PhD offer :

Title: **Study of the implication of ion channels in endothelial mechanotransduction in response to shear stress in the context of Cerebral Cavernous Malformations using an in vitro endothelial model.**

Starting date: October 2023

Scientific context:

The endothelial cells lining the blood vessels are permanently subjected to extracellular mechanical signals generated at their apical side by the blood flow and at their basal side by the stiffness of the extracellular matrix. These mechanical signals are integrated into mechanotransduction pathways to generate appropriate cellular responses.

Our group is focused on better understanding the molecular bases of endothelial mechanotransduction and has identified a complex of proteins called CCM (Cerebral Cavernous Malformations) as a major orchestrator of these pathways. In humans, loss-of-function mutations on the CCM genes lead to the formation of cerebrovascular lesions in which the mutant endothelial cells invade the surrounding neuronal tissue to form stacks of dilated and hemorrhagic vessels. CCMs are present in 0.5% of the worldwide population. Mysteriously, these malformations form only in low blood flow vessels (venous-capillaries), but not in high shear stress which keeps the defects silent. The mechanisms responsible for this hypersensitivity to low flow are still to be discovered. Ion channels are the first molecules activated, within a few milliseconds, when endothelial cells are subjected to flow. We have shown that endothelial cells deficient in the CCM complex overexpress a set of ion channels which are otherwise known to control angiogenesis and vascular permeability. Our first results indicate a functional cross-talk between these channels and suggest that they could lie upstream of the mechanotransduction pathways controlled by the CCM complex.

Objectives and experimental approaches:

The goal of this PhD work will be to study the role of these channels during the onset of CCM defects. For that, mutant endothelial cells placed on substrates of different stiffness will be submitted to decreasing shear stress using microfluidic devices. Fluorescently tagged channels will be followed by live microscopy and their activity monitored using fused ion and ROS sensors. The cellular CCM defects will be followed in parallel to depict the role of each channel on the appearance of the diseased phenotype.

Keywords:

Mechanotransduction, endothelial cells, ion channels, microfluidics, biomaterials, live microscopy.

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Laboratories:
This PhD will be performed in IAB, Grenoble in the group led by Eva Faurobert in DYSAD team. This work will lie in the context of an international collaboration with Prs Hans Van Oosterwyck and Susana Rocha laboratories of the Department of Mechanical Engineering in KU Leuven in Belgium. The PhD student will perform research stays in these laboratories to complete his/her work. Moreover, the student will benefit from the microscopy facility at IAB (MicroCell) which is equipped with confocal microscopes for live and quantitative microscopy.

Requested knowledge and skills:
The project requires that the candidate has very good knowledge in cell biology, cell biomechanics, biomaterials and microscopy. Some skills acquired through internships in either of these domains will be appreciated.
The successful applicant must also have the willingness and enthusiasm to work independently while being able to communicate with the various scientists involved in this project whether they are biologists, engineers, or biomechanicians. The ideal candidate should be curious, and should enjoy solving problems and developing new technologies with personal creativity and innovation.

Publications from the lab:
- Vannier DR, Shapeti A, Chuffart F, Planus E, Manet S, Rivier P, Destaing O, Albiges-Rizo C, Van Oosterwyck H, **Faurobert E*.** CCM2 deficient endothelial cells undergo a ROCK dependent reprogramming into senescence associated secretory phenotype. Angiogenesis, 2021, Nov;24(4):843-860. doi: 10.1007/s10456-021-09809-2
- Manet S, Vannier D, Bouin AP, Lisowska J, Albiges-Rizo C and **Faurobert E**. Morphological study by immunofluorescence of cell-cell and cell-extracellular matrix adhesive defects in *in vitro* endothelial CCM model. Juxtacrine role of mutant extracellular matrix on wild-type endothelial cells. **Methods in Mol Biol** 2020;2152:401-416
- Lisowska J, Rödel CJ, Manet S, Miroshnikova YA, Boyault C, Planus E, De Mets R, Lee HH, Destaing O, Mertani H, Boulday G, Tournier−Lasserve E, Balland M, Abdelilah−Seyfried S, Albiges−Rizo C, **Faurobert E***. The CCM1−CCM2 complex controls complementary functions of ROCK1 and ROCK2 that are required for endothelial integrity. **J Cell Science** 2018 Aug 13;131(15).

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