

Department of Veterinary Medicine

Available PhD Project:

Supervisor: Professor Clare Bryant

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Project Title: The mechanistic basis for inflammasome formation

Description: The inflammasome is a macromolecular protein complex composed of a Nod-like receptor (NLR), an adaptor protein ASC and effector caspases that are responsible for driving the production of pro-inflammatory cytokines and macrophage death in response to infection and damage associated molecules. We showed that NLR-induced inflammasome activation is characterised by formation of an ASC speck within the cell that recruits effector caspases to tailor the inflammatory response (1). Our work has also shown that actin reorganization is a critical process involved in inflammasome activation (2). Dysregulation of inflammasome activity is associated with many common chronic inflammatory diseases for example type II diabetes, atherosclerosis, Alzheimer's disease and gout. Patients with mutations in different NLRs have constitutively active inflammasomes but this differentially affects speck formation (either no speck is formed or many specks are formed). The net result of the NLR mutations is to induce serious auto-inflammatory diseases in these patients. The hypothesis of this project is that the inflammasome will recruit different effector proteins depending upon the functionality of the NLRs and caspases within the cell.

In this project the student will:

1. Determine the constituents of the inflammasome speck in cells from patients carrying NLR mutations (in collaboration with colleagues at NIH, USA and in Dresden, Germany).
2. Investigate how the actin cytoskeleton impacts on inflammasome activation
3. Determine whether the molecular mechanisms by which patients suffering from immune disorders due to actin cytoskeleton dysfunction are linked to NLR activation.

Skills to be learnt by the student:

- Cutting edge imaging techniques (including live single cell imaging, super resolution microscopy and single molecule fluorescence techniques),
- classical biochemical techniques,
- molecular biology techniques
- cell biology studies.

References:

1. Man et al., 2014, Proc Natl Acad Sci 111(20):7403-8.
2. Man et al., 2014, Proc Natl Acad Sci (In press).

Funding:

This project is not funded. Prospective students would be expected to apply for funding opportunities either through the University (<http://www.vet.cam.ac.uk/grad/Prospectivestudents/funding>) or other sources.

How to apply:

Contact the Supervisor to discuss before submitting an application.

More details on how to apply here: <http://www.vet.cam.ac.uk/grad/Prospectivestudents/apply>