2020 IWMF RESEARCH GRANT RECIPIENTS

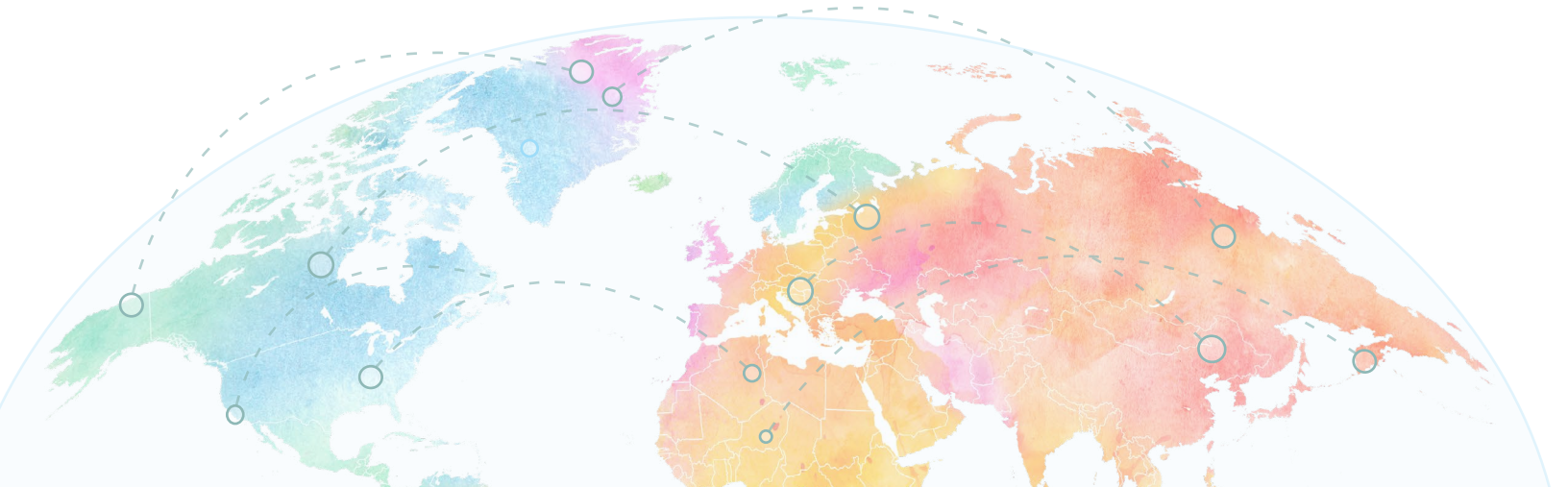
IMAGINE A CURE:

A WORLD WITHOUT WM

(Waldenstrom's macroglobulinemia).

IWMF

International Waldenstrom's
Macroglobulinemia Foundation



Stephen Ansell, MD, PhD

Factors regulating immunoglobulin-producing B-cells in patients with Waldenstrom's macroglobulinemia

IWMF Legacy Grant Renewal, October 2020

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 WM cells are protected in the bone marrow 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.

Ruben Carrasco, MD, PhD

MYD88 L265P signaling-associated multiplex characterization of the bone marrow microenvironment in WM patients for clinical application

In this proposal, Dr. Carrasco, a pathologist at the Dana-Farber Cancer Institute at Harvard, will harness new and powerful digital pathology and artificial intelligence technology for better diagnostics and understanding of WM. He is using two approaches. (1) More than 90% of WM patients have a mutation of the MYD88 gene, resulting in an altered protein, called MYD88 L265P. The altered MYD88 drives abnormal signaling which is key to survival and growth of WM cells. Detection of the MYD88 mutation by PCR is one of the cornerstones of making the diagnosis of WM. Dr. Carrasco has detected a feature of the mutant MYD88 protein, in which it forms microscopic aggregates inside cells. He proposes to detect these aggregates of mutant MYD88 protein with a technique called immunohistochemistry, which could speed up and simplify the diagnosis of WM.

(2) WM cells live primarily in bone marrow (BM), where they interact with other BM cells. Some of the BM cells help maintain a favorable environment for the WM cells to grow, while other BM cells attack the WM cells and prevent excessive growth. Dr. Carrasco's group, in collaboration with Drs. Treon, Hunter, and other state-of-the-art labs at Harvard, will examine BM samples using automated digital pathology to identify WM cells and the specific cell types in their immediate proximity which may be interacting with the WM cells and change during disease progression and development of resistance to conventional therapies. If scientists could understand these local interactions better, it may be possible to identify novel targetable dependencies to treat patients with drugs to make the BM less supportive of WM cell growth or to enhance immune attack on the WM cells.

OUR VISION: A WORLD WITHOUT WM (Waldenstrom's macroglobulinemia).

Zachary Hunter, PhD

Multiomic analysis of DNA, RNA, and epigenomic networks for prognostication and novel identification of WM

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 the vast majority of WM patients and CXCR4 mutations found 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.

CONNECTED BY A UNIVERSAL GOAL: A WORLD WITHOUT WM

As patients with Waldenstrom's macroglobulinemia will know, WM is a unique disease. Particularly unique to this disease is the production of the IgM protein by the cancer cells and the presence of symptoms such as hyperviscosity that develop as a consequence of this protein, as well as the fact that the cancer cells typically grow in the bone marrow and replace the normal cells. Twenty years ago this was mainly all we knew about the disease. Since then, due in large part to funding provided by the IWMF, we have learned a tremendous amount about the genetics and biology of this disease. Research funded by the IWMF has allowed us to understand the mutations in genes that lead to the development of WM, to identify signaling pathways that are overactive in this disease, to determine which proteins present in the bone marrow promote the growth and survival of the cancer cells, and to identify some of the deficiencies in the immune system that prevent eradication of the cancer cells. This work has led to novel therapies to treat WM. While in the past, treatments for WM were borrowed from other diseases, they are now specifically approved for WM based on research supported by the IWMF. While we have gone from almost no knowledge regarding WM in the past to substantial knowledge of this disease at present, we are now poised to make additional breakthroughs that may potentially lead to a cure for WM patients. All this progress is directly due to funding provided by WM patients!

–IWMF Board Member Dr. Stephen Ansell, Mayo Clinic

Guang Yang, PhD and Steve Treon, MD, PhD

Targeting MYD88 signaling in Waldenstrom's Macroglobulinemia

IWMF Legacy Grant Renewal, August 2020

In groundbreaking research supported by the IWMF, Dr. Treon's lab previously discovered that 95-97% of WM patients have mutations of a gene called MYD88 inside WM cells. This change makes the MYD88 protein excessively active, which sends signals for WM cells to grow and survive. Because MYD88 signals to the WM cells through another protein called BTK, Dr. Treon's group reasoned that it would be logical to try to inhibit BTK. This led to his discovery that ibrutinib, a BTK inhibitor, was successful in controlling WM in many patients. Now, a family of other BTK inhibitors are being studied in WM patients. However, in some WM patients, it is not sufficient to block BTK, and resistance to ibrutinib can develop over time. Dr. Treon's group carefully assessed the complicated signaling network of MYD88 and identified another important signaling protein, called HCK, that is also involved in WM. Like BTK, HCK is also activated by the mutated MYD88 which is found in most WM patients. In turn, HCK further activates BTK as well as a number of other key signals that lead to excessive growth and survival of the WM cells. They reasoned that if they could block both HCK and BTK at the same time, they could control WM better than with a BTK inhibitor such as ibrutinib alone. Accordingly, they teamed up with a medicinal chemistry group at the Harvard Medical School and tried to invent a new drug to inhibit HCK. This led to the discovery of a lead candidate, called KIN-8194, that has potent activity against WM cells, including even WM cells in which ibrutinib resistance has developed. At the same time, they also discovered another candidate drug, JH-X-119-01, to inhibit IRAK1, another member of the MYD88 signaling pathway. The current grant will provide funding for testing the preclinical safety and efficacy of these new molecules, a necessary step before any human clinical trials. They will also study additional MYD88-related pathways and the possibility to develop therapeutics targeting these molecules.

CONNECTED BY A UNIVERSAL GOAL: A WORLD WITHOUT WM

"The IWMF support has made some of the most pivotal discoveries in WM possible, including the genomics driving WM, and the development of drugs like ibrutinib, acalabrutinib, zanubrutinib, and tirabrutinib that target MYD88 signaling. These discoveries provide a real example of how basic scientific research is allowing us to make real gains on WM. I am honored to work with the IWMF trustees and scientific advisory committee to continue this progress, and to finding a cure for WM."

– Dr. Steven Treon
Dana-Farber Cancer Institute

HELP US MAKE OUR VISION A REALITY:
A WORLD WITHOUT WM
(Waldenstrom's macroglobulinemia).

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