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

Internship Proposal
Academic Year 2019-2020

1. Host team :

Research Unit (e.g. Department or Institute) : Institut du Fer à Moulin
Research Unit Director : Jean Antoine GIRAULT
Research Team Director : Jean Christophe PONCER
Team name : Plasticity in Cortical Networks & Epilepsy

Address : 17 rue du Fer à Moulin, 75005 Paris

Supervisor of the Research Intern for this project : Jean Christophe PONCER
Telephone : 01 45 87 61 18
E-mail : jean-christophe.poncer@inserm.fr

2. Internship project title:

Targeting cation-chloride cotransporters in Rett Syndrome

3. Internship Description :

Rett syndrome (RTT) is a rare and severe neuropsychiatric disorder and a major cause of mental retardation in females. It is most often associated with mutations in Mecp2, a key epigenetic factor in CNS development and function. Animal models show cellular and synaptic alterations affecting both glutamatergic and GABAergic signaling. However, the underlying mechanism remain unknown and therapeutic options are missing.

Several recent arguments support that alterations in cation/chloride co-transporter (CCC) expression may be causal in RTT. Thus, KCC2 protein levels are reduced in the cerebrospinal fluid of symptomatic RTT patients and in IPS-derived neurons RTT patients. In addition, MeCP2 directly regulates KCC2 expression through interference with other transcription factors. These observations lead us to propose the **main hypothesis that down-regulation of KCC2 expression in MeCP2-deficient neurons may be central in engaging synaptic alterations that underlie some of the defects associated with RTT phenotype**. Compensating for these alterations may then prove beneficial and rescue some synaptic and cognitive functions.

In support of this hypothesis, we have recently obtained evidence that downregulation of KCC2 not only influences GABA signaling through altered chloride homeostasis but also aggregates in dendritic spines and plays a major role in spine maintenance as well as excitatory synaptic function and long term plasticity. In addition, we have shown that chronic KCC2 down-regulation in the dorsal hippocampus also leads to profound alterations of cognitive performances in contextual memory tasks, again similar to those reported in RTT mice models. Our general concept is therefore that KCC2 down-regulation in RTT compromises both GABAergic and glutamatergic transmission through chloride transport-

dependent and independent mechanisms, respectively, and therefore offers converging opportunities for therapeutic intervention.

The proposed project aims at testing this hypothesis and evaluate the potential benefits of acting on KCC2 function expression to rescue RTT phenotype in both *in vitro* and *in vivo* models. For this, we will combine mouse genetics, biochemistry, *in vivo* electrophysiological and behavioral approaches as well as human induced neural cells (iNs) to explore the contribution of altered chloride transporter expression in synaptic and behavioral deficits associated with RTT. Together our experiments may then pave the way towards new therapeutic strategies for treatment of Rett patients, by targeting converging pathways with other neurological and psychiatric disorders.

Recent references from the lab related to the project

- Goutierre M et al (2019) KCC2 regulates neuronal excitability and hippocampal activity via interaction with Task-3 channels. ***Cell Rep*** *(in press)*
- Heubl M et al (2017) GABA(A) receptor dependent synaptic inhibition rapidly tunes KCC2 activity via the Cl(-)-sensitive WNK1 kinase. ***Nat Commun.*** *8:1776*
- Chevy Q et al (2015) KCC2 Gates Activity-Driven AMPA Receptor Traffic through Cofilin Phosphorylation. ***J Neurosci*** *35:15772-86*
- Gauvain G et al (2011) The neuronal K-Cl cotransporter KCC2 influences postsynaptic AMPA receptor content and lateral diffusion in dendritic spines. ***PNAS*** *108:15474-9*