**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:** Unraveling the metacyclic to bloodstream form differentiation of African trypanosomes during the early infection of the Mammalian host.

**Keywords:** African trypanosome, Tsetse flies, Host, Infection, Metacyclic form, Bloodstream form, Virulence factor

**Department:** Parasites and Insect Vectors

**Name of the lab:** Trypanosome Cell Biology Unit

**Head of the lab:** Philippe BASTIN

**PhD advisors:** Brice ROTUREAU

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

**Web site address of the lab:** <http://www.pasteur.fr/en/research/trypa>

***Doctoral school affiliation and University*:** ED515 Complexité du Vivant – UPMC Paris 6

Presentation of the laboratory and its research topics:

Our lab is studying the role and functioning of the trypanosome flagellum, with perspectives in the field of both parasitology and genetic diseases. Indeed, trypanosomes are significant parasites of man and cattle in central Africa and there are currently no efficient vaccines against them. Moreover, trypanosomes are also an excellent model to study human genetic diseases due to defects in cilia and flagella. Our lab is a Pasteur full research unit of about 12 members affiliated to the Department of Parasites and Insect Vectors and the Department of Cell Biology and Infection. We also belong to a larger INSERM unit (U1201, A. Scherf).
In the lab, the Trypanosome Transmission Group investigates the mechanisms by which trypanosomes become infectious and first develop in the mammalian host using the most appropriate models with the bite of the tsetse fly. The group demonstrated recently that trypanosomes transit through the blood to reach multiple tissues and in particular the skin. Importantly, we revealed that these trypanosomes are transmissible to the tsetse fly.

Description of the project:

Human African Trypanosomiasis is a neglected tropical disease caused by the flagellated protist *Trypanosoma brucei* (Rotureau, 2013). The injection of these extra-cellular parasites by the bite of the tsetse fly induces a local inflammatory response. Trypanosomes first settle at the bite site and further transit via the lymphatic system before invading the blood and several tissues where they proliferate. We have recently proven that the skin was a major yet overlooked anatomical reservoir for trypanosomes (Capewell, 2016). However, very little is known about the early steps of infection, especially the mechanisms involved in the initial trypanosome differentiation in the skin. This project aims at unravelling how non-proliferative “metacyclic” trypanosomes injected in the dermis within the tsetse saliva initiate the infection. The metacyclic surface proteins are the first elements encountered by the host immune cells and may therefore act as virulence factors that could represent promising targets for early diagnosis and/or vaccine purposes. Metacyclic parasites then differentiate into proliferative mammalian-adapted bloodstream trypanosomes, a transformation that is critical for host invasion. To decipher the mechanisms of differentiation, we will (1) validate a set of 8 putative metacyclic surface markers *in vitro* (Savage, 2012; Kolev 2012), (2) study the expression (timing, duration and level) of the most highly expressed surface markers *in vivo* after natural transmission (Rotureau, 2014), and (3) unravel their role during the early differentiation by functional approaches *in vivo*. Overall, this study will greatly increase our understanding of African trypanosome biology and pathogenesis at the point of transmission to the mammalian host, and will identify a number of putative proteins which could be investigated further for early diagnosis and/or vaccine targets.

References:

1. *Rotureau, B., and Van Den Abbeele, J. (2013). Through the dark continent: African trypanosome development in the tsetse fly. Front Cell Infect Microbiol 3, 53.*
2. *Capewell, P.\*, Cren-Travaille, C.\*, Marchesi, F., Johnston, P., Clucas, C., Benson, R.A., Gorman, T., Calvo-Alvarez, E., Crouzols, A., Jouvion, G., Jamonneau, V., Weir, W., Stevenson, L.M., O'neill, K., Cooper, A., Kuispond, N., Bucheton, B., Mumba, D., Garside, P., Rotureau, B.\*\*, and Macleod, A.\*\* (2016). The skin is a significant but overlooked anatomical reservoir for vector-borne African trypanosomes. eLife Sep 22;5.*
3. *Kolev, N.G., Ramey-Butler, K., Cross, G.A., Ullu, E., and Tschudi, C. (2012). Developmental progression to infectivity in Trypanosoma brucei triggered by an RNA-binding protein. Science 338, 1352-1353.*
4. *Savage, A.F., Cerqueira, G.C., Regmi, S., Wu, Y., El Sayed, N.M., and Aksoy, S. (2012). Transcript expression analysis of putative Trypanosoma brucei GPI-anchored surface proteins during development in the tsetse and mammalian hosts. PLoS Negl Trop Dis 6, e1708.*
5. *Rotureau, B., Ooi, C.P., Huet, D., Perrot, S., and Bastin, P. (2014). Forward motility is essential for trypanosome infection in the tsetse fly. Cell Microbiol 16, 425-433.*

Expected profile of the candidate (optional):

Skills in parasitology, molecular biology and / or *in vivo* imaging

Contact:

rotureau@pasteur.fr