Funded PhD position :

Single-cell Analysis of Human Airway Regeneration and Remodeling in Asthma

Team: **Dr Pascal BARBRY**
PhD advisor: **Dr Laure-Emmanuelle ZARAGOSI CRCN Inserm**

Our project aims to use single-cell transcriptomics, a powerful and unprecedented approach, to unravel the molecular events that control the balance between the distinct cell types of the airway epithelium and their deregulation in asthma.

The airway epithelium is essential for mucociliary clearance, the process by which inhaled pathogens and pollutants are trapped in mucus and cleared out of the lungs by the coordinated beating of motile cilia which are present at the apical surface of multiciliated cells. In asthma, the airway epithelium is exposed to chronic inflammation and undergoes remodeling, resulting in mucus-secreting cell hyperplasia, defective mucociliary clearance and subsequent worsening of the clinic picture. Our team uses a 3D cellular differentiation model to reconstruct in vitro an airway epithelium with characteristics similar to those of respiratory epithelial tissue in vivo and has already identified several regulators of multiciliated cell differentiation. However, our understanding of epithelial specific mechanisms in asthma is largely insufficient. Yet, deciphering the epithelium-related molecular mechanisms is of paramount importance considering the pivotal roles of this tissue in the inflammatory cascade and the lack of efficient therapies in severe asthmatics.

In this project, the PhD student will establish single-cell transcriptomic profiles of several thousand epithelial cells derived from asthma patients and healthy controls, recovered after 3D in vitro epithelial culture. Novel data obtained in this project should implement this broad picture by revealing inter-individual heterogeneities and by identifying subpopulations at higher resolution. The PhD student will also evaluate the functional contribution of new molecular players in the development of asthma of various severity.

This project is based on the expertise of our consortium, leaders in the field of single-cell transcriptomic analysis (only French team to be selected for the Human Cell Atlas project) which is expert in 3D culture models of respiratory epithelial cells and acknowledged specialist in asthma. Patient recruitment is already possible with close collaboration with clinicians in Nice and Marseille's hospitals and specific equipment as well as the bioinformatics expertise necessary for this project will be in part provided by the UCA GenomiX platform.

Our team has recently published several studies in the field, and has contributed to the understanding of SARS-CoV-2 pathogenicity within the Human Cell Atlas Consortium.

Related publications

A single-cell atlas of the human healthy airways. Marie Deprez †, Laure-Emmanuelle Zaragosi †*, (…), Sylvie Leroy°°, Pascal Barbry°°*, **AJRCCM**, 2020, Minor revision

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SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues. Ziegler CGK, (…) , Zaragosi LE, Barbry P, (…), Ordovas-Montanes J; HCA Lung Biological Network. **Cell**. 2020 Apr 27:S0092-8674(20)30500-6.

SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Sungnak W, Huang N, Bécavin C, (…), HCA Lung Biological Network. **Nat Med**. 2020 May;26(5):681-687.

Using single-cell RNA sequencing to unravel cell lineage relationships in the respiratory tract. Zaragosi LE, Deprez M, Barbry P. **Biochem Soc Trans**. 2020 Feb 28;48(1):327-336.

Novel dynamics of human mucociliary differentiation revealed by single-cell RNA sequencing of nasal epithelial cultures. Ruiz García S*, Deprez M*, (…), Barbry P, Zaragosi LE. **Development**. 2019 Oct 23;146(20):dev177428.

CDC20B is required for deuterosome-mediated centriole production in multiciliated cells. Revinski DR*, Zaragosi LE*, Boutin C, Ruiz-Garcia S, Deprez M, Thomé V, Rosnet O, Gay AS, Mercey O, Paquet A, Pons N, Ponzio G, Marcet B*, Kodjabachian L*, Barbry P*. **Nat Commun**. 2018 Nov 7;9(1):4668.

miR-34/449 control apical actin network formation during multiciliogenesis through small GTPase pathways. Chevalier B*, Adamiok A*, Mercey O, Revinski DR, Zaragosi LE, Pasini A, Kodjabachian L*, Barbry P*, Marcet B*. **Nat Commun**. 2015 Sep 18;6:8386.

Control of vertebrate multiciliogenesis by miR-449 through direct repression of the Delta/Notch pathway. Marcet B, (…), Kodjabachian L*, Barbry P*. **Nat Cell Biol**. 2011 Jun;13(6):693-9.

Necessary skills

- Experience in cell culture and in and molecular biology will be greatly appreciated.
- A strong motivation to partner with the bioinformaticians of our team. No specific bioinformatics training is required, but interest in bioinformatics is mandatory.
- Strong motivation to lead a project combining cell biology, bioinformatics, and partnership with clinicians.

Application process

The position will be funded for 3 years through an ANR grant and a “Region Emploi Jeunes Doctorants” grand. If you are interested, please contact Laure-Emmanuelle Zaragosi (zaragosi@ipmc.Cnrs.fr) or Pascal Barbry (barbry@ipmc.cnrs.fr), with a CV, letter explaining your research motivations, and recommendation contacts.

Deadline: June 1st