Monitoring complex kidney pathophysiological processes in quantitative optical imaging in glomeruli-on-chip devices

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Project description :

In order to monitor numerous pathologies, it is essential to develop technologies to quantitatively probe biological processes from the molecular to the organism scale, at high temporal and spatial resolutions. This is particularly true for Rapidly Progressive GlomeurloNephritis (RPGN) or Focal Segmental GlomeruloSclerosis (FSGS), two major kidney pathologies, which cause the uncontrolled de-differenciation and migration of specialized cells relying on a complex molecular interplay between different local cues (PDGF, EGF,shear stress…), whose action can be mediated by the production of Reactive Oxygen Species (ROS). The lack of efficient quantitative assays, both for cell response in a multicellular environment and for ROS detection, has so far hindered the understanding of its mechanisms.

In this project, we propose to develop (i) biomimetic *in vitro* devices (or "organ-on-chip", see Figure 1A) in order mimic relevant patho-physiological environments, (ii) imaging methods using super-resolution approaches to probe membrane receptor organization, single lanthanide-based luminescent nanoparticles for ROS monitoring[1,2]., and deep 3D fluorescence imaging (Figure 1B) for cell adhesion characterization and filtering function probing. Based on these developments, combining high-content imaging and biomimetic devices, we expect to obtain a molecular and functional assay in order to decipher complex regulation mechanisms of RPGN/FSGS related migration[3].

[1] Abdesselem et al. Nanoscale (2017)
[2] Bouzigues et al. Chem. Biol. (2014)
[3] Lazareth et al. Nat. Comm. (2019)

The main objective of the internship will be the development of the long-term culture of human differentiated cells (PEC, podocytes and vascular endothelial cells) in microsystems in order to recapitulate a functional glomerulus, which will be the framework for further tests.
This experimental project is highly interdisciplinary and will involve notably in cell biology, microfluidics and optical microscopy. The trainee is expected (i) to address technical problems regarding culture microsystems to achieve physiological structures, (ii) to characterize the features of the glomerulus-on-chip, and (iii) to determine the multi-scale response (receptor organization, cell motility and layer permeability) to a single stimulus (PDGF), which will be the basis for the further identification of normal or pathological mechanisms.
Altogether, this project will pave the way for the elaboration of powerful tools (i) to accurately understand molecular signaling in normal and pathological situation (ii) to propose models for pathological transitions, and (iii) to elaborate strategies to non-invasively and quantitatively profile complex pathologies (tumor, auto-immune diseases,…), which are essential for the further conception of personalized treatments. It could be followed by a thesis with a specific focus on the biomedical aspects of signaling in model pathological glomeruli-on-chip.

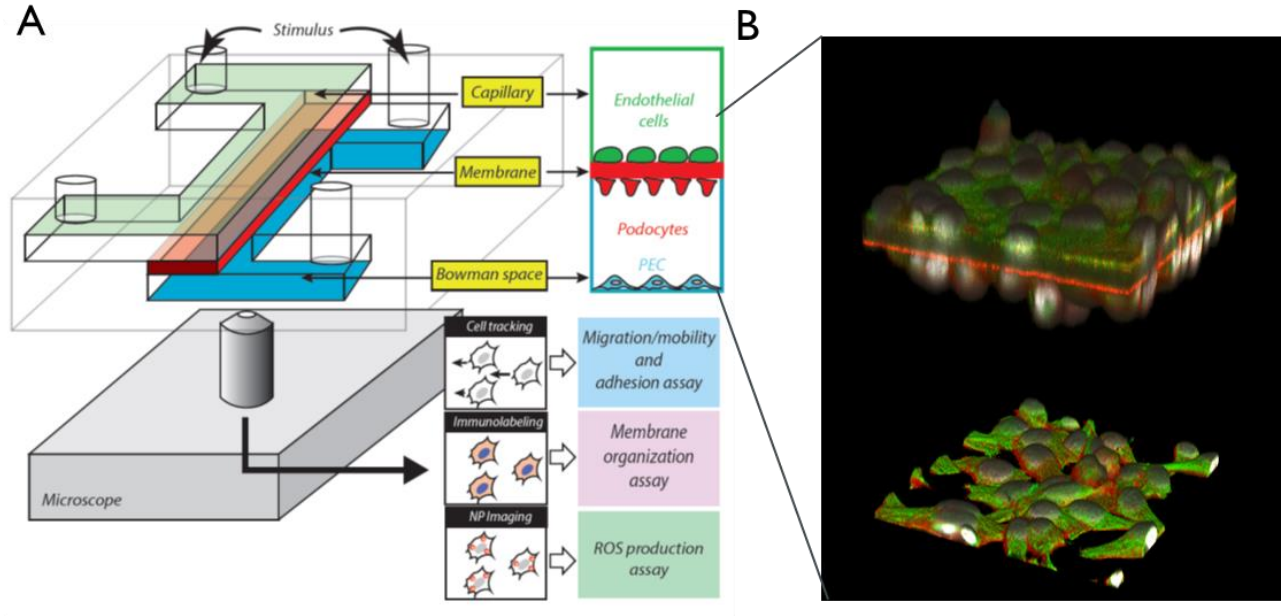

Figure 1. A) Glomerulus-on-chip imaging assay project. B) 3D Fluorescence imaging (tubulin, actin and DNA) of model HeLa cells in microsystem.

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