

Slowing the progression of ALS from the periphery: ALS macrophage intrinsic and extrinsic reactivities for biomarkers and new therapeutic targets

This project focuses on Amyotrophic Lateral Sclerosis (ALS), the most common adult motor neuron (MN) disease leading to progressive paralysis and early death within 3 to 5 years, with no curative treatments available. Although ALS symptoms are the consequence of MN degeneration, our previous work showed that other cell types, especially immune cells, participated in disease progression including microglial cells, the macrophages of the central nervous system (CNS). More recently, we have discovered that modulating macrophages, at the periphery, in ALS models, impacted microglial cells in the CNS and disease progression. ALS, like all other neurodegenerative diseases, suffers from the low accessibility of the neurons in the CNS for therapies. With our discovery that peripheral macrophages were implicated in MN degeneration, our goal is to use these immune cells directly at the periphery to target MN and slow down ALS symptoms.

With this project we want to find out whether peripheral macrophages, in the human context, are also important for ALS and if they could be used as a therapeutic target and a biomarker of the disease. More specifically, we want to know whether macrophages of ALS patients are different than macrophages from control individuals and if this difference is intrinsic to the macrophages or if it needs a second hint, an activation process, the reaction to the disease, to make them different.

We had 3 specific objectives (i) recruit all the needed ALS and control individuals to obtain their blood-derived monocytes/macrophages, (ii) find the deregulated pathways in ALS macrophages and (iii) confirm the candidates.

Objective 1 was planned for the first 6 months of the project. We have indeed recruited all the needed ALS patients and control individuals for the project. We have obtained blood from these individuals and have isolated their blood-derived monocytes. We are very grateful to the patients, their families and all the donors for their participation in this research, which has allowed us to fulfil this first aim on time to be able to pursue the project.

We have already started the second objective, to use these blood monocytes, that we mature to macrophages, in culture to obtain the transcriptome and the secretome of ALS and control macrophages. More specifically, we are currently deriving the blood monocytes of ALS patients and controls towards macrophages and are activating them towards either a pro-inflammatory phenotype, or an anti-inflammatory phenotype or a control phenotype. Using RNA sequencing we will compare all the regulated pathways between ALS and control macrophages in these 3 different conditions. Finalizing this second objective will take one year.

With our third objective that will span the last 6 months of the project, we will confirm our candidate pathways. The goal is to find differently regulated pathways that could be new therapeutic targets.

With this project supported by Ferblanc, we want to find new therapeutic targets that we could use, directly at the periphery without having to reach the CNS to target MN to slow down ALS disease. The importance of this project resides on showing that the mechanisms we described in ALS models are also true in ALS patients to find new therapeutic pathways relevant for ALS. We would therefore like to thank Ferblanc for supporting this ambitious project.