PhD Research Proposal Form
China Scholarship Council (CSC) - ENS Group

FIELD: Biology
(eg: Mathematics, Physics, Sociology, ….)

Thesis subject title: Regulation of inflammation (*in vivo* murine models and cell biology approaches)

Name of the French doctoral school: Ecole doctorale: BMIC (biologie moléculaire integrative et cellulaire)

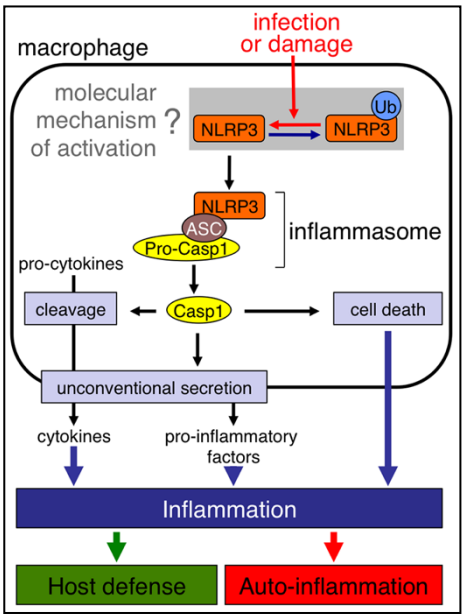
Name of the Research team: Lab CIRI-Team NLRP3 inflammasome
Website: http://ciri.inserm.fr/en/team/all-teams/nlrp3-inflammasome/fields-of-research/

Name of the Supervisor: Dr Bénédicte PY
Email: benedicte.py@inserm.fr

Lab Language: English

Research Proposal Abstract:
Appropriate inflammatory response efficiently participates in protection against infections and mediates tissue repair. Adversely chronic or excessive inflammation fuels pathogenesis of a large set of conditions including gout and Alzheimer's diseases, type 2 diabetes, atherosclerosis and cancer, and causes deleterious genetic autoinflammatory syndromes that can be lethal. Therefore, we decipher the molecular mechanisms regulating inflammation in order to identify new therapeutic targets and genetic susceptibility factors for these multifactorial conditions.

At the molecular level, inflammation is triggered by the detection of pathogen- and damage-associated molecular pattern (PAMP and DAMP) through a repertoire of pattern recognition receptors (PRR). PAMPs are typically molecular structures essential and unique to microorganisms but absent /from the host. DAMPs are inflammatory stimuli resulting from cellular damage or metabolic stress. PRRs are highly diverse in their specificities, subcellular localizations and downstream signaling pathways. We are currently focusing on NLRP3, a cytosolic PRR involved in numerous highly prevalent human pathologies aforementioned. In addition, mutations in *NLRP3* are associated with genetic autoinflammatory syndromes named CAPS. NLRP3 activation leads to the assembly of an oligomeric complex named inflammasome, serving as an activation platform for caspase-1. Caspase-1 protease then controls maturation and secretion of key proinflammatory cytokines and can trigger a proinflammatory form of cell death.



NLRP3 does not directly bind its diverse activators and we still know very little about the molecular mechanism of NLRP3 activation. **We discovered that inflammasome assembly is regulated through NLRP3 ubiquitination level**

and identified a key ubiquitination site. We generated knock-in mice mutant for this ubiquitination site, and mutant primary macrophages from these mice show defect in negatively controlling the inflammasome. These results confirm the key functional role of this modification in NLRP3 biology.

The recruited student will participate in characterizing the role and regulation of this ubiquitination in NLRP3 activation. The student will characterize the inflammatory phenotype of the mutant mice by *in vivo* study (with the help of an assistant engineer), as well as deciphering the signaling pathway in primary macrophages using a variety of approaches including cell biology (macrophages extraction from mice and purification of human monocytes, in vitro cell culture and treatment, siRNA tranfection, immunofluorescence) and biochemistry (co-immunoprecipitation, western-blot, ELISA test).

This project is co-funded by the ERC (ERC-2013-CoG_616986 to BP), the FINOVI foundation, and the IDEX.

References:

Groslambert M, **Py BF** : Spotlight on the NLRP3 inflammasome pathway. **J Inflam Research**. 2018 1:359-374. Review.

- Yuan J, Najafov A, **Py BF** : Roles of caspases in necrotic cell death. ***Cell***. 2016. 167(7):1693-1704. Review.
- **Py BF**, Desai BN, Jin M, Penumaka A, Zhu H, Kober M, Dietrich A, Lipinski MM, Henry T, Clapham DE, Yuan J : Caspase-11 controls interleukin-1beta release through degradation of TRPC1. ***Cell Reports***. 2014 6(6): 1122-8.
- **Py BF**, Kim MS, Vakifahmetoglu-Norberg H, Yuan J : Deubiquitination of NLRP3 by BRCC3 critically regulates inflammasome activity. ***Molecular Cell***. 2013 49(2): 331-8.
- **Py BF**, Gonzalez SF, Long K, Kim MS, Kim YA, Zhu H, Yao J, Degauque N, Villet R, Ymele-leki P, Gadjeva M, Pier GB, Carroll MC, Yuan J : Cochlin produced by follicular dendritic cells promotes anti-bacterial innate immunity. ***Immunity***. 2013 38(5): 1063-72.

Type of PhD :

Full PhD

- Joint PhD/cotutelle (leading to a double diploma): YES
- Regular PhD (leading to a single French diploma) : YES