**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**

Human infection with zoonotic simian foamy retroviruses: role of virological and immunological factors in restricting viral emergence

**Keywords:** Retroviruses, Zoonosis, Emergence, Neutralizing antibodies

**Department:** Virology

**Name of the lab:** Epidemiology and Physiopathology of oncogenic viruses (EPOV)

Head of the lab: Antoine Gessain

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

***Doctoral school affiliation and University*:** BioSPC, Paris-Diderot University (Paris 7).

Presentation of the laboratory and its research topics

The EPOV research unit developed several research programs focusing on epidemiology, physiopathology and immunology of retroviruses – Human T Lymphotropic viruses (HTLV) and their simian counterpart (STLV), simian foamy viruses (SFV) and HIV-- as well as herpesviruses (HHV-8), and more recently some emerging viruses, such as Chikungunya and Zika viruses.

The research unit is composed of three groups. Florence Buseyne is the head of the” Immunity in human retroviral infections” group. The central theme to her research is the **adaptive immune response of humans to retroviruses**. The group works on projects in two clinical contexts. The first is **HIV pediatric infection**, in which virus-specific responses are generated by an immature immune system and in the presence of an immunosuppressive virus. The second context is the **cross-species transmission of simian foamy retroviruses from apes and monkeys to humans**. These viruses can establish a persistent infection in the new human host, but they have not emerged into the human population, probably because of effective restriction by the immune system.

Description of the project

The public health relevance of **retroviruses of zoonotic origin** is illustrated by the human immunodeficiency virus (HIV) epidemic, the worldwide distribution of human T-lymphotropic viruses (HTLVs), and the high morbidity and mortality associated with these viruses. Both HIVs and HTLVs emerged in the human population after several cross-species transmission events involving retroviruses (SIVs and STLVs) endemic in nonhuman primates (NHPs). Moreover, a third genus of complex retroviruses, the foamy viruses, some of which are of simian origin, can also establish persistent infections in humans. **Simian foamy viruses (SFVs)** are widespread and highly prevalent in many NHP species. These viruses can be readily isolated from the saliva and oropharyngeal secretions of infected NHPs. **Penetrating bite wounds** therefore constitute a potential route of transmission to humans, leading to the establishment of **life-long persistent infection**. **Human infection with zoonotic SFVs constitutes a unique, natural model for studies of the restriction of retrovirus emergence in humans**.

The team has recently shown that neutralizing antibodies are present at high titers in most SFV-infected individuals. These antibodies target highly conserved regions of the viral envelope and are associated with the control of SFV replication. The PhD thesis will broaden the knowledge on antiviral antibodies against SFV infecting humans. The project aims are:

**Define the antigenic epitopes targeted by neutralizing antibodies**. A three-step strategy is planned: *in silico* prediction of antigenic peptides, neutralization assay based on competition with linear peptide or protein subdomains, functional validation of virus vulnerability sites using viral vectors. Antibodies are quantified in the plasma of SFV-infected subjects. An SFV microtitration assay is carried out with an indicator cell line containing a β-galactosidase gene under the control of the promoter region of SFV. Viral foamy vector carrying a fluorescent transgene are used in neutralization assays. Their envelope will be modified by PCR cloning and/or mutagenesis.

**Study human monoclonal antibodies specific for SFV**. After identification of immunodominant epitopes, peripheral blood B lymphocytes are stimulated *in vitro* with peptides carrying the neutralizing epitopes and B cell growth factors. Responding cells are labelled with fluorescently tagged epitopes, sorted by flow cytometry. Immunoglobulin chains are amplified by PCR, sequenced and analyzed. Monoclonal antibodies are produced by cotransfection of heavy and light chains. Their sequence and function will be characterized.

**Assess the ability of antibodies to mediate the lysis of infected cells.** A flow cytometry-based assay evaluating the killing of fluorescently labeled target cells is used. Target cells are cell lines infected with primary SFV strains from our study population. They are labeled with carboxyfluorescein succinimidyl ester (CFSE) and a lipophilic dye (PKH-26, Sigma) and incubated with plasma from SFV-infected donors as a source of antibodies. PBMCs from uninfected donors are used as a source of CD16+ (FcγRIII) killer cells for the ADCC assay. After a four-hour incubation period, flow cytometry is carried out to detect cell lysis on the basis of a loss of CFSE cytoplasmic labeling and the retention of PKH-26 membrane staining.

References:

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Expected profile of the candidate

We are seeking a highly motived doctoral candidate to join us and work on highly exciting topics. Applicants should have a solid record of scientific achievement and be highly commited to producing high-quality science. Preference will be given to candidates with e in immunology or virology.

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