AIX-MARSEILLE UNIVERSITE
ECOLE DOCTORALE DES SCIENCES DE LA VIE ET DE LA SANTE – ED62

PROPOSITION SUJET DE THESE

Concours d'attribution des Contrats Doctoraux 2019 – 2022
A renvoyer impérativement **avant le 2 mars 2019** par courriel au format **PDF** à
edsvs-direction@univ-amu.fr

1. Choix du sous-jury (vous ne pouvez cocher qu'une seule case) :

☐ JURY 3 – Neurosciences (Neurobiologie cellulaire – Neurosciences Cognitives et Comportementales – Neuroimagerie – Neurosciences Computationnelles).

Laboratoire	
Nom et N° :	Centre de Génétique Médicale de Marseille - MMG - U1251
Adresse :	Faculté de Médecine de La Timone
	27 bd Jean Moulin - 13005 Marseille
Directeur :	Nicolas Lévy
Website :	www.marseille-medical-genetics.org
Nom de l'équipe	Neurogénétique Humaine
Responsable équipe :	Laurent Villard
Nombre d'HDR dans l'équipe	4
Directeur de Thèse	
Nom :	VILLARD
Prénom :	Laurent
Grade :	DR2
Courriel :	laurent.villard@univ-amu.fr
Téléphone :	04 91 32 49 03
HDR obtenue le :	1997
Nom du Codirecteur éventuel :	/
Nom(s) du(es) doctorant(s) en cours d'encadrement :	/
Nom et date de soutenance du précédent doctorant encadré :	Mlle Affef ABIDI - soutenue le 25 mars 2016
Publication du Doctorant :	• Milh et al. Am J Med Genet A. 2015, 167A(10):2314-8. • Abidi et al. Neurobiol Dis. 2015, 80:80-92. • Abidi et al. Eur J Hum Genet. 2016, 24(4):615-8. • Di Meglio et al. Epilepsia. 2015, 56(12):1931-40. • Devaux J, Abidi A. et al. Epilepsia. 2016, 57(5):e87-93. • Villeneuve N, Abidi A. et al. Eur J Paediatr Neurol. 2017, 21(5):783-786.

PROJET DE THESE

Characterization of a mouse model for Ohtahara syndrome and pharmacological interventions.

During the last few years, our laboratory has built a cohort of 900 patients with early onset epileptic encephalopathies including 103 patients with the most severe form of neonatal epilepsy (Ohtahara syndrome). We have shown that pathogenic variants in the KCNQ2 gene, encoding the Kv7.2 potassium channel subunit, are the major cause of Ohtahara syndrome. We have engineered the first Ohtahara syndrome mouse model by knocking-in a variant present in one typical Ohtahara patient from our cohort. The preliminary characterization of the knock-in animals reveals that they present severe generalized seizures, abnormal learning and motor activity and a high rate of premature death (25%, similar as the one seen for human patients). Similar to what occurs in many patients, seizures are no longer observed in older animals (>P30) and the Kncq2 mutation does not lead to macroscopic brain alterations (unpublished). We also produced induced pluripotent stem cells (iPS) from Ohtahara patients and are able to generated cortical neurons from these cells. We want to use these models (mice and human neurons) to elucidate pathophysiological mechanisms and test pharmacological hypotheses (the patients are resistant to existing anti-epileptic treatments). Upon completion, this project must provide a better understanding of the molecular and cellular mechanisms causing one of the most severe epilepsy phenotype and will generate new data to develop therapeutic approaches for this devastating and currently intractable condition.
We will characterize the motor and cognitive phenotypes of the knock-in model using several tests routinely used in our laboratory, study brain morphology and tissue organization. We will also perform in vivo electrophysiology (EEG) and study RNA/protein expression using omics analyses at different stages of the disease. Finally, we will perform pharmacological interventions in the mouse model to try to prevent seizures.
Our group has been studying mouse models for neurological diseases for the last 15 years. We are familiar with motor and cognitive phenotyping and pre-clinical research using pharmacology or gene therapy. We are also able to perform omics analysis with bioinformatics support. Authorizations from ad-hoc committees have been obtained for our projects.
We are looking for an enthusiastic PhD candidate holding a master degree in neurosciences or molecular/human genetics. He/she must be willing to work with rodents. He/she must be interested in epilepsy, genetic diseases and pre-clinical research, and keen to interact inside and outside our team to perform collaborative work. Multidisciplinary skills inside our group (neurophysiology, molecular genetics, clinical neurosciences) or in collaborators' (high throughput pharmacological screening, proteomics) will ensure an adequate supervision for the various aspects of the project.