International Waldenstrom Macroglobulinemia Foundation (IWMF)

Strategic Research Agenda

August 2025

I. Background

Introduction

Waldenstrom macroglobulinemia (WM) is a rare, indolent, non-Hodgkin lymphoma characterized as a B-cell lymphoid neoplasm resulting from bone marrow infiltration by clonal lymphoplasmacytic cells which secrete a monoclonal IgM paraprotein.

WM patients present with a broad range of clinical issues including fatigue, anemia, peripheral neuropathy, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, hyperviscosity, cryoglobulinemia, nephropathy, pleural effusions, among others. A substantial portion of patients who fulfill the criteria for WM diagnosis are initially asymptomatic and will not require treatment until the disease progresses causing clinical symptoms or cytopenias. The disease is currently considered to be incurable.

Recurring somatic mutations in *MYD88* (95%-97%) and *CXCR4* (30%-40%) are prevalent in WM patients, while *TP53* alterations (as high as 30%) are also found for previously treated patients. Multiple pro-survival signaling pathways are active in WM cells, including those involving BTK, are believed to be driven by expression and activation of HCK through mutated *MYD88* (Treon et al., 2025).

Approved treatment options demonstrating safety and efficacy controlling symptomatic and progressive disease include chemoimmunotherapy (combination of rituximab and nucleoside analogs, and alkylating agent), proteasome inhibitors, or more targeted

therapies with BTK inhibitors (Gertz, 2025). Exploratory studies with agents approved for other B-cell malignancies include next generation BTK inhibitors, BCL2 antagonists, and BTK degraders, alone and in combination, are also showing promising results.

Nevertheless, complete responses in WM are rare, and even with the best novel combination therapies to date, recurrent disease relapses are expected. The IWMF is committed to identifying and supporting new therapeutics that ultimately achieve a cure for WM.

Clinical Development Path – A Successful Past and Promising Future

Over the past 10 years, the WM field has leveraged the development of novel agents used for other hematological cancers; these include covalent and non-covalent BTK inhibitors (BTKis) and venetoclax (a BCL2 antagonist), which have received prior FDA approvals for other indications. Currently, second generation BTK inhibitors, zanubrutinib, acalabrutinib, and tirabrutinib, are deemed safe and effective to treat WM (Buske et al., 2023; Dimopoulos et al., 2023; NCCN guidelines). Third generation BTKis, including non-covalent pirtobrutinib, and more recently, BTK degraders, have also shown promising results in relapsed and refractory WM patients, including those who failed covalent BTKis (Seymour et al., 2024).

Nevertheless, despite improved clinical outcomes for WM patients, significant clinical challenges persist. Specifically, complete response rates with BTKi monotherapies remain elusive, resistance to BTKi therapies is commonly seen over time, there is no standard-of care therapy for relapsed patients who have progressed on BTKi treatments, durable responses with fixed-duration combination treatments have not been validated (despite promising results from the combination therapy of BTKi with venetoclax as approved for CLL), and triplet combination therapy, which has been explored for CLL in a Phase 3 comparator study (Brown et al., 2025), remains to be examined for WM. Additionally, since WM is an indolent disease showing limited complete response rates in clinical studies, molecular markers of durable efficacy such as MRD-negativity that may predict long-term

responses (e.g. studied for CLL – Rios-Olais et al., 2024) may be needed for future WM trials and approvals.

Immunotherapeutics to treat other lymphomas have achieved remarkable success and represent compelling areas to be explored for WM. This is underscored by the plethora of new T-cell immunotherapeutics that have been FDA-approved to treat CLL, multiple myeloma, DLBCL and/or other NHLs including three CD20 x CD3 bispecific antibodies, two BMCA x CD3 bispecific antibodies, three CD19-CAR T therapies, and three BCMA-CAR T therapies. CD20, BCMA, and CD19 are expressed in WM patients (Palomba et al., 2022; Martens et al., 2022) and are relevant targets in WM. In addition, antibody drug conjugates (ADCs), such as CD79b- or CD19-ADCs have been approved for DLBCL (i.e. polatuzumab vedotin, loncastuximab tesirine) and experimental therapies to target CD22 (which are highly expressed on WM cells; see Sourdeau et al., 2025) are in clinical trials. Many of these new agents represent intriguing therapeutic possibilities for WM patients but await the results of on-going trials or the initiation of new trials in WM patients. Immunotherapies for other NHLs have not only been used to effectively treat active disease; they also may safely block progression to full-blown disease (for myeloma see Dimopoulus et al., 2025; Landgren et al., 2025; for follicular lymphoma see Northend et al., 2025). While current consensus guidelines recommend observation rather than treatment for asymptomatic WM patients, and while chemoimmunotherapy has not been shown to increase overall survival in these patients (Castillo et al., 2020), it is conceivable that earlier intervention with fixed-duration novel immunotherapeutics may be safe and beneficial for WM patients who are at high risk of serious disease progression, subject to the development of validated prognostic markers.

With respect to the promising role for CAR T therapies, although 3 WM patients treated with autologous CD19-CAR T did not achieve durable responses (Palomba et al., 2022), exploration of new and improved CAR T strategies are of high interest. Further exploration of highly efficacious new derivatives of CD19-CAR T (Svoboda et al., 2025) or dual BCMA/CD19- CAR T (Qiang et al., 2024) may outperform previously approved autologous CD19-CAR T therapy. In addition, allogeneic CAR T therapy, which derives T-cells from

donors (Locke et al., 2025), may be beneficial for WM patients and offers an off-the-shelf solution to therapy. Understanding the optimal role and timing of CAR T therapy and its potential use as an earlier intervention for WM patients is increasingly important since preliminary studies suggest that patients with depleted T-cells—whether from prior rounds of immunosuppressive therapy (e.g. bendamustine) or from "T-cell exhaustion" due to the disease itself—may exhibit limited responses to CAR T treatment.

Bispecific T-cell engagers offer another promising class of novel therapeutics for relapsed/refractory WM. Approval of several bispecfic antibodies (glofitamab, mosunetuzumab, epcoritamab) have demonstrated significant efficacy in other relapsed and refractory B-cell malignancies and ongoing studies examining the role of bispecifics will likely show safety and efficacy of this novel class of agents for WM (Kapoor and Rajkumar, 2023).

Coupled with the development of new immunotherapies, there has also been great interest in understanding the tumor microenvironment (TME), which can promote malignant expansion and induce resistance to immunotherapies. This is highlighted by a recent report showing that varying TME profiles correlate with differential CD19-CAR T responses (Li et al., 2025). The unique TME in WM cells within the bone marrow has been an active area of research interest. Identifying druggable targets for this milieu remains incompletely explored. However, the ability to study the TME has improved in the past 10 years, especially with single-cell analysis methods applied to clinical samples. Beyond that, therapies that antagonize TME-stimulated tumor progress or therapies that activate the immune environment to recognize and kill tumors may be on the horizon for the treatment of WM. Translational research with a specific focus on understanding how WM escapes detection by the immune system and on identifying specific targets in the TME to interfere with WM cell survival and pathogenesis may lead to new therapeutic approaches to intercept WM at the earliest stages of disease.

IWMF Research Goal: To Accelerate the Cure

IWMF stands at the forefront of a global mission: to transform WM from an incurable malignancy into a disease that can be fully eradicated. The IWMF defines “cure” not simply as remission, but as the achievement of sustained, treatment-free survival—where patients are liberated from both the clinical burden and molecular traces of disease, as confirmed by innovative diagnostic technologies. As the world’s leading patient-centered organization dedicated exclusively to WM, the IWMF leverages its unrivaled network, Scientific Advisory Committee expertise, and global commitment to drive groundbreaking research, fund innovative therapeutic discoveries, advance novel clinical trials, and foster collaborations reshaping the future for all affected by this rare disease.

IWMF’s research funding is focused on advancing translational breakthroughs that elucidate the molecular basis and pathogenesis of WM and on facilitating innovative clinical-enabling studies poised to significantly improve patient outcomes.

The IWMF’s broader strategic research agenda and efforts to support WM patients are driven by several key objectives: (1) expanding philanthropic support to advance all facets of WM research and patient care; (2) demonstrating that both short- and long-term research investments yield measurable and meaningful clinical benefits; (3) attracting and sustaining a cadre of highly skilled investigators and clinicians, including developing early-career talent to ensure ongoing innovation in the WM field; (4) strengthening collaborative partnerships with leading non-profit organizations—including the Leukemia & Lymphoma Society and the Lymphoma Research Foundation—to enhance support resources for WM patients; (5) maintaining active engagement with pharmaceutical and biotechnology companies to encourage continued research, development, and regulatory approvals of novel WM therapeutics; and (6) facilitating targeted funding for premier world-class academic institutions to accelerate the translation of research discoveries into transformative therapies for WM patients.

II. Request for Proposals: Translational Research Goals for the Next 3-5 Years

The IWMF seeks applications for research and clinical studies that will have a meaningful impact on WM patients within the next 3-5 years. Therefore, the proposed preclinical or clinical research studies should demonstrate clear clinical relevance with the potential to improve patient-centered outcomes, inform evidence-based clinical decision making, or address gaps in current therapeutic insights and approaches. Applications lacking a well-defined link to advancing patient outcomes or translating research findings into meaningful therapeutic advances will be considered non-responsive.

The IWMF Request for Proposal (RFP) process seeks *five types* of grant applications:

Pilot Clinical Trial Grant: up to $1 million over 2-4 years. The IWMF seeks to support: a) innovative clinical studies using novel agents, existing agents, novel combination therapies, or immunotherapies with high potential for clinical activity in WM; and b) studies that substantially improve quality of life and/or reduce prevalent disease complications. Importantly, the IWMF seeks to fund research that leads to the clinical application of knowledge, with the goal of clinical trials using novel agents or regimens that result in measurable clinical disease improvement. Clinical studies are likely to demonstrate proof-of-concept of clinical benefit in a limited number of patients. Successful study results should provide validation for larger clinical studies in the future that could support inclusion in NCCN Guidelines, FDA approval, or other comparable regulatory approvals (and likely will require co-funding beyond the means of the IWMF).

Studies designed to achieve complete responses and MRD-negativity are encouraged, as this may lead to the IWMF's goal of enhancing long-term disease control (a functional cure) and ultimately, complete cures (discontinuation of any therapy). Studies that stratify patients by risk (e.g., *CXCR4 /MYD88* double mutants, or neither mutation, TME, prior treatment etc.) are of interest. Applicants should provide a detailed explanation of the proposed project timeline, including a clear rationale for the overall duration and projected schedule for milestone-based payments throughout the grant period.

Companion Grant: up to $250,000 over 2 years. The IWMF seeks to support Companion studies within pharmaceutical and biotechnology company-sponsored trials that may be instrumental in determining the optimal use of new therapeutics under study. These projects leverage biological samples collected during trials to explore and validate biomarkers, mechanisms of response or resistance, or disease biology response to therapeutic intervention that will inform future clinical studies.

Projects may include identifying genetic, proteomic, or immune markers that predict activity profiles, elucidating molecular mechanisms of resistance, TME profiling, MRD assessment, among others. These proposals are intended to leverage clinical research questions not funded by the industry sponsor and deemed critical to advancing the field.

Note: Grant applications that require access to investigational new drugs or approved drugs should have previously secured agreement from the manufacturing sponsor for access to study drug supply. The grant funds should not be used to pay for or offset the cost of the drug.

Translational Research Grant: $500,000-$750,000 over 3-4 years. IWMF seeks proposals to understand the mechanisms of WM pathogenesis with a focus on: a) uncovering new features of WM biology and cellular vulnerabilities; b) laboratory studies investigating mechanisms of WM relapse and therapy resistance; and c) identifying novel, therapeutically exploitable targets that represent previously under-explored opportunities. Such foundational studies should be focused on translational potential and ultimately driven by the goals of improved patient outcomes and reduction or elimination of disease.

It is recognized that the application of new technologies to WM, which often generate descriptive work that lays the groundwork for new therapeutics, are important. Such translational applications will be considered but will be most competitive if clinical

relevance can be shown. If the development of a novel therapeutic is proposed, ideally it will have optimized pharmacologic properties (i.e., a lead candidate) that could enable a clinical trial within 3 years. Applications for the development of preclinical models such as organoids that contain TME elements are of interest (as done for follicular lymphoma; Kastenschmidt et al., 2024), particularly if they include goals to develop new therapeutics.

Acceleration and Expansion Grant(s): **$250,000 over 2 years**. The IWMF seeks to support Acceleration and Expansion Grants. An Acceleration Grant is used to accelerate existing and prior IWMF grants that require further funding based on a novel, testable hypothesis that drives the prior funded research work towards clinical application. In the second type, an Expansion Grant supports novel, translational targets or mechanisms to be explored based on prior proof-of-concept work. No prior IWMF funding is required for the Expansion Grant. For Expansion Grant applications, investigators outside the field of plasma cell malignancies are also encouraged to apply.

Renewal after the first year of these grants will be considered if good progress against the goals, as defined in the application, is demonstrated and would be determined by the IWMF (i.e., this expedited review will not require an expert panel and instead will be considered by an IWMF Scientific Advisory Subcommittee). The work may apply new techniques such as single-cell analysis (Gagler et al., 2025), epigenetic profiling, or state-of-the art cell free DNA methodology applied to WM.

Note: Post-doctoral fellows may not apply for these type of grants.

The Robert A. Kyle Career Development Award Grant: $160,000 over 2 years. IWMF seeks to provide grants to support young investigators, (defined as a junior faculty member, instructor or assistant professor; and/or postdoctoral fellow), who are focused on research in the field of B-cell or plasma cell malignancies. A successful applicant's academic program must have a formal teaching curriculum and mentoring from established

investigators with a proven record of advancing relevant research in the B-cell malignancy or plasma cell malignancy field. Highest priority for Kyle Awards will be given to translational research proposals; however, applications addressing critical questions in basic discovery science relevant to WM biology and pathogenesis will be considered.

Final Thoughts:

In recent years, we have witnessed substantial progress in both the basic biomedical research and clinical management of WM. IWMF-funded research has played a pivotal role in driving these advances, owing in large part to the IWMF's rigorous grant-awarding process. Each grant application undergoes thorough evaluation by an independent committee composed of members of the IWMF Scientific Advisory Committee and other leading experts in the field. Final approval rests with the IWMF Board of Trustees, ensuring strategic oversight from the highest level. This commitment to excellence continues beyond the initial award, as grant recipients are required to submit regular progress reports to the IWMF Research Committee for ongoing review and guidance. Through this comprehensive process, the IWMF ensures that its research investments have a meaningful and lasting impact on the WM community. If you have a compelling opportunity promising to transform the treatment landscape for WM patients, we invite you to join us.

III. References

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