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 1 – Biologie Cellulaire (Développement – Immunologie – Biologie Végétale – Physiologie).~~

~~- JURY 2 – Microbiologie – Génomique (Bioinformatique – Biochimie Structurale – Biochimie).~~

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

~~- JURY 4 – Biologie Santé (Oncologie – Cardiovasculaire – Santé Publique – Maladies Infectieuses – Génétique).~~

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Nom et date de soutenance du précédent doctorant encadré :	Catia Plaminha – 13/06/2018
Publication du Doctorant :	1. Falace A*, Palminha C* et al. FLNA promotes dendritogenesis and synaptogenesis through the ARHGAP24/RAC1 pathway (in preparation).

Résumé du projet de thèse :

Exploring the role of FLNA in cortical development and function

Background : Nodular heterotopia (NH) is highly associated with epilepsy, intellectual disability and, occasionally, with ASD. Mutations in the actin-crosslinking protein FLNA are the main cause of NH. In patients, no correlation between the extent of NH and epilepsy severity was found suggesting that aberrant cortical circuitry rather than nodules is responsible of the disease. Our recent investigations showing that FlnA regulates the morphological and functional maturation of pyramidal neurons support this hypothesis. Moreover, we found that FlnA exerts its role by modulating the activity of the RAC1/ARF6 complex, which is involved in membrane trafficking.

Our main objectives will be to: 1) determine disclose the cell autonomous role of FlnA in synaptic integration and plasticity by using the conditional KO mice that we recently generated in conjunction with Cre driver lines/ electroporation. 2) investigate how *Flna* KO neurons are connected with other brain regions at the synaptic level use a viral tracers based approach. 3) decipher the role of FLNA in network excitability by electrophysiology and by calcium imaging.

Expected Results: 1) To disclose the impact of FLNA dysfunction on neuronal maturation and synaptogenesis; 2) To decode and provide a first connectivity map of *Flna* KO somatosensory cortex; 3) To assess the role of FLNA in the maintenance of excitatory and inhibitory balance.

Références:

1. Falace A*, Palminha C* et al. FLNA promotes dendritogenesis and synaptogenesis through the ARHGAP24/RAC1 pathway (in preparation).
2. Plantier V, Watrin F, Buhler E, Martineau FS, Sahu S, Manent JB, Bureau I, Represa A. Direct and Collateral Alterations of Functional Cortical Circuits in a Rat Model of Subcortical Band Heterotopia. *Cerebral Cortex*. 2018 Dec 7. doi: 10.1093/cercor/bhy307.
3. Guarnieri FC, et al. Disorders of neurogenesis and cortical development. Review. *Dialogues in Clinical Neuroscience*, 2018, 20 (4):255-266.
4. Falace A., Buhler E., Fadda M., Watrin F., Lippiello P., Pallesi-Pocachard E., Baldelli P., Benfenati F., Zara F., Represa A., Fassio A. and **Cardoso C**. TBC1D24 regulates neuronal migration and maturation through modulation of the ARF6-dependent pathway. *Proc. Natl. Acad. Sci. USA***.** 2014, 111 (6): 2337-2342.
5. Carabalona A. et al (2012) A glial origin for periventricular nodular heterotopia caused by impaired expression of FLNA. *Hum. Mol. Genet.* 21(5): 1004-17.