IBEC-VHIR INTERNATIONAL PhD PROGRAMME

Position

1. Project Title/ Job Position title:
   Advancing Asthma Pathology: Insights into Airway Remodeling and Pollution Impacts through Innovative Imaging and Models

2. Research project/ Research Group description

The PhD project will be developed between the group of Pneumology of Vall D'Hebron (VDH) Research Institute and the group of Nanoscale Bioelectrical Characterization of IBEC. The first group is leader in the research on asthma. Asthma is a chronic inflammatory disorder of the airways characterized by symptoms like airway obstruction, bronchial hyperresponsiveness, and underlying inflammation. The pathological hallmarks of asthma include airway remodeling, mucus hypersecretion, inflammatory cell infiltration, and epithelial cell damage. Asthma pathology involves multiple interacting processes at the cellular and biomolecular levels. For example, inflammatory cells (such as T-helper type 2 (Th2) lymphocytes, eosinophils, mast cells, and basophils) release cytokines and mediators (e.g., histamine, leukotrienes) that amplify the inflammatory response, recruit additional immune cells, and induce tissue damage. Airway remodeling is also a key feature of chronic asthma and involves structural changes to the airway wall, such as subepithelial fibrosis, increased smooth muscle mass, angiogenesis, and goblet cell hyperplasia. These changes contribute to persistent airflow limitation, often irreversible despite standard therapies. Epithelial cells in asthmatic airways exhibit increased susceptibility to environmental insults, including allergens, pathogens, and pollutants. *Despite significant advances in understanding the disease,* **several aspects of its physiopathology remain unclear,** *particularly regarding its heterogeneity and the mechanisms driving chronic inflammation and airway remodeling*. The IBEC group is leader in the development of the atomic force microscopy (AFM) technique for the high throughput mechanical characterization of cells and biological tissues for disease detection (Calò et al., Sci Rep. 2020; Tello et al., Immunity 2021). The aim of the project is to shed light into the mechanism of Asthma disease through nano and micromechanical measurements, i.e. across scale lengths that go from single cells to the entire tissue architecture.

3. Job position description

Despite decades of research, several knowledge gaps persist in understanding the asthma pathology. For example, 1) the mechanisms underlying asthma heterogeneity, 2) the factors that

promote progression from acute inflammation to airway remodeling and structural tissue changes and 3) the impact of environmental exposure and air pollution (particulate matter PM, nitrogen dioxide NO_2, and ozone O_3) on asthma are not fully understood. ***In particular, the specific cellular and molecular pathways through which pollutants influence asthma remain unclear*****,** particularly in the context of *long-term exposure* and its *effect on airway remodeling*.

Animal models have been invaluable in advancing the understanding of asthma. These models can recapitulate many features of human asthma, including eosinophilic inflammation, airway hyperresponsiveness, and mucus hypersecretion. However, they often fail to capture the complexity and heterogeneity of human asthma, particularly non-Th2 endotypes and chronic airway remodeling. To address this limitation, the VDH research group developed **advanced mouse models that incorporate chronic allergen exposure and additional environmental factors such as air pollution**, to simulate the prolonged inflammatory and structural changes observed in human asthma, providing a more accurate representation of the disease progression. **Thus, they have the potential to address the critical gaps in asthma research previously mentioned.** For instance, combining allergen sensitization with exposure to pollutants like PM, allowed to study the synergistic effects of these triggers on airway inflammation and remodelling (Homdedeu et al., Environ. Pollut. 2020; Homdedeu et al., Environ Res. 2021). The PhD project will be focused on the preparation of tissue sections from these animal models and their functional imaging through the AFM, to extract mechanical observables (stiffness, viscoelasticity, adhesion) used to investigate the mechanism of asthma disease. ***Specifically, the effect of pollutants on tissue micromechanics will be studied, to gain insights into key environmental effectors on the pathology.***

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