Funded PhD project in Integrated Structural & Cell Biology in Grenoble, France

Title of the PhD project:
Liver-Architecture: Multiscale 3D electron microscopy to decipher Liver Architecture

PhD supervisors:
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Host laboratory:
Chemistry and Biology of Metals laboratory, Met&Or team https://www.cbm-lab.fr/MetOr
Modélisation et Exploration des Matériaux (MEM), LEMMA team https://www.mem-lab.fr/LEMMA

Project summary:
The liver is a major organ for metabolism that possesses a very complex architecture. The liver is organized in hexagonal lobules with the hepatic vein at the center. Blood from both the portal vein and the hepatic artery at the periphery of the lobule mix together in very specific liver capillaries, named sinusoids. Blood then drains out of the lobule through the hepatic vein. Hepatocytes are arranged in hepatic cords separated by adjacent sinusoids. Besides, within each cord and between apical surfaces of adjacent hepatocytes, bile canaliculi are formed and constitute a network of micrometer-sized channels. Hepatocytes thus exhibit a unique polarity phenotype that is obtained thanks to finely orchestrated differentiation mechanisms that remain puzzling up to now.
In the last years, we have developed the use of 3D electron microscopy (3D-EM) for the study of biological samples. 3D-EM is revolutionizing ultrastructural imaging in many fields of biology. It comprises a set of techniques where a sample is cut slice by slice by different means, and each new surface is imaged in series. In SBF-SEM, sample surface is removed by an ultramicrotome, which allows robust access to large volumes but with a limited resolution, while FIB-SEM uses a gallium gun to remove sample surface enabling to reach nanometer range resolution. In Liver-Architecture, we want to take advantage of the combined use of both techniques, to explore hepatic architecture at different scales and in different contexts to answer key biological questions. The first objective tackled will be to obtain healthy adult mice liver architecture from a macroscopic view of the hepatic cord down to the reconstruction of the details of key regions such that the Disse space or bile canaliculi. The second objective will be to delve mice liver morphogenesis thanks to the analysis of liver from mice at different developmental stages. Finally, the third objective will be to explore the role of bone morphogenetic proteins, BMP9 and BMP10, in liver endothelium differentiation thanks to liver from knock out mice. Overall, the methodology developed in this project provides an original approach to explore ultrastructure from tissue to cell level.

Preferred skills: We are looking for a highly motivated student interested by a project at the interface between biology and physics. Knowledge in electron microscopy and image analysis would be an asset.

Student role: The PhD student will mainly focus on ultrastructural data acquisition and analysis. In parallel, discussions with experts in liver biology and angiogenesis will provide the support for the PhD student to efficiently perform data analysis and interpretation. During the first year, the PhD student will firstly be trained to FIB-SEM and data analysis. The recruited PhD student will benefit from the expertise of another PhD student currently setting-up the methodology for liver analysis. Then, the PhD student will implement the coupled SBF-SEM / FIB-SEM data acquisition workflow thanks to exchange with our collaborator at the University of Lausanne. Finally, the PhD student will acquire and analyze data from different mice liver to answer key questions about liver development. The PhD student will thus have to perform 3D reconstruction, segmentation, and finally biological analysis with the help of experts in liver biology.

Keywords:
Liver ultrastructure, Liver morphogenesis, 3D electron microscopy, Sinusoid, Stellate cells

Relevant publications of the team:

Morphological bases of phytoplankton energy management and physiological responses unveiled by 3D subcellular imaging. Uwizeye C, Decelle J, Jouneau PH, Flori S, Gallet B, Keck JB, Bo DD, Moriscot C, Seydoux C, Chevalier F, Schieber NL, Templin R, Allorent G, Courtois F, Curien G, Schwab Y, Schoehn G, Zeeman SC, Falconet D, Finazzi G. **Nat Commun.** 2021; 12(1):1049. doi: 10.1038/s41467-021-21314-0.
Canalicular domain structure and function in matrix-free hepatic spheroids. Sharma V, Shrivastava A, Gallet B, Karepina E, Charbonnier P, Chevallet M, Jouneau PH*, and Deniaud A*. **Biomaterials Science.** 2020; 8(1):485-496. DOI: 10.1039/c9bm01143a.
Bone Morphogenetic Protein 9 Is a Paracrine Factor Controlling Liver Sinusoidal Endothelial Cell Fenestration and Protecting Against Hepatic Fibrosis. Desroches-Castan A, Tillet E, Ricard N, Ouarné M, Mallet C, Belmudes L, Couté Y, Boillot O, Scoazec JY, Bailly S, Feige JJ. **Hepatology.** 2019; 70(4):1392-1408. doi: 10.1002/hep.30655.
Plastid thylakoid architecture optimizes photosynthesis in diatoms. Flori S, Jouneau PH, Bailleul B, Gallet B, Estrozi LF, Moriscot C, Bastien O, Eicke S, Schober A, Bártulos CR, Maréchal E, Kroth PG, Petroutsos D, Zeeman S, Breyton C, Schoehn G, Falconet D, Finazzi G. **Nat Commun.** 2017; 8:15885. doi: 10.1038/ncomms15885.

Grenoble Alliance for Integrated Structural & Cell Biology

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