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

Internship Proposal
Academic Year 2018-2019

1. **Host team : Team of Dr. Séverine BOILLEE, ICM, Paris**
   Research Unit (e.g. Department or Institute) :
   Institut du Cerveau et de la Moelle épinière, ICM (The Brain and Spinal Cord Institute), Inserm U 1127, CNRS UMR 7225, Sorbonne Université, F-75013, Paris
   Research Unit Director : Dr. Alexis BRICE
   Research Team Director : Dr. Séverine BOILLEE (PhD, HDR, CR1 Inserm)
   Team name : " Causes and mechanisms of motor neuron degeneration in ALS "

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   Supervisor of the Research Intern: **Dr. Christian S. LOBSIGER (PhD, HDR, CR1 Inserm)**
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2. **Internship project title:** ***"Analysis of motor neuron degeneration and neuro-immune interactions in a new mouse model of ALS ".***

3. Internship Description : Amyotrophic Lateral Sclerosis (ALS) is a fatal, adult onset neurodegenerative disease that affects brain and spinal cord motor neurons (MNs). Our goal is to understand the mechanisms underlying MN degeneration by using a wide set of experimental approaches including rodent models, human genetics, iPS culture models and postmortem tissue analysis. A significant amount of ALS cases are linked to mutations in a growing set of genes, with most acting by still unknown gain-of-functions, making it often difficult to identify the toxic component. However, recently, dominant loss-of-function (LoF) mutations in a new gene linked to ALS have been discovered, suggesting haploinsufficiency - a study to which our team contributed. Interestingly, the encoded kinase is strongly implicated in the immune system and autophagy. With our team's interest in neuroinflammatory processes and the contribution of microglia/macrophages in ALS, our aim is to analyse how LoF mutations in this new ALS gene could lead to motor neuron degeneration, and whether they could deregulate reactive microglial responses. This project is strongly linked to previous work of the team addressing the cell-specific contribution of ALS toxicity to motor neuron degeneration. To assess these questions, we have already generated conditional knock-out mice of this ALS gene, that will allow for cre/lox mediated cell-specific gene deletion in motor neurons and immune cells.
The student will be implicated in the mechanistic analysis of how partial loss of this kinase leads to motor neuron degeneration. The approaches will include assessing, in vivo, the integrity of the motor neuron unit during aging, as well as determining the global molecular changes in the affected motor neurons using laser-microdissection assisted transcriptomic analysis. With respect to the role of this kinase in immune cells, the student will also be implicated in the analysis of whether its reduction could deregulate motor neuron neighbouring microglia. This will be done both in vitro using primary mouse microglia as well as in vivo, using isolated spinal cord microglia. This project could help understand how LoF mutations in this kinase could lead to ALS, generate a crucially needed new ALS model and show new evidence for a contribution of deregulated neuroinflammatory responses in broader ALS. It is designed as a M2-project but could also be continued as a possible PhD-thesis (we are looking for both types of candidates).