In 2018, Ignacio Criado defended doctoral thesis on **"Phenotypic, cytogenetic and molecular characterisation of Low-count monoclonal B-cell lymphocytosis of healthy individuals vs malignant B-cell Chronic Lymphocytic Leukemia",** co-directed by Professors Alberto Orfao and Julia Almeida from the University of Salamanca.

The general objective was to evaluate over the medium term, the clinical and biological evolution of individuals from general Salamanca population that presented clones classified as MBL ^{low} and determine the status of the immune system in comparison to both, patients with MBL ^{high} and those with CLL.

Specific objectives and *conclusions* obtained were as follows:

1.-**To define the medium-term progression rate of B-cell lymphoid populations in individuals with MBL^{lo} into MBL^{high} and CLL, as well its clinical impact.** *Individuals with MBL^{lo} show the greater risk of death from infection than healthy people. The research results support the hypothesis that MBL^{lo} may constitute an initial phase of CLL. Longitudinal and long-term studies with more subjects involved would be necessary, in order to analyse in depth possible alterations in the existing immunological response, already in the initial stages of MBL^{lo}, as well as their role in the progression into more advanced forms of the disease.*

2.-To identify early stage alterations of the immune response of individuals with MBL^{lo}: *Patients with MBL^{high} or CLL showed significantly reduced both immature and naïve B-cells amount in PB, producing narrower B-cell repertoire. There is a qualitative and progressive alteration in plasma and memory B-cells observed.*

3.-Investigate B lymphocyte response to common and pneumococcus-specific pathogens that we tend to associate with a neoplasic processes or major infectious agents that MBL^{high} and CLL patients suffer. *Ratio between specific immunoglobulin against latent virus, (such as cytomegalovirus and Epstein-Barr virus) has relatively higher levels in MBL^{high} cases (but not in MBL^{low}) and in CLL, versus healthy donors. These relatively high levels of antibodies spe-cific for the latent viruses is accompanied by lower levels of S.pneumoniae-specific immunoglobulins. The reactivation of chronic humoral immune response against those latent virus as cytomegalovirus Epstein-Barr virus could be related to the disease progression.*

Scientific Papers associated:

- Low-count monoclonal B-cell lymphocytosis persists after seven years of follow up and is associated with a poorer outcome, *Haematologica. 2018 Jul.; 103(7): 1198–1208.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6029554/
- Residual Normal B-cell Profiles in Monoclonal B-cell Lymphocytosis Versus Chronic Lymphocytic Leukemia, *Leukemia. 2018 Dec;32(12):2701-2705. doi: 10.1038/s41375-018-0164-3. Epub 2018 Jun 21.* https://pubmed.ncbi.nlm.nih.gov/29930299/
- Host virus and pneumococcus-specific immune responses in high-count monoclonal B-cell lymphocytosis and chronic lymphocytic leukemia: implications for disease progression, *Haematologica. 2017 Jul; 102(7): 1238–1246.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5566034/

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