**Multi-Omics for Deciphering Mechanisms of Progression in Pre-Malignant IgM Gammopathies**

*Simone Ferrero, University of Torino (Italy), Hematology Division, on behalf of Fondazione Italiana Linfomi (FIL)*

In this project will be investigated the biological mechanisms that drive progression from IgM monoclonal gammopathy of uncertain significance (IgM-MGUS) to smoldering WM, to symptomatic WM. We took advantage of sample leftovers already collected in the "FIL BIO-WM trial" (NCT03521596, enrolling a large, prospective, cohort of IgM-MGUS, smoldering and symptomatic WM in Italy and Spain) to better understand why only in some people this disease progressed from non-neoplastic IgM-MGUS to WM.

The well-known *MYD88* and *CXCR4* gene mutations do not fully explain the wide diversity of WM presentations, nor do they explain why some patients progress to serious disease and others do not. Our team is investigating other possible gene mutations that may be involved in the transition to symptomatic WM, including *PRDM1* and *TNFAIP3* genes. Deficiency in such genes may enable B cells to grow without their normal control mechanisms and progress to WM.

Moreover, blood samples will be studied for the still poorly characterized circulating "cell-free RNA" (cfRNA): a better knowledge of them might facilitate WM diagnostics and prognostic evaluation, without the need for bone marrow biopsies.

Finally, clonal hematopoiesis of indeterminate potential (CHIP) will be studied in serial samples. CHIP is a common occurrence in older people, in which non-cancerous blood-forming cells in the bone marrow or certain immune cells accumulate mutations that enable them to proliferate and harmlessly accumulate in the body. Genetic changes in these cell populations might tip them over the edge to become harmful, both facilitating WM progression and/or promoting the occurrence of additional, different tumors.