Project Details	
Project Code	MRCIIAR26Br Cadby
Title	Tackling tick-borne pathogenic bacteria through SLiMs
Research Theme	IIAR
Project Type	Wet lab
Summary	In this PhD you will use molecular and protein biochemistry approaches to understand how Short Linear Motif (SLiM) containing virulence factors contribute to infection by the tick-borne pathogens, Anaplasma, Ehrlichia, and their relatives. You will work at the molecular scale at the host-pathogen interface, uncovering the targets of these virulence factors, how their interactions with host cell components remodels their biology to favour pathogen proliferation. Ultimately, you will uncover novel biology andexploit this information for proof-of-concept development of novel anti-infectives to combat tick-borne disease and tackle antimicrobial resistance.
Description	Tick- and vector-borne pathogens such as Anaplasma and its relatives, Rickettsiales bacteria, cause disease in humans and a wide range of animals and impact on global livestock economies. Many of these bacteria lead an obligate intracellular lifestyle and replicate inside the cells of their animal hosts. To achieve this, the genomes of Anaplasma and its relatives encode virulence factors which interact with- and subvert the biology of- the host, converting host cells to a favourable niche for survival and proliferation. Some of these virulence factors and are proteins that contain Short Linear Motifs (SLiMs), amino acid sequences that enable virulence factors to bind host proteins and have pathogenic and host subversive activities. To bind and subvert the activities of their host targets, SLiMs often use molecular mimicry and resemble house-keeping and signalling proteins that are found in their eukaryotic hosts proteins and which are responsible for normal host biology. Because of their function at the host-pathogen interface, their importance for bacterial survival, and their roles in pathogenesis, SLiM containing virulence factors represent an attractive research target to understand how Rickettsiales bacteria cause disease and for the development of novel host or pathogen directed anti-infectives. Since the use of antibiotics in livestock industries is recognised as a driving factor in the emergence of resistance, any developments in this area will help to also tackle the challenge of AMR. This project will address the over-arching question: how do Anaplasma SLiMs contribute to intracellular survival and pathogenesis, and are these proteins potential therapeutic targets? Specific objectives to address this question include: 1) Identify the host targets of Anaplasma SLiM virulence factors. 2) Determine how SLiMS interact with- and influence the biochemistry of- their cognate host targets, be they proteins or other biomolecules. 3) Explore where else these SLiMs are found, their conservation, and their possible evolutionary origins (work with Prof Preston at the University of Bath) 4) Assess the role of SLiMs in infection and the impact of their targeted inhibition.

	Key approaches in this project include: protein expression, purification, and characterisation; immunoprecipitation and immunofluorescence microscopy with infected host cells; and biomolecular and cellular assays. This list is non exhaustive, we collaborate broadly both nationally and internationally, and you will be supported to pursue your curiosity and develop skills. Current UKRI-funded work in our group includes several SLiM-containing proteins that we have identified in Anaplasma. You will have the chance to contribute to these well-developed projects whilst you train and become equipped with the skills needed to tackle your project, exploring novel SLiMs, and refine hypotheses for you to investigate. During this time and throughout the PhD, you will be supported and encouraged to develop as a researcher and take ownership of your project. Since there are more SLiMs than can be studied in a single PhD project you will be able to shape the direction of your project. Our research approaches afford a great amount of intellectual freedom allowing you to tailor your project and specialise your training to personal preferences as you progress. You will receive extensive training in protein production and structure-function analyses, molecular and cell biology approaches, infections and microscopy, 'omics approaches; and beyond through our network of collaborators (e.g. Dr Jepson, Bristol; the Tick Cell Biobank, Liverpool; Prof Dumler, US). In addition to training as a researcher, you will 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 in and outside of academia.
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