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 : 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 "
   Address : **Pitié-Salpêtrière Hôpitale**, **Bâtiment ICM, 47 Bd de l'Hôpital, 75013 Paris**
   Supervisor of the Research Intern: **Dr. Christian S. LOBSIGER (PhD, HDR, CR1 Inserm)**
   Telephone : 01 57 27 45 33 / **06 31 43 99 28**
   E-mail : **christian.lobsiger@upmc.fr** / christian.lobsiger@icm-institute.com

2. **Internship project title: *"Role of TBK1 in neuro-immune interactions during motor neuron degeneration in ALS"***

3. **Internship Description :** Amyotrophic lateral sclerosis (ALS) is an adult onset neurodegenerative disease affecting both cortical and spinal cord motor neurons (MNs). Our team studies the underlying pathological mechanisms with a specific focus on non-cell autonomous mechanisms and the disease contribution of pathological neuro-immune interactions. We are using mouse modeling and human iPS cells and have a strong link to the local ALS clinics for actual patient samples. A significant amount of ALS cases are linked to mutations in a growing set of genes, with most acting by still unknown gain-of-toxic-functions, making it often difficult to study the pathological mechanism. However, recently, dominant loss-of-function (LoF) mutations in TBK1 (TANK-binding kinase 1) have been linked to ALS. As TBK1 has well described functions especially in immune system regulation and autophagy, it could be easier with it, to assess possible ALS mechanisms, than when trying to assess gain of unknown toxic functions linked to most other ALS genes.
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 TBK1 could lead to MN degeneration, and whether they could deregulate reactive microglial responses. This project is strongly linked to our previous work addressing cell-specific contribution of ALS toxicity to MN degeneration. To assess these questions, we have generated (cre/lox mediated) conditional Tbk1 knock-out mice, and deleted Tbk1 specifically in MNs and/or microglial cells. The focus of this M2-project will be on the role of Tbk1 in microglial cells, but also touch on our ongoing analysis of Tbk1 in MNs. The main approach will be to use primary microglial cells from our Tbk1 mouse model to assess *in vitro*, how loss of Tbk1 would affect microglial functions and reactivity. Complementary, the student will also assess *in vivo*, in mice, the role of Tbk1 in isolated microglial cells, using molecular profiling approaches, as well as, assess if Tbk1 could influence the responses of microglial cells to MN injury. This project could reveal new insights into the pathological mechanisms of ALS, 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).