Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: IBS, SAGAG group

Supervisor: Romain Vivès **Phone:** 0457428508

Email: romain.vives@ibs.fr

Research project title: enzymatic regulation of cell-surface glycanic landscape in human disease

5 Keywords to describe the project: heparan sulfate, interactions, enzymes, structure/function relationships, disease

Description of the project (aims, experimental techniques, recommended background):

Many pathological conditions have been associated with an alteration of cell-surface glycan structure and function. This is particularly relevant for Heparan sulfate (HS), a complex polysaccharide that play key **regulatory roles** in most biological processes, including cell proliferation and development, inflammation and immune response, angiogenesis, tissue repair or **host-pathogen interaction** and **cancer**. HS elicits these activities through the binding and modulation of a wide array of proteins. These interactions depends on specific sulfations of the polysaccharide, which are tightly controlled during both its biosynthesis and
post-synthetically, through the action of extracellular enzymes. The objective of the project is to study the patterning of HS for one type of **sulfation** (6-sulfation), which is critical in many pathologies. For this, we will carry out the structural and functional characterization of the **enzymes** involved in the addition and removal of HS 6-sulfates. The project will thus include recombinant expression of proteins, enzymology, **structural biology** approaches (NMR, X-ray crystallography, SAXS), and functional assays (*in vitro*, *in cellulo*). This study should provide significant insights into this major regulation system of HS activities, and for the design of new HS-based **inhibitors** and therapeutical approaches.

Justification that the internship's subject fits with the general theme of GRAL:

HS is a major cell-surface receptor for many pathogens, including a wide variety of viruses (HIV, HSV, dengue, Ebola…). Understanding the mechanisms regulating HS structure and binding properties is thus fully in the frame of GRAL Axe 1: Host-pathogen interactions.

Relevant publications of the team:

El Masri R., Seffouh A., Lortat-Jacob H. and Vivès R.R. The "in and out" of glucosamine 6 O-sulfation: the 6th sense of heparan sulfate. *Glycoconjugate Journal* **34**, 285-298 (2017).

Heidari-Hamedani G., Vivès R.R., Seffouh A., Afratis N.A., Oosterhof A., T.H. van Kuppevelt T.H., N.K. Karamanos N.K., M. Metintas M., A. Hjerpe A., K. Dobra K. and Szatmári T. Syndecan-1 alters heparan sulfate composition and signaling pathways in malignant mesothelioma. *Cell Signal*. **27**, 2054-67 (2015).

Préchoux A., Halimi C., Simorre J.P., Lortat-Jacob H. and Laguri C. C5-epimerase and 2-O-sulfotransferase associate in vitro to generate contiguous epimerized and 2-O-sulfated heparan sulfate domains. *ACS ChemBiol* **10**, 1064-1071 (2015).