Project Details	
Project Code	MRC21IIRBa Gebhard
Title	Inhibition of signaling pathways as a novel strategy to block antibiotic resistance
Research Theme	Infection, Immunity & Repair
Summary	Antibiotic resistance is a serious threat to public health. Its first step is often through signaling pathways that trigger the bacterium's resistance mechanisms in response to a drug. This project will apply biochemistry, molecular biology and protein modelling to find inhibitors that block signaling and thus prevent activation of resistance.
Description	Antibiotic resistance is one of the grand challenges in modern medicine, with tremendous efforts invested in finding new drugs that can kill resistant microbes. This PhD project will explore an exciting alternative approach: developing anti-resistance drugs that do not directly harm the bacteria but instead reinstate the effectiveness of our existing arsenal of antibiotics. Resistance mechanisms are often tightly controlled by bacteria and only activated if an antibiotic is present. This occurs via signaling pathways that detect the presence of a drug and relay this information into the cell. Signaling can therefore be regarded as the first step of resistance. To date, anti-resistance drugs are mostly designed to disrupt the function of the resistance mechanism itself. A novelty in this PhD will be to instead target the signaling pathways and find inhibitors that block the activation of resistance. The student will focus on a histidine kinase that was shown by the lead supervisor to control resistance in many Gram-positive bacteria, including enterococci. Specifically, we will target the coiled-coil arrangement of helical domains in the kinase's catalytic core. The project's co-supervisor has pioneered the use of peptide antagonists to disrupt coiled-coil proteins, with great success in the context of cancer and neurodegenerative disease. This PhD project now brings this cutting-edge technology to bacterial signaling in a truly interdisciplinary approach to drug discovery. Building on extensive expertise in the supervisory team, the student will initially use in silico predictions to identify the most promising peptide sequences for kinase inhibition and use these as the starting point for targeted and random screens to find effective peptide inhibitors. The established screening platform for coiled-coil inhibitors is based on a bacterial system, ensuring feasibility despite the novelty of the context. Lead peptides will be characterized biochemically and in vivo to test their ability to block signaling and resistance. Using endogenous peptide production in the bacteria vs. addition of synthetic peptides will allow the student to begin exploring aspects of drug delivery, moving closer to application. The broad expertise of the supervisory team will ensure cross-cutting training in all practical and theoretical methodology. Links are in place to companies that specialise in commercialisation of peptide drugs, with expertise in reaching intracellular targets. The project also synergises with a funded international collaboration by the lead supervisor on anti-signalling drugs to target resistance. Histidine kinases are structurally conserved making results highly translatable to other resistance systems. At the same time, protein interactions are very specific allowing targeted inhibitor design to maximize selectivity and

	minimize side effects. The outcomes of this PhD project are therefore expected to open a new perspective on combating resistance.
Supervisory Team	
Lead Supervisor	
Name	Dr Susanne Gebhard
Affiliation	Bath
College/Faculty	Faculty of Science
Department/School	Department of Biology & Biochemistry
Email Address	s.gebhard@bath.ac.uk
Co-Supervisor 1	
Name	Professor Jody Mason
Affiliation	Bath
College/Faculty	Faculty of Science
Department/School	Department of Biology & Biochemistry
Co-Supervisor 2	
Name	Dr Steven Porter
Affiliation	Exeter
College/Faculty	College of Life and Environmental Sciences
Department/School	Biosciences
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	
Co-Supervisor 4	
Name	
Affiliation	
College/Faculty	
Department/School	