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 :**
   Research Unit (e.g. Department or Institute) : **Institut Biologie Paris Seine. Département Neuroscience Paris Seine**
   Research Unit Director : **Dr Hervé Chneiweiss**
   Research Team Director : **Dr Jocelyne Caboche / Dr Peter Vanhoutte**
   Team name : **Neuronal signaling and gene regulation**

   Address : **9 Quai Saint Bernard, Batiment A 3eme étage, 75005 Paris**
   Supervisor of the Research Intern for this project : **Dr Sandrine Betuing**
   Telephone : **0144275344**
   E-mail : sandrine.betuing@upmc.fr

2. Internship project title:

Dysregulation of cholesterol metabolism in Huntington's disease : cellular and molecular aspects of cholesterol hydroxylase (CYP46A1)-mediated neuroprotection

3. Internship Description :

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by abnormal polyglutamine expansion in huntingtin protein (mHTT) leading to degeneration of striatal neurons. The neuropathology of HD first affects the striatum, and can progressively extend to other brain areas. Emerging evidences indicate that the cholesterol homeostasis is impaired in HD. We made the original observation that levels of CYP46A1 the rate-limiting cholesterol hydroxylase enzyme involved in cholesterol conversion in 24S-hydroxy-cholesterol (24S-OHC) were decreased in the striatum of HD mouse models at early stages, and also in the putamen of HD patients. Restoring CYP46A1 expression in cellular models of HD significantly reduced neuronal dysfunctions and death induced by mHtt. Associated-adeno-virus-mediated delivery of CYP46A1 into striatal neurons *in vivo*, results in a significant improvement of motor behavior associated with a significant neuroprotection. CYP46A1 overexpression resulted in cholesterol biosynthesis pathway reactivation in the striatum leading to a normalization of various cholesterol metabolites. We are investigating the molecular and cellular mechanisms involved in CYP46A1-mediated neuroprotection through two axes involving transcriptional regulation and regulation of synaptic connectivity. The internship will be focused on the transcription regulation analysis. CYP46A1 is a key regulator of sterol contents probably through transcriptional activation of key cholesterol enzymes and cholesterol efflux protein (ApoE). The Liver X receptors (LXRα and LXRβ) are master regulators of cholesterol homeostasis in the central nervous system and 24S-OHC, the product of cholesterol hydroxylation by CYP46A1, acts as a ligand of LXRs. ***We propose to study LXR contribution in the molecular and cellular mechanisms that drive the neuroprotective effects of CYP46A1 in HD.***
To address this question we are currently testing new synthetic stéroïdal ligands of LXRs designed by a chemist collaborator (Dr Maura Maronozzi, University Perugia, Italy) on striatal HD primary neurons. This project will aim at investigating the transcriptional regulation mediated by the the LXRs ligands on striatal neurons. These ligands will be further tested in a HD cellular model to adress their effects on mHTT aggregate formation and neuronal survival. A structure-based modeling of the to LXRs ligand binding domain (LXRα and/or LXRβ) will

further be assessed according to the transcriptional regulation analysis. *In vivo* studies on HD mouse model will be the next step to analyse LXRs ligand treatment on HD phenotype.

References

Boussicault et al, Brain 2016
Marinozzi et al, Medicinal Chemistry 2017
Pei et al, Mol Neurobiol 2013