PROGRAMME INTITUTS ET INITIATIVES

Appel à projet – campagne 2021

Proposition de projet de recherche doctoral (PRD)

IUIS - Institut univ d'ingénierie en santé

Intitulé du projet de recherche doctoral (PRD): MIcrofluidic glomerular filtration barrIer-on-Chip with Integrated Sensors (ICIS)

Directeur.rice de thèse porteur.euse du projet (titulaire d'une HDR) :

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Unité de Recherche :
Intitulé : CoRaKiD
Code *(ex. UMR xxxx)* : UMRS 1155

École Doctorale de rattachement de l'équipe (future école doctorale du.de la doctorant.e) : **ED394-Physiologie,Physiopathologie Thérapeu**

Doctorant.e.s actuellement encadré.e.s par la.e directeur.rice de thèse (préciser le nombre de doctorant.e.s, leur année de 1e inscription et la quotité d'encadrement) : 0 doctorant

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Unité de Recherche :
Intitulé : LISE
Code *(ex. UMR xxxx)* : UMR 8235

École Doctorale de rattachement : **ED388-ChimiePhysiqueChimieAnalytique ParisCentre**
Ou si ED non Alliance SU :

Doctorant.e.s actuellement encadré.e.s par la.e co-directeur.rice de thèse (préciser le nombre de doctorant.e.s, leur année de 1e inscription et la quotité d'encadrement) : 1 doctorante,

inscrite depuis Octobre 2018; encadrée à 100%

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Unité de Recherche :
Intitulé : GeePs
Code *(ex. UMR xxxx)* : UMR 8507

École Doctorale de rattachement : **ED391-SMAER**
Ou si ED non Alliance SU :

Doctorant.e.s actuellement encadré.e.s par la.e co-directeur.rice de thèse (préciser le nombre de doctorant.e.s, leur année de 1e inscription et la quotité d'encadrement) :0 doctorant

Cotutelle internationale : ☒ Non ☐ Oui, précisez Pays et Université :

Selon vous, ce projet est-il susceptible d'intéresser une autre Initiative ou un autre Institut ?
☒ Non ☐ Oui, précisez Choisissez l'institut ou l'initiative :

Description du projet de recherche doctoral *(en français ou en anglais) :*

Ce texte sera diffusé en ligne : il ne doit pas excéder 3 pages et est écrit en interligne simple.

Détailler le contexte, l'objectif scientifique, la justification de l'approche scientifique ainsi que l'adéquation à l'initiative/l'Institut.

Le cas échéant, préciser le rôle de chaque encadrant ainsi que les compétences scientifiques apportées. Indiquer les publications/productions des encadrants en lien avec le projet.
Préciser le profil d'étudiant(e) recherché.

Context:

The prevalence increase of Chronic Kidney Diseases (CKD) is becoming a worldwide public health issue because the only treatments of end-stage kidney failure are not only costly but also rely on heavy treatment such as dialysis or kidney transplantation. Since the renal glomerulus is the first structure to perform the blood filtration, it is the main target in the case of kidney injury. In order to understand the physiology and physiopathology of the glomerulus, there is a need for a new generation of in vitro models. Indeed, current in vitro models do not reproduce accurately the in vivo physiology of the glomerulus and the animal models do not only reproduce poorly human physiology but also suffer of ethical issues. New in vitro systems, called MicroPhysiological Systems (MPS) or Organs-on-Chip have been introduced, 10 years ago, by Huh et al. [1]. If MPS represent a very promising technology to enhance the physiological relevance of in vitro models thanks to the microfluidic technologies [2], they still lack of two majors in vivo physiological features: (i) mature cells expressing the specific markers of interest and (ii) basement membrane, an extracellular matrix membrane playing an important role in the glomerular filtration [3]. Further enhancement of MPS should also allow to get real-time readouts, thanks to integrated sensors, in order to monitor the in vitro model and the dynamic effects. Up to now, MPS mimicking the glomerulus, do not implement all these three aspects [4,5] or focus on the use of cells that express a better phenotype than glomerular cell lines [6,7]. The development of a new glomerular filtration barrier-on-chip integrating these different aspects will not only help to perform permeability assays but also to model and understand glomerulopathies. This project will be a part of an ANR JCJC project between the laboratories CoRaKiD, LISE and GeePs.

Objectives and description of the proposal:

The main objective of this PhD thesis proposal is to develop a sensor-integrated microfluidic platform reproducing the glomerular filtration barrier. The platform will be then used to challenge clinical questions notably to investigate the presence or not of factors causing glomerular permeability in the serum of patients suffering from idiopathic glomerulopathy.

Preliminary work on the electrode integration is currently on going. Based on this preliminary work, this proposal is composed of three main tasks:

1: Engineering a physiological relevant glomerular basement membrane within microfluidic device

Currently engineered basement membranes (BM) do not properly mimic the biophysical and biochemical properties [8]. The aim, here, is to develop a hydrogel containing type IV collagen, which is the major component of the glomerular BM. The hydrogel formulation is currently under investigation (CoRaKid and GeePs). The PhD student will characterise the physical properties of the hydrogel using atomic and kelvin force microscopies available in GeePs. The hydrogel will be then extruded within the microfluidic device using the methods developed by Onoe et al. [9].

2: Perfusion of glomerular cell culture within the microfluidic platform

As the established conditionally immortalized glomerular cell lines (endothelial cells and epithelial cells called podocytes) [10,11] do not differentiate and mature well in classical 2D, they will be seeded on each side of the hydrogel membrane previously generated within the microfluidic platform. Cells will be matured under perfusion culture in order to form a physiologically relevant glomerular filtration barrier. Its permeability property will be assessed thanks to: (i) optical methods with fluorescent labelled-proteins and (ii) impedance spectroscopy methods with the electrodes [12] (CoRaKiD and LISE). Cellular phenotype will be assessed by immunofluorescence. Further improvement of the cell phenotype will rely on the induced pluripotent stem cell (iPSC) differentiation into glomerular cells (preliminary work currently on going at CoRaKiD). Differentiated iPSCs into podocytes and glomerular endothelial cells will be seeded respectively on each side of the hydrogel membrane. The permeability property will be assessed using the methods described above. The PhD student will carry out these experiments in CoRaKiD in close collaboration with LISE for the impedance spectroscopy methods and with GeePs for the tissue engineering with microfluidic device.

3: Reproduction of a glomerulopathy with the glomerular filtration barrier-on-chip

Based on the established expertise of CoRaKid in the pathophysiology of glomerular diseases [13–15], particularly, membranous nephropathy where increase permeability of the glomerular filtration barrier is induced by antibodies to podocytes (the external cell layer of the barrier), the PhD student will leverage this platform to model the glomerular events of the disease using the serum (or purified Immunoglobulins) from the patients with membranous nephropathy of from healthy controls or patients with a different mechanism of disease (IgA nephropathy). The aim, here, is to understand the combined effects of the permeability factors (antibodies) and the glomerular microenvironment. The dynamic of these effects will be monitored in real-time with impedance spectroscopy.

Candidate:

We are looking for a candidate with a Master degree in bioengineering, cellular biology or biochemistry. Able to work in an interdisciplinary environment. Experiences in microfabrication, cell culture with induced pluripotent stem cells, RT-PCR and immunofluorescence appreciated.

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