

Internship Proposal Academic Year 2018-2019

1. Host team :

Research Unit (e.g. Department or Institute) : ICM
Research Unit Director : Alexis Brice
Research Team Director : Brahim Nait Oumesmar
Team name : Molecular and cellular approaches of myelin repair

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2. Internship project title: Molecular mechanisms of myelin plasticity

3. Internship Description:

Myelin, produced by oligodendrocytes in the central nervous system (CNS), has been thought for a long time as a static structure. Recent studies demonstrated that myelin is dynamic: myelination increases upon sensitive stimulations and decreases after sensory deprivation [1-3]. Remodeling of actin cytoskeleton might be implicated in this plasticity. Indeed, the first steps of myelination (ensheathment) require actin polymerization, while the next steps (wrapping) switch to actin depolymerization [4,5]. Thus, a precise control of signaling pathways regulating actin polymerization/depolymerization might occur in oligodendrocytes during the myelination process. We identified a protein kinase regulating these processes as a key effector in oligodendrocytes differentiation and membrane maturation. Indeed, we showed that: *i*) this kinase is highly expressed in mature oligodendrocytes, *ii*) its loss-of function leads to an increase of oligodendrocyte differentiation and membrane maturation. We generated a knockout mouse of this kinase in oligodendroglial cells (cKO), and several molecular tools (inducible kinase dead and constitutive active forms) to study the role of this kinase in the dynamic of oligodendrocyte membrane formation and in myelination *in vitro* and *in vivo*. We will analyze oligodendrocyte development and myelination of the kinase cKO mice by immunohistochemistry and electron microscopy. We will also modulate the activity of this kinase in oligodendrocytes *in vitro* and determine the effects on the dynamic of oligodendrocyte membranes by live imaging. The perspective of this project is to analyze how this kinase affects myelin plasticity in the adult CNS and subsequently how it might affect motor skill learning and social interactions.

Literature citations:

1. Young KM, Psachoulia K, Tripathi RB, Dunn SJ, Cossell L, et al. (2013) Oligodendrocyte dynamics in the healthy adult CNS: evidence for myelin remodeling. *Neuron* 77: 873-885.
2. Liu J, Dietz K, DeLoyht JM, Pedre X, Kelkar D, et al. (2012) Impaired adult myelination in the prefrontal cortex of socially isolated mice. *Nat Neurosci* 15: 1621-1623.
3. McKenzie IA, Ohayon D, Li H, de Faria JP, Emery B, et al. (2014) Motor skill learning requires active central myelination. *Science* 346: 318-322.
4. Zuchero JB, Fu MM, Sloan SA, Ibrahim A, Olson A, et al. (2015) CNS myelin wrapping is driven by actin disassembly. *Dev Cell* 34: 152-167.
5. Nawaz S, Sanchez P, Schmitt S, Snaidero N, Mitkovski M, et al. (2015) Actin filament turnover drives leading edge growth during myelin sheath formation in the central nervous system. *Dev Cell* 34: 139-151.