INSTITUT DE PHARMACOLOGIE MOLÉCULAIRE ET CELLULAIRE

IPMC CNRS UMR7275 - Univ. Côte d'Azur
660 Route des Lucioles - Sophia Antipolis
06560 Valbonne – France
http://www.ipmc.cnrs.fr

PhD Fellowship

Rescue of $Na_V1.2$/*SCN2A* sodium channel in neurodevelopmental disorders

A 3-year PhD fellowship is available starting from 01/10/2021, funded by the Laboratory of Excellence "Ion Channel Science and Therapeutics" (LabEx ICST).

- Objectives. Voltage-gated Na^+ channels (NaV) are essential for generation and propagation of action potentials (APs), and mutations of the $Na_V1.2$ isoform (*SCN2A* gene) cause neurodevelopmental disorders with a remarkably large clinical spectrum. In particular, numerous $Na_V1.2$ mutations cause severe late infantile-childhood neurodevelopmental disorders (LICND) with onset between 3 months and few years of age: a) developmental and epileptic encephalopathies (DEE) with various degrees of autism spectrum disorder (ASD) and intellectual disability (ID) b) severe ASD without epilepsy, c) severe ID without epilepsy & d) schizophrenia without epilepsy. Notably, recent large-scale human genetic studies have indicated that $Na_V1.2$ mutations are among those that show the strongest association with ASD. It has been proposed that LICND mutations induce reduction of $Na_V1.2$ function, but mechanisms linking reduced $Na_V1.2$ function to clinical phenotypes are not completely understood yet. In addition, we have identified a novel pathological mechanism for mutations causing LICND with severe ASD, leading to a larger loss of $Na_V1.2$ function. Importantly, there are no effective treatments for LICND and there are no $Na_V1.2$ enhancers available for increasing its function. We aim to: 1) develop and test drugs and strategies for counteracting reduced $Na_V1.2$ function (targeting also the novel mechanism that we identified), which could be used to treat severe LICND; 2) study pathological mechanisms and effects of treatments in vitro, *ex vivo* and *in vivo*.
- Methods. Electrophysiology and imaging in transfected cells and in brain slices (patch-clamp, sodium imaging) and in vivo (video-EEG), behavioral tests, pharmacological experiments and AAV viral delivery; use a new conditional gene targeted mouse model that we have generated (which carries a $Na_V1.2$ human mutation causing the new pathological mechanism that we have identified); use of cre-lox mouse models.

Our group has long lasting expertise in the study of the pathophysiology of ion channels and neuronal excitability, and all the tools and techniques are available. We collaborate with Michel de Waard (Nantes; development of $Na_V1.2$ activators) and Marco Canepari (Grenoble; sodium imaging). The student will be able to spend some time in Grenoble to learn a novel cutting edge sodium imaging technique for optically measuring Na^+ currents in neuronal sub-compartments. The group is part of the Institute of Molecular and Cellular Pharmacology (IPMC; www.ipmc.cnrs.fr), which is affiliated to the Université Côte d'Azur (UCA; http://univ-cotedazur.fr) and the French National Center for Scientific Research (CNRS; http://www.cnrs.fr/), and has state of the art shared research facilities; it is located in the technological park of Sophia Antipolis (https://www.sophia-antipolis.fr/en/), in the French Riviera, near Nice.

A pre-selection will be made according to CV, letter of recommendation and results obtained in the Master program.
Salary according to French standards: around 1450 €/month (health insurance is paid).

Contact: **Massimo Mantegazza**, IPMC, CNRS and Université Côte d'Azur, 660 Route des Lucioles, 06560 Valbonne-Sophia Antipolis, France mantegazza@ipmc.cnrs.fr Tel.+33 493953425

Selected references

- Mantegazza M., Cestèle S and Catterall W.A. (2021) Sodium Channelopathies of Skeletal Muscle and Brain. *Physiological Reviews*. https://doi.org/10.1152/physrev.00025.2020
- Chever O. et al. (2020) GABAergic neurons and $Na_V1.1$ channel hyperactivity: a novel neocortex-specific mechanism of Cortical Spreading Depression. bioRxiv 2020.03.14.991158; Preprint. https://doi.org/10.1101/2020.03.14.991158
- Lena I. and Mantegazza M. (2019) Nav1.2 haploinsufficiency in Scn2a knock-out mice causes an autistic-like phenotype attenuated with age. *Scientific Reports 9(1):12886*. https://doi.org/10.1038/s41598-019-49392-7
- Salgueiro-Pereira et al. (2019) A two-hit story: seizures and genetic mutation interaction sets phenotype severity in *SCN1A* epilepsies. *Neurobiology of Disease* 125:31-44. https://www.ncbi.nlm.nih.gov/pubmed/30659983
- Terragni B. et al. (2018) Post-translational dysfunctions in channelopathies of the nervous system. *Neuropharmacology* 132:31-42. *https://www.ncbi.nlm.nih.gov/pubmed/28571716*
- Mantegazza M. et al. (2010) Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. *Lancet Neurology*. 9(4):413-424. Review. https://www.ncbi.nlm.nih.gov/pubmed/20298965