MASTER 2 Neurosciences Fondamentales et Cliniques

Internship proposal 2021-2022

(internship from January to end of May 2022)

Host laboratory: Institut NeuroMyoGene - INSERM U1217 - CNRS UMR5310 – Lyon 1 Claude Bernard University.
Host team : Synaptopathies and Autoantibodies (SynatAc). Faculté de médecine Rockeffeler, 8 avenue Rockeffeler 69008 Lyon. https://www.inmg.fr/honnorat/
Internship supervisors : Claire Meissirel, PhD, HDR , claire.meissirel@inserm.fr

Project title: Therapeutic potential of peptides targeting Aβ oligomers in Alzheimer's disease models.

Project summary :
Alzheimer's Disease (AD), the most common form of dementia, is characterized by a progressive decline in cognitive function. Soluble aggregates of amyloid beta peptide (Aβ), the Aβ oligomers (Aβo), are considered as an early trigger of the disease underlying synaptic damage and neurodegeneration. Recently, the team demonstrated that the vascular endothelial growth factor, VEGF, is able to rescue synaptic alterations induced by Aβo, limiting synapse loss in AD models. This beneficial action of VEGF could be impaired in AD because it accumulates in Aß plaques and also because Aβo specifically bind VEGF. Taking advantage of this specific interaction, we designed new peptide tools to selectively trap Aβo and restore synapse integrity. Our findings reveal that blocking peptides have the ability to prevent Aβ from associating in aggregates. We propose now to use these blocking peptides to study their impact on synapses and Aβ load in *in vitro* and *in vivo* AD models.

To determine blocking peptide bioactivity in AD models, we will use peptides conjugated to nanoparticles (NP) to limit their degradation and enhance their accumulation in brain tissue. Next, we will develop a suitable *in vitro* model to allow the progressive accumulation of Aβ aggregates in brain tissue, characteristic of AD pathological conditions. This challenging model with increased Aβ load will be obtained by culturing organotypic brain slices derived from the APP/PS1 mouse model of AD for weeks, and by chronically treating slices with peptide-NP conjugates. Next, we will investigate if treatments with blocking peptide-NP conjugates prevent synaptic alterations by monitoring changes in synapse density with bassoon and PSD95 immunoreactivity. Treatment impact on Aβ load will be characterized by quantifying Aβ levels using ELISA assays. In addition, pilot *in vivo* experiments will be performed thanks to the use of fluorescent NP to quantify the efficiency of nose to brain delivery of peptide-NP conjugates using fluorescent brain tomography.
This project will allow determining if this blocking strategy is able to prevent synaptic impairments due to toxic Aβo and to decrease Aβ burden in brain slices. It will also represent an *in vivo* proof of concept of *intranasal* peptide delivery.

3-5 recent publications :

1 – Martin et *al.* VEGF counteracts amyloid-β-induced synaptic dysfunction. **Cell Reports 2021** 35(6)
2 – Naudet et *al.* Transcriptional regulation of CRMP5 controls neurite outgrowth through Sox5. **Cell Mol Life Sci. 2018** *75:67-79.*
3 – De Rossi et *al.* A critical role for VEGF and VEGFR2 in NMDA receptor synaptic function and fear-related behavior **Molecular Psychiatry 2016** 21(12):1768-1780.
4 – Ravassard et *al.* REM sleep-dependent bidirectional regulation of hippocampal-based emotional memory and LTP. **Cereb Cortex 2016** 26(4):1488-500.

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