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 du Fer à Moulin
Research Unit Director : Jean-Antoine Girault
Research Team Director : Matthias Groszer
Team name : Neurodevelopmental disorders

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## 2. Internship project title:

Microglia-neuron interactions in a novel mouse model of schizophrenia

## 3. Internship Description :

Schizophrenia (SZ) is a prevalent and severe disorder but its treatment has suffered from a lack of progress. The role of immune processes in schizophrenia had been long suspected. Epidemiological data indicate that both autoimmune diseases and infections to are causally related to schizophrenia. The identification of genomic polymorphisms and mutations associated with schizophrenia is rapidly advancing. Interestingly, genes involved in the immune response to pathogens were repeatedly associated with schizophrenia in large-scale genome-wide association studies (GWAS). In particular, genetic variants conferring high expression of C4, a member of the classical complement cascade, are strongly associated with SZ.

Microglial cells are part of the brain innate immune system and can be activated by immune challenges, especially by C3a, downstream of C4 in the complement cascade. Microglial activation is associated with neuronal alterations and has been found in subsets of SZ patients. We developed a novel mouse model of elevated C4 expression in the prefrontal cortex (still unpublished), and observed microglial activation along with neuronal alterations consistent with those observed in the brain of SZ patients. We hypothesize that high C4 expression activates microglia via the C3a receptor (C3aR), thereby giving rise to SZ-associated neural endophenotypes. To examine this hypothesis, we propose a master project with a multidisciplinary approach. Cx3CR1-CreERT2 mice, which conditionally express the Cre-recombinase in microglial cells, will be crossed to $C3aR^{lox/lox}$ mice to ablate C3aR specifically in microglial cells. The activation of microglial cells in Cx3CR1-CreERT2:: $C3aR^{lox/lox}$ mice and controls following in utero electroporation of C4 will be investigated using anti-Iba1 immunostainings, confocal imaging and automated morphological reconstructions. In parallel we will study neuronal alterations in C4-overexpressing Cx3CR1-CreERT2::$C3aR^{lox/lox}$ mice and control mice using immunohistochemistry and patch-clamp electrophysiology in cortical pyramidal cells and interneurons ex vivo.

These experiments will shed new light on the neurobiology of schizophrenia, and more generally on the interactions between microglia and neurons during brain maturation.