Research projects 2020-2021

Master M1&M2 – PhD – Post-Doc

Mucociliary clearance-on-a-chip

Supervisor:

Name: Jean-François Berret

E-mail: jean-francois.berret@univ-paris-diderot.fr

Phone: 01 57 27 61 47

Affliliation: Laboratory Matière et Systèmes Complexes, Université de Paris

Host Laboratory:

Affliliation: Université Université de Paris

Lab Name : Laboratoire Matière et Systèmes Complexes

Address : UMR 7057 Université de Paris/CNRS, Batiment Condorcet,
10 rue Alice Domon et Léonie Duquet, F-75205 Paris Cedex 13

Describe the team that the student will join for the project.

Our research group develops novel functional structures, devices and systems with stimuli-responsive features at the nano and microscales. Our objectives also deal with applications in medicine, biology and in the environment. It includes the development of tools for imaging and therapy in vivo, microfluidics and microrheology as well as the study of living system-machine interfaces.

Project description

Fine airborne particulate matter (PM) are released from production facilities, construction sites and wildfire, among other sources, and their inhalation is shown to be a major source of premature mortality in Europe and in the world.[1] Among them, ultra-fine PM and nanoengineered materials (size < 100 nm), namely nanoparticles (NPs), cause the most adverse effects due to their accessibility to the distal ends of the lungs.[2] Luckily, the body has a barrier, or a defense mechanism, along the upper airways which traps and disposes of inhaled NPs. This barrier is called "Mucociliary Clearance" (MCC) and consists of (a) covering the airway epithelium with mucus, (b) trapping inhaled NPs in mucus, and (c) continuous clearance of mucus from the airways via ciliary waves (Fig. 1).[3] Nevertheless, trapped NPs may cross the MCC barrier through mucus' pores and reach the underlying epithelial cell layer[4] or

[1] Lelieveld, J., Evans, J. S., Fnais, M., Giannadaki, D., Pozzer, A., *Nature* **2015,** *525*, 367-371.
[2] Fernandez Tena, A., Casan Clara, P., *Archivos de bronconeumologia* **2012,** *48* (7), 240-6.
[3] Bustamante-Marin, X. M., Ostrowski, L. E., *Cold Spring Harbor perspectives in biology* **2017,** *9* (4).
[4] Kirch, J., Schneider, A., Abou, B., Hopf, A., Schaefer, U. F., Schneider, M., Schall, C., Wagner, C., Lehr, C.-M., *Proceedings of the National Academy of Sciences* **2012,** *109* (45), 18355-18360; Schuster, B. S., Suk, J. S., Woodworth, G. F., Hanes, J., *Biomaterials* **2013,** *34* (13), 3439-3446.

stick to mucus, change its viscosity and hinder its clearance. These adverse effects rely on the specific interactions between mucus and NPs which is aimed to be investigated in this project. A mimic of MCC built on a microfluidic chip is aimed to be developed to serve as a non-biological model for NPs clearance examinations via MCC. Since the role of MCC in NPs inhalation toxicology has received a somewhat incoherent attention in the past, this project will contribute to the existing knowledge, while the developed mimic apparatus will serve as an alternative model for future NPs inhalation toxicology and pharmacology as well as pulmonary disease diagnosis investigations.

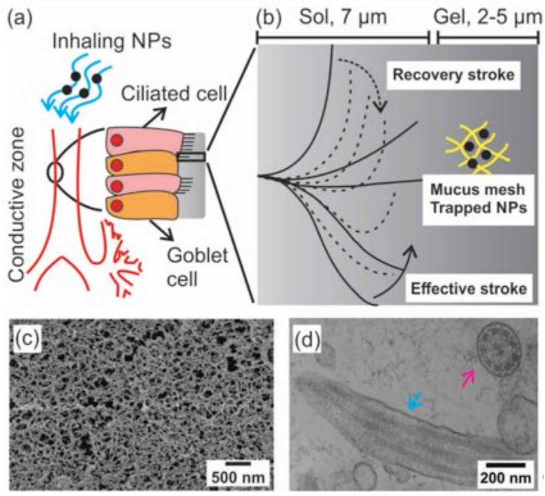

Figure 1: (a) Schematic of conductive zone (trachea, bronchi and conductive bronchioles) and the airway epithelium consisting of goblet cells and ciliated cells. Mucus is secreted by goblet cells via mucus granules as well as by submucosal glands (not shown). (b) Schematic of mucociliary clearance (MCC) whereby mucus and trapped nanoparticles (NPs) are cleared from airways towards gastrointestinal tract. (c) Network microstructure of mucus gel.[4] (d) Cilium (cyan arrow) and its complex protein machinery (pink arrow).

Pulmonary mucus is a viscoelastic, adhesive, permeable gel layer that is mainly composed of water (90-95%), mucin glycoproteins (1-5% by weight), electrolytes and lipids.[5] Over the epithelium, mucus forms a sol layer comprising of electrolytes and a small number of membrane-bound mucins (~ 7 µm thick) and a gel layer composing of a large amount of crosslinked and network-like mucins (~ 2-5 µm thick, pore size 200-300 nm) (Fig. 1b & 1c).3,4 The sol layer facilitates ciliary waves, while the gel layer traps inhaled NPs. Cilia are hair-like organelles of the ciliated cells whose function is to propel mucus out of the lung airways towards the pharynx until it is swallowed or expelled via coughing.3 The cytoskeleton of a cilium consists of 9 pairs of microtubules in the periphery,[2] central singlet microtubules, and proteins that produce the force required for cilia bending (Fig. 1d).3 The coordinated metachronal wave of 3 trillion cilia (more than about 100 per a ciliated cell) results in mucus clearance velocity of about 5.5 mm/min in healthy lungs.3

The objectives of the project are outlined as follows: **Aim 1**: To explore the effect of the physical and chemical properties of NPs on their adsorption kinetics to mucus, as well as the effect of trapped NPs on the viscoelasticity of mucus. **Aim 2**: To develop a mimic of MCC using magnetic micropillars and a chip that integrates electromagnets and accommodates access to mucus deposition and exposure to aerosolized NPs. **Aim 3**: To study the clearance of NPs in MCC mimic apparatus and to explore its potentials for future applications.

[5] Bansil, R., Turner, B. S., *Advanced Drug Delivery Reviews* **2018,** *124*, 3-15.