Internship Proposal

Project's title: Modulation of T cell responses by neutrophils in HIV infection.

Supervisor's name: Benoît Favier (benoit.favier@cea.fr)

Welcoming institution and team: The new research center, ImVA, (directed by Dr Roger Le Grand) brings together more than 100 scientists working on common scientific challenges related to innate and adaptive immunity in the context of viral infections and regulation of autoimmune disorders. ImVA is a mixed research unit (UMR1184) involving CEA, INSERM, Université Paris-Sud and a strong partnership with the Institut Pasteur. Research programs are supported by outstanding technological platforms (in vivo imaging, cytometry, bio-informatics, non-human primate models, pharmacology, biobanks…).
http://www.idmitcenter.fr
The CEA at Fontenay-aux-Roses is close to Paris (15 mn by public transportation).

IDOH co-supervisor : (if you have already identified someone, please indicate the name of the IDOH co-supervisor. If not, please let it empty and we (the IDOH Coordinating office) will identify someone) :

Summary of the project (1page max):
Early immune responses are dysregulated in HIV infection leading to the progression of the disease toward chronic stage[1]. In this regard, neutrophils play an important role in the early immune responses against microbial pathogens[2]. In the context of HIV infection, previous in vitro studies indicate that neutrophils can directly sense and neutralize HIV particles through NETosis and reactive oxygen species (ROS) production[3]. In addition to this effector function, neutrophils can also act as presenting cell to memory T cells[4]. Along with this beneficial role in HIV infection, neutrophils might be detrimental for antiviral response. Indeed, it was reported that neutrophils from HIV-infected patients in chronic phase are dysregulated and express high levels of PD-L1, resulting in the inhibition of T-cell responses and disease progression[5]. Neutrophils functions in vivo, such as phagocytosis and ROS production, are impaired chronically HIV-infected patients[3]. Nevertheless, functional and phenotypic characterization of neutrophils in primary infection and antiretroviral treatment are still missing.

Here we hypothesize that HIV infection induces the early dysregulation of neutrophils leading to HIV escape and T cell response attenuation.
Our aim is to characterize the function and phenotype of peripheral and tissular neutrophils during early immune responses against HIV in vivo. To achieve this goal we will use animal model of HIV infection mimicking human pathogenesis. This study will be a part of p-VISCONTI project, founded by ANRS and MSDAvenir, to explore the impact of treatment initiation on viral reservoir and immune activation. Student will work on neutrophils suppressive activity and phenotypic characterization during primary HIV infection using flow cytometry and RNA-sequencing approaches. He/she will be trained on functional assays and global transcriptomic analysis. The candidate should have a strong background in immunology and skills in cell culture, flow cytometry analysis.

References:

1. Cohen, M. S. M. M. S. *et al.* Acute HIV-1 Infection. *N Engl J Med* **364,** 1943–54 (2011).
2. Nauseef, W. M. & Borregaard, N. Neutrophils at work. *Nat. Immunol.* **15,** 602–11 (2014).
3. Casulli, S. & Elbim, C. Interactions between human immunodeficiency virus type 1 and polymorphonuclear neutrophils. *J. Innate Immun.* **6,** 13–20 (2014).
4. Liang, F. *et al.* Vaccine priming is restricted to draining lymph nodes & controlled by adjuvant-mediated antigen uptake. *Sci. Transl. Med.* **9,** (2017).
5. Bowers, N. L. *et al.* Immune Suppression by Neutrophils in HIV-1 Infection: Role of PD-L1/PD-1 Pathway. *PLoS Pathog.* **10,** (2014).

Supervisor's significant publications (5 maximum)

- Alaoui L, Palomino G, Zurawski S, Zurawski G, Coindre S, Dereuddre-Bosquet N, Lecuroux C, Goujard C, Vaslin B, Bourgeois C, Roques P, Le Grand R, Lambotte O, Favier B. Early SIV and HIV infection promotes the LILRB2/MHC-I inhibitory axis in cDCs. CMLS 2017.

- Damouche A, Pourcher G, Pourcher V, Benoist S, Busson E, Lataillade JJ, Le Van M, Lazure T, Adam J, Favier B, Vaslin B, Müller-Trutwin M, Lambotte O, Bourgeois C. High proportion of PD-1-expressing CD4+ T cells in adipose tissue constitutes an immunomodulatory microenvironment that may support HIV persistence. Eur J Immunol. 2017

- Favier B. Regulation of neutrophil functions through inhibitory receptors: an emerging paradigm in health and disease. Immunological Reviews. 2016 Sep;273(1):140-55

- Damouche A, Lazure T, Avettand-Fènoël V, Huot N, Dejucq-Rainsford N, Satie AP, Mélard A, David L, Gommet C, Ghosn J, Noel N, Pourcher G, Martinez V, Benoist S, Bérézíat V, Cosma A, Favier B., Vaslin B, Rouzioux C, Capeau J, Müller-Trutwin M, Dereuddre-Bosquet N, Le Grand R, Lambotte O, Bourgeois C. Adipose Tissue Is a Neglected Viral Reservoir and an Inflammatory Site during Chronic HIV and SIV Infection. PLoS Pathog. 2015 Sep 24;11(9):e1005153

- Baudhuin J., Migraine J., Faivre V., Loumagne L., Lukaszewicz AC, Payen D., Favier B. Exocytosis acts as a modulator of the ILT4 mediated inhibition of neutrophil functions PNAS 2013. 110:17957-62