**Master 2 internship project**

**Year 2024-2025**

**Laboratory/Institute:** Biosanté U1292 INSERM-CEA-UGA **Director:** Dr. A Andrieux

**Team:** MAB2 **Head of the team:** Dr N Alfaidy

**Name and status of the scientist in charge of the project:** Dr C. Marquette DR CEA

 **HDR: yes X no ☐**

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**Program of the Master’s degree in Biology:**

**☐** Microbiology, Infectious Diseases and Immunology **☐** Structural Biology of Pathogens

**☐** Physiology, Epigenetics, Differentiation, Cancer **X Neurosciences and Neurobiology**

**Title of the project: Impact of preeclampsia in vascular dementia development at long term**

Objectives : The objectives of the thesis project will be to characterize the involvement of the PROKs/PROKRs system in the development of neurological disorders associated with vascular dementia subsequent to preeclampsia, and to determine the potential therapeutic effects of PROKRs antagonists

Abstract: Preeclampsia (PE) is a specific complication of pregnancy characterized by proteinuria, hypertension, and hypoperfusion of the placenta, resulting in an increased risk of adverse fetal and maternal neonatal outcomes. Recent studies have shown that neurovascular functions are directly affected by circulating inflammatory and angiogenic factors in preeclamptic women. Moreover, the vascular consequences of preeclampsia do not appear to be limited to pregnancy: women with a history of preeclampsia are at increased risk for subsequent hypertension, cardiovascular disease, stroke, and diabetes. Clinical studies show that decades after a preeclamptic pregnancy, women are subject to cognitive failures related to symptoms of anxiety and depression affecting memory and concentration. MRI scans of PE women have revealed white matter lesions, like those observed in Alzheimer's disease and vascular dementia. Our team has demonstrated the direct involvement of pro-angiogenic and pro-inflammatory chemokines, called prokineticins, in the symptoms of preeclampsia. In fact, the treatment of preeclampsia model animals with pharmacological antagonists of prokineticin receptors prevents hypertension during gestation. Prokineticins belong to a recently discovered family of proteins that play a crucial role in several biological mechanisms, through their binding to their receptors, PROKR1 and PROKR2, G protein-coupled receptors. Disruption of the PROKs/PROKRs system is implicated in several complications and diseases such as stroke, Aβ toxicity in Alzheimer's disease, and PE. During preeclampsia, maternal hypertension and placental hypoperfusion seem to be mediated by the overexpression of certain inflammatory factors including PROKs, which is supported by the team's new results suggesting that PROK1 could be considered as a biomarker of PE..

Methods: These objectives will be addressed by investigating In vivo, neurological disorders and lesions will be evaluated and analyzed using MRI and cognitive tests, in mice that have had a PE gestation several months earlier, and with the evaluation of the potential therapeutic effect of treatment with PROKRs antagonists. Subsequent analysis of vascular tight junction proteins, and lesions will be performed in different brain regions by immunohistochemistry.

Relevant publications

Younes, et aL; Effects of Prokineticins on Cerebral Cell Function and Blood–Brain Barrier Permeability. IJMS, 2023, 24, no 20: 15428. https://doi.org/10.3390/ijms242015428.

Reynaud et al. Evidence-Based View of Safety and Effectiveness of Prokineticin Receptors Antagonists during Pregnancy. Biomedicines. 2021 Mar 17;9(3):309. doi:10.3390/biomedicines9030309.

Sergent et al. Sustained Endocrine Gland-Derived Vascular Endothelial Growth Factor Levels Beyond the First Trimester of Pregnancy Display Phenotypic and Functional Changes Associated With the Pathogenesis of Pregnancy-Induced Hypertension . Hypertension. 2016, 68(1):148 56. https://doi.org/10.1161/HYPERTENSIONAHA.116.07442.

Requested domains of expertise: The candidate will be a highly motivated M2 student, with a background in neuroscience/immunohistology/biochemistry/animal experimentation, and strong analytical and organisational skills. Certification for animal experimentation will be an additional asset to the application. He/she will be able to work both independently and as part of a collaborative team, with a good ability to interact with people. He/she will be interested in pursuing a PhD after the M2 course.

**Interested candidates** should send their CV, a cover letter (detailing motivation, relevant experiences and availability), and contact information for at least one reference to Christel Marquette: christel.marquette@cea.fr by October 15th, 2024.