2020

Current Research Projects

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Current IWMF Research Projects

IWMF grant funding for research projects has helped to provide an understanding of 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. The goal of our research program is to improve quality of life for WM patients and, ultimately, discover a cure.

The Foundation has a rigorous process in place for all research grant proposals, which includes review by an independent committee composed of selected members of the IWMF Scientific Advisory Committee and other experts in the field. The awarding of research grants is ultimately subject to IWMF Board of Trustees approval. Researchers who receive grant awards must submit periodic progress reports, including a layman's summary, to the volunteer IWMF Research Committee for review and comment.

IWMF / LLS Strategic Research Roadmap Initiative

Because of exciting advances in our understanding of the biological basis of WM, the IWMF decided in 2014 to update its research strategy and enlist the cooperation of many of the major players in the WM research community. To this end, the IWMF partnered with the Leukemia & Lymphoma Society (LLS) to sponsor a Strategic Research Roadmap Summit in New York City in May 2015. Now the summit is held annually and the agenda is divided into five major topics:

Signaling – How do we find and block the pathways that WM cells use for communication?

Immunology/immunotherapy – How can we boost our immune system to fight WM?

Tumor microenvironment – How do we manipulate the bone marrow/tumor environment to kill WM cells?

"**Omics**" – What else can we learn about genomics, epigenomics, and mutations in WM cells that will improve the lives of WM'ers?

IgM Monoclonal Gammopathy of Undetermined Significance (MGUS) - How can understanding changes in the genome, transcriptome, and epigenome that accompany IgM MGUS progression to WM identify patients at risk of progression and interventions that may prevent or suppress progression?

All research projects that are funded by the Strategic Research Roadmap Initiative are marked accordingly.

CRISPR-BASED FUNCTIONAL CHARACTERIZATION OF WM CELLS: INSIGHTS INTO THERAPEUTIC VULNERABILITIES AND STRATEGIES TO OVERCOME RESISTANCE

Project Period 10/ 01/19 – 10/01/21	**Investigator**: Constantine Mitsiades, MD, PHD
$400,000 over two years	**Institution**: Dana-Farber, Boston, USA

This project falls under the IWMF-LLS Strategic Research Roadmap Initiative. The research takes advantage of new technologies, including the gene editing tool CRISPR, improved and powerful computational approaches, and innovative new mouse models. The researchers will conduct a broad, genome-wide search to identify specific genes that are required to allow Waldenström's macroglobulinemia (WM) cells to thrive. Additionally, the researchers will attempt to identify genes that allow WM cells to resist established therapies. The key is to identify specific gene targets that cause death of WM cells, but do not alter normal body cells. Any genes identified will be further tested in laboratory cells and then evaluated in mouse models. This research will hopefully identify new, previously unsuspected molecular targets for WM therapy.

TOWARDS A RATIONAL TARGETED THERAPY FOR WALDENSTRÖM MACROGLOBULINEMIA BY KINOME-CENTERED LOSS-OF-ADHESION AND SYNTHETIC LETHALITY SCREENS

Project Period 03/01/20 – 03/01/22	**Investigator**: Marcel Spaargaren, PhD; Steven T. Pals, MD, PhD; and Marie Jose Kersten, MD, PhD
$398,000 over two years	**Institution**: Academic MC, Amsterdam, The Netherlands

This project falls under the IWMF-LLS Strategic Research Roadmap Initiative. One mechanism of action of ibrutinib is to dislodge WM cells from the bone marrow, where they grow best. This research seeks to identify specific kinases that allow WM cells to remain in the bone marrow. In a second part of the project, the researchers will seek to identify kinases that allow some of the ibrutinib-surviving cells to survive. In previous IWMF-funded research, Dr Spaargaren's group identified a set of kinases with potential as new WM drug targets. In the present grant period, they will continue this work, first by validating the new targets in cellular tests ("in vitro") and then by evaluating the role of the new targets in an innovative mouse model ("In vivo"). Identifying these new protein targets can help determine if there are existing drugs that may be re-purposed to treat WM, or could lead to development of new drugs specific to WM.

DIRECT TARGETING THE MYD88 L265P DRIVER MUTATION IN WALDENSTROM'S MACROGLOBULINEMIA

Project Period 10/15/19 – 10/15/21	**Investigator**: Yong Li, PhD
$400,000 over two years	**Institution**: Baylor Medical School, Houston, USA

This project falls under the IWMF-LLS Strategic Research Roadmap Initiative. More than 90% of Waldenström's macroglobulinemia (WM) patients have an abnormality (mutation) in the MYD88 protein, termed MYD88 L265P. This research aims to discover a drug to specifically block the abnormal MYD88 L265P protein in WM cells, while sparing the body's normal MYD88. The work builds on Dr Li's prior discovery that the abnormal MyD88 L265P, but not normal, wildtype MYD88, interacts with a specific protein called RING finger protein 138 (RNF138), leading to polyubiquitination that stimulates excessive NF-kB signaling. The project will perform a high-throughput screen to identify candidate molecules that either block RNF138 from interacting with MYD88 or inhibit RNF138 directly. Candidate molecules will be tested in additional cellular assays and in a mouse model. A new drug to block the abnormal function of MYD88 L265P would be useful to most WM patients, even though WM patients show a wide diversity of clinical disorders.

FACTORS REGULATING IMMUNOGLOBULIN-PRODUCING B-CELLS IN PATIENTS WITH WALDENSTROM'S MACROGLOBULINEMIA – PART V

Project Period 01/01/19 – 12/31/20	**Investigator**: Stephen Ansell, MD, PhD
$428,146 over two years	**Institution**: Mayo Clinic, Rochester, MN, USA

This is a continuation of previous projects proposed by Dr. Ansell and funded by the IWMF. While recent studies have provided considerable insight into the genetic events occurring in the WM cell, less is known about the influence of the bone marrow

microenvironment on WM development. Myeloid derived suppressor cells (MDSCs) are a group of immature immune cells that can give rise to macrophages, granulocytes, and dendritic cells. They can also strongly expand in disease situations such as chronic infections and cancer and have the ability to suppress T-cell function. Dr. Ansell proposes that these MDSCs are important in the bone marrow microenvironment of WM patients and may be involved in suppression of normal immune cells so that they are not doing their job of killing the cancer cells. To test his hypothesis, Dr. Ansell and his team will define the characteristics and function of MDSCs in the WM bone marrow, determine whether WM cells promote the development of MDSCs, assess whether MDSCs not only suppress immune function but also directly promote WM cell growth, and determine whether MDSCs can be altered so that they can instead become immune cells effective in killing WM cells. This work may lead to a new therapeutic approach for WM patients.

TARGETING MYD88 SIGNALING IN WALDENSTROM'S MACROGLOBULINEMIA

Project Period 9/1/20 – 9/1/22	**Investigator**: Principal Investigator Steven Treon, MD, PhD, and Co-Investigator Guang Yang, PhD
$500,000 over two years	**Institution**: Dana-Farber Cancer Institute, Boston, MA, USA

This is a continuation of previous projects proposed by Dr. Treon and funded by the IWMF. In previous research partially funded by the IWMF, Dr. Treon and his team discovered the highly recurring mutation in the MYD88 gene that occurs in more than 90% of WM patients and showed that mutated MYD88 promoted growth and proliferation of WM cells through the downstream signaling pathways BTK and IRAK1/IRAK4. These findings enabled the pivotal clinical trial that led to approval of the BTK inhibitor ibrutinib (Imbruvica) for the treatment of WM in the US, Europe, and Canada. Resistance to ibrutinib is an emerging problem in WM patients, and Dr. Treon's team has identified mutations in BTK that disrupt ibrutinib-BTK binding in samples from half of WM patients whose disease progressed on ibrutinib. His group has sought novel strategies to overcome the most common type of BTK mutation-related ibrutinib resistance in WM. His group is also working on uncovering the importance of other MYD88 downstream signaling pathways, including HCK, which triggers AKT, ERK1/2, and BTK itself. For this project, Dr. Treon has three principal Aims: 1) to delineate the importance of IRAK signaling to ibrutinib resistance and develop selective IRAK inhibitors based on this work, 2) to clarify whether HCK inhibition can suppress mutated BTK-acquired ibrutinib resistance in WM and develop selective HCK inhibitors, and 3) and to validate these inhibitors alone and in combination using animal models for future translation to clinical trials.

TRANSCRIPTIONAL CHARACTERIZATION OF UNTREATED PATIENTS WITH WALDENSTROM'S MACROGLOBULINEMIA

Project Period 9/1/18 – 8/31/20	**Investigator**: Principal Investigator Steven Treon, MD, PhD, and Co-Investigator Zachary Hunter, PhD
$400,000 over two years	**Institution**: Dana-Farber Cancer Institute, Boston, MA, USA

This project falls under the IWMF-LLS Strategic Research Roadmap Initiative. The genome is made up of DNA, a long, winding molecule that contains the instructions needed to build, maintain, and reproduce cells. For these instructions to be carried out, DNA must be "read" and transcribed—in other words, copied—into RNA molecules, which are called "transcripts." A "transcriptome" is a collection of all the RNA transcripts present in a cell. A comprehensive characterization of the RNA transcriptome provides a snapshot of the inner workings of a cell at a particular moment in time. Studying the RNA transcriptome is a way in which researchers can determine when, where, and how each gene is expressed in a cell. This in turn can provide a basis for comparison between how genes are expressed in normal cells versus how they are expressed in cancer cells. Dr. Treon and Dr. Hunter propose to sequence the RNA transcriptome of a much larger set of WM patient samples than previously studied. Their sample set from 300 untreated patients should provide robust numbers for statistical analysis, thereby leading to better evaluation of gene expression from different types of MYD88 and CXCR4 mutations and better characterization of gene expression of other, less understood mutations in genes such as CD79B, ARID1A, and TP53, among others. Patients who provide samples will continue to be followed over time to investigate whether and how their gene expression patterns correlate with the clinical characteristics of their disease, such as: disease progression, response to therapy, subsequent progression-free survival and overall survival, and other events relevant to the natural course of WM.

EPIGENETIC REGULATION OF WM BIOLOGY

Project Period 9/15/18 – 3/15/21	**Investigator**: Sherine Elsawa, PhD
$400,000 over two & 1/2 years	**Institution**: University of New Hampshire, Durham, NH, USA

This project falls under the IWMF-LLS Strategic Research Roadmap Initiative. Although several genetic alterations in the development of WM have been identified, very few advances have been made in understanding the epigenetic landscape controlling the biology of the disease. The word epigenetics literally means "above genetics." It is the study of variations caused by external factors that switch genes on and off and affect how genes are "read." Like DNA, these epigenetic variations can be passed on from cell to cell. We currently know of several methods by which these epigenetic variations affect genes. One is by histone modification. Histones are spool-like proteins that enable the DNA molecule to be tightly coiled into chromosomes. A variety of chemicals can affect histones, changing how tightly or loosely they package DNA. If the wrapping is tight, a gene may be "hidden" in the DNA strand and consequently switched off; if the wrapping is looser, a gene that was formerly hidden may now be turned on. Many enzymes involved in histone modification have been reported to be abnormally expressed in different malignancies, although most of these are just beginning to be explored in WM. An enzyme called MLL1 is best known for its role in leukemia; however, previously no role for MLL1 in WM has been described. Dr. Elsawa has generated preliminary data indicating that MLL1 is highly expressed in WM cell lines and in WM cells from patient samples, and she suggests that defining the impact of MLL1 in WM could be a possible breakthrough in understanding the epigenetic regulation of the disease. Dr. Elsawa's central hypothesis is that MLL1 activates key genes, particularly IL-6 and CCL2, which play an important role in WM biology through the Toll-like receptor/MYD88 pathway. She will perform several experiments with cell lines, patient samples, and animal models to confirm her hypothesis.

ANTI-TUMOR AND IMMUNE MICROENVIRONMENT RESPONSES FOLLOWING A FIRST-IN-HUMAN DNA FUSION VACCINE FOR ASYMPTOMATIC WM/LPL

Project Period 10/15/17 – 10/15/20	**Investigator**: Larry W. Kwak, MD, PhD
$400,000 over three years	**Institution**: Beckman Research Institute of the City of Hope, Duarte, CA, USA

This project falls under the IWMF-LLS Strategic Research Roadmap Initiative. WM/LPL (lymphoplasmacytic lymphoma) is characterized by an asymptomatic phase during which currently available therapies are associated with toxicities and provide no overall survival benefit – hence the current strategy of "watch and wait." A more efficient, non-toxic alternative therapy is therefore needed in this early disease setting. The surface IgM immunoglobulin of malignant B-cells, formed by the combination of the variable regions of heavy and light chains, can act as a tumor-specific marker of the malignant clone and can thus be used as a target to develop a vaccine therapy. Dr. Kwak's group now has the ability to clone the genes in the variable region of the immunoglobulin and combine them into a single chain antigen format (scFv) to be used as a DNA vaccine. This vaccine is the subject of a cooperative single-center Phase I safety study being conducted at MD Anderson Cancer Center by Dr. Sheeba Thomas. Analysis of pre- and post-vaccination blood and bone marrow samples to determine the vaccine's effectiveness will be performed by Dr. Kwak's group at the City of Hope.

MULTIOMIC ANALYSIS OF DNA, RNA AND EPIGENOMIC NETWORKS FOR PROGNOSTICATION AND NOVEL TARGET IDENTIFICATION IN WALDENSTROM'S MACROGLOBULINEMIA

Project Period 09/01/20 – 09/01/22	**Investigator**: Zachary Hunter, PhD
$400,000 over two years	**Institution**: Dana -Farber Cancer Institute, Boston, Ma, USA

Previously, Dr. Hunter has transformed our understanding and management of WM, including the discovery of key gene mutations in WM cells, such as the MYD88 mutation carried by 90% of WM patients and CXCR4 mutations in 30-40% of WM patients. This discovery led to the development of ibrutinib as one of the mainstays of WM treatment and now has led to clinical trials with CXCR4 inhibitors in WM patients with relevant CXCR4 mutations. However, DNA sequences do not tell the whole story. Genes, encoded by DNA, must be transcribed into RNA strands, which are then translated into proteins. At each step of the way, there are many key regulatory processes. If any of these regulators go awry, cancers—including WM—can ensue. In this project, Dr Hunter's group will go beyond DNA sequence analysis and integrate many different molecular tests to look at WM in a more comprehensive way. The analysis will be powered by a large number of patients, including samples already collected from 300 WM patients. This large-scale approach will combine analysis of epigenetic gene regulation, DNA and RNA sequence, and protein identification, together with

clinical data from each patient. Dr. Hunter has built powerful collaborations with some leading computer groups, which will use newly developed artificial intelligence methods to uncover how the molecular changes interact in networks, both within WM cells and between WM cells and nearby normal cells in bone marrow. Analysis of interactive molecular changes will hopefully aid in understanding differences among WM patients and how to use these differences to personalize the best treatment for each patient. This project falls under the IWMF-LLS Strategic Research Roadmap Initiative.

MYD88L265P SIGNALING-ASSOCIATED MULTIPLEX CHARACTERIZATION OF THE BONE MARROW MICROENVIRONMENT IN WM PATIENTS FOR CLINICAL APPLICATION

Project Period 11/01/20 – 11/01/22	**Investigator**: Rueben Carrasco, MD, PhD
$400,000 over two years	**Institution**: Dana -Farber Cancer Institute, Boston, Ma, USA

WM cells live primarily in bone marrow. The bone marrow is not merely a hollow cavity in which WM cells grow. Instead, bone marrow is a complex environment with many cell types. Collectively, the bone marrow forms a hospitable place for WM cells to survive, grow, and secrete IgM. Dr. Ansell thinks there may be a way to change the bone marrow, to make it less hospitable to WM cells. The bone marrow of WM patients differs from normal bone marrow, making it an even better place for survival and growth of WM cells. Dr. Ansell and his group hypothesize that one feature that makes WM patients' bone marrow such a good place for WM cells is that in the bone marrow, WM cells are protected from the body's normal immune system. In previous IWMF-funded research work, Dr. Ansell's group found specialized cells in the bone marrow of WM patients that prevent the body's normal immune system from killing WM cells. If these specialized cells, called myeloid-derived suppressor cells (abbreviated MDSCs), could be inhibited with appropriate drugs, perhaps the body's immune system would be free to better attack the WM cells in the bone marrow. Moreover, the MDSCs may not only suppress immune killing of WM cells, but may also directly send positive growth signals to the WM cells. Drug therapy in the future could be a two-pronged, combining drugs such as ibrutinib or rituximab to kill WM cells, together with drugs that inhibit MDSCs to make the bone marrow environment less hospitable to WM and allow the body's immune system to attack the WM cells. This project falls under the IWMF-LLS Strategic Research Roadmap Initiative.