**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:** Molecular evolution and viral adaptability in different host environments

**Keywords:** virus, evolution, human genetics

**Department:** Genomes and Genetics

**Name of the lab:** Functional Genetics of Infectious Diseases Unit

**Head of the lab:** Anavaj Sakuntabhai

**PhD advisor:** Etienne Simon-Loriere / Jean-François Bureau (pending HDR for ESL in 2018)

**Email address:** etisl@pasteur.fr

**Web site address of the lab:** https://research.pasteur.fr/en/team/functional-genetics-of-infectious-diseases/

***Doctoral school affiliation and University*:** ED BioSPC - University Paris Descartes

Presentation of the laboratory and its research topics:

The GFMI unit is a multidisciplinary laboratory that includes human geneticists, immunologists, epidemiologists and virologists. We study the basis of human genetic susceptibility to major human pathogens, with a focus on two mosquito-borne infections (malaria and dengue) that impose a heavy public health burden in tropical and sub-tropical regions. We aim to identify genes governing infection outcome and transmissibility, within two important contexts:

* That of the pathogen exploitation of the host and maximization of onward transmission;
* The environmental context, placing emphasis upon the exogenous factors that impact upon the within-host dynamics of the pathogen and thus influence the outcome of infection.

Description of the project:

*(1 page, Arial font size 11: 600 words in total with at least 50% dedicated specifically to the proposed PhD project(s))*

Emerging and re-emerging infectious diseases are major threats to human and veterinary public health. They remain among the leading causes of death and disability worldwide and represent a significant burden on global economies ([Morens and Fauci, 2013](#_ENREF_5)). Most importantly, there is a wide variation in both animal and human risk and outcome of infection, generally encompassing asymptomatic, to more severe and sometimes lethal cases. Genetic epidemiology provides solid evidence that genetic variation in human populations contributes to susceptibility to infectious disease.

This project aims at exploring the question of human differences of susceptibility to infection and severe disease from a novel virological and evolutionary perspective. More specifically, the aim of this project is to better understand how the host environment may influence the evolutionary trajectories, composition and properties of a viral population, notably with respect to pathogenicity and transmissibility.

Dengue virus (DENV) is a perfect example of a pathogen associated with varying degrees of clinical severity, and as such, a highly representative model for this project. Infection with DENV results in a spectrum of clinical outcomes, ranging from self-limiting, uncomplicated dengue fever to the more severe dengue hemorrhagic fever or shock syndrome. In addition, a significant although variable fraction of DENV infections are pauci- or asymptomatic([Grange et al., 2014](#_ENREF_2)), but play a major role in the continued circulation of dengue viruses ([Duong et al., 2015](#_ENREF_1)). Genetic factors have been shown to influence the risk of severe dengue disease ([Rodenhuis-Zybert et al., 2010](#_ENREF_6)), and this translates into strong disparities in individual responses to infection, but also at the scale of human populations. For example, Cuba was the stage of several dengue epidemics, during which the proportion of severe cases observed in populations of African origin was significantly reduced compared to populations of European or Asian ancestry ([Guzman and Kouri, 2003](#_ENREF_3)).

The project will consist of the longitudinal characterization of viral populations evolving in a model of primary cells isolated from blood from donors of different ethnicity. The comparison of properties of these viral populations (fitness, tropism and transmissibility to mosquitoes), in the context of the transcriptomes of cells from different human donors, will reveal the nature and breadth of the constraints due to the different host factors on the viral genomes.

The second half of the project will make use of optimized, amplicon free, next generation sequencing techniques ([Matranga et al., 2014](#_ENREF_4)), to characterize viral populations in samples from patients affected by different degrees of dengue disease severity, as well as in asymptomatic cases. These samples, collected in Cambodia and Senegal in recent years, correspond a recently published transcriptomic study within our EU DENFREE consortium ([Simon-Loriere et al., 2017](#_ENREF_7)).

This project will allow the exploration of fundamental questions of evolutionary processes of RNA viruses that propagate as populations of variants, and that are continuously exposed to environments with different constraints. This work aims notably at exploring how host factors can modulate the dynamics of viral population genetic diversity, and the consequences of such variation on key parameters such as pathogenicity ([Vignuzzi et al., 2006](#_ENREF_8)) or transmissibility to new hosts or species. In addition, the study model for this project is a human pathogen that can cause grave and sometimes lethal symptoms, whose etiology remains poorly understood, and which imposes an increasing burden on public health and economy of many countries.

References:

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Guzman, M.G., and Kouri, G. (2003). Dengue and dengue hemorrhagic fever in the Americas: lessons and challenges. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology *27*, 1-13.

Matranga, C.B., Andersen, K.G., Winnicki, S., Busby, M., Gladden, A.D., Tewhey, R., Stremlau, M., Berlin, A., Gire, S.K., England, E.*, et al.* (2014). Enhanced methods for unbiased deep sequencing of Lassa and Ebola RNA viruses from clinical and biological samples. Genome biology *15*, 519.

Morens, D.M., and Fauci, A.S. (2013). Emerging infectious diseases: threats to human health and global stability. PLoS pathogens *9*, e1003467.

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Simon-Loriere, E., Duong, V., Tawfik, A., Ung, S., Ly, S., Casademont, I., Prot, M., Courtejoie, N., Bleakley, K., Buchy, P.*, et al.* (2017). Increased adaptive immune responses and proper feedback regulation protect against clinical dengue. Science translational medicine *9*.

Vignuzzi, M., Stone, J.K., Arnold, J.J., Cameron, C.E., and Andino, R. (2006). Quasispecies diversity determines pathogenesis through cooperative interactions in a viral population. Nature *439*, 344-348.

Expected profile of the candidate (optional):

Experience in molecular biology, virology and interest for bioinformatics

Contact:

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