**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:** “USF1 transcription factors and the oncogenic response to *H. pylori* infection”.

**Keywords:** *H. pylori*, host-pathogen interaction, gene regulation, DNA repair, oncogenesis, gastric cancer

**Department:** Microbiology

**Name of the lab:** Unit of Helicobacter Pathogenesis, group “Infection, Genotoxicity and cancer”

**Head of the lab:** Hilde De REUSE

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**Web site address of the lab**: <http://www.pasteur.fr/en/research/microbiology/units-groups/helicobacter-pathogenesis>

***Doctoral school affiliation and University*:** Doctoral School BioSPC University Paris Diderot and University Paris Descartes

Presentation of the laboratory and its research topics:

In our unit we study the pathogenesis of *Helicobacter pylori* infection, a bacterial pathogen that colonizes specifically the human stomach of about half of the human population worldwide. Infection by *H. pylori* is chronic and can evolve from gastritis to severe pathologies such as gastric cancer. We develop complementary approaches to analyse the bacterial physiology of *H. pylori* and the mechanisms caused by its interaction with the host that are responsible for its pathogenicity.

One part of the projects aims at understanding what makes *H. pylori* such a successful and persistent pathogen in an hostile niche, the acid stomach. This includes a study of the transport, trafficking and sensing of Nickel which is an essential virulence determinant for *H. pylori.* The analysis of RNA-mediated regulation in *H. pylori* is also investigated.

The second part of the topics is developed by E. Touati ‘s group on “Infection, Genotoxicity and Cancer” and aims to characterize molecular events at the origin of the genotoxic activity of H. pylori infection and its oncogenic consequences. We develop one main project focused on the study of pleiotropic transcriptional regulators, Upstream Stimulating factors (USF) and their involvement in the DNA damaging activity and host genetic instabilities induced by the infection. The USF factors have been previously demonstrated as pleiotropic stress sensors and would be associated with a tumor suppressive activity. A previous study from our group also investigated the consequences of H. pylori at mitochondria and mechanisms related to maintenance of their genome integrity during the infection. Finally, a translational approach is conducted, that aims at identifying biomarkers for an early detection of gastric cancer.

Description of the project:

*Helicobacter pylori* is a gastric pathogen that infects chronically about50% of the human population worldwide. It induces gastric inflammation that can evolve to severe pathologies as peptic ulcers (10% of the infected population) and gastric cancer (1 to 3%). Up to now, *H. pylori* is the only bacteria associated with cancer. We explore the events at the origin of the relationship between this bacterium and gastric cancer development. We previously demonstrated a mutagenic effect in *H. pylori* chronically-infected mice associated with gastric inflammation and an impairment of DNA repair systems (1,2,3). *H. pylori* infection is also a source of epigenetic alterations in gastric epithelial cells. Both genetic instabilities and epigenetic mechanisms are known to occur at the initial steps of the carcinogenic process and play an important role in *H. pylori* associated gastric carcinogenesis. Our previous studies showed that *H. pylori* induces DNA methylation in the promoter region of the Upstream Stimulating Factors USF1 and USF2, leading to the inhibition of their transcription (4). USF1 and USF2 are pleiotropic transcription factors and key regulators of genes related to stress conditions, cell proliferation, immune response and DNA damage and repair response. They act as homo- or heterodimers. USF1 and USF2 interact with specific E-boxes DNA binding sequences in promoter regions of their target genes. They have been proposed as tumor suppressor genes. Their role in the host response during *H. pylori* infection and their impact in the associated gastric carcinogenesis remain to be determined.

The proposed project aims to investigate the consequences of the *H. pylori*-mediated USF1 deregulation on the host response with a special focus on genes related to oncogenesis and associated regulatory pathways. This will be performed on ex-vivo mouse gastric explants cultures under different conditions of *H. pylori* infection and using global transcriptomic and proteomic approaches. The mechanisms of regulation of the identified genes will be investigated by several molecular and cellular approaches. In order to analyze the consequences of USF depletion on the gastric pathogenicity associated to *H. pylori* infection, a mouse model will also be used including USF1 Knock-out and wild-type mice. The second part of the project will compare the deregulation of the USF1 levels by various *H. pylori* clinical isolates from gastritis and gastric cancer patients and will focus on the identification of *H. pylori* factors responsible for the deregulation of USF1 and its target genes. This includes characterization, by biochemical and genetic approaches, of *H. pylori* candidates based on their ability to deregulate USF1 gene expression in gastric epithelial cells *in vitro*.

In conclusion, this project will combine different complementary approaches that will allow further insights in the role of these pleiotropic transcription factors and their involvement in mechanisms leading to severe clinical outcome of *H. pylori* infection. It will also lead to the characterization of new *H. pylori* virulence factors with potential oncogenic properties.

References:

1. *Touati et al, (2003) Chronic Helicobacter pylori infection induce gastric mutations in mice. Gastroenterology,* ***124****, 1408-1419*
2. *Machado AM et al (2009) Helicobacter pylori infection influences genetic stability of nuclear and mitochondrial DNA. Clinical Cancer Research,* ***15****: 2995-3002.*
3. *Touati**E.**(2010) When bacteria are mutagenic and carcinogenic: lessons from H. pylori. Mutation Research.* ***703****: 66-70.*
4. *Bussière et al, (2010) H. pylori-induced promoter hypermethylation downregulates USF1 and USF2 transcription factor gene expression. Cellular Microbiology,* ***12****: 1124-1133.*

*Other publications from the group:*

1. *Majlessi et al, (2017) Colonization with Helicobacter is concomitant with modified gut microbiota and drastic failure of the immune control of Mycobacterium tuberculosis. Mucosal Immunology, Feb 1. doi: 10.1038, PMID:28145441*
2. *Fernandes J et al (2014) Circulating mitochondrial DNA level as a potential non-invasive biomarker to the early detection of gastric cancer. Cancer Epidemiology, Biomarkers and Prevention,* ***23****: 2430-2438.*
3. *Correia M, et al (2013) Crosstalk between Helicobacter pylori and gastric epithelial cells is impaired by docosahexaenoic acid. PLoS ONE****, 8****: e60657.*
4. *Gomes J, et al (2012) Pteridium aquilinum and its ptaquiloside toxin induce DNA damage response in gastric epithelial cells, a link with gastric carcinogenesis. Toxicological Sciences,* ***126****: 60-71.*

Expected profile of the candidate (optional):

The candidate should have solid knowledge on Microbiology, Molecular and Cellular Biology, Host-pathogens interaction. She/he should be able to work with the mouse model.

Contact:

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