Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

Supervisor(s):
Romain Vivès, romain.vives@ibs.fr

Host laboratory:
IBS www.ibs.fr

Host group/team:
SAGAG / Vivès

Title of the M2 research internship:
Enzymatic alteration of cell-surface glycan landscape in human disease

Project summary:
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 how the expression and structure of HS can be modified under pathological conditions, through the combined activities of sulfatases and heparin lyases. For this, we will carry out the structural and functional characterization of key enzymes involved in the remodelling of HS. The project will thus include recombinant expression of proteins, enzymology, structural and biophysical characterization (MP, MALLS, SPR, BLI…), and functional studies (in vitro, in cellulo and in vivo, through our collaboration with the CEA IRIG-IMAC lab). 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.

Keywords:
heparan sulfate, enzyme, disease

Relevant publications of the team:

A. Kennett, S. Epple, G. van der Valk, I. Georgiou, E. Gout, R.R. Vivès, and Angela J. Russell. “Modified minimal-size fragments of Heparan Sulfate as inhibitors of endosulfatase-2 (Sulf-2)”. Chem commun. 60, 436-439 (2023).

C. Marques, J. Poças, C. Gomes, I. Faria-Ramos, C.A. Reis, R.R. Vivès and A. Magalhães . “Exostosin-like 2 and Exostosin-like 3 cellular balance dictates Heparan Sulfate biosynthesis and shapes cancer cell motility and invasion” J. Biol. Chem. 298, 102546 (2022).

R. El Masri*, A. Seffouh*, C. Roelants, I. Seffouh, E. Gout, J. Pérard, F. Dalonneau, K. Nishitsuji, F. Noborn, M. Nikpour, G. Larson, Y. Crétinon, M. Friedel-Arboleas, K. Uchimura, R. Daniel, H. Lortat-Jacob, O. Filhol and R.R. Vivès. “Extracellular endosulfatase Sulf-2 harbours a chondroitin/dermatan sulfate chain that modulates its enzyme activity” Cell reports, 38, 110516 (2022).

A. Seffouh, R. El Masri, O. Makshakova, E. Gout, Z.el Oula Hassoun J.P. Andrieu, H. Lortat-Jacob and R.R. Vivès. “Expression and purification of recombinant extracellular sulfatase HSulf-2 allows deciphering of enzyme sub-domain coordinated role for the binding and 6-O-desulfation of heparan sulfate”. Cellular and Molecular Life Sciences, 76, 1807-1819 (2019).

C. Debarnot, Y.R. Monneau, V. Roig-Zamboni, V. Delauzun, C. Le Narvor, E. Richard, J. Henault, A. Goulet, F. Fadel, R.R Vivès, B. Priem, D. Bonnaffé, H. Lortat-Jacob and Y. Bourne. “Structural insights into substrate binding and catalytic mechanism of human heparan sulfate D-glucuronyl C5 epimerase”. PNAS, 116, 6760-6765 (2019).