MASTER 2 Fundamental and Clinical Neurosciences

Internship proposal 2023-2024

(internship from January to June 2024)

Host laboratory: *Name + address*
STEM CELL AND BRAIN RESEARCH INSTITUTE (SBRI)-INSERM U1208
18 avenue Doyen Lépine
69500 BRON
http://www.sbri.fr

Host team : *team name + website*
CELLULAR REPROGRAMMING IN THE BRAIN
https://sbri.fr/teams/cellular-reprogramming-in-the-brain/

Internship supervisors : *name + position + email*
Christophe HEINRICH, PhD, HDR, Group Leader
Christophe.heinrich@inserm.fr

Project title :
Lineage reprogramming of glial cells into neurons: A new avenue for brain repair

Project summary : *approx 10 lines*
Injury to the human CNS is devastating because our adult mammalian CNS lacks intrinsic regenerative capacity to replace lost neurons. Acute CNS injury and chronic neurodegenerative diseases are associated with irreversible loss of neurons and permanent deficits. Most neurological diseases associated with neuronal death are also accompanied by reactive gliosis. An emerging approach towards replacing lost neurons is to instruct fate conversion of reactive glial cells into clinically-relevant induced neurons (iNs) by direct lineage reprogramming (Heinrich, et al Nat Cell Biol, 2015; Vignoles et al, Trends Mol Med, 2019). We showed that mouse astroglia and NG2 glia can be reprogrammed *in vitro* and *in vivo* to generate functional iNs by forced expression of neurogenic transcription factors (Heinrich et al, PLoS Biol, 2010; Nat Protoc, 2011; Stem Cell Reports, 2014; Gascon et al, Cell Stem Cell, 2016). It remained a crucial question whether iNs are endowed with the capability to promote functional recovery in pathological contexts. We have recently adressed this question in the context of Mesial Temporal Lobe Epilepsy, the most common form of drug-resistant epilepsy. Using a mouse model of epilepsy, we showed that reactive glia can be converted into GABAergic neurons (typically lost in epilepsy) that show a considerable level of synaptic integration within the epileptic brain and reduce seizures (Lentini et al, Cell Stem Cell, 2021).

While glia-to-neuron reprogramming emerges as neuron-replacement strategy, our understanding of this process is very limited. It is a fundamental question to unravel how transcription factors impose on glial cells a new molecular program reassigning the novel neuronal identity. The aim of this project is to decipher the molecular mechanisms underlying glia reprogramming into GABAergic iNs. During his/her internship, the Master student will join forces to study these exciting questions using techniques such as cell culture, immunostaining, confocal microscopy, pharmacological manipulations, time-lapse video microscopy and analysis of single-cell RNA sequencing datasets.

Please send your proposal to marion.richard@univ-lyon1.fr for publication on the Master of Neuroscience website.

3-5 recent publications :

Studer F, Jarre G, Pouyatos B, Nemoz C, Brauer-Krisch E, Muzelle C, Serduc R, **Heinrich C***, and Depaulis A*. Aberrant neuronal connectivity in the cortex drives generation of seizures in rat Absence Epilepsy. **Brain, 2022,** 145(6):1978-1991 - *These authors equally contributed to this work

Lentini C, d'Orange M, Marichal N, Trottmann MM, Vignoles R, Foucault L, Verrier C, Massera C, Raineteau O, Conzelmann KK, Rival-Gervier S, Depaulis A, Berninger B, and **Heinrich C**. Reprogramming reactive glia into interneurons reduces chronic seizure activity in a mouse model of mesial temporal lobe epilepsy. **Cell Stem Cell, 2021,** 28(12):2104-2121.e10

Vignoles R, Lentini C, d'Orange M, and **Heinrich C**. Direct Lineage Reprogramming for Brain Repair: Breakthroughs and Challenges. **Trends in Molecular Medicine**, **2019,** 25 (10): 897-914

Gascón S, Murenu E, Masserdotti G, Ortega F, Russo GL, Petrik D, Deshpande A, **Heinrich C**, Karow M, Robertson SP, Schroeder T, Beckers J, Irmler M, Berndt C, Angeli JP, Conrad M, Berninger B and Götz M. Identification and successful negotiation of a metabolic checkpoint in direct neuronal reprogramming. **Cell Stem Cell, 2016**, 18 (3): 396-409

Heinrich C, Spagnoli F and Berninger B. In vivo reprogramming for tissue repair. **Nature Cell Biology**, **2015**, 17 (3): 204-211

Please send your proposal to marion.richard@univ-lyon1.fr for publication on the Master of Neuroscience website.