ROBERT A. KYLE CAREER DEVELOPMENT AWARD FROM THE IWMF

2023 Request for Proposals

Robert A. Kyle Career Development Award

To fulfill its vision of a world free from Waldenstrom's macroglobulinemia (WM), the International Waldenstrom's Macroglobulinemia Foundation (IWMF) acknowledges the crucial role of nurturing a new generation of WM researchers to ensure continuous progress in the field. The primary objective of the Kyle Career Development Awards is to inspire and provide support to talented young investigators with a background in hematology and/or oncology, encouraging them to either enter or persist in their work within the realm of Waldenstrom's research. In this regard, the IWMF is delighted to announce the third year of the Robert A. Kyle Career Development Award for Waldenstrom's Macroglobulinemia, which serves as a tribute to Dr. Robert Kyle's significant contributions to the field of plasma cell disorders and Waldenstrom's macroglobulinemia over the past 50+ years.

Program Structure

- Each awardee will receive a two-year grant of $75,000 per year for a total of $150,000.
- A 5% overhead for institutional related overhead will also be provided.

Research Focus

The Robert A. Kyle Career Development Award will focus on furthering knowledge in five key domains of Waldenstrom's macroglobulinemia research:

- Genomics and Epigenomics:

Mutations in signaling pathways that drive cancer provide an opportunity to develop targeted therapies to treat Waldenstrom's Macroglobulinemia (WM). Whole genome sequencing has revealed mutations in MYD88 and CXCR4 in 95-97% and 30-40% of WM patients, respectively. Other mutations including those in ARID1A, CD79, TP53 as well as copy number alterations such as 6q deletions are found that impact genes that modulate NFKB, BCL2, Bruton tyrosine kinase (BTK), and apoptosis. Among MYD88 wild-type patients, recurring mutations in TBLXR1, canonical and non-canonical NFKB pathway genes, and genes involved in DNA repair have been identified. The discovery of mutations in MYD88 and CXCR4 enabled the development of targeted inhibitors for WM including BTK-inhibitors, and CXCR4 antagonists. While long term disease control has been achieved in MYD88 mutated patients, complete responses are lacking and patients with CXCR4 mutations, particularly nonsense variants show fewer deep responses and earlier progression.

WM is an ideal disease model for a multi-omic approach given highly recurring somatic activating mutations in *MYD88* and *CXCR4.* Moreover, *MYD88* and *CXCR4* activating mutations are clinically relevant as they associate with important disease presenting features and have prognostic and/or predictive treatment roles. Recent evidence supports that transcriptional regulation of WM is impacted by the epigenome. The methylome stratified WM patients into two camps: one with similar profiling to healthy donor memory B cells while the other profiling similar to healthy donor plasma cells. Those WM patients with MBC-like profiling showed DNA methylation changes that targeted functional domains related to transcriptional activation, while among those with PC-like profiling broader losses in methylation that impacted repressed, heterochromatic, as well as intergenic regions were observed.

While the above studies have provided critical insights into WM, the pathophysiological, diagnostic and clinical implications for these as well as other genomic, transcriptomic-including splicing variations, and epigenomic alterations associated with WM remain to be more clearly defined. Such revelations may further advance targeted treatments for WM

patients, provide personalized approaches for treatment and enable improved diagnostic, prognostic and treatment predictive tools for WM.

- Signaling:

Much of the knowledge for the signaling apparatus of MYD88 has been generated for mutated MYD88. Key discoveries have included the importance of BTK, IRAK1/IRAK4, HCK, and SYK as critical downstream mediators of mutated MYD88 signaling. Other nodal components critical to mutated MYD88 signaling remain to be clarified. Knowledge of mutated Myddosome assembly and identification of other signaling components of mutated MYD88 signaling beyond BTK and IRAK, including scaffold and kinase components are needed for advancing medicinal chemistry campaigns. The creation of 3D-crystal structures of the mutated Myddosome, MYD88/IRAK complex, and MYD88/BTK complex may provide critical information for medicinal chemistry campaigns aimed at disrupting Myddosome assembly and signaling.

The functional consequences of CXCR4 mutations are not well understood. While MYD88 mutations are found in other B cell cancers, CXCR4 mutations are relatively unique to WM. Both AKT and ERK are hyperactivated in response to the CXCR4 ligand CXCL12. CXCR4 mutations, including nonsense and frameshift, have been found to affect response rates and progression-free survival in Waldenstrom patents treated with current BTK inhibitors. Differences in the impact of nonsense versus frameshift CXCR4 mutations, association with homozygous versus heterozygous mutated MYD88, and clonality of CXCR4 mutations have been recognized with BTK-inhibitors, though the underlying pathophysiology for these observations remains to be clarified. Detailed signaling studies aimed at clarifying mutated CXCR4 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. Studies leading to the development and study of CXCR4 inhibitors, and novel and improved means for routine detection of CXCR4 mutations are needed to enable targeted approaches for WM.

While BTK inhibitors are highly active in Waldenström macroglobulinemia (WM) patients, disease progression can occur due to acquired mutations in BTK, the target of ibrutinib, and other covalent BTK-inhibitors. Mutations in BTKCys481 lead to activation of ERK, enabling release of IL-6, IL-10 and other cytokines that can propagate bystander tumor resistance. However, not all resistant patients harbor mutations in BTK. Further understanding of the mechanisms that enable resistance against BTK-inhibitors may enable novel treatment approaches for the prevention and treatment of resistance to

BTK-inhibitors.

- Immunology/Immunotherapy:

There is little published data on the anti-tumor immune response or lack thereof in WM, and potential impact of current therapeutics including BTK-inhibitors. Such studies may lead to new clinical approaches to enhancing anti-tumor responses in WM. Studies characterizing the immune microenvironment in WM, and an improved understanding of immune cell repertoire 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 which may identify high- risk WM patients who would most benefit from immune therapies, such as CAR T cell therapy or immune checkpoint therapy, are needed. Discovery of neoantigens for development of novel immunotherapies are also 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 including mast cell and macrophage/monocyte interactions. 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 also needed.

- IgM MGUS:

IgM Monoclonal Gammopathy of Undetermined Significance (MGUS) involves a clone of lymphoplasmacytic B cells that produces an overabundance of IgM and is usually found in the bone marrow. Normally benign, the clone can evolve into Waldenstrom macroglobulinemia at 2 percent per year. While many patients with IGM MGUS harbor MYD88 mutations, the presence of mutated MYD88 alone is unlikely to explain progression given findings from transgenic animal models. An understanding of changes in the genome, transcriptome, and epigenome that accompany IGM MGUS progression to WM may identify patients at risk of progression, and interventions that may prevent or suppress

progression.

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 and mission:

- Vision – A World Without WM (Waldenstrom's macroglobulinemia).
- Mission – Support and educate everyone affected by Waldenstrom's macroglobulinemia (WM) to improve patient outcomes while advancing the search for a cure.

The IWMF currently has a worldwide membership, 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 and webinars about WM that feature prominent physicians and researchers.
- Publishes booklets and fact sheets on WM and its treatment.
- Supports research aimed at improving treatments and ultimately, finding a cure for WM.
- The IWMF has invested $23 Million dollars on WM basic science research since 1999. Additionally, we currently have 24 active projects that will receive $4.6 Million dollars between now and their completion.

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

IWMF Research

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.

Under the terms of the Robert A. Kyle Career Development Award, the IWMF will confer a

research grant to junior faculty members and/or post-doctoral fellows in the amount of $75,000 each year for a two (2)-year project. The applicant should have a focus in clinical research in the field of B cell or plasma cell malignancies for at least two (2) years. His or her program must have a teaching curriculum and mentoring with well-established investigators with a track record in the B cell malignancy or plasma cell malignancy field.

How to Apply for a Research Grant

The grant application process for the Robert A. Kyle Career Development Award will follow standards that already exist for previous IWMF-funded research grants, as well as NIH review guidelines:

Submissions: An application for a research project can be submitted for the Robert A. Kyle Career Development Award via email (timelines and addresses listed below). The project description, significance, Aims, six-month timelines and scientific approach should not exceed 12 pages in length and follow the guidelines noted below and also located on the IWMF website at www.iwmf.com/research/applying-research-grant. Additional pages should include references, biographical sketches, detailed budget with justification, list of other projects, and appendices as necessary. Following a review process that may take up to 2-3 months, the award will be made to the successful applicant(s).

Who Can Apply: Applicants must hold an MD, PhD, or equivalent degree and work in domestic or foreign non-profit organizations, such as universities, colleges, hospitals, or laboratories, that have a teaching curriculum and mentoring program with senior investigators. Applicants should be junior faculty members and/or post-doctoral fellows who have had a focus in clinical research in the field of lymphoma for at least two (2) years. Applicants need not be US citizens, and there are no restrictions on applicant age, race, gender, or creed. Applications from non-academic facilities and the National Institutes of Health are not eligible.

Review Process: Research proposals are reviewed by an independent committee composed of selected members of the IWMF Research Committee, the IWMF Scientific Advisory Committee (SAC) and other experts in the field. This committee may in turn respond to the research proposal applicant(s) with questions and/or request clarification regarding certain aspects of the proposal itself. The proposals will be ranked using established NIH review criteria. Awards will be made based on funding availability.

Applicants will be notified by the IWMF as soon as a decision is made. Grant recipients will be invited to the IWMF Educational Forum to be acknowledged by and meet the attendees. the IWMF reimburses a grant recipient's expenses for attendance at the Ed Forum.

Payment Policy: The IWMF Treasurer will pay a pro rata amount for six months at the start of the project. Future payments will be made at designated six-month intervals after each Interim or Final Progress Report and accompanying Lay Summary has been received and the IWMF Research Committee has reviewed it for satisfactorily meeting the IWMF reporting guidelines (see below). Payments will be made after all guidelines have been met.

Reporting Requirements: Progress Reports are required to be submitted to the IWMF by the Investigator every six months for the duration of the project. Interim Progress Reports must be submitted no later than 30 days after the six-month period ends. Such Progress Reports will describe the activities and results with respect to each specific Aim that has occurred during the preceding six-month period. Each Progress Report will include a proposed path forward over the next six-month period. Project Aims should not be changed during the research process without prior notification, justification, and agreement of the IWMF Research Committee. The Investigator must show in the reports that he or she is performing the obligations stated in the submitted and approved research proposal for each reporting period. Deviations from the six-month timelines need to be explained to ensure that the project is on track. A Final Progress Report which describes 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 45 days after the project ending date. The Investigator should expect on occasion to receive requests for clarification of Progress Reports. A Lay Summary must accompany each Interim Progress Report and the Final Progress Report. The reports must be submitted in Microsoft Word or PDF file format. A final detailed expenditure report must also be sent no later than 90 days after the project ending date.

Budget

A detailed budget and budget justification should provide itemized detail for each major category for all the years of the project. This budget can be summarized for year one and extrapolated for the remaining year. All totals and subtotals should be included. The maximum annual direct costs cannot exceed $75,000. The Indirect cost will be up to 5% of the project's direct cost. The aggregate costs over two (2) years cannot exceed $157,500.

Permissible direct costs include the following with the specified limitations:

- Personnel expenses including salary 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., MD, PhD, DVM) regardless of function or role. This restriction does not apply to supportive technical staff for the project (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.

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 five percent (5%) 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/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 the investigator.
- Adequacy of resources and environment (facilities, data management data analysis, etc.).
- Adequacy of provisions for protection of human subjects.

Timeline

Email Call for Proposals	August 16, 2023
Application Deadline	January 17, 2024, 3:00 PM US (**No exceptions**)
Review of Submitted Applications Completed & Notification of Awards	March 28, 2024
Award Winners will receive the award at the 2024 IWMF Educational Forum in Seattle	April 2024
Anticipated Funding Start Date	July to September 2024

Submit All Correspondence to

All proposals and other correspondence regarding the Robert A. Kyle Career Development Award should be sent to the following two individuals:

- Dr. Tom Hoffmann, IWMF Research Committee, thoffmann@iwmf.com
- Robin Tucker, IWMF Finance Manager, rtucker@iwmf.com

The IWMF Office will acknowledge receipt of each proposal within one business day via email. If you do not receive such an acknowledgment, please contact Robin Tucker, IWMF Finance Manager, at rtucker@iwmf.com or call the IWMF Office at 941-927-4963.

Good luck and thank you for your interest!