3 years PhD student position in Neurobiology

Mechano-sensing of the axon and its initial segment, links with the nanoscale organization of the membrane periodic skeleton

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Project Summary

Neurons have reached an extreme level of compartmentalization and complexity, with synapses and axons containing micron-scale functional domains, themselves organized into nano-domains in which proteins perform specific functions. The formation and plasticity of a functional neural network is controlled by adhesion and cytoskeletal proteins that coordinate morphological remodeling of synapses, growth cones and axons. In axons and dendrites, a new molecular assembly has been uncovered by super-resolution microscopy, a periodic actin/spectrin network known as the periodic membrane skeleton (MPS) (Xu, Science 2013). In the axon initial segment (AIS), the MPS control the spatial organizations of proteins controlling action potential, signaling pathways and transport, such as sodium channels (Xu, Science 2013), cannabinoid receptors (Zhou, Science 2019) and microtubules. Unsurprisingly, deficits in spectrins underlie several neurodevelopmental and neurodegenerative disorders, including language and motor delays, intellectual disability, seizures and autistic features (Cousin, Nature Genetics 2021). Mechano-sensing is emerging as a key mechanism regulating neuronal functions during physiological processes, including neuronal development (Koser, Nature Neuroscience 2016) and synaptic transmission (Ucar, Nature 2021). While adverse mechanical stimuli are involved during pathophysiological events (e.g. traumatic brain injuries) or during aging which is associated with stiffening of the extracellular matrix (Segel, Nature 2019). Despite the fact that they probably involve adhesion and cytoskeleton proteins, the molecular mechanisms underlying neuronal mechano-sensing remain unknown. The MPS may control neuronal mechano-sensing and mechano-protection during dendrites and axons formation and function (Hammarlund, Journal Cell Biology 2007; Krieg, Nature Cell Biology 2014; Berge, Neuron 2018; Costa, eLife 2020).

The aim of this PhD project is to study the links between the MPS and mechano-sensing and mechano-protection of the axon and its initial segment. To achieve this goal, we will exert mechanical forces on the axon by stretching neurons on deformable substrates, or use substrates of controlled rigidities. We will use advanced microscopy techniques, including super-resolution microscopy and optic-based voltage, mechanical force and protein activity sensors. Using these methods, we will study the effects of mechanical stimuli on the morphology of the axon and its initial segment, the generation of action potential and signaling pathways. We will correlate these

mechanical effects with changes in the nanoscale architecture and dynamics of the MPS and associated functional proteins (e.g. sodium channels, phosphotyrosin signaling, cannabinoid receptors). This way, we will gain a molecular understanding of the mechanisms underlying neuronal mechano-sensitivity and mechano-protection.

This PhD project will be a collaboration between the group of Grégory Giannone 'Spatio-Temporal and Mechanical Control of Motile Structures' in the Interdisciplinary Institute for Neuroscience (IINS, Bordeaux, France), Anna Brachet 'Dynamic Organization and Function of Synapses' (IINS, Bordeaux, France) and Emilie Pacary 'Neurogenesis and pathophysiology'(Neurocentre Magendie, Bordeaux, France).

Environment

The PhD student will benefit from cutting edge facilities and interdisciplinary scientific environment. In particular, the team of Grégory Giannone is expert in cell migration and force-sensing, integrin adhesions and actin-based protrusion. Using super resolution microscopy/single particle tracking, his group unraveled key molecular events leading to: integrins activation and mechano-sensing in normal, and cancer cells; actin assembly in dendritic spines and the lamellipodium (Rossier, Nature Cell Biology; 2012; Paszek, Nature 2014; Chazeau, EMBO J. 2014; Orré, Nature Communications 2021; Mehidi, Current Biology, 2019; Massou, Nature Cell Biology 2020; Mehidi, Nature Cell Biology 2021). Anna Brachet is expert in AIS dynamic organization (Brachet, JCB 2010), electrophysiology and organotypic slice imaging (Brachet, JCB 2015 and Brachet, Cell Report 2021). She is now leading a project on MPS regulation in neurons. Finally, Emily Pacary expertise in *in vivo* cortical neuron migration by cytoskeleton regulators and *in utero* electroporation (Pacary, Neuron 2011; Pacary, Nat Commun 2013; Nicole, Mol Psy 2018; Kerloch Cereb Cortex 2019), IINS facilities (Cell Biology, Molecular Biology) and the Bordeaux Imaging Center will be instrumental for this project.

The PhD student will be encouraged to present their data in international meetings.

Qualification and offer

This project is for a student from a Master of Neuroscience or Cell Biology, with an affinity for the topics at the interface between neurobiology and biophysics. It requires a motivated student, with some knowledge in cell imaging and ready to get trained to new microscopy imaging techniques.

Within the frame of the NanoCoding project funded by the "Grand Programme de Recherche de l'Université de Bordeaux GPRBrain_2030", this position is available for 3-years, with a flexible starting date around October 2022. The salary is in accordance with University policy.

Please send your CV, a cover letter with a description of your research interests and two references to: gregory.giannone@u-bordeaux.fr and anna.brachet@u-bordeaux.fr

IINS web site: http://www.iins.u-bordeaux.fr/