

Internship Proposal Academic Year 2018-2019

1. Host team :

Research Unit (e.g. Department or Institute) : Institut de la Vision
Research Unit Director : J. Sahel
Research Team Director : Filippo Del Bene
Team name : Development and Function of the Vertebrate Visual System

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2. Internship project title:

Meteorin and Meteorin-like proteins in the wiring of the nervous system

3. Internship Description :

Meteorin and Meteorin-like are newly discovered secreted proteins involved in both glia and neuronal cell differentiation (Jorgensen et al., 2012; Nishino et al., 2004). More recently, they have also been implicated in axonal growth in in vitro systems. We have cloned the zebrafish orthologous gene (Meteorin, *Metrn1* and *Metrn2*) and determined their expression during CNS development in larval zebrafish. Each *Meteorin* gene codes for a small protein (of about 300 amino acids) containing an N-terminal signal peptide and a predicted C-terminal Netrin-like domain that we identified using bioinformatic sequence analysis. Interestingly, we have obtained preliminary data showing that both *Metrn* and *Metrn1* mRNAs are highly expressed by floor plate cells and in other midline structures in the zebrafish. We have also created null alleles of all three genes via CRISPR/Cas9 technology. Although the mutant fish are viable they show very penetrant and specific axonal growth defect. Preliminary work has demonstrated that these axons fail to innervate the proper brain areas and establish the correct synaptic connectivity. The student will characterize in detail these defects in trigeminal ganglion neuron axons using transgenic lines, in vivo imaging and immunohistochemical analysis. He/she will as well analyze double and triple mutants for these genes that have already been generated, to

unmask new phenotypes, including abnormalities in commissural axon crossing and visual perception defects via calcium imaging of behaving animals. A biochemical screen has also been initiated to identify the receptor of Meteorin proteins in vivo and the best candidates from the screen will be functionally validated in vivo by the student. In parallel we have generated a transgenic line to overexpress a GFP-tagged Meteorin protein in various part of the central nervous system. The analysis of axonal growth and development in this transgenic model will also be performed. This work will be the first characterization of the role of Meteorin in CNS development via loss-of-function analysis in a vertebrate model.