



MASTER 2 Neurosciences Fondamentales et Cliniques

Internship proposal 2021-2022

(internship from January to end of May 2022)

Host laboratory: Centre Recherche Neuroscience Lyon (CRNL), Centre Hospitalier Le Vinatier, NEUROCAMBUS Michel Jovet, 95 boulevard Pinel - 69675 BRON Cedex, FRANCE

Host team : SLEEP team (<https://lyonsleeplab.cnrs.fr/>)

Internship supervisors : Dr FORT Patrice, Research Director CNRS, patrice.fort@univ-lyon1.fr

Project title : Deciphering the neuronal networks involved in the expression of paradoxical sleep by using the powerful genetic TRAP method in mice.

Project summary : REM sleep behavior disorder (RBD) is a parasomnia characterized by loss of muscle atonia during paradoxical sleep (PS). We recently demonstrated in rats that the genetic inactivation of glutamate neurons within the pontine sublaterodorsal nucleus (SLD) is sufficient to reproduce RBD symptoms. The other major cue from this work is that SLD may generate muscle atonia but not PS *itself* which is still present, in contrast to the consensual hypothesis suggesting its crucial role in generating this state. In that context, our ongoing goal is to decrypt neural networks recruited during PS to identify its generator timely controlling the matched occurrence of muscle atonia, REMs, cortical and hippocampal activation. We use TRAP2-Red-cFos transgenic mice in which glutamate PS-on SLD neurons can be selectively "TRAPed" (induction of tamoxifen-dependent expression of *cre*-recombinase and reporter protein dtTomato). Thanks to pertinent viral tools (*cre*-dependent AAVs for opto-chemogenetics, retro AAVs for connectomics, AAV-diphtheria for targeted lesion), we will manipulate SLD TRAPed neurons to confirm their functional role in PS in freely-moving mice prepared for polysomnography. In a bottom-up strategy, we will then circumscribe among brain inputs targeting TRAPed neurons in SLD, those involved in PS induction and expression.

3-5 recent publications :

- 1) Valencia Garcia S, Libourel PA, Lazarus M, Grassi D, Luppi PH, Fort P. Genetic inactivation of glutamate neurons in the rat sublaterodorsal tegmental nucleus recapitulates REM sleep behaviour disorder, *Brain*, 2017, **140** :414–428.
- 2) Valencia Garcia S, Brischoux F, Clément O, Libourel P-A, Arthaud S, Luppi PH, Fort P. Ventromedial medulla inhibitory neuron inactivation induces REM sleep without atonia and REM sleep behavior disorder. *Nature Com*, 2018, **9**: 504-14.
- 3) Lee HS, Yamazaki R, Wang D, Arthaud S, Fort P et coll. Targeted recombination in active populations as a new mouse genetic model to study sleep-active neuronal populations: demonstration that Lhx6+ neurons in the ventral zona incerta are activated during paradoxical sleep hypersomnia. *J Sleep Res*, 2020, **29**:e12976.
- 4) Maciel R, Yamazaki R, Wang D, De Laet A, Cabrera S, Agnorelli C, Arthaud S, Libourel Pa, Fort P et coll. Is REM sleep a paradoxical state? Different neurons are activated in the cingulate cortices and the claustrum during wakefulness and paradoxical sleep hypersomnia. *Biochem Pharmacol*, 2021, 14514.
- 5) Risa Yamazaki, Dianru Wang, Anna De Laet, Renato Maciel, Claudio Agnorelli, Sébastien Cabrera, Sébastien Arthaud, Paul-Antoine Libourel, Patrice Fort et coll. Granule cells in the infrapyramidal blade of the dentate gyrus are activated during paradoxical (REM) sleep hypersomnia but not during wakefulness: a study using TRAP mice. *Sleep*. 2021, **10**:zsab173.

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