Grenoble Alliance for Integrated Structural & Cell Biology

GRAL Research proposal for PhD projects

Institute and Group: BIG-BCI-BAL

Supervisor: Bailly Sabine Contact information: sabine.bailly@cea.fr

Co-Manager: Bouvard Claire Contact information: Claire.bouvard@cea.fr

Title of the thesis project: **Deciphering BMP9/10 signalling**

Keywords: BMP, signalling, mass spectrometry, assembly of protein complexes, rare vascular diseases,

Summary of the project:

Bone morphogenetic proteins (BMPs) belong to a large family of growth factors that play multiple roles. Ten years ago, our team identified BMP9 and BMP10 as key factors in vascular development. Indeed, we found that BMP9 and BMP10 bind with a very high affinity to the endothelial receptors ALK1 and BMPR2, which are present within the same signalling complex. Interestingly, these two receptors, when mutated, lead to two different rare vascular diseases (the Rendu-Osler disease and pulmonary arterial hypertension, respectively).

At the molecular level, BMPs bind to type 1 and 2 transmembrane receptors with serine/threonine kinase activity and induce the activation of transcription factors (Smads) by phosphorylation. However, there also exist non-Smad signalling pathways that remain to be characterized. This project aims to characterize for the first time Smad-independent BMP signalling pathways using mass spectrometry based proteomics. We will map phosphorylated proteins in response to BMP9 and BMP10 and we will characterize the different partners of the signalling complex. We will then study the status of the newly identified targets in mutated cells from patients and perform mechanistic and functional studies. The aim is to understand how mutations in this same pathway can lead to two different diseases in order to be able to propose new therapeutic approaches.