Available PhD Project:

**Supervisors:** Dr Steve Webster and Professor Clare Bryant

**Project:** Exploring aberrant inflammasome activation in chronic granulomatous disease

Innate inflammatory responses are essential for host defence against microbial pathogens. However, chronic or dysregulated innate inflammation underpins a multitude of human and animal intractable diseases such as; cancer, cardiovascular disease, diabetes, rheumatoid arthritis and inflammatory bowel disease. Studying inflammatory responses in humans with defective innate immune systems is a powerful way of determining how innate immunity is regulated. Individuals with genetic mutations in the genes that comprise the NADPH oxidase system develop a primary immunodeficiency called chronic granulomatous disease (CGD). Affected individuals are immunocompromised as a result of their inability to generate reactive oxygen species (ROS) within their phagocytic cells. Paradoxically, despite their immunocompromised state, CGD patients display a hyper-inflammatory phenotype, resulting in granuloma formation and colitis that bears strong resemblance to Crohn’s disease. Importantly, studies have identified that IL-1 receptor signalling may underpin CGD patient colitis. The IL-1 family of cytokines require proteolytic maturation and secretion via a non-classical pathway that is dependent on membrane gasdermin D pore formation. Inflammatory caspases are central to this process and are activated by intracellular protein molecular scaffolds termed inflammasomes. This indicates that aberrant inflammasome activation in CGD, and possibly other chronic diseases, causes dysregulated inflammation and hence disease. Interestingly, we have identified that inflammasome responses to live, intracellular bacterial infection, but not sterile agonists, are significantly elevated in macrophages from NADPH deficient mice and myeloid cells from CGD patients compared with healthy donors. Additionally, we have identified that mitochondrial ROS drives the excessive inflammasome activation. There are two specific aims of this project: (1) identify which inflammasomes are aberrantly activated in the absence of NADPH oxidase activity following intracellular bacterial infection and (2) investigate the molecular mechanisms that contribute to mitochondrial ROS generation and excessive inflammasome activation in CGD patients. We will adopt a candidate gene approach and use genetically deficient mice and specific pharmacological inhibitors to probe mechanisms of inflammasome regulation which will be then be expanded in to include tissue from human CGD patients. The outcome of this project will provide valuable information about potential therapies for a debilitating human disease i.e. CGD colitis, and will also provide information which helps us understand how innate inflammatory responses are regulated at the molecular level in humans.

This project will provide opportunities to learn skills in (but not limited to): Microbiology, host:pathogen interactions, genetic manipulation, microscopy/imaging techniques, general molecular biology techniques, data presentation and statistical analysis.

**Funding:**

This project is not funded. Prospective students would be expected to apply for funding opportunities either through the University or other sources. ([https://www.vet.cam.ac.uk/study/postgrad/funding](https://www.vet.cam.ac.uk/study/postgrad/funding))

**How to apply:**

Contact the Supervisor to discuss the project before submitting an application.

More details on how to apply here: [https://www.vet.cam.ac.uk/study/postgrad/apply](https://www.vet.cam.ac.uk/study/postgrad/apply)