Project Details	
Project Code	MRCIIAR24Ba Hunt
Title	Genetic signatures of parasitism in clinically important strains of a gastrointestinal parasite
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Strongyloides stercoralis is an intestinal parasite infecting over 600 million people. This project will investigate genetic features associated with the severity of infection using genome sequences from S. stercoralis collected from patients. We will also use a laboratory model for infection with S. ratti (close relative of S. stercoralis) to further test genotype-phenotype associations.
Description	Strongyloides stercoralis is a gastrointestinal parasitic nematode that infects >600 million globally and can be asymptomatic or can cause a range of gastrointestinal and skin complaints. In some cases e.g. where the patient is treated with immunosuppressants, a hyperinfection can occur which can be fatal. The aim of this project is to (i) identify genetic signatures e.g. SNPS or patterns of gene organisation associated with the severity of S. stercoralis infection, and (ii) to test the genotype-phenotype links identified in (i) using a lab based model for Strongyloides infection. We are collecting S. stercoralis nematodes from infected patients along with matched clinical data e.g. symptoms indicating the severity of infection, place of infection, parasite burden, measures of immune response, drug treatment. The genomes of S. stercoralis collected from patients will be sequenced using short and long read sequencing technologies. These data will be used to identify genetic features associated with characteristics e.g. severity of S. stercoralis infection. This project is part of a collaborative project between the Hunt lab, Dora Buonfrate (strongyloidiasis WHO liaison, IRCCS Sacro Cuore Don Calabria Hospital, Italy) and Richard Bradbury (Federation University, Australia). The laboratory methods have been established for part (i) of this project and sample collection and DNA extraction is in progress. Samples will continue to be collected throughout the duration of the proposed PhD project. Depending on the students interests, there is opportunity for the student to visit the labs of the collaborators for training in wet-lab methods such as DNA extraction from single S. stercoralis larvae. Aim (i) will focus on analysing the data generated from genome sequencing of these parasites. Aim (ii) will use the parasite S. ratti, a close relative of S. stercoralis, to further investigate the consequences of genetic signatures on infection phenotypes. Key objectives are: 1. Are specific haplotypes associated with infection severity of origin of infection? Genomic data collected for >200 S. stercoralis isolates using Illumina short read sequencing. These data will have matched clinical data (see above). Single Nucleotide Polymorphisms analysis will be carried out to identify haplotypes associated with specific features of infection e.g. severity of infection or particular immune responses. 2. Is the arrangement and organisation of 'parasitism genes' associated with infection severity? Up to 20 strains (from the 200 above) will be selected for long read sequencing using PacBio HiFi. These genomes will be assembled and annotated. We recently discovered that in S. ratti 'parasitism genes' i.e. genes upregulated during parasitism and most likely to be involved in

	manipulation of the host environment by the parasite, are physically clustered in 'parasitism islands' in the genome. We will investigate parasitism islands i.e. are they also present in S. stercoralis? What genes are clustered in these islands? 3. Using a rat-parasite lab in vivo model we will test associations and hypothesises established in #1 and #2. We will either select strains of S. ratti (maintained in the Hunt lab) with characterised genotypes or use CRISPR to test hypothesises from (1) and (2). For example, if we identify SNPs in a particular region of the genome/ particular genes we investigate strains of S. ratti will different levels of variation on the orthologous region by measuring phenotypes of infection under laboratory conditions. The balance between objectives (1), (2) and (3) can vary depending on the students' interests. For example, if they take more of an interest in bioinformatics aspects of the projects then they can focus more on (1) and (2), and they can spend more time on (3) if they are interested in developing the in vivo model. Full training will be provided for all aspects of the project.
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