

Supervisor(s):

Nadia Alfaidy, nadia.alfaidy-benharouga@cea.fr
Dr Tiphaine Barjat, Tiphaine.Barjat@chu-st-etienne.fr

Host laboratory:

Biologie et Biotechnologie pour la Santé
<https://biosante-lab.fr/en>

Title of the M2 research internship:

Informational value of prokineticins as biomarkers and targets of preeclampsia during pregnancy and beyond.

Project summary:

Preeclampsia (PE) is a significant pregnancy disorder, which genetic « mutation in the gene STOX1 » association has recently been reported. However, PE pathogenesis still lacks reliable biomarkers for prediction and for therapies. Beside its established adverse effects, long-term brain-associated pathologies have been recently reported in PE women. Using clinical and in vitro studies, we have recently identified the prokineticins (PROKs) as potential biomarkers and targets to treat PE. The objectives of the proposed PhD project are the following, i) to confirm the predictive value of PROKs in two large PE cohorts (600 patients/ 1200 time points), our cohort developed with the center of clinical investigation at Grenoble hospital and the cohort of a clinician Dr T. Barjat in our group (ANGIOpred), ii) to characterize the biological significance of PROKs using placental organoids in collaboration with Dr Xavier GIDROL at Biomics laboratory; iii) and to characterize using an in vivo genetic model of PE, the STOX1 model developed by our group, the effects of PROK antagonization (use of antagonists for PROKs receptors and the blocking developed monoclonal antibodies by our group) on the pregnancy outcome. As PROKs are also involved in the development of inflammatory-associated brain diseases, the project proposes to characterize their role in the brain of STOX1 mice and in PE patients during and beyond pregnancy (10-20 years later in PE women and 6-18 months later in mice). This part of the project will be conducted in collaboration with Dr J. Molet at clinattech, CEA Leti.

Keywords:

organoids, biomarker, preeclampsia

Relevant publications of the team:

Abi Nahed R, Reynaud D, Lemaitre N, Lartigue S, Roelants C, Vaiman D, Benharouga M, Cochet C, Filhol O, Alfaidy N. Protein kinase CK2 contributes to placental development: physiological and pathological implications. *J Mol Med.* 2020 Jan;98(1):123-

Alfaidy N, Brouillet S, Rajaraman G, Kalionis B, Hoffmann P, Barjat T, Benharouga M, Murthi P. The Emerging Role of the Prokineticins and Homeobox Genes in the Vascularization of the Placenta: Physiological and Pathological Aspects. *Front Physiol.* 2020 Nov 12;11:591850.

Alfaidy N, Baron C, Antoine Y, Reynaud D, Traboulsi W, Gueniffey A, Lamotte A, Melloul E, Dunand C, Villaret L, Bessonnat J, Mauroy C, Boueihl T, Coutton C, Martinez G, Hamamah S, Hoffmann P, Hennebicq S, Brouillet S. Prokineticin 1 is a new biomarker of human oocyte competence: expression and hormonal regulation throughout late folliculogenesis. *Biol Reprod.* 2019 Oct 25;101(4):832-841.

Alfaidy N, Chloé B, Yannick A, Déborah R, Wael T, Aurore G, Anna L, Eve M, Camille D, Laure V, Julien B, Charlotte M, Thomas B, Charles C, Guillaume M, Samir H, Pascale H, Sylviane H, Sophie B. Prokineticin 1 (PROK1) is a new biomarker of human oocyte competence: expression and hormonal regulation throughout late folliculogenesis. *Biol Reprod.* 2019

Reynaud D, Sergent F, Abi Nahed R, Brouillet S, Benharouga M, Alfaidy N. EG-VEGF Maintenance Over Early Gestation to Develop a Pregnancy-Induced Hypertensive Animal Model. *Methods in molecular biology.* 2018;1710:317-324.

Traboulsi W, Sergent F, Boufettal H, Brouillet S, Slim R, Hoffmann P, Benlahfid M, Zhou QY, Balboni G, Onnis V, Bolze PA, Salomon A, Sauthier P, Mallet F, Aboussaouira T, Feige JJ, Benharouga M, Alfaidy N. Antagonism of EG-VEGF Receptors as Targeted Therapy for Choriocarcinoma Progression In Vitro and In Vivo. *Clin Cancer Res.* 2017 Nov 15;23(22):7130-7140.

Sergent F, Hoffmann P, Brouillet S, Garnier V, Salomon A, Murthi P, Benharouga M, Feige JJ, Alfaidy N. 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 Jul;68(1):148.

Garnier V, Traboulsi W, Salomon A, Brouillet S, Fournier T, Winkler C, Desvergne B, Hoffmann P, Zhou QY, Congiu C, Onnis V, Benharouga M, Feige JJ, Alfaidy N. PPAR γ controls pregnancy outcome through activation of EG-VEGF: new insights into the mechanism of placental development. *Am J Physiol Endocrinol Metab.* 2015 Aug 15; 309(4): E357-69.