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 (e.g. Department or Institute): **Neuroscience Paris Seine (NPS), INSERM U 1130, CNRS UMR 8246, Sorbonne Université**
Research Unit Director: **Hervé Chneiweiss**
Research Team Director: **Stéphanie Daumas**
Team name : **Neuropharmacologie des VGLUTs**

Address: **9 quai Saint Bernard, Bât. B - 75252 PARIS CEDEX 05**

Supervisor of the Research Intern for this project: **Véronique Fabre and Stéphanie Daumas**
Telephone: **01 44 27 39 28**
E-mail: veronique.fabre@upmc.fr and stephanie.daumas@upmc.fr

2. Internship project title:

VGLUT3 as a marker of vulnerability to stress and associated psychiatric diseases

3. Internship Description:

Alteration of glutamatergic systems are linked to stress-related brain disorders including anxiety, depression and addiction. Our team has accumulated preclinical evidences showing that the atypical vesicular glutamate transporter VGLUT3, is a vulnerability marker for anxiety[1] and addiction[2]. We further established that malfunctioning VGLUT3 could be causal for a pathological use of substances in humans[2]. In this study, we screened patients with severe addiction and identified several mutations in *SLC17A8*, the gene encoding VGLUT3. Interestingly, among several rare missense variations identified in the cohort of subjects with severe addictions, the mutation p.T8I was present in 12 human subjects and was significantly more frequent in drug abusers than in general population. To further address the role of this mutation, we generated a mouse line expressing the VGLUT3-p.T8I variant (VGLUT3$^{T8I/T8I}$).

Here, we will test whether VGLUT3 dysfunction is associated with mood disorders and insomnia. To tackle this issue, we will take advantage of the VGLUT3$^{T8I/T8I}$ mouse line. Our current hypothesis is that individual carrying the VGLUT3-p.T8I allele will be more prone to develop maladaptive stress responses including anxiety- and depression-like phenotype as well as an insomniac-like profile after a sustained stress.

In this context, we will study the vulnerability of VGLUT3$^{T8I/T8I}$ mice to stress. VGLUT3$^{T8I/T8I}$ mice will undergo a chronic social defeat stress (CSDS). Polygraphic sleep recordings will be performed at different time-points throughout the 10-day CSDS and during the recovery period as described by our team[3]. At the end of the CSDS paradigm, social behavior will be assessed to identify susceptible and resilient mice. Although the majority of defeated mice express passive coping responses and are considered as susceptible, some show stress resilience manifested by resistance to defeat-induced social avoidance[4]. Despair-and anxiety-related tests (such as the elevated-plus maze; dark-light box;

open-field, tail suspension test; forced swim test) will be performed at the end of the CSDS. We predict that VGLUT3$^{T8I/T8I}$ mutation will promote stress susceptibility and stress-induced sleep alterations.

The present proposal is designed to fully characterize the impact of the p.T8I allele in stress vulnerability by studying the VGluT3$^{T8I/T8I}$ mice. It is a first step prior to the identification of the underlying mechanisms that will focus on dopaminergic neurotransmission.

References

1 Amilhon, B. *et al. J Neurosci* **30**, 2198-2210, (2010).
2 Sakae, D.Y. *et al. Mol psychiatry* **20**, 1448-1459, (2015).
3 Henderson, F., *et al*. *Front Behav Neurosci* **11**, 227, (2017).
4 Krishnan, V. *et al. Cell* **131**, 391-404, (2007).