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

Mechanisms of neuronal hyperexcitablity and therapeutic approaches in mouse models of the epileptic encephalopathy Dravet syndrome

A 3-year PhD fellowship is available starting from 01/06/2021, funded by the European Joint Program on Rare Diseases SCN1A-UP! project (https://www.ejprarediseases.org/funded-projects-2020/) including five European laboratories.

- Objectives. Dravet syndrome (DS) is a devastating encephalopathy characterized by drug-resistant epileptic seizures and cognitive deficits, caused by loss-of-function mutations of the *SCN1A* gene, encoding the main Na^+ channel of GABAergic neurons ($Na_V1.1$), which lead to widespread disinhibition of neuronal networks in mouse models that recapitulate DS phenotype. Anti-epileptic drugs are only partially effective against seizures and not against other symptoms. An effective disease-preventing or -modifying treatment for DS will most likely need a polytherapy with different approaches and drugs. The overall objectives of the project are: 1) to better understand pathological mechanisms in mouse models, in particular modifications of different signaling pathways leading to further pathological modifications in neuronal networks (pathological remodeling). 2) to develop more effective treatments for DS by targeting directly the initial genetic dysfunction, SCN1A loss-of-function, as well as pathological remodeling.

- Methods. Experimentation with mice, in vivo and ex vivo, by electrophysiological recordings (video-EEG and depth electrode recordings in vivo; patch-clamp recordings in brain slices), behavioral tests and AAV viral delivery, immunohistochemistry and western blot. Techniques for manipulating neuronal activity in vivo (optogenetics and/or chemogenetics) could be used for testing specific hypothesis.

Our group has long lasting expertise in the development and study of Dravet syndrome models, and all the tools and techniques are routinely used. 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 www.ipmc.cnrs.fr/?page=mantegazza&lang=uk

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

- Mantegazza M. and Broccoli V. (2019) *SCN1A*/$Na_V1.1$ channelopathies: mechanisms in expression systems, animal models and human iPSCs models. *Epilepsia 60(S3):S25-S38*. Invited review. https://doi.org/10.1111/epi.14700

- 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

- Hedrich U.B.S, et al. (2014) Impaired action potential initiation in GABAergic interneurons causes hyperexcitable networks in an epileptic mouse model carrying a human $Na_V1.1$ mutation. *Journal of Neuroscience* 35(45):14874-14889. *https://www.ncbi.nlm.nih.gov/pubmed/25378155*