**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 PhD project:** Identifying factors that affect the interplay between *M. tuberculosis* and human macrophages

**Keywords:** Tuberculosis, Innate immunity, Host-pathogen interactions, Macrophage

**Department:** Genomes and Genetics

**Name of the lab:** Integrated Mycobacterial Pathogenomics

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***Doctoral school affiliation and University*:** BioSPC (University Paris VII)

Presentation of the laboratory and its research topics:

Tuberculosis (TB), which is caused by *Mycobacterium tuberculosis* (MTB), is the deadliest disease due to a single infectious agent, ahead HIV/AIDS and malaria. According to the most recent WHO report, 10.4 million new TB cases occurred and the disease killed 1.5 million individuals in 2015. Despite considerable efforts, TB remains a major public health problem. An effective vaccine against TB is still not available and multidrug resistant (MDR) strains of MTB are continually emerging. The fight against TB requires new strategies and a better understanding of host-pathogen interactions.

In the unit for Integrated Mycobacterial Pathogenomics, complementary and innovative approaches are developed to understand mycobacterial pathogenicity.

Research strategies are oriented towards:

- the study of mycobacterial type VII / ESX secretion systems (Gröschel MI et al., Nat Rev Microbiol 2016 ; Simeone R et al., Tuberculosis 2015).

- the patho-evolution of the *Mycobacterium tuberculosis* complex (Boritsch EC et al., Nat Microbiol 2016 ; Boritsch EC et al., Proc Natl Acad Sci U S A. 2016 ; Supply P et al., Nat Genet. 2013).

- the study of the anti-mycobacterial immunity, using animal and human models (Majlessi L et al., Mucosal Immunol. 2017 ; Sayes F et al., PLoS Pathog. 2016 ; Polena H et al., Sci Rep. 2016 ; Majlessi L et al.,Immunol Rev. 2015 ; Simeone R et al., PLoS Pathog 2015 ; Siddle KJ et al., PLoS Genet. 2015; Dubois-Colas N et al., J Infect Dis. 2014 ; Barreiro LB et al., Proc Natl Acad Sci U S A. 2012).

- the development of new tuberculosis vaccines (Gröschel MI, Cell Rep 2017)

The main expertise of our laboratory is both the manipulation of tubercle bacilli and the culture and manipulation of phagocytic cells. We combine cutting-edge genomic techniques, cell and molecular biology and immunological tools in order to understand the immune response to bacterial infection and to identify virulence factors of *M. tuberculosis*.

Description of the project:

Tuberculosis (TB) is initiated when *M. tuberculosis* (MTB)-containing droplets are inhaled into the pulmonary alveoli. After encountering the bacillus, alveolar macrophages (Ms) invade the subtending epithelial layer and secrete several cytokines and chemokines, which allow the recruitment and activation of inflammatory cells1. This host response against the bacteria results in the formation of the granuloma. The granuloma consists of concentric layers of infected Ms, foamy Ms, epithelioid cells and multinucleated giant cells surrounded by a mantle of activated T lymphocytes1. Although the bacteria are not cleared, granulomas are generally considered as host-protective structures, containing the primary infection2,3. This dogma has been challenged in recent years with studies in zebrafish embryos infected with *M. marinum* showing that mycobacterial growth is indeed facilitated during the early granuloma formation 4. Ms infected with virulent mycobacteria together with the neighboring epithelial cells promote both the recruitment of new uninfected Ms and the formation of Ms aggregates, which facilitate phagocytosis of infected apoptotic cells and increase the bacterial burden4-6.

Ms are central to TB pathogenesis. They are the primary cell target of MTB, which has developed different strategies to survive and to multiply inside the Ms phagosome (such as prevention of phagosome acidification7 and inhibition of phagolysosomal fusion8). In addition, Ms play a key role in the outcome of the infection, by orchestrating the formation of granulomas, by presenting mycobacterial antigens to T cells and by killing the bacillus upon IFN- activation. One of the major virulence features of the tubercle bacillus is thus its ability to parasitize Ms. The mechanisms underlying this peculiar host-pathogen interaction are not fully understood. A better understanding of this process might help to develop innovative tools to treat TB.

Here, we propose to use a combination of immunological, genomic and high-throughput approachesto identify host and bacterial genes and regulatory pathways that contribute to the intracellular parasitism by MTB and to immune evasion by the bacteria.Specifically, we will (i) study the cell and bacterial responses during MTB infection and (ii) decipher how MTB-infected cells communicate with bystander uninfected Ms.

Briefly, human monocytes will be purified and differentiated into different Ms subtypes, mimicking the ones found in granulomas. These cells will be then infected with virulent strains of MTB (including MTB mutants). After different time post-infection, the cells will be sorted and the host and bacterial responses will be analyzed using global approaches (such as mRNA sequencing). This will allow the identification of key host and bacterial genes or pathways, involved in host-pathogen interactions. These genes or pathways will be studied more in-depth using for example gene silencing and imaging technologies.

Our project is a knowledge-generating project. It requires expertise in the fields of immunology, microbiology and genetics.

References:

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3 Seiscento, M. *et al.* Pleural fluid cytokines correlate with tissue inflammatory expression in tuberculosis. *Int J Tuberc Lung Dis* **14**, 1153-1158 (2010).

4 Volkman, H. E. *et al.* Tuberculous granuloma formation is enhanced by a mycobacterium virulence determinant. *PLoS Biol* **2**, e367 (2004).

5 Davis, J. M. & Ramakrishnan, L. The role of the granuloma in expansion and dissemination of early tuberculous infection. *Cell* **136**, 37-49 (2009).

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7 Sturgill-Koszycki, S. *et al.* Lack of acidification in Mycobacterium phagosomes produced by exclusion of the vesicular proton-ATPase. *Science* **263**, 678-681 (1994).

8 Armstrong, J. A. & Hart, P. D. Phagosome-lysosome interactions in cultured macrophages infected with virulent tubercle bacilli. Reversal of the usual nonfusion pattern and observations on bacterial survival. *J Exp Med* **142**, 1-16 (1975).

Expected profile of the candidate (optional):

Contact:

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