| Project Details | |
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| Project Code | MRC21IIRBa Sheppard |
| Title | Strain wars and the evolution of opportunistic pathogens. |
| Research Theme | Infection, Immunity & Repair |
| Summary | Many serious diseases (e.g. meningitis, pneumonia, blood/wound infections) are caused by commensal bacteria that are common on the skin or in the guts of healthy people. But what makes good strains go bad? Trained by academics and clinicians (Bath/Bristol/Cardiff), you will use laboratory techniques and state-of-the-art genome analyses to identify pathogenicity genes, strains, and evolutionary forces that cause harmless bacteria to become opportunistic pathogens. |
| Description | SIGNIFICANCE: Bacteria live in complex communities with multiple species and strains competing with each other. Victories and defeats within these microbial wars are largely ignored unless they have a noticeable impact on the environment or the host, for example when a disease causing strain emerges as a winner. Typically, people think of pathogens being transmitted from person-to-person where they cause disease in the newly infected individual. However, most pathogens do not conform to an obligate closed-system infection model. Rather, they are symbionts that have followed a new ecological trajectory. In fact, many serious diseases (e.g., meningitis, pneumonia, blood/wound infections) are caused by bacteria that are common on the skin, mucous membranes, or in the guts of healthy humans. Because of this, bacterial species such as Streptococcus pneumoniae, Neisseria meningitidis, Staphylococcus aureus, and Staphylococcus epidermidis (all of which inhabit human epithelia commensally) are often described as 'opportunist' or 'accidental' pathogens. The prevailing view, that infection is an accident of surgery, host factors or other perturbations, means that the spread of so called opportunistic pathogens are far less well understood than some more infamous pathogens, despite being (arguably) of greater clinical significance in many countries. However, pathogenicity is not an accident. In fact, the assumption that all strains in one niche (skin or mucosal epithelium) are equally able to colonize a second (subcutaneous) niche (eg. blood, meninges, lung), contradicts accepted evolutionary theories of niche transition and adaptation. By improving understanding of the strains and pathogenicity genes responsible for infection, we will inform enhanced infection control and treatment of some of the UKs most persistent and pernicious pathogens. INTERDISCIPLINARY TRAINING THROUGH COLLABORATION: The student will gain an understanding of the evolution and emergence of disease causing S. aureus, S. epidermidis, N. meningitidis, S. pneumoniae. Building on UKRI-funded work in the Sheppard lab and across the supervisory team, this interdisciplinary studentship will combine clinical expertise in microbiology and diagnostics (MacGowan, Bristol) and epidemiology (Cowley, Bath), with molecular microbiology and big data science (Connor & Sheppard; Cardiff and Bath). Using large bacterial strain (and genome) collections and novel bioinformatics approaches, including genome-wide association study approaches (GWAS) and machine learning linked to laboratory phenotypes and metadata, the candidate will identify genetic determinants of pathogenicity in commensal populations and high risk strains. Following on from the |

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| | genomic analysis, laboratory competition experiments (in vitro and ex vivo - human epithelial tissue), involving knockout mutant strains, will investigate how competition in a fluctuating immune environment leads to the maintenance of potentially pathogenic strains and genes in the population. Specifically, how pre-adaptation to low-level immune response (minor epidermal damage) allows the co-existence of strains with adaptations that are potentially beneficial in invasive disease.<br>RESEARCH WITH IMPACT: Broad expertise of the supervisory team will ensure training for the candidate in state-of-the-art practical and theoretical methodology. This program will improve understanding of why opportunistic bacteria become pathogens, when they are likely to do this and how we can interfere with their plastic responses to control virulence in a sustainable manner. Collaborations are in place within Public Health England and Wales, will test the relevance of the findings informing risk assessment, diagnosis, pre- and post- operative procedure, and targeted interventions providing immediate application of this study in a clinical context. |
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