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 : NeuroDiderot, UMR1141-Inserm/Université Paris-Diderot
Research Unit Director : Pierre GRESSENS
Research Team Director : Pascal Dournaud/Pierre Gressens
Team name : NeuroKines : glial homeostasis, neuroinflammation, neuroprotection

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2. Internship project title:

Fine tuning of brain circuitry during rodent development in interaction with the serotonergic system: outcome in autistic-like syndrome

3. Internship Description :

Fetal and perinatal periods are a particularly sensitive time-window in the functional programming of normal developing brain which may constitute a target that later leads to pathological conditions such as those implicated in the onset and progression of autistic spectrum disorder (ASD) (Bortolato et al. 2018; Khanzada et al., 2017). Serotonin (5-HT) is known as a trophic factor of brain development *in utero* before it acts as a neurotransmitter (Gaspar et al. 2003; Vitalis et al. 2013) and up to 45% of patients suffering from ASD display increased levels of blood 5-HT. In humans, links have been demonstrated between the emergence of ASD and intake of selective serotonin reuptake inhibitors (SSRIs) during gestation, or polymorphisms in the genes of *MAOA*, *SERT*, *TPH2* and some *5-HT* receptors (Khanzada et al., 2017). Circulating 5-HT is synthesized by tryptophan hydroxylase type 1 (TPH1; Côté et al. 2003) and represents up to 95% of the total amount of 5-HT present in the body. However, to our knowledge, its role in the emergence of ASD has not been investigated.

The proposed project aims at studying in our original mouse model the influence of the lack or lowered-levels of maternal 5-HT during pregnancy on the progeny's brain structure and function during development. We have previously shown that a 50% depletion of 5-HT in dams' blood impacts the development of wild-type progeny. Actually, our results show altered anxiety-like and emotional behaviors in the adult progeny associated to an imbalance in brain concentrations of neurotransmitters and their metabolites. However, further characterizations are required in the adults to assess a link between maternal 5-HT deficit and an ASD-like phenotype. The trainee will determine to what extent and how brain structures are affected throughout development in wild-type progeny born to hyposerotonergic dams. The screening of brain regions will be performed to pick out the prominent modified structures and the brain cyto-architecture will be investigated. The expression profile of the serotonergic components, such as TPH2, 5-HT receptors or its transporter SERT, and those of other neurotransmitter systems will be determined. Neurogenesis at different embryonic stages will also be investigated. The following exploratory approaches will be used: biochemical and molecular measurements (HPLC, RT-qPCR, and protein detection), histology, immunohistochemistry, *in situ* hybridization, microscopy. This ambitious project will benefit from the help of dedicated platforms and human environment. The issues that will be tackled in this project should give a comprehensive overview not only on how neurodevelopment is disarrayed in the absence of maternal 5-HT contribution during fetal life, but should also emphasize on 5-HT as an environmental factor which participates in the emergence of the offspring's ASD-like behavior.