Internship/PhD in System Biophysics of membranes

SIM microscopy for the study of the multi-scale dynamics of Huntington's neurons

Contact : Stéphanie Bonneau (stephanie.bonneau@sorbonne-universite.fr)

Project and objectives

Metabolic activity, by which living systems maintain their out-of-equilibrium state, takes place in a highly dynamic, crowded and structured environment. Today, the multi-scale spatiotemporal organization emerges as organizing and coordinating cellular behaviour. A major challenge now is to link the nano-scaled and molecular levels with the classical micron-scale cell description, in terms of dynamics, mechanics and remodelling. In particular, insight are lacking for the 50-500 nm scale (corresponding to the so-called meso-scale biology).

We will focus on a comparison of healthy and Huntington neurones, of which both cholestol and oxidative metabolisms are strongly impaired from the early stages of the pathology. Important subsequent malfunctions such as decrease of the energy production, increase of the oxidative stress and dis-assembly of the synaptic structure induce alterations of the axonal transport and synaptic signalling. Associated to this neurodegenerative disease, a triad of symptoms affects the psychiatric cognitive and motor behaviours.

Internship/PhD programm

The goal of the internship if to track the nano-scalled cholesterol-lipid rafts (R) and their dynamics. Rafts represent the so-called lateral compartmentalization of lipids and protein-receptors at the cell surface. Internalization of ligands and receptors by these domains occurs via a specific process defined as raft-dependent endocytosis (E).

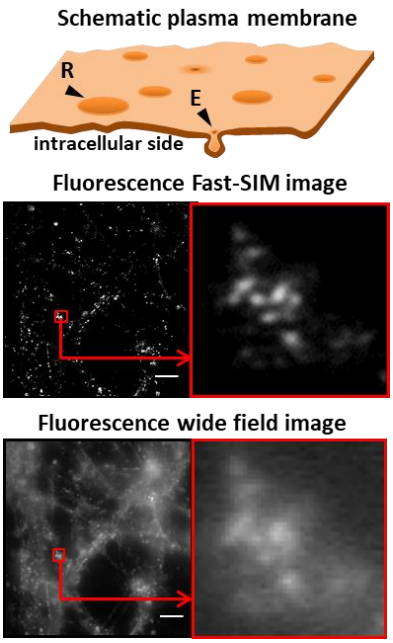

Fig. *Schematic of lipid rafts and comparison between WF and Fast-SIM in primary HD neurons. Bar 10µm.*

The successful candidate will be in charge of the experimental part of the project, in particular super-resolution imaging. She/he will work in the Laboratoire Jean Perrin (UMR 8237 CNRS and Sorbonne University) in the Biomembrane group, under the supervision of Prof. S. Bonneau. The team has a homemade Fast-SIM set-up, of which innovative approach increases the acquisition rate and enable fast, large field and non-aggressive (low light) imaging of the samples. Experiments on living cells already demonstrate a lateral resolution of ~100 nm at raw data acquisition rate of 15 frames per second for a wide field of 85µmx85µm. In collaboration with the Neuroscience Lab of IBPS (Prof S. Betuing), experiments will be performed on primary cells cultures of cortical neurons, from wild type mice and from models of Huntington Disease (HD). Our strategy is to track the cholesterol-rich lipid rafts (Cholera-toxin B Alexa-488) and the receptors (GluN2B-Cherry subunit). Quantitative data will be derived from image analysis (rafts number and size distribution, mean square displacement, fission/fusion events, dif-fusion mode…) to analyse topology and dynamics. Those data are characteristic of reprogramming of the cell and describe its state. They will be correlated with data obtained from biochemical analysis and functional imaging, which give access to the biological activity.

Extends of this work can conduct to a PhD program involving SIM developments, statistical and numerical modelling and extend of the approach to the study of the oxidative metabolisms and mitochondria.