PROPOSITION SUJET DE THESE

Concours d'attribution des Contrats Doctoraux 2019 – 2022
A renvoyer impérativement **avant le 2 mars 2019** par courriel au format **PDF** à edsvs-direction@univ-amu.fr

1. Choix du sous-jury (vous ne pouvez cocher qu'une seule case) :

☐ JURY 1 – Biologie Cellulaire (Développement – Immunologie – Biologie Végétale – Physiologie).

☐ JURY 2 – Microbiologie – Génomique (Bioinformatique – Biochimie Structurale – Biochimie).

☒JURY 3 – Neurosciences (Neurobiologie cellulaire – Neurosciences Cognitives et Comportementales – Neuroimagerie – Neurosciences Computationnelles).

☐ JURY 4 – Biologie Santé (Oncologie – Cardiovasculaire – Santé Publique – Maladies Infectieuses – Génétique).

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Publication du Doctorant :	

Project Abstract :

Understanding Schwann cell-axon interaction through human and rodent models of Charcot-Marie-Tooth disease 4H

Introduction and context

Myelin is required for neuronal development, integrity and function. Defects in myelin include a myriad of hereditary debilitating leukodystrophies and dysmyelinating neuropathies, including Charcot Marie Tooth disease (CMT). CMT is one of the most common inherited neurological disorders, characterized by length-dependent progressive degeneration of the Peripheral Nervous System (PNS). The disease may affect either motor and/or sensory neurons, or Schwann cells (SC) which form PNS myelin, or both. Understanding the nature of the signals controlling SC-neuron association and myelination is key to unravel the mechanisms disturbed in myelin diseases.

Objectives

In this project, we propose to study neuronal-glial interactions required for proper PNS myelination using *in vitro* and *in vivo* models of CMT4H, an autosomal recessive demyelinating CMT, for which we have identified *FGD4* as the culprit gene in 2007. FGD4 encodes FRABIN (FGD1-related F-actin binding protein), a GDP/GTP nucleotide exchange factor, specific for Cdc42.

Methods

To do so, we will perform:

1) The analysis of axon-SC interactions, ***in vitro***, in hiPSC-derived SC-neuron cocultures from patients affected with CMT4H, as compared to controls.

To this purpose, control SCs or SCs knockdowned for *Fgd4*, will be seeded with mutant or control human neuronal membranes (from hiPSC-derived sensory neurons), respectively, in a modified Boyden chamber system. SC pseudopods will be collected and analysed by mass spectrometry.

2) The identification of molecular regulators and signaling pathways existing during initiation and maintenance of peripheral myelin, ***in vivo***, in sciatic nerve of our CMT4H mouse model (*fgd4*$^{-/-}$). Here, both mass spectrometry and RNA-seq studies will be performed on sciatic nerves from wild-type (WT) or fgd4 knock-out mice at two time-points corresponding to the peak of myelination production and adult stages, where myelin is established and need to be continuously maintained. We will validate the selected candidates by various means.

Expected results. We expect to identify novel molecules important in Schwann cell-axon interactions that are regulated by the presence/absence of FRABIN. We believe that this project will not only highlight key actors of the pathophysiological mechanisms in CMT4H, but also bring new insights into the mechanisms and molecular contributors involved in SC-neuronal crosstalk in the PNS and eventually open new therapeutic perspectives in CMT.

The candidate should be interested in neurobiology and diseases of the peripheral nervous system. He should be able to learn and develop many technics ranging from molecular biology to cell culture, and interested to work in a translational research environment.