**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:** How can *Yersinia pestis* become invisible to the host immune system?

**Keywords:** Plague, *Yersinia pestis*, host cellular immune response, immune evasion

**Department:** Microbiology

**Name of the lab:** *Yersinia* Research Unit

**Head of the lab:** Dr Javier Pizarro Cerda

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**Web site address of the lab:** https://research.pasteur.fr/fr/team/yersinia/

***Doctoral school affiliation and University*:** Université Paris BioSPC

Presentation of the laboratory and its research topics:

The activities of the *Yersinia* Research Unit are primarily devoted to the analysis of:

- Comparative genomics and transcriptomics between *Y. pestis* and *Y. pseudotuberculosis*.

- Molecular bases for the exceptional pathogenicity of *Y. pestis*.

- Pathophysiology of *Yersinia* infections.

- Host's mechanisms of innate and adaptive immunity.

- Genetic bases of host susceptibility to plague.

- Evolution of pathogenic *Yersinia*.

The Unit is also developing:

- A vaccine against plague and pseudotuberculosis.

- Typing tools for molecular epidemiology.

- Real time *in vivo* imaging technologies for pathogenic *Yersinia*.

- Tools for stable gene complementation and gene expression *in vitro* and *in vivo*.

- Techniques for molecular characterization of the various *Yersinia* species.

The Unit participates actively to the surveillance and control of enteropathogenic *Yersinia* through its activities at the National level (Reference Laboratory and French Surveillance Network), and to the fight against plague at the international level (World Health Organization Collaborating Center for *Yersinia*).

Description of the project:

*Y. pestis* is the agent of plague, a disease transmitted from rodents to humans by fleabites. Bubonic plague is fatal for 50-70% of patients in the absence of treatment. Pneumonic plague results from inter-human contamination through aerosols and is an acute and fulminant pneumopathy, which is systematically lethal in usually less than 3 days. *Y. pestis* is thus among the most pathogenic bacteria for humans. Despite considerable progress in plague prevention and cure, this infection has not been eradicated and natural plague foci exist in Africa, Asia and the Americas.

The key to *Y. pestis* virulence is its capacity to escape host immunity. During the first 48h of infection, the host's innate immune response is defective (pre-inflammatory phase), allowing the bacteria to multiply and invade tissues. How *Y. pestis* prevents this response and what are the bacterial virulence factors responsible for this inhibition remain open questions. Because its recent ancestor *Y. pseudotuberculosis* (a much less virulent enteropathogen) does not exert these mechanisms, they are specific to *Y. pestis*. We will take benefit from the very close genetic relationship between the two species to identify mechanisms of immune response inhibition that are specific to *Y. pestis*.

Among the mechanisms blocked by *Y. pestis* during early plague that we will study is the inhibition of IFNγ production. This cytokine is essential to phagocytes activation and cell-mediated adaptive immunity, and IFNγ injection reverts mouse plague mortality. During a normal immune response, sentinel cells (dendritic cells /DC, macrophages) detecting bacteria recruit and activate cells such as natural killer (NK) and T lymphocytes which produce IFNγ, among other cytokines. *Y. pestis* therefore blocks one or more steps of this cascade. The proposed project will aim at deciphering the bacteria-cell and cell-cell interactions that occur early during the infectious process to paralyze this host defense system.

NK and DCs recruitment to infected lymph nodes will be characterized using the mouse experimental model of bubonic plague. The dynamics of recruitment and expansion or destruction of these populations in the lymph node infected with *Y. pestis* will be analyzed (flow cytometry and fluorescence microscopy). Production of cytokines and chemokines activating/attracting NK cells will be examined. Immunohistology will be used to define cell localization and cell-cell contacts in the lymph nodes. The presence and source of NK-activating factors will be determined (Immunofluorescence). Cell depletion in vivo will be used to confirm the roles played by the identified cell populations. Once specific cells and factors targeted early by *Y. pestis* are identified, the interactions between these targets and the bacteria will be deciphered using in vitro cultures of single and mixed cell populations. Cell survival, mechanisms of cell death, levels of cytokine production and activation markers will be examined.

A set of *Y. pestis* and *Y. pseudotuberculosis* mutants devoid of various genetic elements (already available in the laboratory) will be used to determine which factors (present or absent) cause the observed phenotypes. If necessary, additional mutants will be constructed. This study should provide new understanding on how a highly pathogenic bacterium circumvents innate host defense mechanisms to invade and kill its host extremely efficiently.

References:

* Guinet, F., Ave, P., Jones, L., Huerre, M., and Carniel, E. (2008) Defective innate cell response and lymph node infiltration specify *Yersinia pestis* infection. ***PLoS One*** **3**, e1688
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* Pachulec E, Ben Abdelwahed Bagga R, Chevallier L, O'Donnell H, Guillas C, Jaubert J, Montagutelli X, Carniel E, Demeure CE. (2017) Enhanced Macrophage M1 Polarization and Resistance to Apoptosis Enable Resistance to Plague. **Journal of Infectious Diseases**. Online.

Expected profile of the candidate (optional):

The project is proposed for a PhD or post-Doc. The candidate will have interest for host-pathogen interactions, and a training in immunology. Some knowledge in bacteriology would also be appreciated. The candidate should be ready to work on highly pathogenic bacteria, in biosafety level 3 environments and on animal models.

Speaking either English or French is mandatory.

Contact:

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