Master Biologie Moléculaire et Cellulaire 'BMC',
Université de Paris - *UFR Sciences du Vivant*

Parcours : **Biologie et Développement Cellulaires 'BDC'**
http://www.master2bdc.fr/
Fiche de Projet de Stage M2, Année 2022-2023

Unité INSERM ou CNRS ou Université : **UMR-1270, Inserm, Sorbonne université** **Intitulé Equipe : Stem cells and Neurodevelopment** **ED d'appartenance : ED CDV 515** **Responsable de l'Equipe : Stéphane Nedelec**	**Responsable du Stage :** **Contacts Stéphane Nedelec** Adresse : Institut du Fer à moulin, 17 rue du Fer à Moulin 75005 Paris Email : stephane.nedelec@inserm.fr Tel : +33145876159 (email de préférence)

Titre du projet: Developing human embryoid/organoid models to study cell fate specification in normal and pathological development

Résumé du Projet de Stage

The generation of organoids, embryoids or specific cell types from human pluripotent stem cells has opened a new era to study human development with important repercussions for cell and tissue engineering to model and treat diseases. Using in vitro models (organoids, embryoids…) coupled to transcriptomic, genetic, pharmacology and live imaging technics, our team seek to decode principles controlling the specification and organization of cell types that form sensory and motor circuits and how genetic mutations perturb these events to cause neurodevelopmental disorders (see Mouilleau, Vaslin et al, 2021, Nedelec & Martinez-Arias, 2020, Duval et al, 2019, Maury et al, 2015)

We recently developed a new embryoid model (see for instance Fu et al, nature materials, 2020) in which multiple lineages develop to recapitulate the 3D morphogenesis and cell type specification observed in the caudal region of the developing human embryo. In particular, a folded neural tube is forming along which neuronal subtypes organize as in the human spinal cord. This unique *in vitro* model opens avenues to study the cellular and molecular mechanisms controlling the normal and pathological formation of the human neural tube and sensory-motor circuits.

We are thus developing new approaches to track specific cell types as well as conditionally-express or remove genes to study cell fate specification and morphogenesis in normal conditions and in presence of disease causing-mutations. For that, we are collaborating with the labs of Jean Livet (Institut de la vision, Paris) and Xavier Morin (ENS, Paris) to genetically modify human pluripotent stem cells using Crispr/Cas9 and iON systems (see below Kumamoto et al, 2020). We wish to recruit a master 2 student with a strong interest in cellular and molecular aspect of development. The project will involve molecular biology with the most recent technics, generation of genetically modified induced pluripotent stem cell lines (iPSCs) followed by differentiation into embryoids. Cell fate and embryoid morphogenesis will be monitored upon loss and gain of function of candidate genes identified in a previous single cell RNA sequencing experiment or mutated in congenital neurological disorders (in particular genes inducing early onset motor neuron diseases). The successful candidate will benefit from direct training on culturing human iPSC and generating/analyzing embryoids/organoids as well as a very collaborative environment within the team and between different labs of the Paris area (see website for more info https://ifm-institute.org/en/equipe/team-nedelec/). A previous experience in cell culture and molecular biology will be a plus.

Publications de l'équipe relatives au projet de stage (max 5)

- *Dynamic extrinsic pacing of the HOX clock in human axial progenitors control motor neuron subtype specification.* Mouilleau V*, Vaslin C* et al. **Development.**148. **2021**

- *In vitro models of spinal motor circuit's development in mammals: achievements and challenges.*

Nedelec S and Martinez-Arias A. **Current Opinion in Neurobiology**. 66:240-249. **2021**

- *Direct readout of neural stem cell transgenesis with an integration-coupled gene expression switch.* Kumamoto T, Maurinot F, Barry R, Vaslin C, Vandormael-Pournin S, Le M, Lerat M, Cohen-Tannoudji M, Rebsam A, Loulier K, **Nedelec S**, Tozer S, Livet J. **Neuron**, 19;107(4), **2020**

- *BMP4 patterns Smad activity and generates stereotyped cell fate organization in spinal organoids*. Duval N. et al. **Development**, Jul (14);146, **2019**.

- *Combinatorial analysis of developmental cues efficiently converts human pluripotent stem cells into multiple neuronal subtypes.* Maury Y et al, **Nature Biotechnology**. 33 :89-96, **2015**