

Honours Projects available in 2014.

Study the microbiology of chronic middle ear infection by participating in an Ear Surgery Trial

Summary

Hearing impairment is a serious problem in Indigenous populations living in remote communities due to the high incidence of middle ear infection. A clinical trial is underway to compare the effects of two surgical interventions in the management of chronic . There is an Honours opportunity to use microbiological analyses of nasopharyngeal swabs, middle ear effusion, auditory canal, and adenoid tissue from children undertaking these treatments to determine bacterial composition and diversity at these sites, and implications for treatment.

Supervisors:

Dr Heidi Smith-Vaughan/Dr Robyn Marsh

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Scholarship opportunities available.

Statin use in sepsis, implications for immune modulation

Summary

The tropical “Top End” of Australia (pop. 140,000) has high rates of severe sepsis and septic patients admitted to Royal Darwin Hospital (RDH) ICU have, an over-representation of Indigenous and younger patients, and several causative organisms that are rare elsewhere in Australia. The high prevalence of sepsis and its high mortality despite current treatments mean that more effective adjuvant therapies are needed. “Statins” (HMG CoA reductase inhibitors), commonly used to treat hypercholesterolaemia, have been shown to have multiple effects apart from lipid lowering. These include anti-inflammatory, immunomodulatory, and anticoagulant effects. A large retrospective cohort study (69,168 patients) has shown that those on regular statins have a significantly lower risk of sepsis and death. However, there are no published randomized controlled trials of statins for the prevention or treatment of sepsis. The immune system plays a central role in the pathogenesis of sepsis. Regardless of the cause of the infection, there are similar symptoms and sequelae in sepsis patients including dysfunctional T cells and widespread apoptosis of lymphocytes. The mechanisms underlying sepsis-related T cell dysfunction are not well understood. Our research recently described, for the first time, significant reductions in T cell zeta chain expression and T cell dysfunction in sepsis patients. We now aim to assess the impact of statin therapy in ICU patients with severe sepsis on T cell zeta chain expression and T cell function. Cells have been cryopreserved from RDH patients who participated in a multi-centre stratified prospective, randomised double-blind, placebo-controlled, phase II trial of of statins for

the prevention or treatment of sepsis. These unique laboratory based projects are suited to a person who has a passion for clinical immunology and an understanding or preferably experience with flow cytometry.

Supervisors:

Dr Tonia Woodberry/Prof Nicholas Anstey

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Malaria T cell function, why don't immune cells respond appropriately?

Summary

Malaria is a global disease caused by Plasmodium parasites with 0.5 billion clinical cases each year and a death toll of 2 million people annually. While much attention has been given to *P. falciparum* infection (which accounts for the majority of malaria-associated morbidity and mortality in sub-Saharan Africa), *P. vivax* and *P. knowlesi* are less intensively studied. *P. vivax* causes at least half of all malaria cases in Asia, with increasing evidence for severe disease manifestations and death. *P. knowlesi* is a major cause of severe and fatal malaria in Sabah, Malaysia. Acute *P. falciparum* malaria causes reductions in plasma arginine concentrations and low levels have been associated with increased mortality. Arginine is a conditionally essential amino acid that is required to maintain surface expression of a fully functional T cell receptor (TCR). Extended exposure of lymphocytes to reduced concentrations of arginine in-vitro, leads to down-regulation of one chain of the TCR receptor, CD3 zeta and T cell dysfunction. This project will examine CD3 zeta expression and T cell function in longitudinal cryopreserved PBMC samples from adults with uncomplicated vivax, falciparum and knowlesi malaria. T cell function will be compared to HPLC plasma arginine values to determine relationships between in vivo arginine concentrations and cell function.

Supervisors:

Dr Tonia Woodberry/Dr Gabriela Minigo

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Investigating the diversity of *Staphylococcus aureus* in native wildlife

Summary

Staphylococcus aureus is typically seen as a pathogen causing human disease. Based on genomic data from disease causing *S. aureus* isolates, we hypothesise that recent *S. aureus* clones have entered the human population in the Top End from animal reservoirs. This project will explore this hypothesis by sampling for *S. aureus* in bat, canine and marsupial populations and then genotyping cultured isolates.

Supervisors:

Dr Steven Tong / Dr Philip Giffard / Dr Deborah Holt

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Whole genome sequencing of epidemic Staphylococcus aureus lineages to determine patterns of local and international transmission

Summary

Recently, epidemics of different clones of Staphylococcus aureus have occurred in the community setting (as compared to within hospitals). We have obtained whole genome sequence data from >400 isolates of the ST93 clone that is currently spreading across Australia. This project will involve the bioinformatic analysis of this sequence data to determine the origins of ST93 and its subsequent spread in Australia and overseas.

Supervisors:

Dr Steven Tong / Dr Philip Giffard / Dr Deborah Holt

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Possible scholarship opportunities available.

Determining genetic susceptibility to severe influenza infections through sequencing the IFITM3 gene and HLA region

Summary

In the Top End, Indigenous Australians had 12x the risk of hospitalization compared to non-Indigenous Australians due to infections with the 2009 pandemic H1N1 influenza. It is not known whether Indigenous Australians are more genetically susceptible to severe influenza infections. This project will involve recruiting hospitalized patients with and without influenza infections and investigating their underlying DNA sequence for regions of the genome hypothesized to be associated with susceptibility to influenza.

Supervisors:

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Scholarship opportunities available.

The Australian *Leishmania* parasite: utilising PCR to study the prevalence of infection in the day feeding midge *Lasiohelea* in the Darwin region.

Summary

The parasite *Leishmania* was first discovered in Australia in 2003, infecting macropods in the Darwin region. Subsequent research revealed evidence that a novel vector, the day feeding midge *Lasiohelea*, was involved in transmission of the parasite. This project will utilise PCR and high resolution melt analysis to further examine the prevalence of infection of day feeding midges collected in the Darwin area.

Supervisors:

Dr Deborah Holt

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Investigation of the utility of a sero-diagnostic assay for evaluating scabies control programs at the population level.

Summary

Scabies is a severely itching and irritating skin disease caused by infestation with the “itch mite” *Sarcoptes scabiei*. Clinical diagnosis of scabies can be difficult due to the disease often appearing similar to other skin diseases. Population based control programs using mass drug administration need to estimate the disease prevalence in order to assess the success of the program. This project will investigate the utility of using a sero-diagnostic assay to determine the incidence of scabies at a population level.

Supervisors:

Dr Deborah Holt

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Bacteriophage immunity and staphylococcal virulence

Summary

Genes that confer virulence on the bacterium *Staphylococcus aureus* are sometimes carried on viruses (bacteriophage) that infect the bacteria. We have obtained evidence that some lineages of *S. aureus* carry a gene that may confer immunity to these bacteriophage, and this may have a significant effect on their virulence properties. This project will encompass laboratory work to determine the susceptibility of a large number of *S. aureus* isolates to several bacteriophage that

carry virulence genes, and bioinformatic analyses to identify genetic correlates of bacteriophage resistance and susceptibility. This will reveal major drivers of the evolution of bacterial virulence.

Supervisors:

Dr Philip Giffard / Dr Steven Tong/Dr Deborah Holt

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Possible scholarship opportunities available.

Transformation of *Staphylococcus argenteus*

Summary

Staphylococcus argenteus is a newly discovered taxon that is allied to the bacterial pathogen *Staphylococcus aureus*. It was discovered by this research group, and is common in the Top End, associated with skin lesions on people. We have an interest in using genetic modification methods to study the virulence properties of these bacteria. This requires the development of methods to transform isolates with foreign DNA. To date, transformation has only been possible in a small minority of isolates. The objective of this project is to perform a systematic survey of the transformability of *S. argenteus* isolates at Menzies, and to identify genetic correlates of transformability. In addition, strategies to improve transformability will be explored.

Supervisors:

Dr Philip Giffard / Dr Steven Tong/Dr Deborah Holt

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Possible scholarship opportunities available.

Factors that influence the reproducibility of high resolution melting analysis.

Summary

High resolution melting analysis (HRMA) is an increasingly popular method for performing genetic analysis. It relies on the interaction between amplified DNA and a conditionally fluorescent dye. We have recently found that the melting characteristics of the DNA are greatly affected by the DNA concentration, in the presence of LCGreenPlus, a commonly used dye. This phenomenon is highly novel and has great potential to confound HRMA. The objective of this project is to further investigate this phenomenon, and to determine if the same or similar phenomenon are observed

with other HRMA dyes such as Eva Green. This project will involve careful laboratory work and data analysis. It will assist in making HRMA validation and optimization a much more rational and evidence based process.

Supervisors:

Dr Phil Giffard, Dr Deborah Holt

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Scholarship opportunities available.

Immunological correlates of melioidosis survivors

Summary

This project will compare risk factors, clinical disease presentations, treatment and outcomes in over 800 cases of melioidosis from the 24-year Darwin Prospective Melioidosis Study. Long term survivors will be asked to consent to blood tests looking at various parameters of immunological responses to *Burkholderia pseudomallei*.

Supervisors:

Mr Mark Mayo/Prof Bart Currie

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Redesigning the *Burkholderia pseudomallei* Multi-Locus Sequence Typing (MLST) scheme to encompass Burkholderia near-neighbours

Summary

Burkholderia pseudomallei is a bacterium endemic in northern Australia, and causes the deadly disease melioidosis. The 'gold standard' method for genotyping (genetic fingerprinting) of *B. pseudomallei* strains is Multi-Locus Sequence Typing (MLST). However, the current MLST scheme does not work well in near-neighbour *Burkholderia* species, many of which reside in the same clinical and environmental niches as *Bpseudomallei*. As such, their genetic diversity is poorly understood. The aim of this Honours project will be to redesign an MLST scheme that encompasses a greater breadth of *Burkholderia* spp. The student will use genetic data obtained from next-generation whole genome sequencing to design PCR-based assays, followed by validation across *Burkholderia* species panels and DNA sequencing. It is expected that a peer-reviewed manuscript will be generated from this work.

Supervisors:

Dr Erin Price

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Whole genome analysis of *Burkholderia pseudomallei*

Summary

This project will use next-generation whole genome sequencing technology and bioinformatics to look for genetic determinants of virulence in *B. pseudomallei* that correlate with disease outcome or environmental features

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