**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Single-cell analysis of macrophage-bacterium interaction at the organ level to understand infection |
| **Project Summary** | |
| Throughout their evolution, bacteria and eukaryotes have interacted setting up complex relationships. Humans and animals live in a non-sterile environment and harbour a multiplicity of bacteria. This is possible since mechanisms are in place to maintain sterility in some body compartments. The prime cell type involved in this innate cellular immunity are tissue resident macrophages. Still, there are a few occasions when bacteria escape this highly efficient monitoring causing invasive disease. This project aims to uncover the molecular and cellular events at the start of invasive infection.    Previous PhD students and post-docs working in the Department of Genetics and Genome Biology of the University of Leicester have shown that bacterial replication in specific subsets of tissue macrophages in spleen (Ercoli et al, Nature Microbiology 2018) and liver (Wanford et al., Lancet Microbiology 2021) are the initial events leading to invasive infection. To study this, the students have set up ex vivo organ perfusion models to characterise the infectious process at the whole-organ level using porcine organs from the abattoir (Chung et al., ALTEX 2019) and more recently human organs (Carreno et al., EBioMedicine 2021). The opportunity to work with human organs is a world-wide unique opportunity to investigate the dynamics of bacterium-host interaction at the organ level (Clinicaltrilas.gov NCT04620824 and NCT05255042). To be able to generate globally relevant data, the student will test multiple bacterial pathogens including *Staphylococcus* *sp*. and bacterial mutant strains in a whole panel of in vitro cell culture and in vivo infection models (Schilcher et al., mBio. 2020; Schilcher et al., The Journal of Infectious Diseases 2014) before validation in the ex vivo human organ perfusion model.    We hypothesise that there are specific events which “go wrong” in the interaction between bacteria and the tissue macrophages in spleen and liver, which then leads to invasive disease. The objectives of this PhD project are to provide qualitative and quantitative data by confocal microscopy to characterise the fate of bacteria in the first hours of infection within tissue macrophages, to characterise the mechanism of microbial killing of the different macrophage subsets using microscopy, single cell sequencing and bacterial genetics. The project will not only characterise macrophage activity, but also analyse which bacterial virulence factors and signalling systems are key players in the (re)action the bacteria put in place to escape killing. This fundamental information on cellular processes should lead the student to test known inhibitors of those processes for their ability to change the outcome of the bacterium-host interaction and prevent invasive infection. The work at the organ level will be complemented by work on primary cells in vitro and selected in vivo infection experiments in mice, to test respectively in greater detail the cellular events and the outcome of interventions. The project is designed to investigate basic molecular and cellular processes at the intersection between microbiology and immunology with a long-term aim to provide the knowledge to meliorate prevention and treatment of infectious diseases.    The project will provide the student with an excellent set of skills in many disciplines which facilitates subsequent career options. Students working previously on aspects of this project had also excellent opportunity to publish in high ranking 4-star publications which are consistently generated by the research teams.  Techniques that will be undertaken during the project:  The student will receive formal training in Good Clinical Practice and will be trained to obtain a Home Office personal licence. These courses will be completed by supervised training on specific tasks relative to human organ perfusion and animal experiments. In addition, training will be provided for biosafety bacteriological work and cell cultures. For the analysis of gene expression data, training will be provided for linux, high performance computing and command line bioinformatic analysis. Confocal and scanning microscopy training provided by the imaging facility will allow the student to become proficient in microscopy. These diverse sets of skills ranging from human organ work to microscopy and bioinformatic analysis will provide the student with a robust training highly requested in academia and industry  BBSRC Strategic Research Priority: Understanding the Rules of Life – Immunology, Microbiology | |
| **References** | |
| * Wanford et al., Lancet Microbe. 2021 Dec;2(12):e695-e703. doi: 10.1016/S2666-5247(21)00195-6. * Carreno et al., EBioMedicine. 2021 Oct 4;72:103601. doi: 10.1016/j.ebiom.2021.103601. * Musser et al., Science 2021. 374, 717–723. DOI: 10.1126/science.abj2949 * Ercoli et al., Nature Microbiology. 2018 May;3(5):600-610. doi: 10.1038/s41564-018-0147-1. * Manso et al., 2014. Nature Commun. 5:5055 doi: 10.1038/ncomms6055 | |