Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2019-2020

1. **Host team :**

Research Unit: Inserm U 1127 - CNRS UMR-7225 - Sorbonne Université
Research Unit Director: BRICE Alexis
Research Team Director: BOILLEE Séverine
Team name: ALS causes and mechanisms of motor neuron degeneration

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2. Internship project title:

Study of motor neuron defects and the role of myeloid cells in Amyotrophic Lateral Sclerosis using human induced pluripotent stem cell models

3. **Internship Description :**

Amyotrophic Lateral Sclerosis (ALS) is a fatal progressive neurodegenerative disease affecting upper and lower motor neurons (MN). This is a very aggressive disease and patients die within 2 to 5 years after diagnosis. Despite many trials, there is today no curative treatment and the mechanisms leading to MN degeneration remain elusive. While 90% of ALS cases are sporadic, 10% have a familial origin and this already allowed the identification of at least 20 different genes responsible for ALS. While initiation of the disease seems to be intrinsic to MNs, its progression seems to involve non-neuronal cells in the MN environment, and in particular myeloid cells. A specificity of the spinal MN is that while its cell body is surrounded by microglial cells in the spinal cord, its axon lies in the periphery surrounded by macrophages. Today, the exact roles of these both inflammatory cell types in disease progression are not well understood.
In order to analyze the contribution of the different ALS causing mutations directly in human MNs and in myeloid cells, we have generated induced pluripotent stem cells (iPSc) from ALS patients carrying mutations in different genes responsible for ALS (C9ORF72, SOD1, TARDBP, UBQLN2) and patients with sporadic forms. We have set up protocols to generate pure cultures of human iPSc-derived MNs, as well as iPSc-derived macrophages and we are currently developing a protocol to generate microglia-like cells. The objectives of the project are to (i) study intrinsic defects in human ALS MNs, macrophages and microglia and (ii) the respective and synergistic contribution of these myeloid cells to MN degeneration. On a more global, we will perform RNA-seq analysis of ALS MNs and myeloid cells to identify affected target genes and inflammatory pathways, which could help to define new therapeutic options. As ALS is diagnosed once symptoms are already present, acting on disease progression by modulating microglia/macrophages could benefit to all ALS cases.