Candidate Information

Position:	Research Fellow
School/Department:	School of Medicine, Dentistry and Biomedical Sciences
Reference:	19/107521
Closing Date:	Monday 1 July 2019
Salary:	£33,199 - £34,189 per annum
Anticipated Interview Date:	Wednesday 10 July 2019
Duration:	12 months

JOB PURPOSE:

A Postdoctoral Research Fellow position for an PhD with training and demonstrated abilities in cell biology/cellular immunology/cellular microbiology is available in the Valvano group to investigate the inflammasome in human CFTR-defective macrophages and monocytes. Infection and chronic inflammation in patients with cystic fibrosis (CF) lead to progressive lung damage. CF-defective macrophages fail to kill engulfed opportunistic pathogens such as Burkholderia cenocepacia. Engulfed pathogens disarm macrophages and counteract immunity by deploying proteins (effectors) that alter central cellular pathways including actin cytoskeleton remodelling. Pathogen-induced disorganization of the actin cytoskeleton is both a remarkable anti-host strategy and a danger signal driving inflammation and cell death. However, the actin cytoskeleton dynamics in the context of the CF defect has not been explored. We hypothesize that intracellular opportunistic pathogens engulfed by macrophages, in combination with the CF genetic defect, induce disorganization of the actin cytoskeleton that leads to a highly proinflammatory state. Our research established B. cenocepacia as a model organism for cellular microbiology. We discovered that a B. cenocepacia type VI-secretion system (T6SS) disrupts the macrophage's actin cytoskeleton and elicits pyroptosis (proinflammatory cell death), and we recently identified TecA as the T6SS protein responsible for these phenotypes by causing the direct inactivation of Rho GTPases, which in turn activates the Pyrin inflammasome and the ASC complex formation. We will investigate here the relationship between inflammation and B. cenocepacia-mediated modulation of macrophages' actin cytoskeleton in CFTR-defective human monocytic macrophages. We will address 2 specific aims: (1) To assess the status of the pyrin inflammasome in B. cenocepacia-infected, CFTR-defective peripheral monocytes; and (2) To evaluate the role of the B. cenocepacia T4SS and T2SS systems in the activation of ASC-dependent inflammasomes upon infection in human macrophages. The successful candidate will work in partnership with members of the Valvano group, plan and perform experiment and will also be involved supervision and training of junior lab members.

MAJOR DUTIES:

1. Design and construct gene deletions in Burkholderia secretion systems, appropriate effector proteins.
2. Undertake the preparation and differentiation of human peripheral lymphocytes into monocytic macrophages.
3. Perform assays to determine the status of the inflammasome in these cells upon infection with wild type bacteria and specific mutants.
4. Characterize the intracellular bacterial trafficking by fluorescence microscopy.
5. Cell fractionation of cellular compartments to identify inflammasome components.
6. Undertake experimental protocols to ensure delivery of experimental data in a timely and rigorous manner. Where possible, these should be done according to existing Standard Operating procedures and the Good Laboratory Practice-like standards.
7. Prepare and maintain adequate laboratory records of methods, sample details and results in a timely fashion within specific studies.
8. Adequately operate analytical instruments, and when required, contribute to the development of new or improved methods/techniques to assess protein quality, level of glycosylation, immune responses, and infection based on technical knowledge and experience.
9. Undertake development/training courses as necessary to keep knowledge and skills up to date and relevant for subject specialism. Apply working knowledge of theory and practice, sharing this knowledge with others as appropriate.
10. Provide training to other members of the Valvano group in related projects.

11. Where necessary, prepare and/or update Standard Operating Procedures for protocols related to the research in the laboratory.
12. Comply with Health and Safety procedures affecting self and others and ensure Health and Safety practices and abidance to SOPs by lab members are maintained to the highest possible standards.
13. Carry out any other duties which are appropriate to the post, as may be reasonably requested by the Supervisor.

Planning and Organising:

1. Carry out without supervision a range of tasks largely but not exclusively according to established procedures.
2. Prioritise own work within a general plan to meet targets and deadlines.
3. Ensuring reagents, consumables and equipment are available for experiments.
4. Assist in the optimisation of new techniques or use of new reagents and troubleshoot as required.

Resource Management Responsibilities:

1. Support student learning through the development and demonstration of standard equipment and techniques.
2. Where appropriate carry out some training of laboratory staff.

Internal and External Relationships:

1. Daily contact with Supervisor, work colleagues, University staff and students.
2. Some contact with laboratory sales representatives and maintenance engineers.
3. Attendance and involvement at seminars and research meetings in the CEM.

ESSENTIAL CRITERIA:

1. PhD in microbiology, immunology, innate immunity, cell biology or equivalent subject.
2. At least 3 years recent relevant work experience to include:
   â€¢ microbiology/immunology/biochemistry research including general experience in a wide range of laboratory methods.
3. Well-developed understanding of relevant regulations and procedures including Health and Safety requirements and of COSHH regulations.
4. Good communication and interpersonal skills.
5. Ability to develop proficiency in and demonstrate standard equipment and techniques.
6. Ability to prioritise own work within a general plan to meet deadlines.
7. Ability to carry out practical laboratory tasks to a consistently high standard.
8. Ability to keep accurate records and provide reports on project progress.
9. Ability to train junior staff and allocate work.
10. Analytical and problem-solving skills.
11. Ability to work in a team and independently.
12. Due to the nature of the projects, flexibility of working hours will be required.

DESIRABLE CRITERIA:

1. PhD in cellular microbiology or inflammation biology/innate immunity or equivalent qualifications in microbiology, molecular genetics, biochemistry or another similar subject.
2. Experience in microbial culture, microbial genetics, Crispr-cas mutagenesis, cell culture, cell flow, immunology methods, western blot analyses, phosphorylation pathways, protein purification.
3. Understanding of Good Laboratory Practice.