IWMF
International Waldenstrom's Macroglobulinemia Foundation

Accelerate the Cure: Three Research Opportunity Funds



The Accelerate the Cure Campaign offers three Research Opportunity Funds (A, B, and C). These funds detail types of research grants that IWMF will fund in its new five-year plan that began in 2024. One hundred percent of the funds raised for Accelerate the Cure research will go directly to that research. The International Waldenstrom's Macroglobulinemia Foundation (IWMF) expects the Opportunity Funds to move us powerfully forward in better understanding and treating WM.

Fund A — A Global Strategic Research Portfolio *with support from the Leukemia & Lymphoma Society (LLS)* — Price Tag (5 years): USD 12 Million

Fund A Investment supports a Global Strategic Research Portfolio designed in coordination with the Leukemia & Lymphoma Society to advance the understanding of the biological basis of WM. Research experts met in 2015, with Scientific Co-Chairs, Dr. Stephen Ansell of Mayo Clinic and Dr. Steven Treon of Boston's Dana-Farber Cancer Institute. The research experts decided that the path to a WM cure required better mapping of research priorities and a razor-like focus on central research questions. They framed these central questions as the Pillars of WM Research.

Pillars of WM Research

IWMF immediately aligned all grant guidelines to the Pillars of WM Research. An annual process of soliciting, screening, and funding research proposals was designed. And then, the pace of global WM exploration exploded. In nine years, the International Workshop on WM quadrupled its attendees. Through 2024, IWMF funded 46 research projects to tackle the central questions, funded by approximately USD 16 million. The redesigned research effort spawned 27 first-time grantees, 24 new institutional partners, and 21 newly funded international partners. Collectively, researchers made quantum leaps in their understanding of WM genetic mutations and the biologic underpinnings of the disease.

In the summer of 2024, a new set of Pillars for WM Research was launched to re-define the next high-value targets on the path to a cure. As research maps the disease process, there are even more ideas for development of therapeutics.

The new Pillars of WM Research ask these central questions:

- **WM Cell Biology –** How do mutated cells signal to other cells and drive the growth and survival of WM in the bone marrow? This pillar includes the development of novel therapeutic strategies that will interrupt aberrant signaling.
- **T-Cell Based Therapeutics –** How can we further CAR-T therapy for WM? CAR-T therapy is about re-engineering patients' own immune cells to attack mutated cells. This pillar includes novel strategies to promote the immune system's fight against WM mutations and strategies to turn off mechanisms that suppress immune cells from doing their job.
- **Microenvironmental Research –** WM cannot survive without the support of the local bone environment, so what are those WM dependencies? What are the therapeutic ways to block them?
- **Genomic Research (study of genetic material and genetic instructions) –** What is the biology of WM evolution from a slumbering state to a symptomatic disease? What mechanisms drive resistance to therapeutic drugs? This pillar includes research about high-risk features.
- **Proteomics –** Distinct from underlying genetics, what is the structure and function of proteins that have an impact on WM signaling pathways and prognostic testing? This pillar includes protein-based research into the causes and treatment of cryoglobulinemia, cold agglutinins, amyloidosis, demyelinating neuropathy, and other complications associated with the uncontrolled proliferation of the IgM protein characteristic of WM.

Research Proposals

Research proposals must be focused and meet the highest standards of design. The IWMF Scientific Advisory Committee and field experts annually review proposals from MDs and PhDs in academic hospitals and laboratories worldwide. Proposals are ranked according to review criteria of the National Institutes of Health. The Scientific Advisory Committee scores the proposals for near-term chances of advancing prevention, diagnosis, or treatment. The IWMF Board's Research Committee recommends awards based on

project quality and fund availability. About one third of the proposals meet the acceptance bar today, with a well-ranked proposal yet to be turned away. Final approval of grants is the IWMF Board's responsibility.

Grant Types

Strategic Research Roadmap Grants are funded at USD 400,000 for two years, with an additional 20% for indirect costs. IWMF selects two to four new projects each year. Applications are reviewed in April, with notifications sent each May.

The New Enhanced Roadmap Grant requires more effort and resources than two-year grants. A first Enhanced Grant was selected, May 2024, with funding of USD 1.5 million for four years.

The Seed Money Initiative enables global investigators to test hypotheses or novel ideas during a one-year time frame. Preliminary data informs and spawns major proposals for future research. Grants fund up to USD 90,000.

The IWMF Companion Initiative funds basic science projects that are clinic-facing, including projects linked to clinical trials. Grants fund up to two years at USD 100,000, plus indirect costs.

Fund B | **Multi-institutional Network (WM-NET)** *Coordinated across 18 US hospitals* | **Price Tag (5 years): USD 2.3 Million**

The Challenge

Clinical trials evaluate a new treatment agent, or combination of treatment agents, to discern whether they are safe and effective in treating patients with a disease. With a broad array of traits in human beings, a trial must demonstrate an exact understanding of the research question, a detailed protocol for enrollment eligibility, and a precise, defined execution plan. There are always multiple unknowns about treatment side effects in any trial, and patient responses must be rigorously studied and recorded for comparison across statistically valid sample sizes. To increase process standardization, clinical trials are typically offered at single institutions.

Geographically spread-out WM patients face challenging obstacles (travel, time, finances) to participate in a single institution trial. Many are treated in community health settings, where local doctors and their patients don't know that trials exist. In the population matched to a trial, there is always a good percentage who are afraid of the unknowns and understandably uninterested in the additional body-probing and testing. As we speed up the search for a cure, we need to expand and speed up clinical trials; yet these trials already compete for the rare WM patient. The annual incidence of WM in the US is just 1500 to 3,000 new patients per year.

The Solution

One of our research partners, the Dana-Farber Cancer Institute (DFCI), recently devised a way to address this rare disease challenge of trial enrollment. This innovative solution, WM-NET, is a US-based think tank aimed at sharing scientific clinical trials for WM, across 18 US hospitals. Practicing WM clinician-researchers in these hospitals have identified critical clinical questions. Collaboratively designed clinical trial plans and protocols are under construction. Patients will be able to enroll in a WM-NET trial at selected sites across 18 locations, expanding participation in underrepresented populations, greatly speeding up timetables, and accelerating access to novel treatments. The clinical trials will include cutting-edge genomic testing of patients and bio-banking—the collection of large samples of human materials for future study. The WM-NET also creates new leverage with pharmaceutical companies in coordinated design of trials. IWMF and WM specialists from outside the US are advisors to the multi-institutional WM network.

IWMF has made a USD 2.5 million commitment to Dana Farber Cancer Institute to fund WM-NET. This initiative represents the largest single research grant ever from IWMF—and the first project outside a long-standing practice of focusing solely on basic science. In the words of Newton Guerin, IWMF President and CEO, "Success in today's ever-changing, global environment depends on agility and requires a capacity for rapid change and flexibility. WM-NET is designed to facilitate a more rapid translation of clinical trials and study results into practice, resulting in better treatment options."

We need a much larger number of clinical trial participants than we traditionally recruit, to get to a cure. Even with our brilliant and dedicated WM research community, new drugs and a cure cannot be approved by the FDA and the European Medicines Agency (EMA) without proof from clinical trials. In the rare disease field, with 7,000 rare disorders identified by the US National Institute of Health, IWMF has a track record of leading the way. As this new WM-NET clinical trial methodology evolves, other rare diseases can emulate our model.

Fund C	Career Development of Next-Generation Researchers *Fields of B-Cell or Plasma Cell Malignancy*	Price Tag (5 years): USD 2.3 Million

It's vital that IWMF encourage the careers of junior faculty investigators and post-doctoral fellows in the WM space. We seek to expand three prongs of this path that encourages next-generation researchers to expand their experience of scientific discovery and spawn medical innovations for B- cell and plasma cell malignancies.

Robert A. Kyle Career Development Awards

Created in 2021, the *Robert A. Kyle Career Development Award* recognizes the 50+ years of impactful contributions by Dr. Robert Kyle, formerly of Mayo Clinic, to the field of plasma cell disorders and WM. Dr. Kyle knew and worked with Dr. Jan Waldenstrom, who discovered this disease.

When junior faculty members or post-doctoral students pursue their careers, it is important that they select a field of concentrated study and find financial resources to support them. This award encourages the best and brightest minds in the world to select WM as their area of concentration.

A USD 150,000 grant (with an additional 5% indirect cost) invests in two-year projects of junior researchers who are engaged in a teaching curriculum and mentoring with a well-established investigator—someone with experience in B-cell or plasma cell malignancies. The researcher must have focused on B-cell or plasma cell malignancy for at least two years. IWMF has funded seven Kyle awards to date—four in the US and three internationally. IWMF seeks to expand funding to add more exceptional minds to the search for a cure.

Young Investigator—Continuing Education Awards

Young Investigator Awards are a second prong of support for next-generation WM investigators. These awards are presented by IWMF to fund investigators' participation in the International Workshop on WM. For the twelfth Workshop in Prague, Czech Republic, October 2024, we expect investigators from 30 countries. They will participate in 90 or more technical presentations. The Workshop enriches each attendee's understanding of disorders affecting the blood, bone marrow, and the immunologic system, and fosters lifetime collaborations in support of a WM cure.

Since its first year in 2000, the Workshop has spawned publication of 8,700 articles in top journals. This is exciting progress when we consider that the Workshop in 2000 was attended by only 18 doctors. As one IWMF board member summarized: "Pretty good for a little rare disease that is funded almost entirely by WM patients and their friends and family!"

Last year, 18 next-generation investigators were honored for their abstracts, working at 20 international institutions in Spain, Greece, Canada, Britain, Germany, the Netherlands, and seven centers of excellence in the United States. Each year the young investigators' research is presented at poster sessions, and top-scored abstracts have separate plenary sessions in the program.

In closing...An investment in next-generation researchers brings a catalytic mix of new insights and creative energy to the global team effort. The path to a cure is difficult and demanding. As discoveries unfold, they unveil new complexities that require further insight from various cellular-biology and medical fields. This fund encourages more researchers to decide that WM-linked science is their lifetime work.

When you invest in IWMF to accelerate a cure...

- You invest in the best minds in the world for WM; they provide input to guide our research investment choices.
- You invest in our track-record at funding ambitious goals, promoting strong global collaborations and managing an accountability-for-results process. Less than 10% of 7,000 Rare Diseases have an FDA-approved drug. Thanks to the IWMF, we have two!
- You invest in this well-organized fight that discovered the exact genetic mutations causing nearly all WM cancer. That discovery is rare in incurable cancer, and odds are increasingly in our favor that we ***will find a cure.***