**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:** Genomic portrait of a neonatal pathogen**.**

**Keywords**: *Streptococcus agalactiae*, Tn-Seq, essential genes, metabolism, host-pathogen interaction

**Department:** Microbiology

**Name of the lab**:Biology of Gram-positive Pathogens

**Head of the lab:** Prof. Patrick TRIEU-CUOT

**PhD advisor:** Arnaud FIRON (HDR 2018) / Patrick TRIEU-CUOT

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**Web site address of the lab**: <https://research.pasteur.fr/en/team/biology-of-gram-positive-pathogens/>

***Doctoral school affiliation and University***:BioSPC (Paris Diderot)

Presentation of the laboratory and its research topics:

Our laboratory investigates new pathways and mechanisms involved in the pathogenesis of low GC % Gram-positive bacteria focusing on the major human pathogens *Streptococcus agalactiae* and *Staphylococcus aureus*. More recently, we have also initiated a research on *Streptococcus gallolyticus*, an emerging cause of septicemia and infective endocarditis in the elderly, which has been consistently linked to colorectal cancer (CRC).

Our current research topics include the study of i) relationships between metabolic adaptation and virulence, ii) bacterial surface components involved in interaction with the host, iii) gene regulation in relation to host environment and adaptation to stress responses, and iv) genomic biodiversity and the evolution of opportunistic pathogens. To this end, we have developed numerous collaborations with internationally recognized groups working in complementary fields in an effort to understand how these opportunistic pathogens adapt so successfully to their hosts.

Description of the project:

*Streptococcus agalactiae* [Group B Streptococcus (GBS)] is a Gram-positive commensal bacterium of the human intestine, also present in the vagina of 15–30% of healthy women. However, GBS is the leading cause of pneumonia, septicemia and meningitis in the first months of life in high-income countries. In most cases, infection of neonates occurs during delivery by direct mother-to-baby transmission in the case of vaginal colonization of the mother. Despite antibiotic prophylaxis measures, the incidence of GBS diseases remains a major public health concern.

Our global project is aimed at discovering the main determinants of the commensal and pathogenic lifestyles of GBS with the following key questions: What are the main virulence factors used by GBS to adhere, invade, survive, and multiply in the host? How does GBS resist and manipulate host immune defenses? How does GBS adapt its metabolism and genetic programs to the different environmental niches encountered during colonization and invasive diseases? How does GBS establish itself as a commensal in the competitive microbiota environment? By answering these questions, we believe that we can contribute to the development of innovative diagnosis tools and/or preventive strategies against GBS infections.

The aim of the PhD project is to define at the genome-level the genetic repertoire necessary for GBS pathogeny. The approach will be based on the development of TnSeq in GBS [1]. This genome-wide approach used a saturating collection of random insertional mutant to identify the whole set of gene essential in a given experimental condition. Basically, a collection of 100 000 random mutants is generated with a modified mini-transposon. Chromosomal positions of the 100 000 mini-transposon insertions are then identified en masse by next generation sequencing (Illumina) before (TO) and after (T1) growth of the pooled collection into a given condition. Genes having transposon insertion at TO and no insertion at T1 are considered necessary for the given condition. This qualitative approach is refined by the quantification of sequencing reads for each insertion allowing to determine the fitness of each of the 100 000 mutants, and thus the contribution of every gene for a given phenotype.

This global approach will be implemented gradually to 1) define the core set of essential gene in GBS for *in vitro* growth in rich and synthetic media; 2) identify the metabolic requirement necessary for anaerobic and aerobic growth; 3) characterize the mechanisms of resistance to selected compounds (lysozyme, heme); 4) identify the genetic specificities of hypervirulent, virulent and avirulent strains; and 5) identify the genes necessary for colonization and invasive infections in animal models of infection.

Overall, this PhD project will quantify the contribution of each gene for GBS growth and pathogeny. Targeted validation of the most promising essential (or conditionally essential) genes will be done in collaboration (ANR-funded project on heme toxicity) and with a special emphasis on the genes specifically necessary during the activation of the master regulator of GBS virulence gene expression.

Reference:

1. Chao MC, Abel S, Davis BM, Waldor MK: **The design and analysis of transposon insertion sequencing experiments**. *Nat Rev Microbiol* 2016, **14**:119-128.

Expected profile of the candidate (optional):

The PhD candidate should have a background on bacterial genetics. He/She should have or will acquire experience in bioinformatics.

Contact:

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