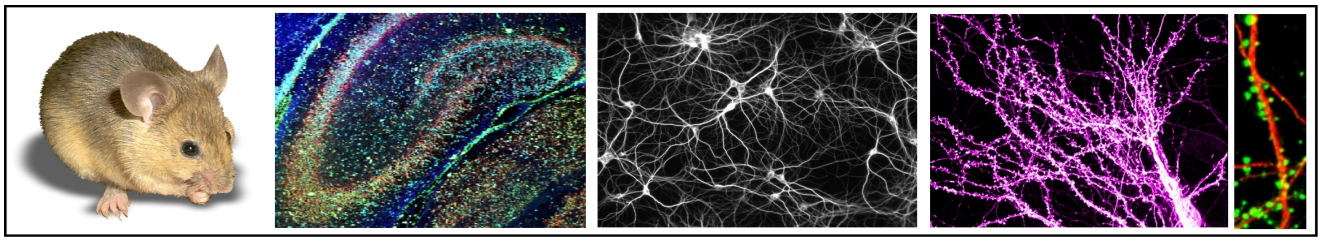

PhD fellowship (M/F): Fragile X missense mutation in glutamate receptor trafficking

Duration 36 months / *Starting date: Around mid-September 2021*

Institut de Pharmacologie Moléculaire et Cellulaire – UMR 7275 CNRS – Sophia-Antipolis

Autism Spectrum Disorders (ASD) and Intellectual Disability (ID) affect millions of individuals worldwide and represent a major health and economic burden. Both disorders are characterized by compromised brain and cognitive functions and impaired social behaviours, representing a leading cause of handicap in children. Fragile X syndrome (FXS) is the most common inherited form of ID and the first-described monogenic cause of autism (**1**). This neurodevelopmental disorder results from mutations within the Fragile X Mental Retardation *FMR1* gene leading to the lack of function of its protein product, the RNA-binding protein FMRP.

We recently demonstrated that FMRP is sumoylated in vivo and that its activity-dependent sumoylation is critical to the neuronal function (**2**). Sumoylation is the covalent conjugation of the Small Ubiquitin-like MOdifier (SUMO) protein to lysine residues of target proteins. It modulates the dynamics of multi-protein complexes by preventing and/or promoting protein-protein interactions, which is essential to establish a functional neuronal network (**3**).

Several FXS missense mutations lead to amino-acid changes that are close to the active SUMO sites of FMRP. This raises the exciting possibility that these mutations directly affect the regulation of FMRP sumoylation, impacting its function, and consequently leading to FXS. In the lab, we focused on the recurrent FXS R138Q mutation, which is located just 8 residues away from the main active sumoylation site of FMRP. We generated a Knock-in mouse model expressing the FXS R138Q mutation in FMRP (R138Q-KI) to study its pathophysiological impact. We measured an increase in the density of dendritic spines and critical alterations in the surface levels of glutamatergic AMPA receptors (AMPAR) leading to significant synaptic plasticity defects and to impaired cognitive and social behaviours (**10**). Therefore, the selected student will use state-of-the-art biochemical and cell-imaging techniques to unravel the molecular basis of these receptor trafficking defects. To achieve this aim, the PhD student will work on two complementary tasks to:

1- Characterize the activity-dependent AMPA receptor trafficking defects in R138Q-KI neurons.
2- Explore the efficacy of pharmacological drugs to restore the AMPA receptor trafficking defects in R138Q-KI neurons.

This project is completely innovative and we are uniquely placed to undertake the work proposed since we have a clear expertise in receptor trafficking (**4-6**), cell imaging (**2, 6-10**) and have a unique access to the FXS KI model.

Publications related to the project:

1- Darnell J et al. ***Nature Neuroscience*** *16:1530 (2013).*
2- Khayachi A., Gwizdek C., et al. ***Nature Communications*** *9:757 (2018).*
3- Schorova L. & Martin S. ***Frontiers in Synaptic Neuroscience*** *8:9 (2016).*
4- Martin S et al. ***Embo Journal*** *23:4749 (2004)*
5- Martin S et al. ***Nature*** *447:321 (2007)*
6- Martin S et al. ***J Biol Chem*** *283:36435 (2008)*
7- Cassé F. & Martin S. ***Frontiers in Cell Neuroscience*** *9:367 (2015)*
8- Loriol C. et al. ***Nature Communications*** *5:5113 (2014)*
9- Schorova L. et al. ***Cellular & Molecular Life Sciences*** *76:3019 (2019)*
10- Prieto M., Folci A., et al. ***Nature Communications*** *12:1557 (2021)*

Contact: martin@ipmc.cnrs.fr

Application *via*: https://bit.ly/3dwLrAV