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): **UMR9199: Neurodegenerative Disease Laboratory**
Research Unit Director: **Emmanuel Brouillet**
Research Team Director: **Gilles Bonvento**
Team name: **Cell-Cell interactions in neurodegenerative diseases**

Address : **MIRCen 18 route du Panorama. 92260 Fontenay-aux-Roses**

Supervisor of the Research Intern for this project: **Carole Escartin**
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2. Internship project title:

Reactive astrocytes as anti-aggregation partners for neurons in Huntington's disease

3. Internship Description:

Astrocytes are essential cellular partners for neurons. In pathological conditions, astrocytes change and become reactive. This occurs in Huntington's disease (HD), a hereditary neurodegenerative disease caused by a mutation in the Huntingtin (*Htt*) gene. Astrocyte reactivity is characterized by morphological changes. However, the functional changes associated with reactivity are still unclear (Ben Haim *et al*. *Front. Cell. Neurosci*. 2015). To better understand the roles played by reactive astrocytes in HD, our team has developed viral vectors that infect astrocytes selectively *in vivo* and either block or induce reactivity, through manipulation of the JAK2-STAT3 pathway. We show that reactive astrocytes reduce mutant Htt aggregation in neurons, a key pathological hallmark of HD (Ben Haim *et al. J. Neurosci*. 2015, and unpublished data). Our data suggest that reactive astrocytes are not only defective cells as usually reported, but can also acquire enhanced capacities to promote mHtt clearance, which has strong therapeutic relevance for HD. The objective of this project is to determine the mechanisms involved in this anti-aggregation effect of reactive astrocytes.

Our transcriptomic data obtained on acutely isolated astrocytes show that several candidate proteins with anti-aggregation properties or involved in intracellular protein degradation are induced when astrocytes become reactive. First, we will confirm the changes of expression and activity of these candidate in reactive astrocytes of HD mouse models and in patient samples. Second, to demonstrate the involvement of some candidates, we will express by viral gene transfer in astrocytes their dominant-negative or inactive mutants in mouse models of HD and measure the effects on mutant Htt aggregation and neuronal indexes.

The Master student will perform transcriptomic (qPCR on fluorescence activated cell sorted astrocytes), biochemical (western blot), histological (immunolabeling, functional probes, confocal imaging) analysis. He will also participate in stereotactic injections of viral vectors in HD mice.

This multidisciplinary project will be carried out in MIRCen (Molecular imaging Research Center), on the CEA campus in Fontenay-aux-Roses, which offers state-of-the-art facilities. We are looking for a strongly motivated, reliable student ready to work in a multidisciplinary environment.