**University of Leicester**

**Future 50 PhD Scholarship**

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| **Project Reference** | RS Yesilkaya |

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| **First Supervisor** | Dr Hasan Yesilkaya |
| **School/Department** | Life Sciences/Respiratory Sciences |
| **Email**  | Hy3@le.ac.uk  | **Telephone Ext** | 1401 |

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| **Second Supervisor** | Dr Primrose Freestone |
| **School/Department** | Life Sciences/Respiratory Sciences |
| **Email**  | ppef1@leicester.ac.uk | **Telephone Ext** | 5656 |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | **How does host stress transform a commensal to a pathogen?** |
| **Project Highlights:** | 1. | Determine how chemical and nutritional factors intersect with stress hormone responses to enable a shift from commensal to an invasive phenotype |
| 2. | Identify the effector and regulatory mechanisms responsive to stress hormones |
| 3. | Evaluate the impact of stress hormones on host response to Spn and determine the *in vivo*importance of the pneumococcal effector and regulatory mechanisms |
| **Project Summary**  |
| Stress is a significant pre-disposing contributor and enhancing factor for infectious diseases. Our understanding of the mechanistic basis for the effects of stress is sparse but revolves around the stress hormones’ impact on bacterial and host cells. The identification of mechanisms that allow bacteria to recognise and respond to host stress signals is a major advance raising the potential for predicting when individuals are susceptible to infections and for developing therapeutic treatments. Achieving these goals requires an enhanced understanding of the mechanistic basis of pathogen stress responsiveness. Bacterial pathogens can detect and respond to the catecholamine stress hormones, norepinephrine (NE), epinephrine (Epi), and dopamine (Dop). The knowledge of the genetic basis for microbial stress hormone responses is limited. Using *Streptococcus pneumoniae* (Spn) as a model system, we have shown that stress hormones increase the rate and yield of pneumococcal growth and reduce capsule production. Critically, NE treatment promotes pneumococcal translocation from the nasopharynx into the lungs. In a major breakthrough (1), we have identified TCS09 two-component response regulator responsible for stress hormone recognition in this Gram-positive species. We are now in a position to dissect the key mechanistic details of this interkingdom signaling phenomenon and to take a major step forward in understanding how stress induces a heightened propensity to cause disease in a major Gram-positive pathogen. In this study, we will build upon our existing work and test the hypothesis that pneumococcal translocation from the nasopharynx into the lungs is enhanced by stress hormone recognition by a complex genetic network under the environmental conditions of the respiratory tract.The project will utilise a wide range of assay platforms including microbiology, molecular biology, cell culture techniques as well as biochemical assays and mouse models of infection. Hence, both from conceptual and methodological perspectives, it offers and excellent opportunity for training. This project aims to investigate the biology of a respiratory pathogen that is the biggest cause of **bacterial** **pneumonia** focusing on **host-pathogen** **interactions** using **infection models**. 1. F. Alghofaili et al., Host Stress Signals Stimulate Pneumococcal Transition from Colonization to Dissemination into the Lungs 2021 mBio. DOI: https://doi.org/10.1128/mBio.02569-21.
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