**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:** Zika virus replication and antiviral responses

**Keywords:** Zika, virus, restriction factors, cytopathic effect, cell death

**Department:** Virology

**Name of the lab:** Virus & Immunity Unit

**Head of the lab:** Olivier Schwartz

**PhD advisor:** Olivier Schwartz

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

**Web site address of the lab:** https://research.pasteur.fr/en/team/virus-and-immunity/

***Doctoral school affiliation and University*:** ED Bio Sorbonne Paris Cité - IFD – Université Paris Descartes

Presentation of the laboratory and its research topics:

We are studying interactions between viruses and their host. Our work focuses on cellular and molecular aspects of viral replication, and on the mechanisms of the triggering of an immune response by infected cells. Our ongoing and future research is aimed at elucidating new biological processes and understanding how viruses shape the host’s intracellular environment to optimize viral propagation. We are mostly studying HIV and Zika virus (ZIKV).

We are currently studying:

* HIV replication and interaction with the immune system
* Strategies to visualize and eliminate the HIV-1 reservoir
* Zika virus multiplication and cytopathic effects

The recent Zika virus (ZIKV) epidemics in South East Asia, French Polynesia, the Caribbean islands and the Americas, and its association with neurological disorders including Guillain-Barré syndrome and microcephaly and other defects in newborns have triggered a global public health response in 2016. ZIKV infection mainly occurs after a bite by infected Aedes mosquitoes, through maternal–fetal transmission, and less frequently by sexual transmission. Evidence of ZIKV transmission have been reported in about 85 countries or territories. The biology and physiopathology of ZIKV infection is thus under intense scrutiny.

Description of the project:

**Study of ZIKV multiplication and antiviral responses.** The innate immune response controls ZIKV spread and disease development in most of infected individuals, through mechanisms that are not clearly understood. We are studying viral replication and the cytopathic effect of the virus. We are also examining the role of interferon-induced transmembrane proteins (IFITM), a family of broad-spectrum antiviral factors, during viral replication. We recently reported that ZIKV induces massive vacuolization followed by “implosive” cell death in human epithelial cells, primary skin fibroblasts and astrocytes, a phenomenon which is exacerbated when IFITM3 levels are low. It is reminiscent of paraptosis, a caspase-independent, non-apoptotic form of cell death associated with the formation of large cytoplasmic vacuoles. We further show that ZIKV-induced vacuoles are derived from the endoplasmic reticulum (ER) and dependent on the PI3K/Akt signaling axis. Inhibiting the Sec61 ER translocon in ZIKV-infected cells blocked vacuole formation and viral production. Our results provided mechanistic insight behind the ZIKV-induced cytopathic effect and indicate that IFITM3, by acting as a gatekeeper for incoming virus, desensitizes the cell to death following virus takeover of the ER. These results have been recently published (1).

 The global aim of the PhD project is to further characterize ZIKV-induced paraptosis and its importance during viral replication. The two complementary axes of research are:

1. **Mechanisms of ZIKV replication and paraptosis.**

Our aim is to understand how ZIKV replicates despite this cytopathic effect, and to further describe the protective innate response of the host. While the cytopathic eventswere detectable in cells containing IFITM3, these phenomena were more apparent upon IFITM3 silencing. This suggests that once incoming ZIKV virions have surmounted the intracellular barrier mediated by IFITM3 at the vital entry step, a pathway leading to ER stress and cell death is triggered.

We will examine how IFITM3 inhibit ZIKV entry. We will also characterize the role of cellular proteins involved in ER function and paraptosis during viral replication. We intend to further determine how small molecules modulating paraptosis and/or apoptosis impact ZIKV production by infected cells. Other questions that deserve further attention are whether paraptotic signaling suppresses or modulates apoptosis in ZIKV-infected cells and whether apoptosis occurs among non-infected bystander cells.

1. **ZIKV-induced cell death and immune responses.**

Dying cells actively regulate immune responses and provide inflammatory and immunogenic signals to the host. These processes have been characterized for apoptotic or necroptotic cells, but not for paroptotic cells. We intend to examine how ZIKV infected cells modulate innate and adaptive immune responses in bystander cells. ZIKV infected cells will be cocultivated with DCs or other immune cells and their ability to induce cytokine production will be compared to cell-free virions. We will silence proteins of interest, either in ZIKV infected cells or in DCs, to describe the links that may exist between ZIKV infection, cell death, and host responses.

References: 5 selected publications

1. Monel B, Compton AA, BruelT, AmraouiS, Burlaud-Gaillard J, Roy N, Guivel-BenhassineF, Porrot F, Génin P, MeertensL, SinigagliaL, JouvenetN, WeilR, CasartelliN, DemangelC, Simon-LorièreE, Moris A, RoingeardP, AmaraA and SchwartzO Zika virus induces massive cytoplasmic vacuolization and paraptosis-like death in infected cells. *EMBO Journal* **2017** May 4.
2. Descours B, Petitjean G, López-Zaragoza JL, Bruel T, Raffel R, Psomas C, Reynes J, Lacabaratz C, Levy Y, Schwartz O, Lelievre JD, Benkirane M. CD32a is a cell surface marker of CD4 T cell HIV-1 reservoir harboring inducible replication-competent provirus*. Nature***. 2017** Mar 23.
3. Bruel T, Guivel-Benhassine F, Amraoui S, Malbec M, Richard L, Bourdic K, Donahue DA, Lorin V, Casartelli N, Noël N, Lambotte O, Mouquet H, Schwartz O. Elimination of HIV-1 infected cells by broadly neutralizing antibodies. *Nature Communications*, **2016** Mar 3.
4. Compton A, Bruel T, Porrot F, Mallet A, Sachse M, Euvrard M, Liang C, Casartelli N, and Schwartz O Interferon-induced transmembrane proteins incorporate into HIV-1 virions and impair viral cell-to-cell spread. **2014** *Cell Host & Microbe* Dec 10.
5. Malbec M, Porrot F,Rua R, Horwitz J, Klein F, Halper-Stromberg A, Scheid J, Eden C, Mouquet H, Nussenzweig MC, Schwartz O**. 2013**. Broadly neutralizing antibodies that inhibit HIV-1 cell-to-cell transmission. *J. Exp. Med.* Dec 16.

Expected profile of the candidate (optional):

Contact: Olivier Schwartz. Email: schwartz@pasteur.fr