



## Master 2 research internship (1<sup>st</sup> semester 2022)

### Project: Epigenetic reprogramming of brain function by opioids

Opioids, such as morphine or heroin, are powerful drugs that have been used for centuries for hedonic or medicinal purposes. While they remain the most efficient painkillers in modern medicine, their chronic use is also associated in susceptible individuals with the development of tolerance, physical dependence, and addiction.

These deleterious effects, which progressively emerge during chronic consumption, are associated with profound reprogramming of brain function and behavioral responses, which frequently persist throughout life.

Recently, epigenetic mechanisms have been proposed as a form of genomic memory that may help explain such prolonged consequences. In this context, the goal of this master 2 internship will be to contribute to our group's current work, which aims at understanding the role of epigenetic mechanisms in opioid addiction.

The project will focus on DNA methylation, a major epigenetic mark that contributes to the structural and functional organization of the genome. Our goal will be to test and compare 2 strategies to achieve the conditional knockout of the 2 main enzymes responsible in the adult mouse brain for methylating the DNA, the methyltransferases Dnmt1 and Dnmt3a:

- 1) A first viral strategy based on the Crispr/Cas9 system;
- 2) A second strategy based on the use of genetically modified mice and the inducible CreERT2-lox system.

In the futur, results from this project will allow us to characterize the role of Dnmt enzymes, and associated DNA methylation plasticity, in behavioral models of opioid addiction.

### Training

We are looking for a motivated student enrolled in a master degree in neuroscience or molecular biology, with an interest in bioinformatics, and a desire to follow-up with a PhD.

### Location

Institut de Neurosciences Cellulaires et Intégratives (INCI CNRS UPR 3212)  
8 allée du Général Rouvillois, 67084 Strasbourg, France

### Supervisor

Pierre-Eric Lutz, [pierreeric.lutz@gmail.com](mailto:pierreeric.lutz@gmail.com) – website: [inci-en.u-strasbg.fr/?page\\_id=1969](http://inci-en.u-strasbg.fr/?page_id=1969)

### References

- 1) Non-CG methylation and multiple epigenetic layers associate child abuse with immune and small GTPase dysregulation. Lutz P-E, Chay M-A, Pacis A, Chen GG, Aouabed Z, Maffioletti E, Theroux J-F, Grenier J-G, Yang J, Aguirre M, Ernst C, Redensek R, van Kempen L, Yalcin I, Kwan T, Mechawar N, Pastinen T, Turecki G. **Nature Communications** (2020) 12(1):1132
- 2) Increased functional coupling of the mu opioid receptor in the anterior insula of depressed individuals. Lutz P-E, Almeida D, Filliol D, Jollant F, Kieffer BL, Turecki G. **Neuropsychopharmacology** (2021) 46(5):920-927
- 3) Focusing on the opioid system for addiction biomarker discovery. Belzeaux R, Lalanne T, Kieffer BL, Lutz P-E **Trends Molecular Medicine** (2018) 4(2):206-220
- 4) Epigenetic regulation of the kappa opioid receptor by child abuse. Lutz P-E, Gross JA, Dhir SK, Maussion G, Yang J, Bramouille A, Meaney MJ, Turecki G. **Biological Psychiatry** (2018) 84(10):751-761

