Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2018-2019

1. Host team:

Research Unit (e.g. Department or Institute): Institut du Fer à Moulin, UMR 839
Research Unit Director : Jean-Antoine Girault
Research Team Director : Stéphane Nedelec
Team name : Stem cells in neurodevelopment and disease

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2. Internship project title:

Decoding the cellular and molecular basis of the temporality of human nervous system development with stem cells

3. Internship Description :

During embryogenesis, the formation of multicellular tissues is a progressive process occurring over an extended period of time which requires a precise coordination of cell proliferation and differentiation. In the nervous system, in which the cellular diversity reaches its apogee, this coordination ensures the generation of thousands of distinct neuronal and glial subtypes at the right time and correct position[1]. Imbalance in this process is at the basis of numerous neurodevelopmental disorders.

This large cellular diversity is generated, during embryonic development, from a relatively small pool of stem progenitors that goes through sequential, stereotyped changes in their competence to progressively give rise to distinct cell types. This temporal patterning is conserved across the animal kingdom[1]. Yet, the dynamics of the differentiation programs is species-specific and have been proposed to account for the diversification of the nervous system during evolution[2]. However, despite the importance of these mechanisms during development and evolution, the underlying molecular and cellular mechanisms, remain poorly understood. This not only impairs our understanding of human nervous system development in health and disease but also prevents the engineering of specific cell types for clinical applications

Using stem cells, transcriptomic and bioinformatics approaches we are developing a collaborative research program between three teams (Vanessa Ribes group, Institut Jacques Monod, Paris and Jacques van Helden group, TAGC, Marseille) aiming at deciphering and comparing **the genetic and epigenetic mechanisms controlling the temporality of mouse and human neurogenesis.**

To approach this question, we rely on the *in vitro* **targeted differentiation of pluripotent stem cells** of embryonic origin (ES cells) or reprogrammed from somatic cells (iPS cells)[3].

In the past years, differentiation of stem cells in specific cell populations and organs is revolutionizing development biology, cell engineering, and disease modeling and provide the first experimental model of human development. We developed *in vitro* 3D-organoid-like differentiations of mouse and human pluripotent stem cells in equivalent neuronal populations (Nedelec and Ribes team unpublished results). These differentiations follow the species-specific temporality of *in vivo* development and thus provide experimentally accessible models to compare mouse and human differentiation.

During his internship the student will differentiate mouse and human pluripotent stem cells to compare the temporality of differentiations in both species using immunohistochemistry for specific transition markers, cell cycle assays, genetically modified stem cell lines, as well as bulk and single cell transcriptomic data generated at different time points of differentiation.

Approaching these questions might have profound consequences for our understanding of human brain formation and improve cell and tissue engineering strategies from stem cells for basic and clinical applications.

Selected publication of the team

- Serotonin neurons in a dish
Gaspar P, Nedelec S
Nature Biotechnology, 2016, Jan 34(1):41-2

- Combinatorial analysis of developmental cues efficiently converts human pluripotent stem cells into multiple neuronal subtypes.
Maury Y, Côme J, Piskorowski R, Mohellibi N, Chevaleyre V, Peschanski M, Martinat C, Nedelec S.
Nature Biotechnology. 2015 Jan;33(1):89-96.

- Synergistic binding of transcription factors to cell-specific enhancers programs motor neuron identity.
Mazzoni EO, Mahony S, Closser M, Morrison CA, Nedelec S, Williams DJ, An D, Gifford DK, Wichterle H.
Nature Neuroscience 2013 Sep;16 (9):1219-27.

- Genetically-modified human pluripotent stem cells: new hope to understand and treat neurological Diseases ?
Nedelec S, Onteniente B, Peschanski M, Martinat C.
Curent Gene Therapy. 2013 Apr; 13 (2):111-9.

- Differential requirement for local protein synthesis In Motor neuron subtype specific response to axon guidance cues. Nedelec S, Peljto M., Peng S.i, Amoroso M.W., Kam LC, Wichterle H.
Journal of Neuroscience, 2012 Jan 25; 32 (4):1496-506.

- An alternative splicing switch regulates ES cells pluripotency and reprogramming.
M.Gabut, P.Samavarchi, X.Wang, V.Slobodeniuc, D.O'Hanlon, H.Sung, M.Alvarez, S.Talukder, Q Pan, E.Mazzoni, S. Nedelec, H. Wichterle, K.Woltjen, TR Hughes, PW Zandstra, Nagy, JL Wrana, BJ Blencowe.
Cell, 2011, 147:132-46

References for project

1. Kohwi, M. *Nat. Rev. Neurosci.* **14**, 823–838 (2013).
2. Namba T, H.W. *Wiley Interdiscip Rev Dev Biol.* (2016).doi:10.1002/wdev.256
3. Maury, Y. *Nat. Biotechnol.* **33**, (2015).