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 du fer à moulin, INSERM UMR 1270
Research Unit Director : Jean-Antoine Girault
Research Team Director : Stéphane NEDELEC
Team name : « Stem cells in neurodevelopment »
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2. Internship project title:

Investigating the neurodevelopmental basis of a rare neurological disorder using human pluripotent stem cells

3. Internship Description :

The differentiation of human pluripotent stem cells (hPSC) opens new avenues to study the development, evolution and diseases of the human nervous system. Using targeted and organoid-like differentiation of of hPSCs our team is, on one hand, deciphering the mechanisms controlling the formation of human neuronal diversity and, on the other hand, studying the basis of differential vulnerability of neuronal subtypes in neurodevelopmental diseases.
We propose a project, in collaboration with a post-doctoral fellow in the lab, aiming at studying the differential vulnerability of spinal motor subtypes in a group of developmental motor neuron diseases called spinal muscular atrophies. The project is conducted in collaboration with the group of Alexandra Baffet (Curie Institute, Paris) specialized in neuronal cell biology and the Professor Nadia Bahi-Buisson (Imagine Institute, Paris) who coordinates a group of clinicians following patients.

Context:

In the nervous system, the generation of thousand distinct types of neurons in appropriate numbers and at precise locations underlies the formation of neural circuits encoding behaviors. Functional impairment or degeneration of discrete neuronal populations leads to the symptoms characterizing individual neurological disorders. Paradoxically, neurodegenerative diseases are often caused by mutations in ubiquitously expressed proteins. The basis of the differential vulnerability of neuronal subtypes is currently unknown. A major challenge in Neurosciences is thus to understand how neuronal subtypes are specified during development, acquire and maintain distinct properties and how genetic mutations or environmental factors challenge subtype specific features to cause diseases. This is well illustrated in motor neuron (MN) disorders that target muscle innervating neurons located in the hindbrain and spinal cord.
The formation of specific motor circuits depends, early in development, on the generation of hundreds of MN subtypes that send their axons toward the periphery to form connections with their muscle targets. Depending on their position in the hindbrain and spinal cord, MNs acquire subtype specific molecular properties that instruct their cell body position, axon pathfinding, muscle target and electrophysiological properties. MN disorders are symptomatically heterogeneous due to the selective degeneration or

dysfunction of specific MN subtypes in individual diseases. For example, spinal muscular atrophies (SMAs) are a group of neurodevelopmental disorders that preponderantly target spinal MNs (sMN) and represent the most common genetic cause of infant mortality affecting ~1:6000 newborn[3]. However, SMAs are divided in proximal SMAs (pSMA) displaying greater proximal than distal muscle weakness and distal SMAs (dSMAs) with limb predominance. 95% of SMAs are pSMAs due to mutations in SMN1 gene while dSMAs are caused by mutations in proteins involved in RNA biogenesis, axonal transport or protein translation. The basis of the differential sensitivity of MN subtypes in SMAs is currently unknown. Deciphering features providing resistance or sensitivity to specific MN subtypes has obvious therapeutic potentials. Therefore, investigating the mechanisms controlling the acquisition and maintenance of MN identities and their erosion in pathological contexts is critical for the understanding of motor circuit formation and diseases. However, these questions are currently difficult to address due to the limited access in animal models let alone in human to normal and pathological MN subtypes to define their molecular and functional differences and understand the basis of their differential sensitivity in MN diseases. We have thus created a consortium of clinicians, cell and stem cell biologists to study the clinical, cellular and molecular basis of SMAs. We have obtained human induced pluripotent stem cells (hiPS) from patients with SMA causing mutations and developed the first methods to differentiate them in differentially affected neuronal subtypes in order to study the impact of the mutations on MN development and the basis of MN subtype differential vulnerability.

Goal of the internship:

The internship will consist in differentiating control and patient derived iPS cell lines in different motor neuron subtypes to perform live imaging in microfluidic chambers (collaboration with C. Villard, IPGG, Paris) and analysis of single cell gene expression profiling to study the defects in intracellular transport and their consequences on motor neuron subtype development.

References

Maury, Y et al. Combinatorial analysis of developmental cues efficiently converts human pluripotent stem cells into multiple neuronal subtypes. Nat Biotechnol 33, 89 (2015).

Nedelec, S et al. Concentration-dependent requirement for local protein synthesis in motor neuron subtype-specific response to axon guidance cues. J Neurosci 32, 1496 (2012).