CMD InnoCARE (Innovation pour les maladies CArdiovasculaires, métaboliques et REspiratoires)

Master 2 Internship proposal (2025-2026)

1 page maximum

Profile(s) linked to the project:
☒ Experimental Biology *(Recherche expérimentale)*
☐ Research and Biological Data Analysis *(Recherche et analyse de données biologiques)*
☐ Clinical Research *(Recherche clinique)*

Lab: Inserm U1087, l'institut du thorax

Team: Team 3

Name and position of the supervisor: Sarah Beck-Cormier

Email of the supervisor: sarah.beck@univ-nantes.fr

Title of the internship: **Understanding the role of mural cells in pathogenesis of Primary Familial Brain Calcification**

Summary of the internship proposal:

Primary Familial Brain Calcification (PFBC) is a rare genetic neurological disorder associated with psychiatric and motor symptoms and characterized by calcium phosphate deposits along microvessels, with an impact on quality of life. Despite the discovery of eight genes responsible for PFBC, current knowledge of the mechanisms by which cerebral calcification is induced remains limited, representing a major obstacle to the development of preventive and therapeutic strategies. Of the three genes most frequently mutated in patients, two, SLC20A2 and XPR1, allow the import (SLC20A2) or export (XPR1) of phosphate. We have been working on the Slc20a2-/- mice, known to be a valuable model for PFBC, for several years. Recently, we have generated a new mouse model carrying the *Xpr1* mutation most frequently found in PFBC patients (Xpr1-L145P). The student will characterize this model, by assessing and quantifying the progression of cerebral vascular calcification using microtomography and histomorphometry techniques. The environment of the neurovascular unit will also be evaluated by 3D immunofluorescence analyses on thick brain slices, labelling mural cells, endothelial cells, astrocytes, microglia and osteogenic cells. Phosphate homeostasis will be assessed by biochemical and hormonal assays and by gene and protein expression analyses (qPCR, western blot).
To understand the role of mural cells in pathogenesis of PFBC, we have generated two conditional KO mice allowing the invalidation of *Slc20a2* and *Xpr1* specifically in mural cells. Characterization of these models will be performed as described for the Xpr1-L145P model.
Finally, the student will also use primary culture of cerebral microvessels to analyze the effect of the absence of Slc20a2 and Xpr1 on Pi-induced calcification *in vitro*.
This work is part of a major project that aim to elucidate the molecular and cellular mechanisms involved in this rare and poorly understood genetic disease and to identify new therapeutic strategies.