PASTEUR PARIS UNIVERSITE (PPU) INTERNATIONAL DOCTORAL PROGRAM 2020

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PROJECT

- **FILE #05**
- **ACRONYM:** SiCIntest
- **TITLE:** Single cell approaches for the study of inflammatory intestinal disease

LABORATORY

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LABORATORY PRESENTATION AND RESEARCH TOPICS

- **SUPERVISOR HDR:** Nadine Cerf-Bensussan, nadine.cerf-bensussan@inserm.fr

- **SPECIFY THE TEAM NAME:** Laboratory of Intestinal Immunity

- **CO-SUPERVISOR:** Anais Levescot, anais.levescot@inserm.fr

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DESCRIPTION OF THE PROPOSED PROJECT

- **KEYWORDS:** inflammatory bowel diseases, monogenic disorders, single cell approaches

- **ABSTRACT**

Herein we intend to use single cell approaches in order to establish an atlas of cells and pathways dysregulated as a consequence of single gene defect causing severe intestinal inflammation. This atlas should be an important reference dataset to stratify patients with inflammatory intestinal disorders of unknow origin and to guide the choice of the most pertinent targeted therapy.

- **DESCRIPTION OF THE PROJECT**

Considerable effort has been made over the past 20 years to dissect genetic factors predisposing to common polyfactorial forms of inflammatory bowel diseases (IBD). Genome-wide association studies in IBD have identified over 230 susceptible genetic polymorphisms (McGovern, 2015). Those variants have provided insight into IBD pathophysiology and pointed to genes controlling the epithelial barrier, innate immunity toward the microbiota as well as T-helper cells function among many others. Yet, individual variants have very limited contribution to IBD development and inheritability; many are located in intergenic regions and overall their contribution to the development of intestinal inflammation is still unclear. As a consequence, it has been difficult to define personalized anti-inflammatory therapies and treatment of IBD remains largely based on drugs with broad and unspecific effects. The genetic landscape of IBD has recently broadened with the discovery of an increasing number of monogenic diseases. Monogenic IBD are usually characterized by a very early onset (VEO-IBD). We have recently shown that systematic screening for genetic defects of VEO-IBD patients, using TNGS and WES, resulted in a significant number of genetic diagnoses (Charbit-Henrion F et al, J Crohns Colitis. 2018) and in the identification of novel genetic etiologies

(Parlato M et al, EMBO Mol Med. 2018; Parlato M et al, Gastroenterology in press), respectively. Preliminary results also indicate that monogenic disorders of late onset can be identified in a substantial fraction of adult patients with severe intestinal inflammation either complicating common variable immunodeficiency or associated with immune dysfunction without immunoglobulin deficiency. This project stems from our recent analysis suggesting an overlap between mono and polygenic IBD (Parlato M et al, bioRxiv 768028. 2019) and will take advantage of the power of single cell transcriptomics and to our access to biopsies and blood from patients with monogenic forms of IBD to establish a detailed single cell resolution analysis of known monogenic disorders and to construct models of disease gene-associated cell types, their expression profiles and putative interactions. So far, this approach has been used to dissect in depth cells and pathways differentially activated between homeostasis and pathological conditions. We expect that the establishment of a single cell-based atlas of cells and pathways dysregulated as a consequence of a defect in one single key gene in monogenic IBD will provide an important reference dataset to guide the stratification of patients with undiagnosed IBD and to potentially reveal subgroups of patients with similar signatures who could benefit from targeted treatments.

- **REFERENCES**

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EXPECTED PROFILE OF THE CANDIDATE

- **EXPERIENCE REQUIRED**

  Eligible candidates should have experience with immunological and molecular biological techniques. English language skills written and spoken (EU level B2 or equivalent) are mandatory. The successful candidate should hold a master degree in Immunology or in Genetics or related fields. A background in machine learning and/or statistics and good programming skills will be helpful. Previous internship experience with next-generation sequencing data analysis and/or single cell data analysis would be a plus.