mercredi, août 31, 2022

INTERNATIONAL PhD PROPOSAL

PhD Supervisor full name **Frédéric Rieux-Laucat**

PhD PROPOSAL IDENTIFICATION

PhD Project title	Inborn Errors of activated JAK/STAT pathway: consequences and mechanisms underlying autoimmunity and lymphoproliferation
Project Acronym	HYPERJAK/STAT
Project Keyword	JAK/STAT signaling- Autoimmunity

LABORATORY PRESENTATION

Laboratory Team Name	Immunogenetics of pediatric autoimmune diseases
Department IP	immunology
Doctoral school	BioSP
University	University of Paris Cite
Laboratory website	https://www.institutimagine.org/fr/users/fredericrieux-laucatinsermfr

PhD PROPOSAL

PhD Supervisor full name	Frédéric Rieux-Laucat
PhD Supervisor position	DRCE
PhD Supervisor email	frederic.rieux-laucat@inserm.fr

PhD Proposal abstract (1000 characters maximum)

The - Immunogenetics of pediatric autoimmune diseases Lab - headed by Frédéric Rieux-Laucat is interested in the identification and molecular characterization of pathways that contribute to control self-tolerance in humans through the genetic dissection of a cohort of patients with primary immunodeficiencies and hyper immune syndromes. This PhD project aims at identifying and characterizing novel variants and genes controlling self-tolerance via activation of the JAK/STAT pathway. Within this frame, we will take advantage of the recently identified GOF variants in JAK1, STAT1, STAT3, STAT5B and LOF variants in SOCS1 and PTPN2 to provide mechanistic insights into the regulatory mechanisms evolved to fine-tune the cytokine-mediated activation of the pathway in human T cells. Besides bringing unique insights into the non-redundant layers of regulation of this emblematic signaling pathway, the present project is expected to improve clinical management of these rare but severe diseases.

PhD Proposal (4000 characters maximum)

Autoimmune-lymphoproliferative primary immunodeficiencies (AL-PID) are a group of rare inborn errors of immunity featuring a combination of autoimmune, inflammatory, lymphoproliferative and infectious manifestations. A subgroup of these patients carries germline mutations in a yet incompletely described group of genes that regulate JAK/STAT signaling, resulting in pathway overactivation. Accordingly, we have recently shownthat loss of function variants in SOCS1, a negative regulator of the JAK/STAT signaling, are associated with dominantly inherited early onset autoimmunity and lymphoproliferation in ten patients (Hadjadj J et al, 2020). The goal of this project is 1) to study the molecular and cellular consequences of novel variants in genes (previously or not) associated with JAK/STAT hyperactivation identified in our cohort of patients with familial autoimmune diseases and 2) to leverage these rare carrier patients to both unravel the fundamental bases of JAKs kinase transcriptional and biochemical function and to unveil the respective contributions of JAKs and STATs to cytokine signaling in human T cells. Within this frame, preliminary work of the laboratory has already identified a large group of patients with genetic variants affecting the JAK/STAT pathways, namely GOF variants in JAK1, STAT1, STAT3, STAT5B and heterozygous LOF in SOCS1, PTPN2 and in genes encoding other negative regulators of the pathway. The PhD candidate will carry out the molecular and cellular characterization of the variants at RNA and protein levels (q-RT-PCR, WB) in patient's cells and in overexpression system in HEK293T cells carrying luciferase STATs reporters. Gene variants will be also modelled in primary T cells by using the CRISPR-Cas9 editing technology. In addition, by integrating mass cytometry (CyTOF) immunophenotyping and single cell- transcriptomic approaches, the PhD candidate will define the potential regulatory networks underlying inflammatory rewiring in hyperactivated JAK/STAT signaling conditions. Finally, possible therapeutic strategies to rescue the disease phenotype will be explored in vitro. The successful applicant will have access to state-of-the-art core facilities at the Imagine Institute - Necker campus. This project is expected not only to define novel monogenic etiologies associated with severe autoimmune manifestations but also to provide mechanistic insights into the non-redundant role of the different members of the JAK/STAT pathway in the development of autoimmunity in humans. Lastly, this project will allow to in vitro assess the efficiency of multiple biologics, already available, specifically targeting this pathway, paving the way to personalized medicine in patients with JAK-STAT overactivation.

Expected profile of the candidate

The candidate should have a validated M2 master degree with a strong background in immunology/ familiar with cell culture, cell and molecular biology techniques.