**University of Leicester**

**Future 50 PhD Scholarship**

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| **Project Reference** | GGB Schilcher |

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**Section 2 – *Project Information***

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| **Project Title** | Mining the bacterial lipoproteome to identify novel regulatory networks |
| **Project Highlights:** | 1. | Novel regulatory networks in the human pathogen *Staphylococcus aureus* |
| 2. | Distinct biological role of bacterial lipoprotein components  |
| 3. | Interference with bacterial regulatory networks as antivirulence strategy  |
| **Project Summary**  |
| **Background:** Lipoproteins (Lpp) are present in all bacteria and play important roles in bacterial physiology and pathogenesis (1). Besides the lipid moiety and the protein part, Lpp include a third component, a small linear peptide derived from the secretion signal sequences of Lpp precursors. The latter was shown to be involved in the dissemination of antibiotic resistance in *Enterococcus* spp. (2) but the biological role of linear peptides in the human pathogen *Staphylococcus aureus* is poorly understood. We recently discovered a dedicated processing and secretion pathway for Lpp-derived linear peptides in *S. aureus* (3).In addition, preliminary data indicate distinct regulatory networks exist for the protein and linear peptide component of staphylococcal Lpp.**Objectives:** The project seeks to decipher regulatory and communication networks governed by bacterial Lpp components. While the protein component of bacterial Lpp can have diverse binding and enzymatic activities, an intriguing question is whether the secreted linear peptides act as extracellular signalling molecules. To delineate their regulatory networks, bacterial Lpp components will be analysed by an integrated -omics approach, including transcriptomics, proteomics and mass spectrometric analysis. Subsequent verification will be achieved by genetic and biochemical experiments, phenotypic screening, and *ex vivo* model systems. The objectives of this PhD project are to: ***i)***characterize the regulatory networks of Lpp components***ii)***gain a molecular understanding of their contribution to bacterial physiology and/or virulence***iii)***determine potential communication networks driven by small linear peptides**Significance:** The project will provide the student with an excellent set of skills in microbiology and host-pathogen interaction including training in bacterial genetics, transcriptomics, proteomics, protein purification, and *ex vivo* model systems.Due to the emergence of multi-drug resistant bacteria, many antibiotics have lost their effectiveness in treating life-threatening diseases. A comprehensive understanding of bacterial communication and regulatory networks is needed for the development of new therapeutics. This project will provide the foundation for new strategies to interfere with bacterial signalling and regulatory networks which can be further developed into anti-virulence therapies. (1) Braun and Hantke, Subcell Biochem. 2019.92:39-77.(2) Dunny and Berntsson, J Bacteriol. 2016.198:1556-1562. (3) Schilcher *et al*., mBio. 2020.11:e00112-20.  |