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) : Institut de la Vision
Research Unit Director : Jose-alain Sahel
Research Team Director : Filippo Del Bene
Team name : Development and function of the vertebrate visual system

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Supervisor of the Research Intern for this project : Filippo Del Bene
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2. Internship project title:

Analysis of Reelin Functions in Circuit Wiring and Neurodevelopmental Disorders

3. Internship Description :

Functional brain circuits arise through a series of sequential steps including neurogenesis, migration, axonal navigation and synaptogenesis. Perturbations of this sequence, which starts during embryogenesis, have been linked with the etiology of neurodevelopmental disorders. Reelin (RELN) is an extracellular glycoprotein that acts as a key regulator of different steps of brain wiring. In the mammalian neocortex, RELN regulates neuronal migration and layer formation, dendritic arborization and synaptogenesis. Autosomal recessive RELN mutations lead to severe cortical malformations with lissencephaly (LIS) and cerebellar hypoplasia (LCH) in humans. However, heterozygous variants or changes in RELN protein levels were also reported to be associated with multiple neuropsychiatric disorders such as epilepsy and Autism Spectrum Disorders (ASD). Recent studies in our laboratory in zebrafish highlight a novel role for this secreted protein in the organization of superficial axonal projections as well as the related synaptic laminar architecture. In collaboration with the laboratory of Alessandra Pierani (institut Imagine) we are analyzing novel reelin mutant variants identified in patients as recessive (compound heterozygous) and dominant (heterozygous) *RELN* mutations associated with a spectrum of neurodevelopmental disorders, epilepsy and intellectual disabilities. The student will will use a combination of GOF and LOF analyses to assess the activity of these mutant variants in zebrafish. In a first step we will test whether the human variants associated with different pathological phenotypes can rescue the zebrafish mutant for *reln* and guide normal synaptic development. We are also generate these mutations in zebrafish using a novel CRISPR/Cas9 precise base editing technique and we will assess the phenotypic consequences of the introduction of the equivalent amino acid (aa) change seen in the human mutations and to investigate the biological function *in vivo* in our optically accessible preparation. Overall our

study aims to decipher the functional role of RELN in human synaptic organization as well to understand its involvement in disease development.