MASTER 2 Neurosciences Fondamentales et Cliniques
UCB Lyon 1, Lyon, France

Internship proposal 2020-2021
(internship from January to end of May 2021)

Host laboratory:
Institut NeuroMyoGene (INMG), dir. L. Schaeffer
Université Claude Bernard Lyon 1
Faculté de Médecine
8 Avenue Rockefeller
69008 LYON France

Host team :
Team: Autoantibodies and Synaptopathies, dir. J. HONNORAT
https://www.inmg.fr/

Internship supervisors :
NORAZ Nelly, CR1 Inserm. nelly.noraz@inserm.fr

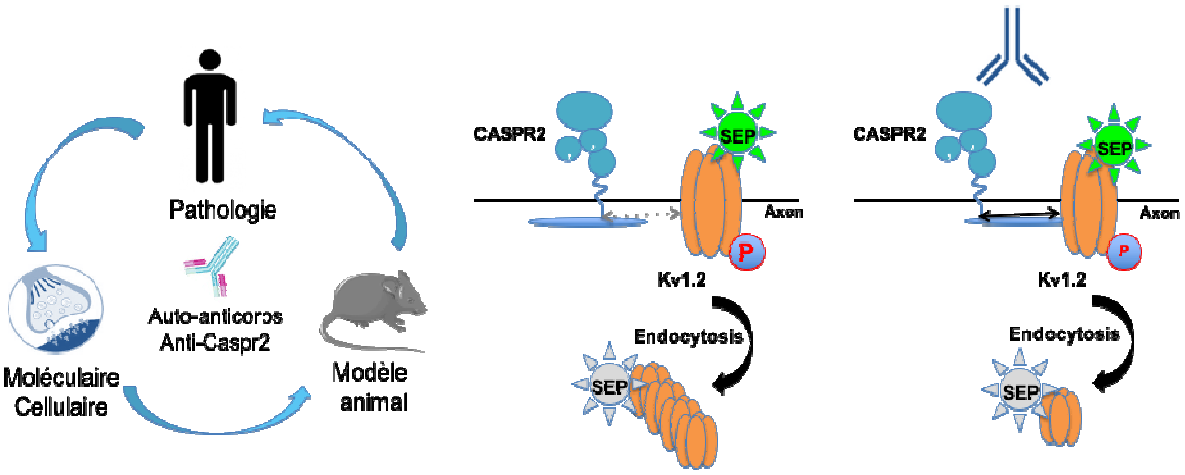
Project title :
Anti-CASPR2 autoantibodies in limbic encephalitis: impact on neuronal excitability through Kv1 potassium channel modulation

Project summary :

Autoantibodies (autoAbs) against CASPR2 (contactin-associated protein-like 2) are found in a subtype of limbic encephalitis (LE) involving men around 60 years of age with prevalent amnesia and temporal lobe epilepsy. Increasing evidence indicate that autoAbs have a direct pathological role in the disease -i.e. autoAb binding to its target protein disrupts its function-. We propose to use this powerful tool to better understand CASPR2 functions and to specify the role of CASPR2 Abs in the pathophysiology of LE.

Numerous data support the idea that CASPR2, by interfering with the activity of type 1 voltage-gated potassium channels (Kv1), is a modulator of neuronal excitability. In hippocampal neurons fully differentiated *in vitro*, CASPR2 is essentially expressed at the axonal membrane of inhibitory neurons which strikingly, express high levels of Kv1.2. Moreover, in regards to autoAb pathogenicity, a 24-hours incubation with CASPR2-Abs increase Kv1.2 expression and decrease Kv1.2 phosphorylation level, a potential cause for reduced Kv1.2 endocytosis rates. We therefore postulate that in the hippocampus, CASPR2 selectively modulates endocytosis rates of Kv1 channels in inhibitory neurons. In CASPR2 encephalitis patients, CASPR2 Abs may alter this function, which would lead to disinhibition and ultimately result in temporal lobe seizures and impaired memory functions. To test these hypotheses, first, changes in Kv1.2 membrane expression and level of phosphorylation will be assessed in mice expressing variable amounts of CASPR2. Second, to assess the impact of CASPR2 Abs on Kv1.2 expression and activity, autoAbs will be infused into the brain of

pHluorin SEP-Kv1.2 KI/CD65-tomato mice in order to selectively visualize the membrane pool of Kv1 and its endocytosis in inhibitory neurons. All analyses will be performed on acute hippocampal brain slices. The following methods will be used: brain slice preparation, biochemistry, optical microscopy (bi-photon & confocal), image analysis (ImageJ, ICI), electrophysiology.



3-5 recent publications :

(1) PINATEL D et al. 2015. Inhibitory axons are targeted in hippocampal cell culture by anti-Caspr2 autoantibodies associated with limbic encephalitis. Front Cell Neurosci. 9:265.

(2) JOUBERT B et al. 2016. Characterization of a subtype of autoimmune encephalitis with anti-contactin-associated protein-like 2 antibodies in the cerebrospinal fluid, prominent limbic symptoms, and seizures. JAMA Neurol. 73(9):1115-24.

(3) SAINT-MARTIN M et al. 2018. Contactin-associated protein-like 2, a protein of the neurexin family involved in several human diseases. Eur J Neurosci. 48(3):1906-1923. Review.

(4) VOGRIG A et al. 2019. Seizure specificities in patients with antibody-mediated autoimmune encephalitis. Epilepsia 60(8):1508-1525.

(5) SAINT-MARTIN M et al. 2019. Impact of anti-CASPR2 autoantibodies from patients with autoimmune encephalitis on CASPR2/TAG-1 interaction and Kv1 expression. Journal of Autoimmunity 103:102284.

Please send your proposal to emiliano.macaluso@univ-lyon1.fr and marion.richard@univ-lyon1.fr for publication on the website.