Project Details	
Project Code	MRCIIAR24Br Cadby
Title	Unlocking immune cells with tick-borne pathogens
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Tick-borne Anaplasma are bacteria that infect the immune cells of diverse organisms. To achieve this feat, they produce specialised proteins that reprogram these host cells, disabling multiple innate immune functions and turning normally hostile cells into a permissive niche for pathogen replication. In this project you will use multi-disciplinary approaches to discover the specific mechanisms underpinning these phenomena.
Description	In this project we will use tick-borne pathogenic bacteria as a molecular tool-kit for unlocking immune cells. These discoveries will help us combat tick-borne disease and provide a basis for manipulating immune cells, impacting on a wide range of diseases. Anaplasma are tick-borne pathogens that cause disease in a wide range of different organisms including humans and have massive impacts on global livestock industries. These bacteria are experts at manipulating host cells for survival and proliferation and can only replicate inside the cells of host organisms. Anaplasma phagocytophilum infects the neutrophils and hemocytes of their mammalian and tick hosts, respectively. This is a remarkable lifestyle as these are front line immune cells that are equipped with potent microbe-killing activities. As such, A. phagocytophilum is able to modulate the innate immunity of diverse organisms to enable its survival. To achieve this, A. phagocytophilum produces an array of specialised proteins that it secretes into host cells and which target host signalling proteins, modifying their activities to favour the bacteria and cause disease. A. phagocytophilum cause extensive changes in immune cell functions including inhibition of apoptosis, loss of phagocytosis, and modified chemokine and cytokine production. Understanding how these specialised proteins function is crucial for us to understand how A. phagocytophilum cause disease, for directing novel host- and pathogen-directed therapeutic strategies, and for identifying new diagnostic markers. In addition, these proteins represent a molecular tool kit for manipulating neutrophils and, since these cells are involved in a wide range of different diseases, have great potential as research tools or as therapeutics in their own right. In this project, you will use multi-disciplinary approaches including molecular-, micro-, cell- and structural-biology to uncover how A. phagocytophilum proteins manipulate immune cells. Your objectives are: 1) Determine what host targets Anaplasma proteins bind to and where this occurs in host cells. Key approaches: microscopy and immunoprecipitations. 2) Identify the molecular basis for Anaplasma protein interactions with host targets. Key approaches: protein expression, purification and interaction assays. 3) Uncover the how Anaplasma proteins influence immune cell functions. Key approaches: phagocyte assays and mutagenesis. At the beginning of the project you will learn some of the key approaches using tried and tested systems, and use bioinformatics approaches to explore Anaplasma proteins of interest. During this period you will get equipped with the basic skills needed to tackle the project and how to generate hypotheses for you to investigate. Our research approach affords a great

	amount of intellectual freedom allowing you to tailor your project and specialise your training to personal preferences as you progress. During this training period you will contribute to an existing research project, allowing you the chance to contribute to a manuscript, develop writing skills, and be an author on high-impact publications. Following this initial training period, we will support you as you drive your project. You will be afforded training opportunities in our laboratories at the University of Bristol (Cadby, Mann), the University of Exeter (Ballou), and beyond (for example, with our international collaborators, such as Prof Dumler, US). During the project you will learn how to be a researcher but also learn a wide-range of transferrable skills (presentation, data analysis/statistics, writing retreats), and skills highly desirable for an industry position (e.g. protein purification and biophysical characterisation). At the close of the project you will be equipped to pursue a wide range of career directions, both within and outside of academia.
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