**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:** Generation and Identity of long-lived B cell Plasmocytes

**Keywords:** Plasmocytes, B cell memory, autoimmune diseases, rituximab treatment

**Department:** Immunology

**Name of the lab:** Antibodies in Therapy & Pathology

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***Doctoral school affiliation and University*:** ED 394 - UPMC Sorbonne Universités

Ecole Doctorale Physiologie, Physiopathologie et Thérapeutique

Presentation of the laboratory and its research topics:

**Antibodies in Therapy & Pathology**: Our research unit is composed of 14 members (4 researchers, 2 post-docs, 5 PhD students, 2 technicians, 1 engineer) that work on both human samples and mouse models. We specialize in antibodies and their functions in disease and therapy: Antibodies are key effectors of the immune system. They are responsible for disease induction (autoimmunity, allergy) and can provide protection against infections and tumors. The Unit of Antibodies in Therapy and Pathology proposes to (1) decipher the role of human antibodies, human antibody receptors (FcRs), and the cells expressing them, in the induction of allergic shock (anaphylaxis), rheumatoid arthritis and in immunotherapy of tumors or inflammatory diseases using mainly mouse models; (2) to map and track antigen-specific antibody production *in vivo* using microfluidic technologies. Since 2015 we have indeed developed droplet microfluidics capabilities in the lab to address biological question with high-throughput single cell technologies. We believe this technology pipeline to allow us to address novel biological questions on the immune system and, as a first focus, on antibody diversification and plasma cell biology.

*For more info, refer to the lab website.*

Description of the project:

*(1 page, Arial font size 11: 600 words in total with at least 50% dedicated specifically to the proposed PhD project(s))*

**Generation and Identity of long-lived B cell Plasmocytes**

**Background**: In both mice and men, B cell memory is maintained by two distinct cell populations, acting differently: long-lived memory B cells (LMB) and long-lived plasmocytes (LLP):

- LMB express but do not secrete antibodies, and are mainly localized in the spleen. They have been subjected to affinity maturation and selection and, following a novel encounter with the antigen, they are able to quickly generate an efficient secondary response by producing high affinity antibodies of the IgG class. Depending on the type of antigen, LMB can display a very long lifespan, up to a human lifespan.

- LLP continuously secrete high level of antibodies and are preferentially localized in the bone marrow. Their persistence depends upon the presence of a given cellular and cytokine environment, including CXCL12, BLyS and APRIL. Their precursors, generation and the maintenance of LLP remain poorly described.

B cells are responsible for autoreactivity and autoantibody production in several autoimmune diseases. A clinically approved therapeutic antibody targeting a B cell marker, CD20, is used to treat some autoimmune diseases, such as autoimmune pemphigus and idiopathic Purpura (ITP). Massive injection of the anti-CD20 antibody rituximab leads to the depletion of most circulating B cells. However, it is not effective in all patients and in some cases following rituximab treatment the development of new population of LLP is induced in the spleen, hypothetically due to the change of the cytokine environment provoked by the treatment. These LLP are thought to be responsible for renewed autoantibody production and disease.

In this context, understanding the generation of LLP and their repertoire is of acute interest and could have profound implications in the treatment of human autoimmune diseases.

**AIMS OF THE PhD PROJECT**:

* Understand the mechanisms underlying LLP generation.
* Identify LLP precursors
* Characterize the affinities and repertoire of LLP antibodies
* Define the LLP cytokine niche and its impact on the development of splenic LLPs.

**METHOD**:

I. Mouse models

To achieve these goals, we will use a mice model expressing human CD20 and inject anti-CD20 (rituximab) to deplete B cells. We will then analyse the generation of LLP in the spleen of rituximab-treated mice as compared to control mice, treated with an irrelevant antibody. We will study the repertoire of the newly produced LLP, at the single cell level, and will compare the repertoire of both LLP and SLP, aiming to determine if one can be generated from the other. In addition, we will alter the cytokine niche (injection of blocking antibodies) to try to modify/block/enhance LLP generation, and understand the precise cytokine combination necessary for LLP development.

II. Human samples

What happens during rituximab treatment in humans? Our laboratory has already set up collaboration with nearby hospital department allowing us an access to samples from rituximab-treated autoimmune patients. Patients that are resistant to rituximab therapy are splenectomized as a last-chance treatment. We will therefore evaluate if the success (or not) of rituximab treatment is correlated (or not) with the apparition of LLP in the spleen (from splenectomised patients where the rituximab treatment has failed). Lastly, we will study how to efficiently neutralize the production of the potentially harmful LLP.

From both species (mouse and human) sorted LLPs will be screened for affinity of their antibody for the target antigen, and their repertoire characterized by single-cell sequencing of their variable antibody genes.

EXPECTED OUTCOME:

This PhD project aims at understanding LLP generation by identifying their precursors, the required cytokines and their repertoires. The translational part of this project should enable to understand the current limitations in anti-B cell treatment in patients suffering from autoimmune diseases, and understand the cellular source of treatment resistance.

References:

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Expected profile of the candidate (optional):

Candidates should be highly motivated and enjoy working in a stimulating and international environment. Training in immunology is required; experience with B cells or antibody repertoires is a plus. Proficiency in English is required. The candidate will be trained on the appropriate technologies in the lab or partner labs on campus.

Contact: **Dr François Huetz**

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