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) : UMR8246, Neuroscience Paris Seine
Research Unit Director : Hervé Chneiweiss
Research Team Director : Bertrand Lambolez and Bruno Cauli
Team name : Cortical network and neurovascular coupling

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Supervisor of the Research Intern for this project: Régine HEPP
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2. Internship project title:

Study of glutamate receptor GluD1 signaling alterations caused by a missense mutation identified in patients with intellectual disabilities

3. Internship Description :

Glutamate is the main excitatory neurotransmitter in the brain. It binds ionotopic receptors (iGlu) and metabotropic receptor (mGlu). Among iGlus, GluD1 and GluD2 subunits are peculiar as they do not directly bind glutamate. Mutations in the *GRID1* gene coding for GluD1 have been identified in patients suffering schizophrenia or autistic disorders. The phenotype of GluD1 knock out (KO) mice resembles that of patients. Interestingly, GluD subunits are implicated in the development and maturation of synapses due to their interactions with pre-synaptic released cerebellins (Cbln). Our team has recently demonstrated that GluD1 is widely expressed in the brain and interacts with mGlu1/5 receptors. We showed that activation of mGlu1/5 induces the opening of the GluD1 channel and that the GluD1 current is involved in slow synaptic transmission. The loss of the current in GluD1KO mice strongly disturbs the firing properties of dopaminergic neurons in vivo. In the hippocampus, it has been shown that AKT and mTOR signaling mediated by mGlu5 was altered in KO mice, disturbing the trafficking of AMPA receptors. Our collaborators have recently identified a rare missense mutation in *GRID1* in patients with intellectual disability (ID). We showed that the mutation does not alter membrane expression or the interaction of GluD1 with mGlus. However, when overexpressed in primary hippocampal culture, mutant GluD1 leads to a reduced number and length of neurites and an increase of the number of immature spines.

The present master's project is part of a wider project aiming at understanding the role of GluD1 in synaptogenesis, mGlu signaling and studying the effect of the ID mutation on GluD1 functions.

Depending on the progress of the project, the student will be involved in one or more of the following aspects:

- Regulation of mGlu5 signaling by wild type and mutant GluD1. The activation of AKT, mTOR, ERk signaling pathways will be investigated by western blotting and biosensor imaging.
- Study of the binding of Cbln to mutant GluD1 using immunocytochemistry, in cell western blotting and surface plasmon resonance.
- Analysis of the GluD1 interactome: Wild type and mutant GluD1 binding partners will be identified using immunoprecipitation and mass spectrometry. Binding partners will be validated using transfected HEK cells and functional significance evaluated accordingly.

GluD1 and type I mGlus are key player in synaptopathies associated diseases but the molecular mechanism linking GluD1 mutations to mental disorders remains largely unknown. This proposal aims to understand how mutant GluD1 leads to synaptic deficits causing ID. Identification of new GluD1 interacting partners and disturbances caused by the mutation will help understand the pathophysiological mechanisms linking GluD1 to synapse formation, function and plasticity. Elucidation of the molecular cascade that links GluD1 to ID has enormous potential to identify new therapeutic targets relevant ID models.

IMPORTANT NOTE: GluD1 being an iGlu, alteration of the channel properties by the mutation will also be examined using patch-clamp recordings. This technique is widely used in the laboratory. Students motivated by this aspect of the project are welcome to postulate.