**PhD PROPOSAL FOR THE**

**PASTEUR - PARIS UNIVERSITY INTERNATIONAL DOCTORAL PROGRAM**

Time for applicants to contact host laboratories: September 13 – November 2, 2017

Deadline for full application: November 13, 2017

Interviews: January 30, February 2, 2018

Start of the Ph.D.: October 1, 2018

**Title of the Full Ph.D. project:** Modulation of the human T cell response by type I interferon

**Keywords:** human immunology, autoimmunity, inflammation, gene regulation

**Department:** Immunology

**Name of the lab:** Unit of Cytokine Signaling, INSERM U1221

**Head of the lab:** Sandra Pellegrini

**Ph.D. advisor:** Frédérique Michel

**E-mail address:** frederique.michel@pasteur.fr

**Web site address of the lab:** <https://research.pasteur.fr/fr/team/cytokine-signaling/>

<https://research.pasteur.fr/en/program_project/milieu-interieur-labex/>

***Doctoral school affiliation and University*:** ED 394 Physiology, Physiopathology and Therapeutic, UPMC University

Presentation of the laboratory and its research topics:

Work in the Unit of Cytokine Signaling aims at deciphering molecular mechanisms that govern protective and pathogenic effects of type I interferons in the human immune system. Our research topics are mainly focused on the IFN signaling pathway and its regulation, the functional impact of polymorphism of genes associated with inflammatory diseases, and the immunomodulatory activity of IFN-I.

Description of the project:

The type I IFN family (IFN-α/β) exerts a complex immunomodulatory activity which can be beneficial or deleterious according to the pathophysiological context. The project aims at understanding the role of IFN in the development and function of T helper and regulatory CD4+ T cell subsets. This objective is pursued by studying the T cell adaptive immune response of healthy individuals and patients with multiple sclerosis (MS). The relapsing-remitting form of this chronic neuroinflammatory and autoimmune disease is commonly treated by IFN-β.

One objective is to pursue our study on the molecular mechanisms by which IFN promotes the expression of the anti-inflammatory cytokine IL-10 in CD4+ T cells stimulated through the T cell receptor (TCR). Using large scale transcriptomic and RNAi approaches, we have identified some transcription factors and STAT family members that are involved in the IFN-dependent enhancement of IL-10 expression. Mechanistic insights into the activation and transcriptional role of these transcription factors will be gained through studies of the TCR and IFN signaling pathways, chromatin immunoprecipitation and RNAi assays, using primary CD4+ T cells and CD4+ T cell lines. A second objective is to characterize IFN-induced type 1 regulatory-like cells (Tr1-like cells). Based on our RNA-seq data, a molecular signature of IFN-Tr1 cells will have to be validated., Multiplex qPCR will be set up in bulk and at the single cell level. The functional activity and stability of IFN-Tr1 cells will be also investigated. Insights from this project with healthy donors will be translated to multiple sclerosis patients, taking advantage of the translational project that we are developing.

References:

1. *U. Govender, B. Corre, Y. Bourdache, S. Pellegrini and F. Michel. Type I interferon-enhanced IL-10 expression in human CD4 T cells is regulated by STAT3, STAT2, and BATF transcription factors. J Leuco Biol., 2017. Doi :10.1189/jlb.2A0416-187RR. PMID:28242623*
2. *Zhang X., Bogunovic D., Payelle-Brogard B., Francois-Newton V., Speer S, Yuan C, Volpi S, Li Z, Sanal O, Mansouri D, Tezcan I, Rice GI, Chen C, Mansouri N, Mahdaviani S, Itan Y, Boisson B, Okada S, Zeng L, Wang X, Jiang H, Liu W, Han T, Liu D, Ma T, Wang B, Liu M, Liu J, Wang QK, Yalnizoglu D, Radoshevich L, Uzé G, Gros P, Rozenberg F, Zhang S-Y, Jouanguy E, Bustamante J, García-Sastre A, Abel L, Lebon P, Notarangelo L, Boisson-Dupuis S, Crow YJ, Casanova J-L and Pellegrini S. 2015. Human intracellular ISG15 prevents IFN-α/β over-amplification and auto-inflammation. Nature, 517 : 89-93.*

# *B. Corre, J. Perrier, M. El Khouri, S. Cerboni, S. Pellegrini and F. Michel. 2013. Type I interferon potentiates T-cell receptor mediated induction of IL-10-producing CD4⁺ T cells. Eur. J. Immunol., 43(10):2730-40. Doi: 10.1002/eji.201242977.*

1. *Z. Li, M. Gakovic, J. Ragimbeau, M-L Eloranta, L Rönnblom, F Michel and S Pellegrini. 2013. Two rare disease-associated Tyk2 variants are catalytically impaired but signaling competent. J. Immunol., 190(5):2335-44.*

Expected profile of the candidate:

Skills in transcriptome analysis, regulation of gene expression, bioinformatics and cellular immunology are strongly wished.

Fluency in English is required.

Contact:

frederique.michel@pasteur.fr