IgM MGUS to WM) and resistance to treatment remains an important goal, as does an evaluation of the nature of the crosstalk between WM tumor cells and the associated microenvironment, including the effects of the stroma on immune cells. The development of a better model system of the bone marrow microenvironment to understand interactions between WM cells and the microenvironment is needed.

The International Waldenstrom's Macroglobulinemia Foundation (IWMF)

The IWMF is a patient-founded and volunteer-led, nonprofit organization that is dedicated to a simple but compelling vision: Support everyone affected by Waldenstrom's macroglobulinemia (WM) while advancing the search for a cure.

The IWMF currently has a worldwide membership of over 8,000, with Support Groups and affiliate organizations on virtually every continent.

Today the IWMF:

- provides support to patients and their caregivers
- enables patients to communicate with one another
- sponsors patient educational forums about WM that feature prominent physicians and researchers
- publishes booklets on WM and its treatment
- supports research aimed at improving treatments and ultimately, finding a cure for WM
- has invested over $8.1 million dollars in research on WM since 1999

For more information, visit the IWMF website at http://www.iwmf.com/

The Leukemia & Lymphoma Society (LLS)

LLS is a US-based foundation focused on developing, and providing access to, therapies to cure or control leukemia, lymphoma, Hodgkin's disease and myeloma as well as improve the quality of life of patients and their families. The organization has funded blood cancer research for the past 60 years to strive toward these goals.

For more information, visit the LLS website at http://www.lls.org/

IWMF Research and the Strategic Research Roadmap

The IWMF supports research to understand the biology of WM, with the goals of improving quality of life for WM patients, discovering new treatments, and ultimately, finding a cure.

IWMF funding for research has helped to provide insight into understanding the basic biology and genetics of WM. This research in turn has played a significant role in the development of treatments and treatment guidelines in current use, as well as potential new drugs still in the pipeline.

On May 16-17, 2015, distinguished WM researchers and officers from the IWMF and the LLS met in New York City to determine the next phase of research priorities focused on improving our understanding of WM. Based on discussions during the meeting in New York, the Scientific Co-Chairs, Dr. Stephen Ansell of Mayo Clinic in Rochester and Dr. Steven Treon of Dana-Farber Cancer Institute, defined in more detail the four priority areas where additional research is needed to advance our knowledge of WM.

The recommended plan is to fund and implement up to 4-5 new research projects for 2 years, with the possibility of an extension for 1-2 additional years depending on the progress achieved, at a cost of up to $200,000 per year per project for a total annual cost of up to $1,000,000. This dynamic plan would initially seek to fund 2-4 research projects in year one (with the possibility of additional research projects in subsequent years depending on available funding).

How to Apply for a Research Grant

The grant application process for the Strategic Research Roadmap Initiative will follow the standards that already exist for previous IWMF-funded research grants:

Submissions: An application for a research project can be submitted within the Strategic Research Roadmap Initiative via email (timelines and addresses listed below). Applications should be no longer than 12 pages in length and follow the guidelines as noted on the IWMF webpage (www.iwmf.com/research/applying-grant). Following a review process that may take up to four to six months, awards will be made to successful applicants.

Who can apply: Applicants must hold an M.D., Ph.D., or equivalent degree and work in domestic or foreign non-profit organizations, such as universities, colleges, hospitals, or laboratories. Applications may involve multiple such institutions, and the applicant should have an independent research or academic position. Applicants need not be U.S. citizens, and there are no restrictions on applicant age, race, gender, or creed. Applications from non-academic facilities, postdoctoral positions, and the National Institutes of Health are not eligible.

Review Process: Research proposals are reviewed by selected members of the IWMF Scientific Advisory Committee (SAC) or other experts in the field. The SAC may in turn respond to the research proposal applicant(s) with questions and/or request clarification regarding certain aspects of the proposal itself. The SAC comments and recommendations are thereafter evaluated by the IWMF Research Committee which in turn may submit further questions to the applicant. Once both the SAC and the Research Committee approve the application, a recommendation for funding is forwarded to the IWMF Board of Trustees and the LLS Oversight Committee, where applicable. Generally speaking, at this stage a decision to fund a SAC/Research Committee-approved proposal is based on fund availability. Applicants will be notified by the IWMF Vice President for Research as soon as a decision is made.

Payment Policy: IWMF research payments are made on a six-month basis. The IWMF Treasurer will pay a pro rata amount for six months at the start of the project. Future payments will be made every six months after receipt of a six-month Progress Report. Ten percent (10%) of the last payment will be withheld until the IWMF Research Committee approves a Final Report. Within a grant, eight percent (8%) of the actual costs is the maximum amount permitted for indirect costs.

Reporting Requirements: Progress Reports are required to be submitted to the IWMF by the Principal Investigator every six months for the duration of the project. Progress Reports must be submitted no later than 30 days after the six-month period ends. Progress Reports will describe the activities and findings of the previous six months and provide a plan for the next six-month period. A Final Report which shall describe the results and findings as they relate to the stated goals of the project for the full term of the project is required no later than two months after the project ending date. The Principal Investigator should expect on occasion to receive requests for clarification of Progress Reports. A layperson summary shall accompany each Progress Report and the Final Report; this often results in fewer queries from IWMF Research Committee members and ensures minimal delay to any of the scheduled research payments.

Budget

A detailed budget and budget justification should provide itemized detail for each major category for all the years of the program. This budget can be summarized for year one and extrapolated for the remaining year. All totals and subtotals should be included.

The maximum annual total costs (direct and indirect) cannot exceed $200,000. The aggregate costs over two (2) years cannot exceed $400,000.

Permissible direct costs include the following with the specified limitations:

- Personnel expenses including salary, wage, or stipend with fringe benefits. In total, no more than forty percent (40%) of the direct costs may be requested for the salary and fringe benefit expenses of professional staff with a post-graduate degree (i.e. M.D., Ph.D., D.V.M.) regardless of function or role. This restriction does not apply to technical staff (lab assistants, nurses, etc.).
- Supplies and materials requests should be itemized by category.

- Equipment purchase requests must identify each item of equipment with an acquisition cost of more than $500.
- Travel expense requests cannot exceed $1000 per year of the award.
- Other direct cost requests can include patient care costs.

Permissible indirect costs (often referred to as institutional overhead, IDC, M&A, G&A, or pooled costs) are those costs incurred for common or joint objectives that cannot be readily identified with a particular project (general maintenance, utilities, library, etc.). Indirect costs are limited to eight percent (8%) of total direct costs. For sponsoring institutions that do not choose to use these funds for indirect costs, these funds can be applied to the Grantee's/Principal Investigator's stipend or fringe benefits cost.

Impermissible costs include membership dues, tuition, books, journals, and publication costs.

Review Criteria

An application will be judged on these criteria:

- The probability of an advance in prevention, diagnosis, or treatment in the near-term.
- The conceptual basis upon which the proposal rests.
- The novelty of the concept and strategy.
- Thoughtful and clear presentation.
- The overall plan for bringing the research findings to clinical application.
- Experience, background, and qualifications of investigator(s).
- Adequacy of resources and environment (facilities, data management, data analysis, etc.).
- Adequacy of provisions for protection of human subjects.

Timeline

Call for Proposals	November 12, 2015
Application Deadline	February 19, 2016, 3:00 PM ET
Review of Submitted Applications Completed	May 2016
Notification of Awards	June 2016
Anticipated Funding Start Date	July-October 2016

Submit All Correspondence to

- Dr. Guy Sherwood, IWMF Vice President for Research, foxfiremedic@gmail.com
- With a copy to Sara McKinnie at the IWMF Office, info@iwmf.com