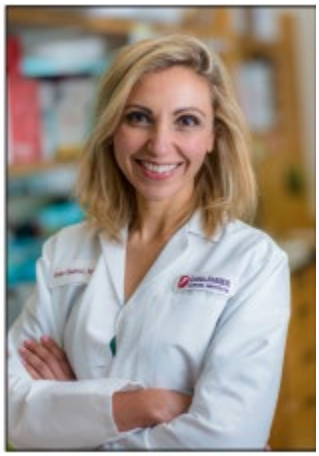
FROM PRECURSORS TO PROGRESSION: THE NEED FOR MORE RESEARCH

BY DR. IRENE GHOBRIAL, MD; ANNIE COWAN
DR. CATHERINE MARINAC, PHD; NADER SHAYEGH


Dr. Irene Ghobrial

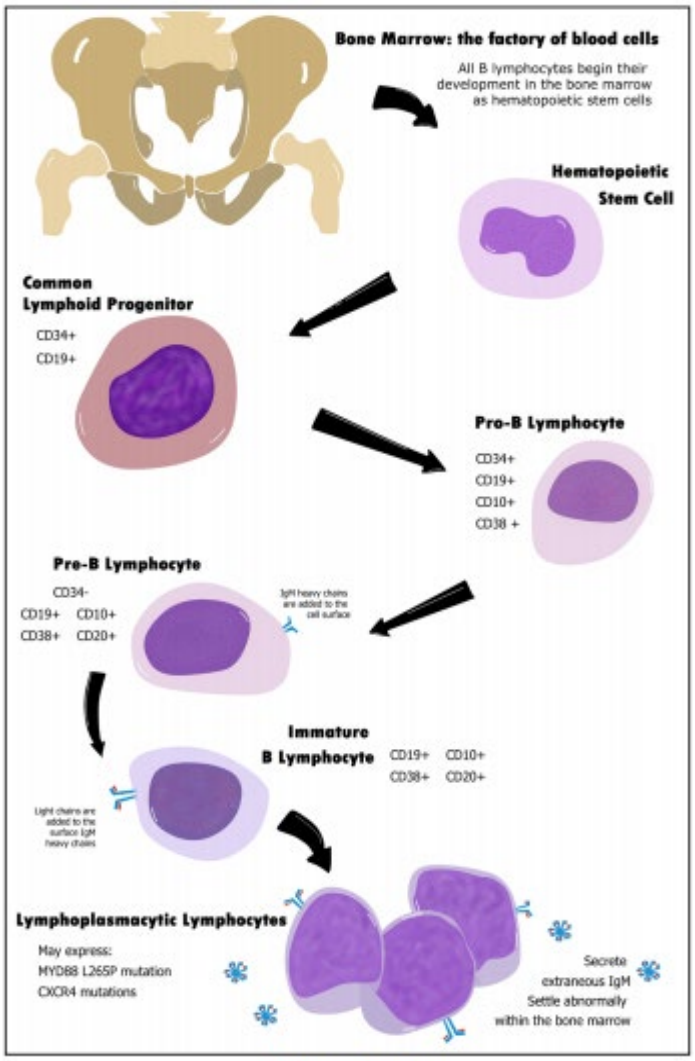
Dr. Irene Ghobrial is a professor at Dana-Farber Cancer Institute (DFCI), Harvard Medical School, Boston, MA and an associate member of the Broad Institute, Cambridge, MA. She is the director of the Clinical Investigator Research Program at Dana-Farber Cancer Institute, co-director of the Center for Prevention of Progression (CPOP), and co-leader of the Blood Cancer Research Partnership (BCRP). She is also the director of the Michele & Stephen Kirsch Laboratory.

She has authored or co-authored over 250 publications and book chapters and has received funding support from the National Cancer Institute as well as multiple foundations, including Stand Up To Cancer, Leukemia & Lymphoma Society, Multiple Myeloma Research Foundation, and International Myeloma Foundation. She has received multiple awards, including the Ken Anderson Young Investigator Award, Robert A. Kyle Award for Research in Waldenstrom Macroglobulinemia, and Mentor of the Year Award at DFCI.

Imagine you have boarded an airplane for a trip across the country. If you've flown before, you know exactly what to expect. You'll settle into your seat as the pilot introduces himself and the flight attendants check your seatbelt. Then, you'll be throttling down the runway, lifting suddenly off the ground with a lurch. It will take a while to reach cruising altitude. When you do, you're offered a cup of water and snacks as you weather through some turbulence. The pilot comes over the intercom to let you know when to put your seatbelt back on; the descent begins. It is a bit of a relief when you finally touch ground.

For those afflicted with Waldenstrom's macroglobulinemia (WM), the diagnosis, treatment, and (hopefully) remission process can be quite long, much like a flight. For some, it initially involves the diagnosis of a "precursor" condition, or one that can develop into WM. Specifically, WM always evolves from the premalignant conditions of IgM monoclonal gammopathy of undetermined significance (MGUS), and smoldering WM (SWM). These precursor conditions are often asymptomatic, and their diagnosis may feel like they have come out of thin air, suddenly, like the lifting of the wheels off the tarmac. Patients with a diagnosis of IgM MGUS or SWM want to know if or when they will "reach altitude" and be diagnosed with symptomatic WM—and if treatment should begin before that point is reached, thus preventing the dreaded "watch-and-wait" ascent and the turbulence that can come with a cancer diagnosis. As the medical community learns more about the precursor conditions which precede WM, we are approaching a crossroads in the discussion of WM prevention and clinical care—one in which the question of early treatment enters center stage. Before this critical conversation can proceed, it is important for us to define these precursor conditions and examine how and why progression to WM may occur in the first place.

Waldenstrom's Macroglobulinemia and the Evolution of the B-Lymphocyte



WM cell evolution

WM is a non-Hodgkin's lymphoma of the bone marrow defined by the abnormal development of B-lymphocytes (B-cells) and the extraneous secretion of IgM monoclonal protein. Because WM cells have features of lymphocytes and plasma cells, WM is sometimes referred to as a "lymphoplasmacytic lymphoma." We can illustrate the origination of WM by walking through the development of a healthy B-lymphocyte, examining when and how alterations to this developmental process result in the evolution of tumor cells.

Bone marrow is the spongy tissue located, in adults, within the interior of the larger bones of the body and is known colloquially as the "factory of blood cells." A single type of cell, deemed the hematopoietic stem cell, produces the three cell types present in blood: white blood cells, red blood cells, and platelets. Platelets are involved in the blood-clotting process and are essential to the healing of wounds. Red blood cells carry oxygen and are involved in respiration.

White blood cells comprise the body's immune system and include, among other infection-fighting cells, B-lymphocytes and plasma cells, the two cells associated with WM.

The hematopoietic stem cell is capable of dividing for a prolonged period of time without differentiating or developing into a more specialized blood cell. Because these stem cells have the ability to propagate indefinitely, they serve as the starting point for all blood cells. An important note about the developmental process is that cells are identified by the presence or absence of specific receptors on their surface called "clusters of differentiation" (CD). CDs are protein units that help cells attach to one another, "talk" with one another, and identify foreign elements, such as bacteria and viruses. Researchers are able to define the developmental pathway

of the plasma cell by examining the changes in the type and number of CDs present on the cell surface; a change in CD pattern indicates the development of a new cell type.

In WM, B-lymphocyte maturation begins normally with the hematopoietic stem cell differentiating into a common lymphoid progenitor (or precursor) with CD34 and CD19 receptors. The common lymphoid progenitor cell then differentiates into a new cell type called the pro-B-cell with CD34, CD19, CD10, and CD38 receptors. The pro-B-cell develops into a pre-B-cell when the CD34 receptors are lost from the cell surface, CD20 receptors are gained, and, importantly, the cell begins to express heavy-chain IgM antibodies (or immunoglobulins) on its surface. The switch from pro-B-cell to pre-B-cell occurs as the cell begins to generate an enormous repertoire of unique antibodies that the cell will eventually use to recognize foreign material (this process is called VDJ recombination). Pre-B-cells develop into immature B-lymphocytes when light chains are added to their membrane-bound IgM heavy chains.

Immature B-lymphocytes move out of the bone marrow and into the body's circulation. There, they interact with foreign materials such as viruses and bacteria, identify them as foreign, and become "educated" to that foreignness. Once educated, the B-lymphocyte is mature, loses its enormous repertoire of antibodies, and begins producing only one unique antibody shaped perfectly to match and identify the foreign material to which it was educated; at this point, the B-lymphocyte has officially become a plasma cell. As part of its development into a plasma cell, the B-lymphocyte must go through a process known as "class switching" where the immunoglobulin heavy-chain class on the B-lymphocyte is changed from IgM to IgG, IgA, or IgE. The plasma cell is then able to clone rapidly and produce large amounts of unique immunoglobulin with heavy and light chains, thus spreading the message of the foreign material quickly throughout the body to fight the infection.

The Pathophysiology of IgM MGUS and SWM

The immunophenotypic (or surface protein expression) profile of a WM cell is unique from normal lymphoid cells as it resides in some intermediate state between the B-lymphocyte and the plasma cell. In simpler terms, this means that the malignant cells involved in WM look structurally like plasma, lymphocyte, *and* lymphoplasmacytic cells with varied patterns of cell-specific receptors. Because this developmental interruption occurs prior to or independent of class switching, WM malignant plasma cells only produce IgM immunoglobulin. Consequently, IgM is secreted prematurely, in the bone marrow and in abundant quantities, leading to several of the symptoms commonly associated with WM, including hyperviscosity ("thick" blood) and anemia.

The evolution of IgM MGUS to symptomatic WM is the consequence of an accumulation of mutations that drive cell division and prevent cell death. MYD88 is an adaptor protein that functions as the connection between two other proteins within a cellular pathway. Crucially, MYD88 operates in a critical signaling pathway in B-lymphocytes that promotes proliferation and cell survival. Recent research has shown that in many IgM MGUS, SWM, and WM clinical cases, a single amino acid of the MYD88 protein is mutated from a leucine (L) to a proline (P) at position 265. This MYD88 L265P mutation results in the overactivation of the MYD88 protein, the overstimulation of the signaling pathway, and the corresponding proliferation of the cell.

Mutations in the CXCR4 protein are also common in IgM MGUS, SWM, and WM. CXCR4 is a cell surface receptor that helps to facilitate cell migration; abnormal forms of CXCR4 found in WM cause WM cells to migrate to and take up residence in the bone marrow where they continue to expand. While the MYD88 L265P mutation occurs in about 50% and CXCR4 mutations in about 15% of IgM MGUS cases, abnormal forms of these proteins appear in even higher rates in SWM, about 80% and 24%, respectively, and in WM, 90% and 27%, respectively. This suggests not only that the presence of these mutations in IgM MGUS and SWM increases the risk of progression, but also that combinations of these mutations may multiply that risk.

At this point in the history of WM (discovered by Dr. Jan Waldenström in 1944) and the even younger history of IgM MGUS (discovered by Dr. Robert Kyle of the Mayo Clinic in 1978), there is enough clinical data to group patients based on their probability of progressing to WM. Current algorithms or formulas to determine the risk of progression utilize standard clinical information, including bone marrow infiltration and IgM, beta-2 microglobulin, and albumin volume. Recently, a team from the Dana-Farber Cancer Institute designed an asymptomatic WM (AWM) risk calculator for both patients and physicians to use to identify their progression risk based on those variables; this calculator is available online at *www.awmrisk.com*. Progression risk algorithms like these may help hematologist-oncologists make decisions about when treatment should begin and are an important clinical component of an IgM MGUS and SWM diagnosis. Incorporating the genetic profile of a patient's specific disease will have an impact on classification systems of high-, intermediate-, and low-risk and thus will likely become a critical variable for improving progression risk classification moving forward.

What Can You Do?

In the general population, IgM MGUS and SWM have been shown to progress at rates of around 1.5% and 12%, respectively, per year, with most IgM MGUS patients never developing symptomatic WM. Specifically, Dr. Robert Kyle, the Mayo Clinic physician who discovered and coined the term MGUS, recently published an analysis on the risk of IgM MGUS disease progression in *The New England Journal of Medicine*. This work found that progression risk is directly tied to M-protein and serum free light chain volume, with the risk of progression at 2% per year for the first ten years following the diagnosis and dropping to 1% per year after that point. But percentages are often difficult to extrapolate to real life, and patients would prefer to be told their personalized risk of progression as well as how to diminish that risk. As our research community works on better describing the variables which impact progression, here are some lifestyle changes you can make following a diagnosis.

1. **Eat well and take care of your body.** A common question that newly-diagnosed IgM MGUS and SWM patients have is how diet impacts progression. While there is research connecting high body mass index to an increased risk of progression from MGUS to lymphoproliferative diseases like WM, there is no special diet or exercise plan that has been shown to specifically counteract progression. As with any chronic condition, the best advice that hematologist-oncologists can give is to eat healthy and exercise daily. Work with your support team to develop better lifestyle habits, such as minimizing sugar, getting at least 150 minutes of moderate intensity or 75 minutes of vigorous intensity

exercise (or a combination of both) per week, and sticking to a schedule that includes 7-9 hours of sleep per day.

2. **Visit a hematologist-oncologist every 6-12 months (for IgM MGUS) and 3-4 months (for SWM) to monitor your numbers**. Research has shown that simply visiting a hematologist-oncologist regularly improves prognosis for patients with hematological precursor conditions. Regular visits to a hematologist-oncologist will ensure that lab result trends are supervised over time and new or worsening symptoms are attended to.

3. **Seek therapy and/or learn a stress management technique to deal with anxiety**. Precursor conditions and "watch and wait" treatment approaches can be difficult to process and may negatively impact mental health. Now is a great time to incorporate stress management techniques into your daily life, such as finding a therapist, picking up meditation, or journaling. You may be surprised how these routines help with other parts of your life as well!

4. **Talk with your hematologist-oncologist about treatment options *before* symptoms begin**. Communicating with your oncologist about when treatment is expected to begin (if ever) and what treatment options are available can help patients better understand what to expect after a new diagnosis. This conversation will also help your physician select clinical trials and/or treatment plans that will work best for you.

The Imperative Need for Research

While the past decade has provided enormous developments in our understanding of WM biology and treatment, there is still much that is poorly understood about the evolution of the disease. Importantly, many clinical trials focus on the treatment of symptomatic WM, with few enrolling IgM MGUS and SWM patients. For example, while there are many clinical trials offered at the Dana-Farber Cancer Institute and other large cancer centers for asymptomatic smoldering multiple myeloma, trials for high-risk SWM are only just beginning. It is crucial that the medical community increase support to IgM MGUS and SWM patient populations by leading and encouraging participation in research studies. Such research may not only provide the basis for developing new therapies to prevent WM in patients with these early precursor conditions, but may also facilitate advanced screening techniques for early diagnosis and allow us to continue to improve the algorithms we use to predict the risk of progression to WM.

Importantly, patients with hematological precursor conditions often require unique clinical management compared to those patients with an active cancer diagnosis. The Dana-Farber Cancer Institute Center for Prevention of Progression of Blood Cancers (the CPOP Clinic) was established to provide multidisciplinary care for patients with hematological precursor conditions like IgM MGUS and SWM. The genetic risk factors, lifestyle, and psychology of patients with precursor conditions can vary immensely across individuals and have a tangible impact on prognosis. The CPOP Clinic allows physicians who specialize in precursor conditions to refer patients to expert cardiologists, psychologists, social workers, and genetic counselors and thus create tailor-made experiences for each patient to improve health outcomes and quality of life. Individuals with precursor conditions deemed higher risk have the opportunity to participate in

the latest treatment options and clinical trials. Tissue banking studies are also available to help improve our understanding of precursor conditions such as IgM MGUS and SWM and how we can prevent them from progressing. The best way for patients to contribute to these advances is to participate in a research project, such as the PCROWD Study and the PROMISE Study, which are further described below.

The PCROWD Study is an international tissue banking project that works with patients diagnosed with hematological precursor conditions, including IgM MGUS and SWM, to generate a database of samples for a wide variety of research projects. Importantly, the PCROWD Study allows researchers to evaluate how these conditions and other monoclonal protein disorders evolve over time. The PCROWD Study supports several progressive projects that are designed to enhance the understanding of WM biology and treatment, including studies that analyze and compare the genetic information of different cell types by using a technology called single-cell sequencing. This is one example of a technology that may help researchers understand how cancer cells interact with other cells in their environment (e.g., the bone marrow) to influence prognosis, as well as how different cells in the body respond to treatment. Patients can join the PCROWD Study by enrolling online at *www.enroll.pcrowdstudy.org*.

Because research has shown that families with a history of WM or IgM MGUS have a significantly increased risk of developing WM or a related blood condition, there may be a benefit for first-degree family members (parents, siblings, and children) to undergo screening for these conditions. The PROMISE Study is a national screening study led by the Dana-Farber Cancer Institute and funded by Stand Up to Cancer that was designed to give family members of patients with WM, multiple myeloma, and their precursor conditions the opportunity to screen for the asymptomatic blood conditions, including IgM MGUS and SWM, that may develop into cancer. Individuals between the ages of 40 and 75 with a first-degree relative with a diagnosis of WM, multiple myeloma, or their precursor conditions, but without a diagnosis themselves, are eligible to participate. Participants who are eligible can enroll online and are sent the necessary instructions and materials to collect their blood for free at a local lab and send it back to the research team. Blood samples are screened for the presence of a monoclonal protein which may indicate the individuals have a precursor condition like IgM MGUS or SWM; those who test positive are assisted with finding a local hematologist-oncologist so that they can receive appropriate clinical follow up, and those who test negative remain in the study and are rescreened every three years. If your parents, siblings, or children qualify for the PROMISE Study and would like to contribute to WM research, they can register online at *www.enroll.promisestudy.org*.

Large research initiatives such as the PCROWD and PROMISE generate the data that researchers and physicians need to advance the understanding of an intricate disease like WM. The precursor patient community is ready to learn more, and our research teams are determined to help. Together, we can work to stop WM before it starts!