Investigation of CpG-decoy STAT1 immunotherapy in Waldenström disease

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Waldenström macroglobulineminia (WM) is defined as an incurable Lymphoplasmacytic lymphoma and represents approximately 2% of all hematologic malignancies. This disease is typically characterized by aberrant plasma cell (PC) differentiation in the bone marrow associated with a high monoclonal immunoglobulin M (IgM) secretion. These two aspects induce two distinct disruptions. Indeed, lymphoplasmacytic infiltration may cause anemia while IgM accumulation into blood may cause hyperviscosity syndrome (Yun S. *et al*., Clin. Lymphoma Myeloma Leuk, 2017).

To better understand the corrupted PC differentiation in WM disease, we have set up an *in vitro* model to differentiate primary WM B cell into PC and study transcriptomic changes at the single cell resolution as well as cell signalling driving cell behaviour over time. It reveals an important increase of STAT1 and STAT1-targeted genes transcription in WM B cells compared to normal B cells that may favor an alternative differentiation pathway. However, the modulation of STAT1 signaling is limited due to the lack of STAT1 specific inhibitor.

The purpose of this project is to develop an innovating CpG-STAT1 decoy immunotherapy in WM. CpG-decoy technology has recently emerged as a promising lymphoma immunotherapy (Soldevilla MM. *et al*, Mol. Ther., 2018). This dual-function molecule allows a decoy internalization by TLR9 cells, such as WM B cells, and STAT inhibition thanks to STAT-decoy interaction. The first step of my project is to design an efficient CpG-decoy against STAT1 that can prevent WM B cell differentiation *in vitro*. Then, we want to test this approach in Waldenström preclinical mouse model. A good efficiency of this immunotherapy would limit PC infiltration and hyper IgM secretion in WM through a reduced capacity for PC differentiation. The support of LabexIGO will provide me with the challenge and opportunity to develop this original research using decoy technology.