Offre de stage de Master/Master Internship offer

Tuteur du stage et Laboratoire d'acceuil/ Internship supervisor and Host laboratory:

CIRI, Centre International de Recherche en Infectiology, Inserm U1111, CNRS UMR5308

Team: Inflammasome, bacterial infections and auto-inflammation, PI: Thomas Henry

http://ciri.inserm.fr/en/team/all-teams/inflammasome-bacterial-infections-and-autoinflammation/research-themes/

Research project: **Identification of a phosphatase regulating the Pyrin inflammasome: implication for Familial Mediterranean Fever**

Description du projet/Project description: Familial Mediterranean Fever (FMF) is a human auto-inflammatory disease associated with inflammatory flares, recurrent fevers and abdominal pain. If untreated, the chronic inflammation can lead to kidney failure. The recurrent inflammation observed in FMF patients is due to mutations in the *MEFV* gene encoding Pyrin. Pyrin is an inflammasome sensor, which detects bacterial toxins leading to activation of the pro-inflammatory caspase, caspase-1, the release of inflammatory cytokines and cell death. The inflammasome is the multi-molecular complex in which caspase-1 activation takes place. Pyrin deregulation is associated with recurrent inflammation and is causing the symptoms in FMF patients.

The Pyrin inflammasome is highly regulated and it is known that the kinases PKN1/2 are required to maintain the Pyrin inflammasome inactive. We have strong preliminary evidence indicating that a phosphatase is balancing the activity of the kinases and is required for Pyrin inflammasome activation. The goal of this project is to identify the molecular nature of the phosphatase and to understand its role in regulating the Pyrin inflammasome in normal (response to bacterial toxins) and deleterious contexts (FMF).

The candidate will perform a subgenomic CRISPR/Cas9 screen to identify the phosphatase and the proteins involved in targeting the phosphatase to the Pyrin inflammasome. The candidate will perform molecular and cellular techniques (cloning, cell culture, lentiviral transduction, western blotting). Inflammasome activation will be monitored by confocal microscopy (Formation of the multi-molecular complex), real time cell death and ELISA.

The long-term goal of this project is to be able to assess the therapeutic potential of the identified phosphatase to treat FMF patients or bacterial infections.

Recent publications of the team (see https://scholar.google.fr/citations?user=-qfgJYsAAAAJ&hl=en for full list):

1-The Pyrin inflammasome: from sensing RhoA GTPases-inhibiting toxins to triggering autoinflammatory syndromes (Review)- Jamilloux Y, Magnotti F, Belot A, Henry T. **Pathogens and Disease**, 2018 March 28

2-LPS targets host guanylate-binding proteins to the bacterial outer membrane for non-canonical inflammasome activation. Carlos Santos J, (...), Henry T, Broz P. **The EMBO Journal**, 2018 Feb 19

3-Human caspase-4 detects tetra-acylated LPS and cytosolic Francisella highlighting functional differences with murine caspase-11. Lagrange B, (...), Henry T. **Nature Communications**, 2018 Jan; 9 (1), 242

4-Familial Mediterranean fever mutations are hypermorphic mutations that specifically decrease the activation threshold of the Pyrin inflammasome. Jamilloux Y (...) Henry T. **Rheumatology**, 2018 Jan 1.

5-IFN-γ extends the immune functions of Guanylate Binding Proteins to inflammasome-independent antibacterial activities during *Francisella novicida* infection. Wallet P, (...), Henry T. **Plos Pathogens**, 2017 Oct2;13(10).

Please apply by sending your CV and a motivation letter to mailto:thomas.henry@inserm.fr