**University of Leicester**

**BBSRC MIBTP Studentship Project 2025-6 entry.**

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**Section 2 – *Project Information***

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| **Project Title** | How does stress make us sick? |
| **Project Summary** | |
| Stress is a potent driver of various diseases. There is strong evidence that stress decreases the effectiveness of the immune response. Much less well understood is whether and how stress directly modulates pathogens via alterations in their gene expression, phenotype, and pathogenic potential. Multiple studies suggest links between stress hormones and bacterial pathways in Gram-negative pathogens. Specifically, catecholamines (CA) released by the host can modulate the expression of virulence determinants and promote iron uptake. Further, a limited number of recent studies suggest that CAs also modulate the physiology of Gram-positive pathogens by promoting biofilms, growth or iron uptake. However, the methods by which Gram-positive bacteria detect and react to CAs signals are still unknown. The objective of this proposal is to gain basic understanding of the regulatory mechanisms, both in vitro and in vivo, that underpin the bacterial response to stress and how host cues affect them. We want to gain insights into how important human pathogen Streptococcus pneumoniae (Spn) responds to stress using in vitro, ex-vivo, and in vivo models of disease. The study builds on our recent work where we demonstrate that Spn senses CAs via a two-component system and responds by changes in growth, biofilm development and iron uptake. Moreover, we find that Spn exposure to a CA (neuroepinephrine norepinephrine (NE)) increases bacterial titres in the lung, while maintaining comparable titres in the upper respiratory tract (URT). Spn colonizes the nasopharynx as a commensal, yet it can also disseminate from the URT to the lungs, middle ear, blood, heart or brain causing mild to severe disease. We hypothesize that stress promotes the transition of Spn from a commensal to a pathogen and propose three aims to address the interaction of stress and Spn biology.    Aim 1: Characterize the molecular circuit(s) that confers responsiveness to NE and its phenotypic consequences using mutant analysis and gene expression studies.  Aim 2: Establish whether and how NE-sensing influences biofilm development and adhesion to host cells.  Aim 3: Evaluate the impact of stress hormones in a murine model of Spn infection and stress. We will use in vivo and ex-vivo studies to uncover how stress-exposed immune cells interact with Spn.    Our results could inform the development of strategies that act by disrupting damaging aspects of the hormonal-to-bacteria information exchange, and in so doing, provide new areas for prevention or treatment of Spn infections, for example by reducing stress induced infection susceptibility.    Techniques that will be undertaken during the project  Microscopy  Microbiology techniques  RNAseq  Flow cytometry  Phagocytosis assay  Array tomography  Animal models of infectious disease | |
| **References** | |
| Alghofaili F, Najmuldeen H, Kareem BO, Shlla B, Fernandes VE, Danielsen M, Ketley JM, Freestone P, Yesilkaya H. Host Stress Signals Stimulate Pneumococcal Transition from Colonization to Dissemination into the Lungs. mBio. 2021 Dec 21;12(6):e0256921. doi: 10.1128/mBio.02569-21. Epub 2021 Oct 26. PMID: 34696596; PMCID: PMC8546540. | |