Caveolin Expressions & Functions in Activated B Cells and Plasma Cells

- ANR-2019 project sCAV-BandPC -

Inserm U1236 (University of Rennes) & Inserm U1143 (Curie Institute, Paris)

Post-Doctoral Fellowship

CSS	**5**
Offer description	B cells are the main cells of the adaptive immune response being able to give rise to antibody-producing effector cells, plasma cells (PC), or to memory B cells. Understanding the B cell differentiation into PC is essential because this complex process, which involves a great diversity of tissues (blood, spleen, bone marrow), induces deep cellular modifications including vast internal membranes reorganizations necessary for the acquisition of immunoglobulin (Ig) secretion. Thanks to transcriptomic and functional experiments, we identified *CAV1*, the gene encoding Caveolin1 protein (Cav1), as one of the first genes induced in PC progenitors after B cell activation, this expression being maintained in mature PCs. After siRNA blocking of *CAV1* expression, cells showed several modifiedfunctions, including Ig secretion, PC responses to TGFβ and cell response to the endoplasmic reticulum stress and autophagy. Cav1 is known as a mandatory constituent of caveolae, invaginations of the plasma membrane characterized by their capacity to impact cell response to mechanical constraints [ref?]. Our preliminary analyzes on PC progenitors revealed two unusual facts: 1) expression of the rarer and under-studiedCav1-beta isoform, and 2) a lack of expression of other proteins constitutive of caveolae. These results signify a peculiar situation for Cav1 in the B cell lineage and prompted us to address a provocative hypothesis that this protein would act in internal membranes via a free form, forming clusters that could disassemble after mechanical stress. This project gives the opportunity to join two complementary expertise, B cell immunology (U1236) and cell biology (U1143), to explore new cellular mechanisms driven by Cav1 in the context of B cell differentiation, PC development and PC identity maintenance. We will focus our work on human B cells and primary cell cultures as well as PC cell lines. Several tools have been developed to modulate the expression of selected genes, which makes it possible to dissect various steps characterizing B cell commitment in PC. **Three main objectives will be followed**: **1**) To characterize the regulation of *CAV1* gene expression during the B cell differentiation, the goal is to decipher the connection between the transcriptional cascade governing the step-wise differentiation process and the emergence/maintenance of *CAV1* expression in cells that initially lack its expression; **2**) To study the role of non-caveolar Cav1 protein in internal membranes dynamics and cell signaling, with a special interest for the JAK / STAT and TGFβ / BMP signaling; **3**) To explore the role of Cav1 in Igs secretion, autophagy, UPR response and cell survival, all these functions being required for PC long-term maintenance. **The post-doctoral fellow will be fully in charge of the first objective, largely implicated in the second and partially in the third.**
Researcher profiles	☐ First-Stage Researcher *(PhD candidate)* X Young Researcher (*with less than 4 years research experience after PhD)* X Established Researcher *(with more than 4 years research experience)* ☐ Senior Researcher
Research Fields (2 max.)	x Biological Sciences ☐ Chemistry ☐ Computer Science x Medical Sciences ☐ Neurosciences ☐ Pharmacological Sciences

	☐ Engineering ☐ Physics ☐ Environmental Science ☐ Technology ☐ Ethics in Health Sciences ☐ Other (specify):
Main Activities	**1)** To characterize the regulation of *CAV1* gene expression using genomic and molecular approaches **2)** To study functional aspects of modified B and PC primary and cell lines and especially on the JAK/STAT and TGFß pathways.
Associated Activities	This project is part of a collaboration and a gathering and sharing of skills between two Partners: Thierry Fest (INSERM U1236, university of Rennes) and Christophe Lamaze (INSERM U1143, Institute Curie, Paris). Our consortium represents a perfect combination of expertise and advanced technologies including: primary human B cell differentiation, NGS, Bioinformatics, tools for endocytosis and membrane trafficking studies, Ig investigations, cell signaling. Teams have access to updated research facilities that allow to perform original studies. The post-doctoral fellow will be under the direct supervision of Thierry Fest. The work will be mainly localized in Rennes' lab but some techniques and insights may be performed in Paris. English & French are the commonly used languages in the lab.
Specific Requirements or Constraints	The post-doctoral candidate will have excellent knowledge in molecular biology, gene transcription & regulation, mutagenesis, functional genome explorations and knowledge to decipher a cell signaling pathway (ideally JAK/STAT or TGFß/BMP).Knowledge in bioinformatic and immunology (ideally B-cell biology) are not a requisite but would be appreciate.
Skills/Qualifications	Position open for French, people form European Community and people outside Europe. This post-doc position could also be an opportunity for young researcher to complete their CV and compete for a permanent research position in France and elsewhere.
Required Experience	X 0 to 2 years X 2 to 4 years X 4 to 10 years ☐ >10 years **Fields: Cell Biology & Gene Regulation**
Required Education Level or Diploma	• Ph.D.
Required Languages	• English
Hosting Unit	
Code	UMR INSERM U1236
Name	MICMAC - MIcroenvironment, Cell differentiation, iMmunology And Cancer
Director	Pr Karin Tarte
Composition	https://micmac.univ-rennes1.fr
Address	Faculté de médecine - Bâtiment 2 - Etage 1 2 avenue du professeur Léon Bernard - CS 34317 35043 Rennes, FRANCE
Website	https://micmac.univ-rennes1.fr/differenciation-lymphocytaire-b-normale-et-tumorale-0
Contract	
Type	The post-doctoral fellow will be employed by INSERM
Duration	Initial contract of 24 months (+ 12 months secured)
Salary	2200 to 2500 € per month, depending on previous experience.
Envisaged Start Date	**Sometimes in 2020**

Application

Applicants must send a CV and a cover letter to:

Thierry Fest thierry.fest@univ-rennes1.fr,

Contact for further information:

https://micmac.univ-rennes1.fr/differenciation-lymphocytaire-b-normale-et-tumorale-0

Deadline for application:

February 2020