MONASH University

MONASH BIOMEDICINE DISCOVERY INSTITUTE

Department of Microbiology

2027 Honours Programs in Microbiology

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GROUP OF EIGHT AUSTRALIA

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2027 Honours Programs in Microbiology

The Honours programs for both Bachelor of Biomedical Science (BBiomedSci) and Bachelor of Science (BSc) contain coursework and an independent research project. The objectives of these courses are to develop the laboratory skills required for research in microbiology and the ability to critically evaluate microbiological research. Students also achieve a detailed understanding of specialised topics in microbiology and enhance their communication skills in written and oral presentations.

The Department looks forward to welcoming you in 2027. We feel that our friendly, constructive and highly productive working environment provides an excellent opportunity for honours students to develop an understanding of the research process and to achieve their full research potential.

Formal Application Process

Application for Microbiology Honours entry involves a two part application process.

1. Formal application to the relevant faculty by

   B. Sc (Hons): November 13, 2026
   www.monash.edu/discovery-institute/honours/so-how-do-i-apply

   B. Biomed. Sci (Hons): November 13, 2026
   www.monash.edu/discovery-institute/honours/so-how-do-i-apply

2. Submission of project preferences to Professor John Boyce (no later than November 13, 2026).

Research Projects

The research project is the major component of both programs. All efforts are made to accommodate students in the laboratory of their choice, and to develop research projects that take into account the student's, as well as the supervisor's, interests. Brief outlines of the available projects for 2027 are in the following section.

Supervisor Interviews

Applicants must find a supervisor and a project before applying for Honours. Applicants are encouraged to discuss research projects with potential supervisors at any suitable time, by appointment. Following these discussions, students should apply online at the relevant faculty site and give Professor John Boyce a copy of their application forms: www.monash.edu/discovery-institute/honours/so-how-do-i-apply indicating their project preferences, and any additional documentation required. The project preference form must be signed by the prospective supervisor. You do not need to wait until November 13th to hand in your preference forms, the earlier the better.

Projects Outside the Department

It is possible for students to complete their coursework within the Department of Microbiology at Clayton, and their research project off-campus , e.g. with selected supervisors working at the Burnet or Hudson (see projects at the end of this booklet). Under these circumstances, students must travel between locations when required. The thesis examination takes place at Clayton and at the same time for all students enrolled through Microbiology.

BBiomedSci and BSc Coursework

The coursework component of the honours year for both BSc and BBiomedSci students in the department of microbiology consists of short courses called colloquia, a statistics course and seminars. Coursework is usually completed, and students receive some feedback on their progress, by mid-year. The format of the colloquia will vary. Most involve reading recent research papers, an oral or poster presentation, and/or a written assignment.

Literature survey

During first semester the students must submit a literature survey on their research project. The literature survey which can be used as the basis for the introduction in the final report, allows the identification early in the year of those students who have problems with English expression so this can be addressed by directed English writing instruction. It also, of course, compels the students to become thoroughly conversant with their area of research.

Additional requirements

The programs will commence on February 22, 2027 (mid year begins July 19) with a series of compulsory introductory modules and sessions, before the students start work on their research projects. These sessions contain information on the course, departmental facilities and occupational health and safety. In the second half of the year students may be given specific training in the presentation of written reports, and in oral presentation of their work. It is compulsory for students to attend the introductory lecture course, all departmental seminars, and any short courses on written and oral presentations.

Assessment

The assessments for the BSc and BBiomedSci Honours programs follow the format:

Literature survey	7.5%
Research report/report review	60%
Seminar	7.5%
Coursework (including statistics)	25%

Eligibility

Monash BSc Students

Entry to the course is restricted to those students who have qualified for the award of the pass degree of BSc (all subjects completed before enrolment), and have an average of at least 70% in 24 points of relevant level-three science units. This generally includes at least 18 points of Microbiology units. Students studying combined Science degrees must be eligible for the award of BSc.

BSc Graduates of Other Universities

As for Monash students, applicants are required to have a BSc and at least distinction grades in Microbiology or closely related subjects. A certified copy of the applicant's academic record and a statement to the effect that they have qualified for a pass degree are required as soon as they are available.

Monash BBiomedSci students

Students must have completed all requirements for the award of the pass degree of Bachelor of Biomedical Science offered at Monash University. They must also have an average of 70% or higher in at least 24 points at third year level, with 12 points from third year core units.

BBiomedSci graduates from other universities

Students applying for admission based on a qualification other than the pass degree of Bachelor of Biomedical Science offered at Monash University will need to demonstrate that they have achieved an appropriate standard in studies comparable to 24 points of BBiomedSci subjects as stipulated above.

Part-time study and mid-year entry

The department prefers students to study on a full-time basis. However, it may be possible under special circumstances to complete the Honours degree in two consecutive years by doing the coursework and research project in separate years. It is also possible to start the course mid-year. In both of these circumstances, the arrangements are made on an individual basis between applicants and supervisors.

Research Projects 2027

Professor John Boyce

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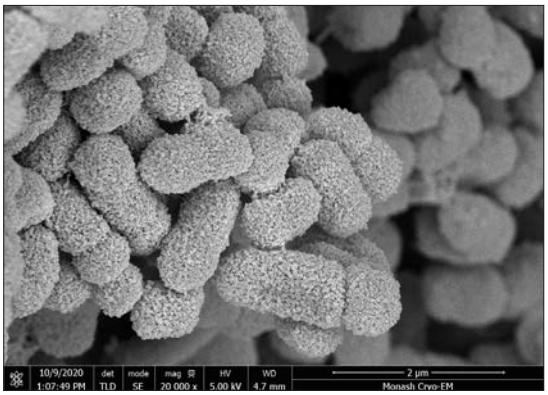
Dr Marina Harper



Scanning electron microscope image of *Pasteurella multocida*

Understanding how *Acinetobacter baumannii* controls firing of its Type VI Secretion System

Prof John Boyce, Dr Marina Harper, Abbey Allgood, Amy Wright

Acinetobacter baumannii has been identified by the WHO as a priority 1 pathogen for which new intervention strategies are desperately required. *A. baumannii* is responsible for a large number of life-threatening infections, especially in hospital ICU settings, and the majority of strains are now resistant to multiple antibiotics.

A. baumannii uses a Type VI Secretion System (T6SS) to deliver antibacterial toxins to kill competitor bacteria. This helps it survive in mixed species infections. We have identified two proteins (TagF and TagZ) that act to repress T6SS firing. Co-immunoprecipitation experiments have identified a number of proteins that directly interact with TagF, but we do not know what proteins interact with TagZ nor understand the mechansims by which these proteins silence T6SS activity.

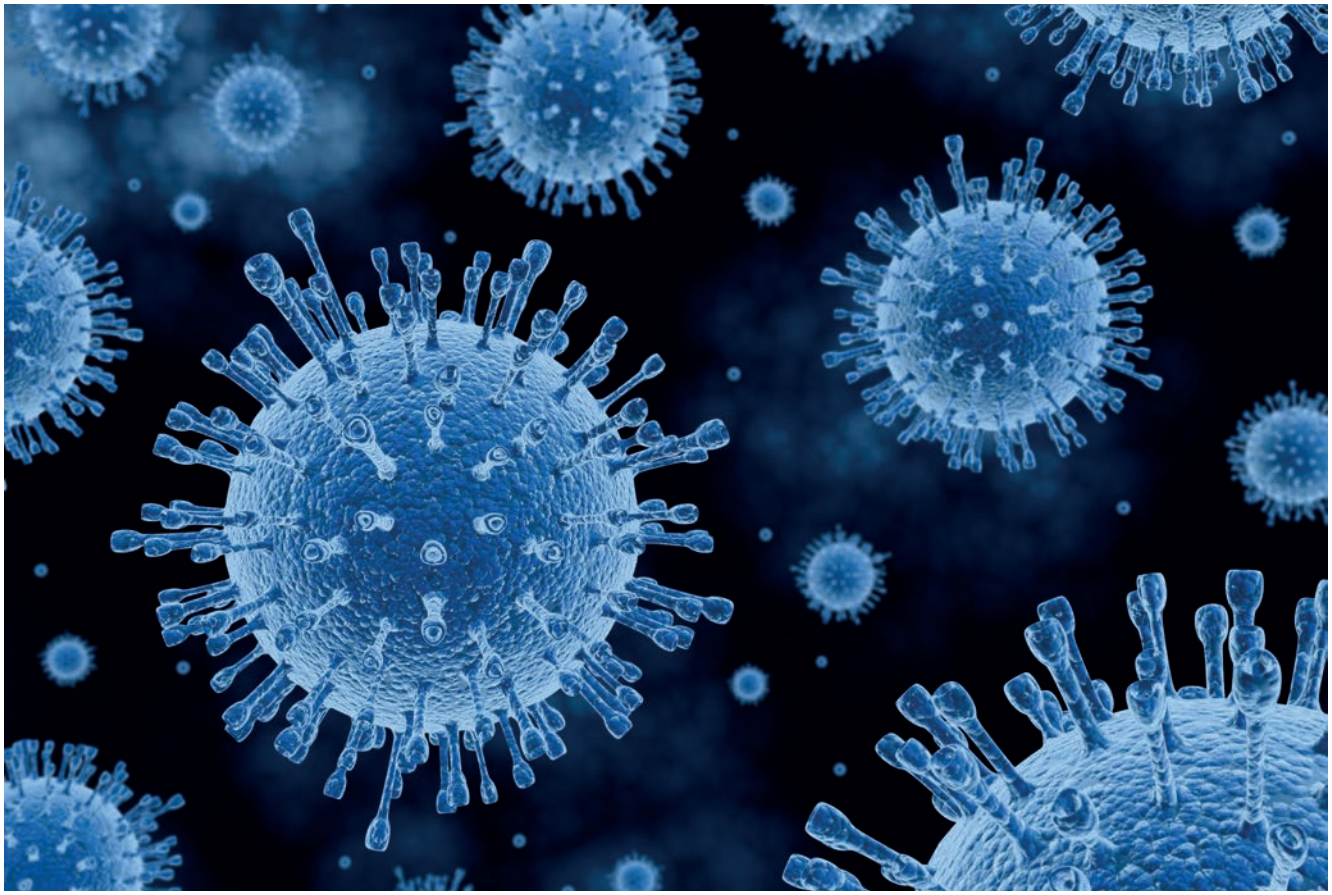
In this project you will use cutting-edge molecular biology, mutagenesis, high-throughput transcriptomics and proteomics methods, and live fluorescent microscopy, to determime how *A. baumannii* controls firing of its T6SS. These studies may lead to the identification of targets for future intervention strategies aimed and inactivating the T6SS and reducing the fitness, and therefore health burden, of this problematic nosocomial pathogen.

Characterising new antibacterial toxic effector proteins delivered by the *Acinetobacter baumannii* Type VI Secretion System

Dr Marina Harper, Prof John Boyce

The *Acinetobacter baumannii* Type VI Secretion System (T6SS) is a multiprotein nanomachine that is used as an antibacterial weapon via delivery of toxic effectors directly into competitor bacteria. We have shown that different *A. baumannii* strains deliver a diverse range of effectors that target essential cell structures such as peptidoglycan, DNA, RNA and bacterial membranes. We propose that many of these antibacterial effectors will have novel modes of action and that understanding their specific functions will allow us to re-purpose them as novel antibacterial molecules.

In this project you will characterise novel toxic effectors using heterologous expression, protein purification, site-directed mutagenesis and utilise a range of phenotypic assays to identify the targets and modes of actions of these novel antibacterial molecules. You will assess how the proteins are delivered by the T6SS and test the activity of selected proteins and bioengineered derivatives against important Gram-positive, Gram-negative and fungal pathogens.



Defining the mechanisms of *Pasteurella multocida* pathogenesis and improving vaccines

Dr Thomas Smallman, Dr Marina Harper, Prof John Boyce

Pasteurella multocida is a Gram-negative bacterial pathogen that causes a range of diseases in humans, cattle, pigs and poultry. These diseases result in serious economic losses worldwide in multiple food production industries. We are interested in understanding the molecular mechanisms of pathogenesis in this bacterium with an aim to developing new, more effective and widely applicable vaccines or antimicrobial drugs.

Recent work in our lab, using comparative genomics and transposon insertion-site mutagenesis, has allowed us to comprehensively define the *P. multocida* genes essential for a range of virulence phenotypes, including growth in serum and production of the anti-phagocytic bacterial capsule. With this crucial data as a base, in this project we will use directed mutagenesis, complementation, whole-genome transcriptomic and proteomic techniques, and established *in vitro* and *in vivo* phenotypic assays, to define the molecular mechanisms by which this important pathogen avoids killing by the host immune system and causes disease. In particular, we will assess the role of quorum sensing in controlling the expression of virulence factors, including crucial surface structures such as capsule and LPS. Finally, we will test selected mutants as live-attenuated vaccine candidates.

Professor Mariapia Degli-Esposti

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Professor Mariapia Degli-Esposti

Dr Iona Schuster

Dr Christopher Andoniou

MCMV, Immunity and Ageing

Prof Mariapia Degli-Esposti, Dr Christopher Andoniou, Dr Iona Schuster

With average life spans increasing we face novel challenges in managing age-associated health decline. A key factor in maintaining overall health is a well-functioning immune system. However, as we age the immune system becomes less functional with reduced production of T and B cells, as well as changes in the quality and composition of respective memory subsets. How immunological challenges such as viral infections impact and shape the aging immune system is not well understood. In this regard, we are particularly interested in cytomegalovirus (CMV), a virus that is never fully cleared and remains with its host life-long. CMV infection causes the gradual expansion of certain CD8+ T cell memory populations, a phenomenon that has been linked with both limiting and enhancing immune responses to other challenges. Using the well-established mouse model of murine CMV (MCMV) infection we aim to examine the impact of this in immune compartments during ageing. Approaches will include high-parameter multicolour flow cytometric analysis of immune cell subsets as well as bulk and single cell assays of immune functionality. The ultimate aim is to gain a better understanding of how CMV infection shapes the immune system over time and how this affects the aging immune system.

Viral Infection and Autoimmunity

Prof Mariapia Degli-Esposti, Dr Iona Schuster

Viral infections have long been suspected to play a role in autoimmunity, with members of the herpes virus family such as cytomegalovirus (CMV) specifically implicated. We use the model of murine CMV, a natural pathogen of the mouse with high similarity to its human counterpart, to investigate the mechanisms underlying the generation of protective antiviral responses and how these correlate with the onset of autoreactive responses. We have shown that a strong anti-viral T cell response generated in the absence of certain immune regulatory mechanisms improves viral control. However, once the virus is controlled, this strong anti-viral response leads to increased generation of auto-specific immune responses resulting in a loss of tissue function. The autoimmune disease generated represents the best available model of the second most common autoimmune disease of man, Sjogren's Syndrome, a condition that affects overall health by severely compromising exocrine gland function. Experimental approaches will include *in vitro* and *in vivo* techniques using wildtype as well as gene-targeted mouse strains. Techniques include the preparation of different tissues for histological analysis of tissue pathology, characterization of infiltrating cell types, and assessment of changes in tissue architecture. Furthermore, we use flow cytometry to characterize and quantify immune cell populations isolated from different tissues at various times post infection. The goal of this project is to further extend our understanding of the processes and mechanisms underlying the generation of autoreactive immune populations in the context of viral infection.

Professor Chris Greening

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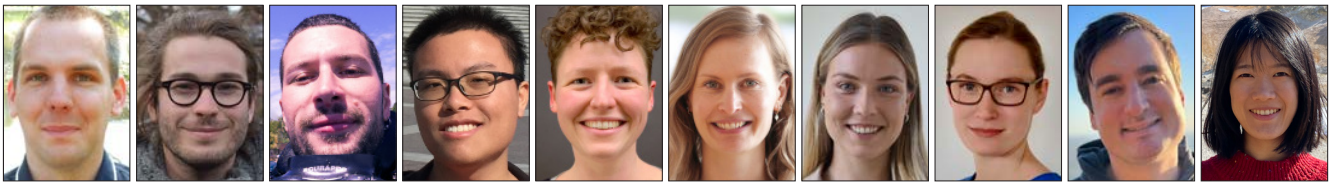
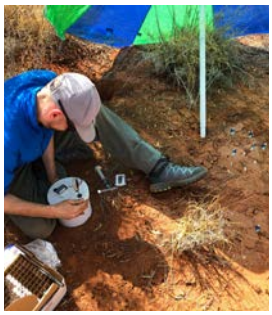


Professor Chris Greening | Dr Tom Watts | Dr Francesco Ricci | Dr Pok Man Leung | Dr Sophie Holland | Dr Marion Jespersen | Dr Caitlin Welsh | Dr Astrid Stubbusch | Dr Anthony Kohtz | Dr Yuka Katayama

The impact of short- and long-term warming on Antarctic soil microbes

Prof Chris Greening, Dr Tess Hutchinson, Dr Francesco Ricci, Dr Sophie Holland

Antarctica is one of the harshest environments on the planet, where soils are subject to freezing temperatures, low water bioavailability, and scarce nutrients. Nonetheless, the small proportion of the continent that is ice-free hosts a range of microbial biodiversity. Many of these microbes can use trace atmospheric gases to generate energy, carbon and water, making them important primary producers in a continent depleted in photosynthetic life. However, Antarctica is increasingly subject to heatwave events and we lack an understanding of how these unique microbial communities will respond to sudden, short-term temperature increases. In this project, you will use our collection of Antarctic soils to investigate how heatwaves will affect the taxonomic and functional diversity of soil microbes and their primary production strategies. You will carry out biogeochemical assays to analyse rates of trace gas oxidation and carbon fixation, as well as using meta-'omics data to analyse the microbial community before, during, and after warming. Bioinformatic and statistical analysis of 'omics data will be required, using the command line and/or R.



Gas metabolism: a new frontier in the human microbiome revolution

Prof Chris Greening, Dr Astrid Stubbusch, Dr Caitlin Welsh, Dr Yuka Katayama, Dr Tom Watts

The recent 'microbiome revolution' has revealed a range of microbiota-derived metabolic by-products that have links with gut dysregulation and disease. Yet the mediators of gas metabolism, an important process performed by gut microbes, are still largely unresolved. Bacterial fermentation within the human gut produces hydrogen gas (H_2), and other groups of microbes are responsible for its subsequent disposal. A delicate balance of these processes must be achieved to prevent accumulation of H_2 and other potentially harmful metabolic by-products, which are linked to colorectal cancer, IBS and IBD. Additionally, carbon monoxide (CO), often labelled a harmful gas, is consistently produced via haem degradation by both host and microbial cells. Emerging evidence suggests that CO-utilizing bacteria are present within the human gut microbiome; however, the enzymes and pathways associated with these processes are largely uncharacterised. Furthermore, exploring these processes in commensal microbes can aid in our understanding of how opportunistic gut pathogens use them during infection. In this study, you will use culture-dependent and culture-independent methods to investigate how H_2- and CO-related metabolic processes occur within the human gut, who the key bacterial players are, and how these processes affect overall human gut health and disease.

Characterizing the metabolism of novel archaea

Prof Chris Greening, Dr Anthony Kohtz, Dr Marion Jespersen

Archaea, only discovered in the 1970s, are an enigmatic third domain of life that includes our ancient ancestors. Many archaea have unusual forms of metabolism compared to bacteria and eukaryotes, including methanogenesis, a process where they generate methane gas as a by-product of growth. Diverse methanogens are found in places from soil and the human gut to extreme habitats like hot springs and salty lakes, where they contribute substantially to global methane emissions. Methane is a powerful greenhouse gas, making these microbes especially important in climate science and mitigation strategies. This project focuses on newly discovered non-traditional methanogens, cultivated from hot springs, that use unique enzymes to oxidize hydrogen and produce methane. You will learn how to cultivate these strict anaerobic methanogens and use cutting-edge approaches (transcriptomics and proteomics) to gain an understanding of how they grow under varying conditions. Depending on your interests, you can also focus on native protein purification and develop assays for studying their unique enzymes.

From symbiosis to stress: does nutrient pollution destabilise the coral microbiome and their vital reef functions?

Prof Chris Greening, Dr Francesco Ricci

Coral reefs are among the most biodiverse and valuable ecosystems on the planet, but they are increasingly threatened by human activities, one of the most pervasive being nutrient pollution. Excess nitrogen and phosphorus from coastal runoff can disrupt the delicate balance of coral holobionts, yet the specific impacts on coral-associated microbial communities and their functional contributions to the host remain poorly understood. This project will investigate how microbial communities associated with reef-building corals respond to nutrient enrichment and whether shifts in microbiome composition and function ultimately impair coral health. Particular focus will be placed on identifying microbial taxa and metabolic pathways that may support coral nutrient acquisition, stress resistance, or resilience in eutrophic environments. We will analyse the taxonomic and functional profiles of coral-associated microbiomes using metagenomics and biogeochemistry, comparing samples collected from nutrient-impacted and pristine reef environments. In this study, you will participate in fieldwork, laboratory analyses (including DNA extraction and biogeochemical assays), data processing (bioinformatics, functional annotation, and statistical analyses), and contribute to the preparation of a scientific manuscript. This project is ideal for students with an interest in marine microbiology, coral reef microbial ecology, and host-microbe symbioses in the context of global environmental change.

Novel microbial catalysts for waste gas conversion into bioproducts

Prof Chris Greening, Dr Anthony Kohtz, Dr Pok Man Leung

Anthropogenic greenhouse gases (GHGs) emission is the leading cause of global climate change. While generally considered a waste, numerous microbes can harness these gases as their energy and carbon sources. They can produce useful microbial bioproducts from single-cell protein to bioplastic, presenting a promising solution to mitigate and make use of GHG emission. However, existing industrial strains are often limited by their sensitivity to inhibitory compounds, modest substrate conversion efficiency, and inability to use multiple gases. In this project, you will lead isolation of novel gas-metabolizing microbes naturally adapted to high fluxes of reduced gas substrates, including from coal seam fire and hydrogen seep ecosystems. You will use cutting-edge systems biology (genomics, proteomics, metabolomics), microbiology (e.g. microscopy), and biogeochemistry (gas chromatography) to characterize the ability of the isolates to grow on waste gases. This project has a potential for discovery of novel gas metabolizing pathways and microbial catalysts that enable sustainable industrial processes.

Conserving energy from atmospheric hydrogen

Prof Chris Greening, Dr Tom Watts, Dr Marion Jespersen

Hydrogenases are enzymes that allow microbes to use hydrogen gas as an energy source. Some microorganisms produce special [NiFe]-hydrogenases that enable them to survive in harsh environments with low levels of nutrients and oxygen. One such enzyme is Hhy, which can function in the presence of oxygen - a poison for most hydrogenase enzymes - and is believed to play a role in bacterial persistence, although the molecular mechanism is unclear. In this project, you will purify and study the Hhy hydrogenase from *Mycobacterium smegmatis*. You will learn to grow this bacterium, isolate the enzyme, and analyse its activity using hydrogen-based assays, artificial electron acceptors, and gas chromatography. To understand its structure and composition, you will use spectroscopic techniques, native gel electrophoresis and cryo-electron microscopy (cryo-EM). This project will provide hands-on experience with microbial cultivation, protein purification, enzymology and structural biology. Your work will improve our understanding of how mycobacteria use this hydrogenase to their advantage to survive in oligotrophic environments.

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Dr Meiling Han


Dr Wayne Lin


Professor Tony Velkov


Dr Gavriel Olshansky

The Antibiotic Resistance and Bacterial Metabolism Group

Our laboratory investigates how bacteria remodel their lipid metabolism to survive antibiotic stress and host immune responses, with a particular focus on the relationship between antimicrobial resistance and changes in bacterial membrane lipids and intracellular metabolites. Over the past three years, we have established an independent research program to characterise the composition and biological functions of key bacterial lipids and metabolites using integrative multi-omics approaches, particularly comparative metabolomics and membrane lipidomics. We also employ advanced biophysical techniques, including neutron reflectometry, alongside computational modelling to investigate interactions between antimicrobial peptides and remodelled bacterial membranes. Our findings have advanced understanding of the roles of small molecules in bacterial physiology and antibiotic resistance and may inform the development of novel therapeutic strategies targeting lipid-associated resistance mechanisms.

Unravelling the complex metabolic interplay between bacteria and host microenvironment

Dr Meiling Han, Prof Tony Velkov

Pseudomonas aeruginosa has been highlighted by the World Health Organization (WHO) as one of the most significant pathogens that can cause life-threatening respiratory tract infections, especially in patients with inflammatory airway diseases such as cystic fibrosis. Due to its high level of antibiotic resistance, infections caused by *P. aeruginosa* have posed significant treatment challenges over the last decades. However, it remains largely unknown how the host metabolic environment influences *P. aeruginosa* infections.

Employing cutting-edge techniques, including metabolomics, stable isotope labelling, and MALDI-MS Imaging, this project aims to establish a host-pathogen-antibiotic tripartite model to investigate metabolic perturbations in the host microenvironment during *P. aeruginosa* infection. Notably, essential metabolite biomarkers that modulate antibiotic efficacy will be identified, with the aim of enhancing the antibiotic effectiveness against *P. aeruginosa*. This research will provide novel mechanistic insights to optimise antibiotic use in clinical settings and combat multidrug-resistant bacterial infections.

Constructing a systems pharmacology model of lipid A modification in Gram-negative bacteria

Dr Meiling Han, Dr Wayne Lin

The bacterial membrane plays a crucial role in protecting bacterial cells from harsh environments, including exposure to harmful compounds and host immune responses. Integral to this function is the lipid A component of lipopolysaccharide in the outer membrane of Gram-negative bacteria, which densely packs the outer layer and forms a critical permeability barrier. Alarmingly, bacterial cells can modify their lipid A molecules with chemical groups (e.g. phosphoethanolamine or 4-amino-4-deoxy-L-arabinose) to evade immune recognition and develop antibiotic resistance. Understanding the kinetics of these modifications and their relationship with antibiotic concentration is crucial for developing strategies to combat antibiotic resistance and improve therapeutic outcomes.

To enhance our understanding of the regulatory impact of individual processes involved in lipid A modification and their relationship with antibiotic concentrations, this project will develop a comprehensive systems pharmacology kinetic model. This model will encompass the pathways of lipid A synthesis and modification. Following this, in silico clinical trial simulations will be conducted to assess the impact of different clinical dosing regimens on lipid A modification. This research will offer insights into optimising dosing regimens for clinical settings, highlighting the significance of the model-informed drug development.

Discovery and validation of metabolic targets associated with antibiotic resistance

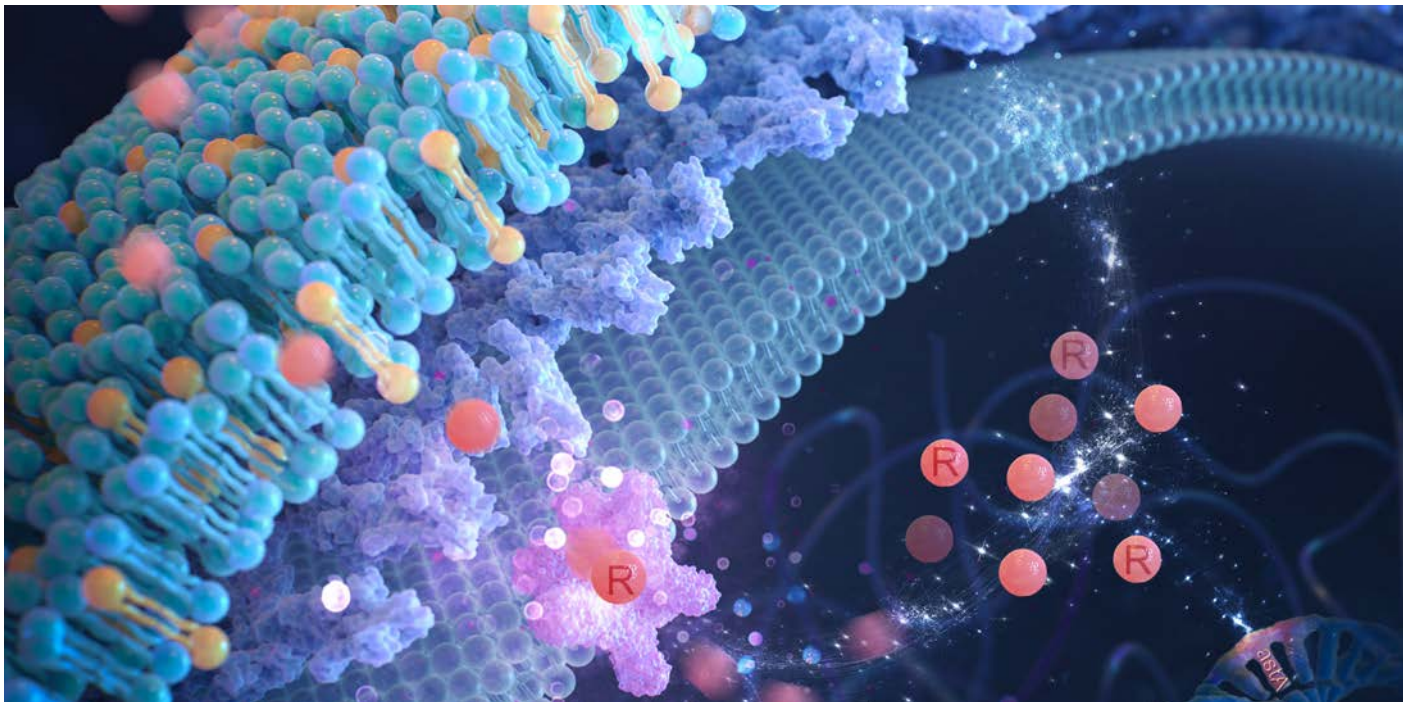
Dr Meiling Han, Dr Gavriel Olshansky

Gram-negative bacteria are major contributors to the global antimicrobial resistance crisis. Despite ongoing efforts to develop new therapeutic strategies, *Acinetobacter baumannii* remains classified as a critical priority pathogen by the World Health Organization due to its high mortality rate, capacity for transmission, and limited treatment options. Studies conducted in the Han laboratory have characterised the metabolic profile of multiple *A. baumannii* strains and assessed the effects of a range of genomic knockouts on bacterial physiology.

The aim of this project is to identify metabolic biomarkers associated with antibiotic resistance using in-house datasets and an AI-informed metabolic model. Following data analysis, the most promising candidates will be prioritised based on their potential as targets for metabolic supplementation strategies. Selected metabolites will then be validated *in vitro* to assess their effects on bacterial growth and antibiotic resistance phenotypes.

This project will involve analysis of metabolomics data, including isotopically labelled and longitudinal data, interpretation of findings within the context of Gram-negative bacterial metabolism, and a wet lab component focused on biomarker validation studies.

The outcomes of this project are expected to improve our understanding of the metabolic mechanisms underlying antibiotic resistance and may identify novel metabolic intervention strategies to enhance effectiveness of existing antimicrobial therapies.



Impact of arginine on bacterial membrane architecture. *Link to article: https://doi.org/10.1016/j.celrep.2024.114410*

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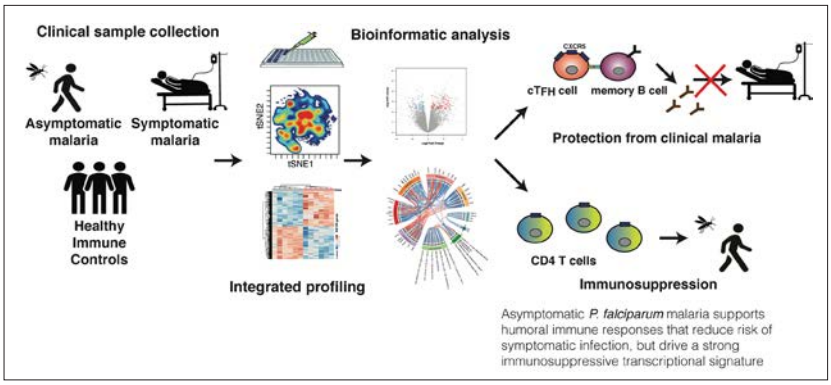
Dr Mariam Bafit

Dr Stephanie Studniberg



Workflow for understanding pathogenesis and immunity to malaria and severe dengue fever

Mechanisms of pathogenesis and immunity to malaria and severe dengue fever

Our research focuses on finding solutions to tackle two devastating mosquito-borne infectious diseases: malaria and dengue. Together these account for 600 million clinical cases worldwide annually

Unlike other infections in which one single encounter with the pathogen is enough to induce long-lasting protection, immunity to malaria might take decades to develop in endemic areas. The Hansen lab investigates mechanisms by which *Plasmodium* infections prevent the acquisition of immunity. This work is undertaken in order to design therapeutic approaches to improve the induction of immune responses to the *Plasmodium* parasite, including effective anti-malaria vaccines.

Clinical immunity to malaria is largely dependent on effective antibody responses. In collaboration with partners in malaria-endemic countries, our group investigates how the induction of antibody-mediated immunity is dysregulated during symptomatic as well as asymptomatic malaria and how constant exposure to *Plasmodium* parasites over time modulates the development of these responses.

There is no specific treatment for dengue and no validated way to predict which patients will progress to life-threatening manifestations of disease. The clinical course for dengue is difficult to predict mostly because the specific pathways influencing severity to disease are not understood. To address this challenge, our group pursues a comprehensive immunological and molecular approach to uncover key mechanisms involved in the development of severe dengue. Obtaining this information is of vital importance to design novel diagnostic tools for early detection of complicated cases, as well as therapeutic approaches to treat severe dengue.

Effect of acute and persistent malaria infection on host immunity to infection and vaccination

Prof Diana Hansen, Dr Stephanie Studniberg

Despite constant exposure to *Plasmodium* parasites, immunity to malaria takes many years to develop for individuals living in endemic areas. This form of protection is not sterilising but prevents clinical episodes by substantially reducing parasitaemia, with adults often experiencing non-febrile malaria infections. Naturally acquired immunity is known to require antibody responses. The acquisition of antibody-mediated immunity requires generation of high-affinity antibody-secreting cells and memory B cells, a process that is facilitated by T follicular helper cells in secondary lymphoid organs.

Using infection models as well as field studies in malaria endemic areas we are investigating how *P. falciparum* and *P. vivax* infections influence these responses and the immunological and molecular factors that modulate the outcome to these processes.

Our team pursues a systems biology approach to address these questions, combining wet lab immunology with bioinformatics analysis of host transcriptional responses. We have available both wet and dry lab projects.

Identification of cellular and molecular pathways predisposing to severe dengue fever

Prof Diana Hansen, Dr Mariam Bafit

Typical symptoms of dengue include sudden onset of fever accompanied by headache, muscle pains, rash, cough, vomiting and haemorrhagic manifestations. Hospitalisation may be required depending on signs of severity such as dehydration, bleeding or comorbidities.

There is no specific treatment for dengue, and care is mainly supportive. To date, there is no validated way of identifying which patients will progress to severe disease, meaning that in endemic areas, health facilities are often overwhelmed with patients admitted for inpatient observation, costing millions of dollars to health systems.

To address this issue, this project undertakes a comprehensive immunological and transcriptional analysis of individuals with mild versus severe dengue fever recruited at local hospitals in different regions of Southeast Asia and South America.

The project will uncover key mechanisms involved in progression towards severe disease after initial patient presentation. Our team pursues a systems biology approach to address these questions, combining wet lab immunology with bioinformatics analysis of host transcriptional responses We have available both wet and dry lab projects.

Dr Simone Li

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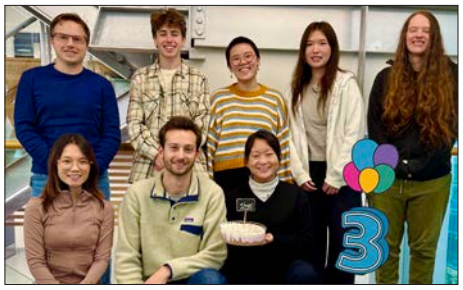
ONE VACANCY



Our lab turns 3!

Professor Trisha Peel

Dr Sam Palframan

Our recent study on faecal microbiota transplantation was featured on the cover of *Nature Medicine* (2022).

Microbiome Systems Lab

We are a young research group in the Biomedicine Discovery Institute, with a focus on creating multidisciplinary, data-oriented approaches to study and compare the evolution of microbial communities in natural environments, such as soil and the human gut. Our goals and contributions are far-reaching – from new ways to combat antimicrobial resistance and treat chronic diseases, to designing sustainable solutions to produce biomolecules that are essential to our daily lives.

New developments in DNA sequencing technologies have advanced the field of metagenomics, enabling innovative ways to study the full genomic diversity of microbes that thrive in different ecosystems (our recent work published in *Nature Commun* 2025). This has revealed an intriguing dual role of the microbiome not only in disrupting but also maintaining health in clinical, industrial and planetary settings.

A recent example is our work on the human gut microbiome, which revealed ecological patterns of engraftment whereby new microbes could thrive in faecal microbiota transplantation (FMT) patients (*Science* 2016, *Nature Medicine* 2022). Here, we developed new computational methods and tools to accurately profile the thousands of microbial species in the gastrointestinal tract and identify and track donor strains over time. By integrating our results with clinical data, we discovered certain bacteria that are more likely to persist in patients (irrespective of disease) and identified aspects of the medical procedure that would facilitate this phenomenon. These findings transformed our lasting impact on the microbes in our gut. It also motivated the use of precision medicine approaches to increase the success of therapies that target the microbiome – a growing global market that is estimated to exceed $21.5 billion USD by 2030.

By unravelling the complex layers of biology contained within microbiomes in their native context, we aim to discover new approaches for preventing and treating disease, and introduce ways to improve and enhance current practices in clinical, biotechnology and environmental bioremediation settings.

We use advanced bioinformatics, machine learning and high-performance computing to test our biological hypotheses on terabytes of new and existing data, generated by both established and emerging ‘omics technologies.

Our team collaborates with experts around Australia and internationally to develop, contextualise and build the biological picture around our findings and further our impact. Lab members have the opportunity to be part of the ARC Centre of Excellence on Peptide & Protein Engineering, the European Alliance for Rheumatology, and Monash Uni Centre to Impact Antimicrobial Resistance.

We are a growing lab and keen students with a good grasp of microbiology, genome analysis, molecular biology and/or computer science are welcome and encouraged to get in touch. All projects involve a substantial bioinformatics component and can be tailored according to your research experience and goals.

Antimicrobial resistance in the human microbiome: transmission and persistence

Dr Simone Li, Dr Sam Palframan

Antimicrobial resistance (AMR) is one of the greatest threats to human health and recognised by the World Health Organisation as a Global Health Challenge. There is an urgent need for new ways to stop its emergence, transmission and persistence. This is especially critical in clinical settings, where patient recovery is often complicated by acute and chronic drug-resistant infections caused by pathogens of unknown origin.

In this project, you will leverage metagenomic and clinical data to monitor and track AMR microbes in the microbiomes of various body sites. Do the same microbes that thrive in our gut also persist on our skin? Does this change when we get sick, and what other factors promote the spread of AMR in the microbiome?

Students will develop data skills in AMR research, metagenomics analysis and computational microbiology in this project that could drive the design of more targeted therapeutics to prevent the spread of antimicrobial resistance.

Large-scale comparative genomics of *S. aureus* isolates from post-surgery patients

Dr Simone Li, Prof Trisha Peel

Patients are often prescribed antibiotics immediately after surgery to prevent and control infection. There are ongoing efforts to optimise this treatment, and avoid inadvertently creating conditions that favour the growth and persistence of superbugs such as methicillin-resistant *Staphylococcus aureus* (MRSA).

In this project, you will analyse and compare 100s of *S. aureus* genomes and AMR profiles. These represent DNA-sequenced isolates that we collected from patients who received antibiotic treatment after surgery, in a recent clinical trial led by Prof Peel (Dept of Infectious Diseases, Alfred Hospital & Monash Uni).

Students will gain experience in bioinformatics as well as unique insights into clinical science in this project that bridges antimicrobial stewardship, computational microbiology and infection prevention.

Faecal microbiota transplantation: why does it work and is it safe for your microbiome?

Faecal microbiota transplantation (FMT) involves the transfer of gut microbes from (the stool of a) healthy donor to patient. The medical procedure is well-known for its high success rates in treating recurrent *C.difficile* infection and has become a potential therapeutic option for an increasing number of chronic diseases. However, we still don't know how it works and there exists a risk of undesired side effects. For example, infections and other diseases have been described in some patients soon after they received FMT treatment for unrelated illnesses – whether this was pure coincidence or caused by FMT is unclear.

In this project, we will study the genomic diversity in the gut microbiome of FMT patients and their donors. What could drive a successful FMT? Can we design a safer treatment for patients with chronic conditions with no alternative treatment?

Students can tackle these questions or pursue their own, gaining experience in data science, statistics and comparative metagenomics in this exciting project at the nexus of discovery and clinical sciences.

Where on Earth are carbon-fixing microbes?

CO_2 is being produced faster than the rate we can remove it from the biosphere. There is a global need for new and innovative solutions to augment carbon fixation processes that already exist in nature. Recent studies suggest that microbes from diverse, unexpected environments could possess as yet undiscovered mechanisms to convert CO_2 – but we don't know where to find them.

In this project, we will study 1000s of microbes captured in metagenomes from samples collected around the world to identify hotspots of carbon-fixing microbes. Are they enriched in certain geographies or ecosystems? Where could we potentially discover new microbial CO_2 conversion pathways?

Students will be able to apply their genomics skills and molecular biology knowledge while gaining experience in integrating and analysing large biological datasets in this international collaboration project.

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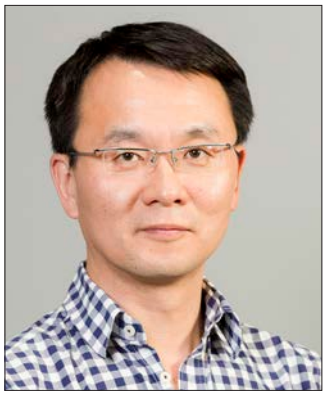


Professor Jian Li

Dr Sue C. Nang

Dr Jinxin Zhao

Laboratory of Antimicrobial Systems Pharmacology

My lab focuses on antimicrobial discovery and pharmacology against Gram-negative 'superbugs' (namely *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*). There has been a marked decrease in the discovery of novel antibiotics over the last two decades. As no novel class of antibiotics will be available against Gram-negative 'superbugs' in the near future, it is crucial to optimise the clinical use of 'old' polymyxins using systems pharmacology and to develop new-generation antimicrobial lipopeptides and innovative therapeutics.

My major research programs include:

(1) optimising clinical use of antimicrobial and phage therapies using pharmacokinetics/pharmacodynamics/ toxicodynamics (PK/PD/TD) and systems pharmacology;

(2) elucidation of mechanisms of antibacterial activity, resistance, and toxicity of antimicrobials and phages; and

(3) discovery of novel safer polymyxins and innovative therapeutics against multidrug-resistant (MDR) Gram-negative bacteria.

My lab is funded by the US National Institutes of Health (NIH) and Australian NHMRC.

Deciphering the Mechanisms of Antimicrobial Resistance and Phage Infection in Gram-negative bacteria Using Computational Biology

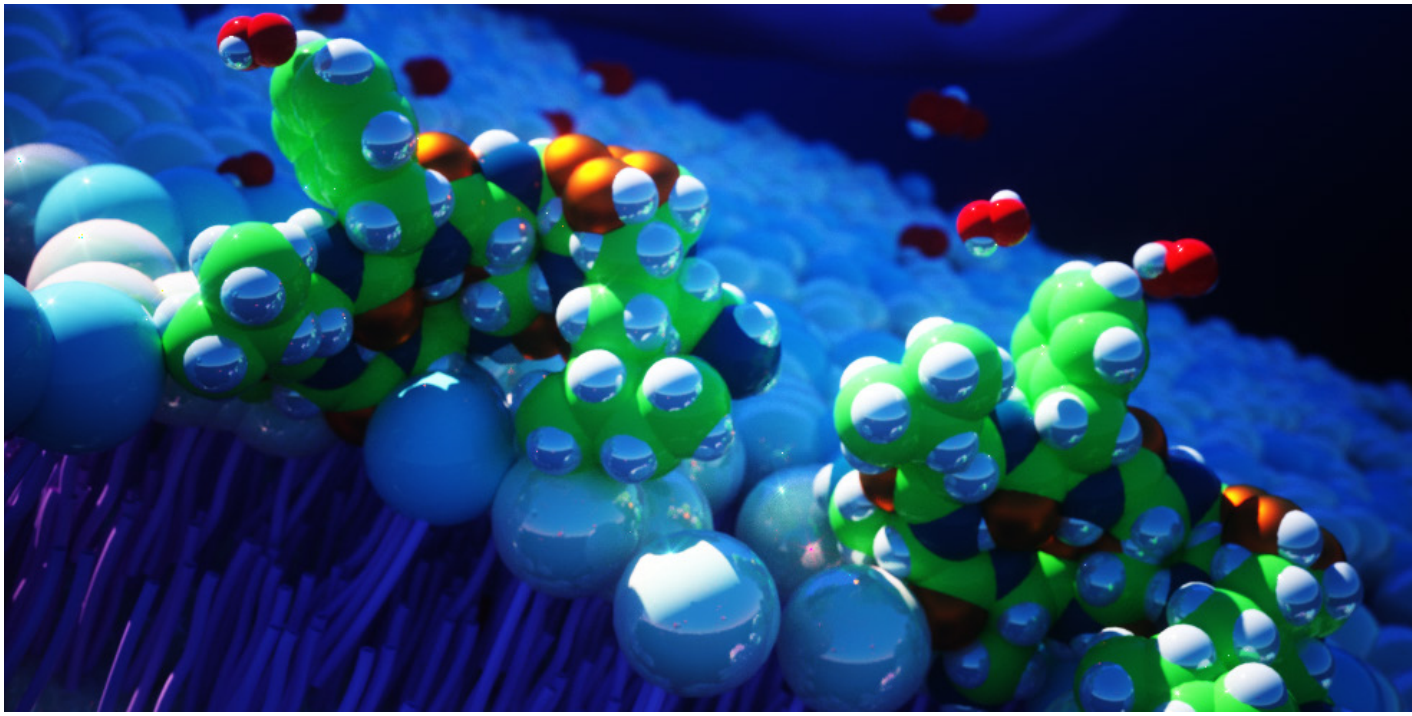
Dr Mei-Ling Han, Dr Jinxin Zhao and Prof Jian Li

Antimicrobial resistance is a critical threat to human health worldwide. Polymyxins are a group of last-line antibiotics against Gram-negative 'superbugs', including MDR. *Acinetobacter baumannii, Klebsiella pneumoniae* and *Pseudomonas aeruginosa.*

We are integrating genomics, transcriptomics, proteomics, metabolomics, and lipidomics to systematically examine bacterial responses to antimicrobial treatment and phage infection.

This project aims to:

1. conduct comparative genomic analysis for phages to predict critical genetic determinants of infection;
2. construct genome-scale models for *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* using multi-omics data;
3. employ the constructed genome-scale models to simulate bacterial responses to antimicrobials and phage infections;
4. predict key genes and pathways contributing to bacterial resistance to antibiotics and phages and validate their functions with our comprehensive mutant libraries.



This multidisciplinary project will characterise the complex interplay of signaling, regulation and metabolic pathways involved in resistance to antimicrobal killing and phage infection, thereby optimising antimicrobial combination and bacteriophage therapies in patients.

Phage-Antibiotic Therapy in the Postantibiotic Era

Dr Sue C. Nang, Prof Jian Li

Antimicrobial resistance has become one of the greatest global threats to human health and pandrug-resistant (PDR) *K. pneumoniae* has been identified by the WHO as one of the 3 top-priority pathogens urgently requiring novel therapeutics. These 'superbugs' cause life-threatening infections, particularly in the critically ill, and polymyxins are often used as the last option. Worryingly, increasing emergence of polymyxin resistance highlights the urgency to develop novel therapeutics to treat PDR *K. pneumoniae*. Bacteriophage (i.e. phage) have recently attracted substantial attention as a potential alternative against PDR bacterial infections; however, resistance to phage therapy (including cocktails) in *K. pneumoniae* can rapidly develop. Fortunately, phage resistance may restore bacterial susceptibility to certain antibiotics and therefore, optimal phage-antibiotic combination therapy provides a superior approach to fight against these superbugs. Contemporary antimicrobial pharmacology plays a critical role in optimising antibiotic dosage regimens, but lacks systems and mechanistic information. Importantly, antibiotic dosing strategies cannot be easily extrapolated into phage therapy, mainly due to the complex disposition, host specificity and self-replication of phages.

As the optimal phage-antibiotic combination and dosage regimens also depend on the dynamics of infection and host responses, innovative strategies incorporating systems pharmacology and host-pathogen-phage-antibiotic interactions have a significant potential in optimising phage-antibiotic combinations. This project will employ cutting-edge systems pharmacology to generate urgently needed information for rationally optimising novel phage-antibiotic combinations in patients.

Pulmonary Toxicity of Novel Polymyxin Combination Therapies

Prof Jian Li

Current dosing recommendations of parenteral polymyxins are suboptimal for treatment of respiratory tract infections due to poor drug exposure at the infection site. Moreover, nephrotoxicity is the dose-limiting factor and can occur in up to 60% of patients. Pulmonary delivery of polymyxins as monotherapy and in combination with other antibiotics has offered a great promise for bacterial eradication in the respiratory tract. However, we have shown that polymyxins localise in mitochondria of human lung epithelial cells and activate multiple apoptotic pathways. This multi-disciplinary project aims to investigate the effect of polymyxins and their synergistic combinations with other key classes of antibiotics on human lung epithelial cells, using fluorescence activated cell sorting (FACS), metabolomics, proteomics, transcriptomics and cutting-edge imaging techniques. This project will provide the much-needed pharmacological information for safer and more efficacious use of polymyxin inhalation therapy against life-threatening lung infections.

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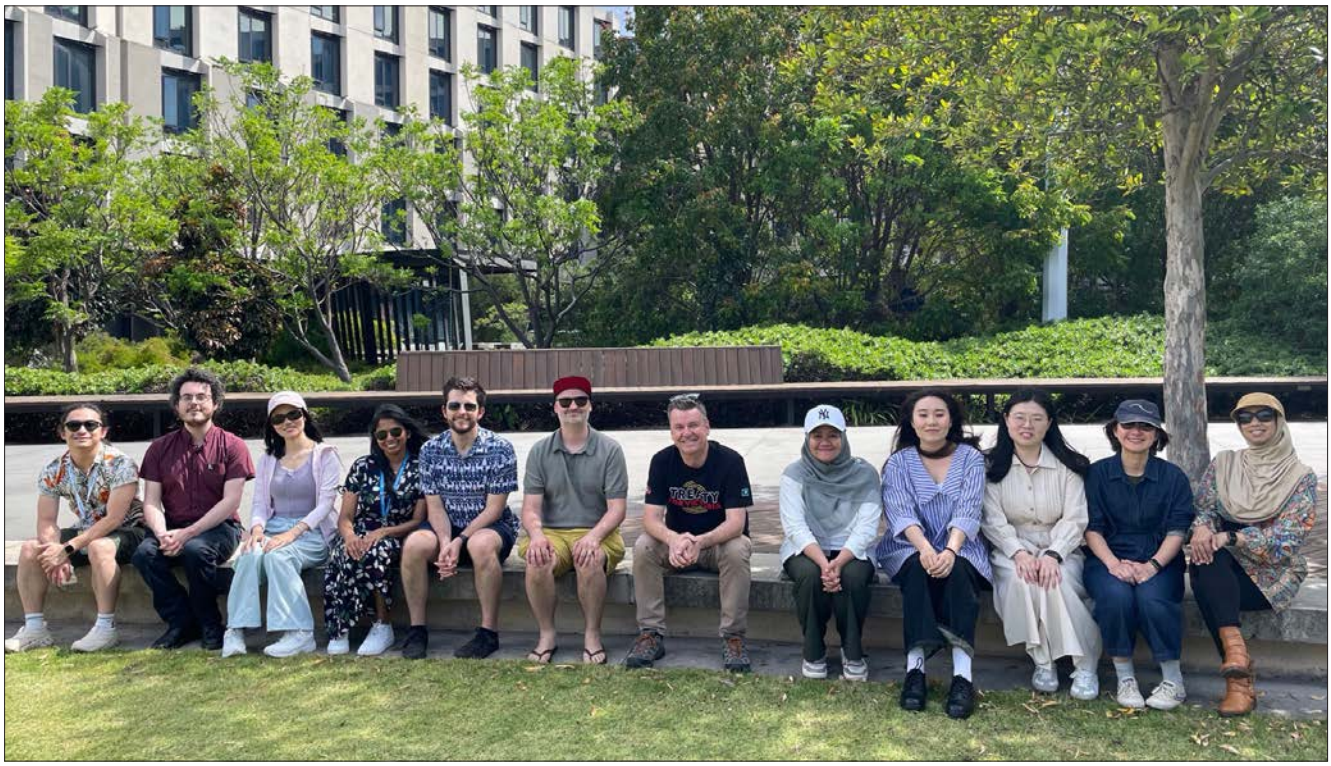


Lithgow lab group

Bacterial Cell Biology Laboratory

Bacterial cells are dismissed in textbooks as having simple and uniform cell surfaces, but we now know this to be far from the truth. The surface "cellscapes" of bacteria show extraordinary topological features that uniquely distinguish the cells within a population (Lithgow, Stubenrauch & Stumpf 2023 *Nature Reviews Microbiology* 21:502). The Bacterial Cell Biology Lab uses all the tools of molecular cell biology to study and image bacteria at the sub-cellular level, and students in this lab are trained how to manage their project work towards at least one first-author paper in a major journal. This is a critical outcome to ensure that graduates from the lab are offered exciting jobs, as indicated on the Lab Alumni page (https://www.monash.edu/discovery-institute/lithgow-lab/members).

Examples of our recent PhD student publications include Sally Byers' paper revealing the secret life of telomere phages (Byers et al 2025 *Science Advances* 11:eadt1627), Sabrina Suhani's paper on a whole new class of phages (Suhani et al *mBio* 17:e0382925), Natalia Rosas' paper on the evolution of non-carbapenemase carbapenem-resistant *Klebsiella* (Rosas et al 2023 *eLife* 6:12:e83107), Eric Mandela's paper on spatial control that bacteria exert on their cell walls (Mandela et al. 2022 *eLife* 11:e73516); Manasa Bharathwaj's paper on how carbapenemases are secreted by *Klebsiella pneumoniae* (Bharathwaj et al. 2021 *mBio*12:e0130221), and Dilshan Gunasinghe's paper on the spatial aspects of outer membrane protein assembly in *Escherichia coli* (Gunasinghe et al. 2018 *Cell Reports* 23:2782).

Student projects in the Bacterial Cell Biology lab can be designed within one of our four areas of activity:

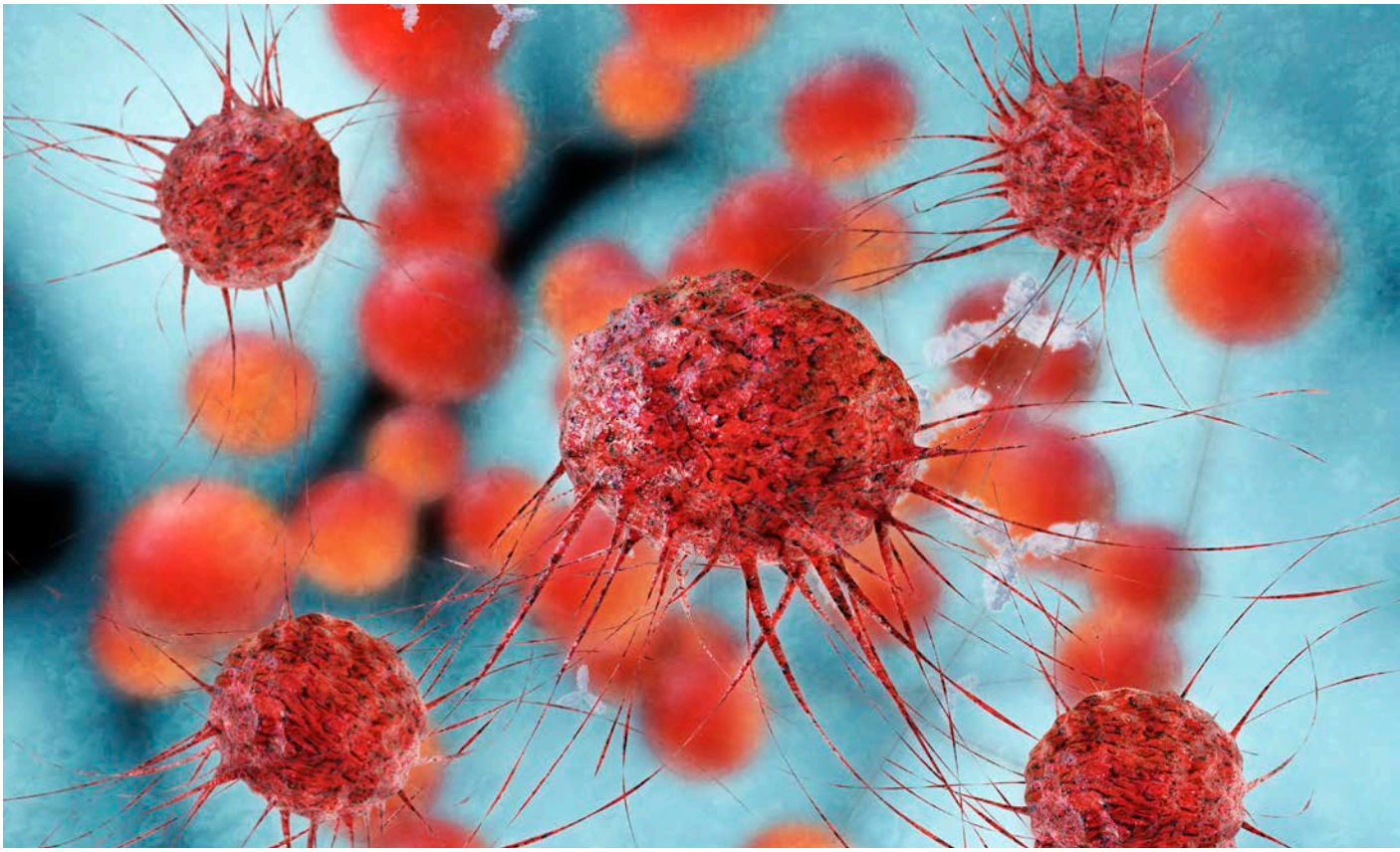
1: **Assembly of proteins into the outer membrane of *Klebsiella.*** This area of molecular microbiology includes projects on (i) assessment of the outer membranes in wild *Klebsiella*, (ii) how two-partner signalling controls outer membrane remodelling, and (iii) mathematical modelling of protein assembly into the bacterial outer membrane.

2: **Structure-function of a bacterial protein import machine.** This area of molecular microbiology and structural biology work includes projects on (i) genetic-biochemical characterization of the protein import pathway into bacteria, and (ii) single-particle analysis of the protein import translocase.

3: ***Klebsiella oxytoca* and other microbes collected on Country.** This molecular microbiology and biotechnology area of work includes projects on (i) a new model organism for biotechnology applications, (ii) cellulose degradation by secreted cellulases, including evolution of enhanced versions of these biotech-relevant strains, and (iii) re-programming of transcription-translation programs in wild *Klebsiella* by their natural phage predators.

4: **Phage stability assessments for phage therapy.** This molecular biology or bioinformatics area of work includes projects on (i) cryoEM of phage virions to explore their stability and other structural features, (ii) using a fluorescence-based disruption assay to rapidly assess phage stability, leading to a scoring system for phage "armour", and (iii) using machine learning to develop PhageArmour as a predictor of phage stability.

We are one of three labs in the Monash node of the Centre of Excellence in Mathematical analysis of Cellular Systems (MACSYS), that brings together research teams at five universities using molecular biology, systems biology and computational science to build whole cell models of bacterial cells. At MACSYS (https://macsys.org/) Honours and PhD students work with interstate and international partners to contribute to multi-disciplinary research outcomes. For PhD students, scholarships are available to support projects aimed at understanding bacterial cell surfaces and subcellular features of bacterial cells.



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Dr Milena Awad


Dr Ashleigh Rogers


Dr Jack Waters


Dr Lena Le


Dr Houdaii Khalil


Dr Irene Alevizos


Dr Desirel Ng

Understanding the impact of *Clostridioides difficile* infection on gut motility

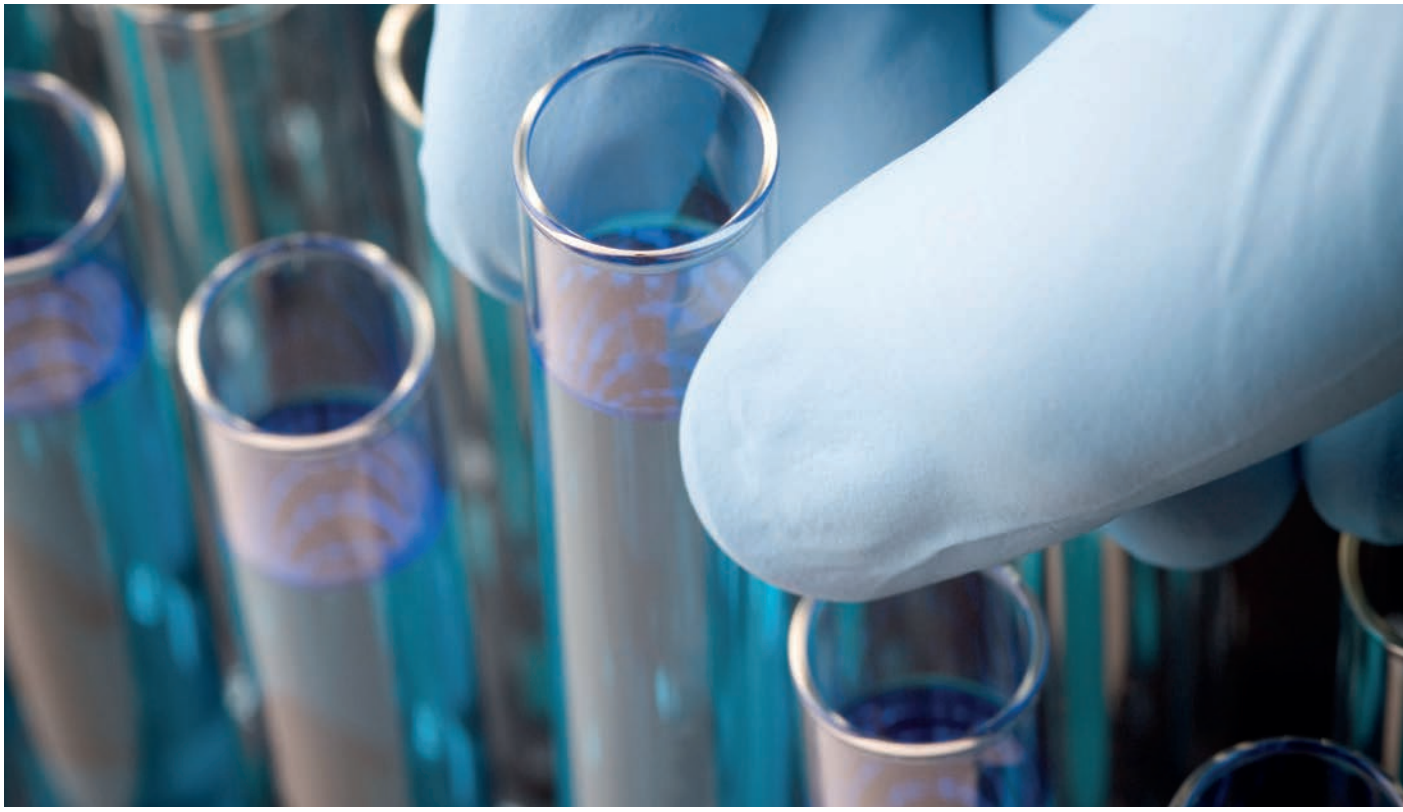
Prof Dena Lyras, Dr Steven Mileto, Dr Jack Waters, Dr Ashleigh Rogers

A defining characteristic of clinical diagnosis of *Clostridioides difficile* infection (CDI) is the development and presentation of diarrhoea, resulting from the disruption and destruction of the colonic epithelial lining by the *C. difficile* toxins TcdA and TcdB. The breakdown of the gut epithelium exposes the underlining layers of the gut to toxin mediated damage, which is a significant problem as the gastrointestinal tract (GIT) is responsible for essential for gastrointestinal motility, and vital homeostatic gut activity. These functions are in part coordinated by a network of neurons and glial cells embedded in the gut wall, termed the enteric nervous system (ENS), which communicate with the gut smooth muscle to generate force for the transit of intestinal contents through the gut. ENS dysregulation and dysmotility trigger various gastrointestinal disorders, however, whether ENS dysregulation and altered gut motility contribute to enteric infection has not been explored in depth. In this project we will use our novel mouse model of CDI to determine if infection with *C. difficile* affects the ENS and the smooth muscle layers of the gut and explore how ENS dysregulation contributes to disease. Findings from this project may aid in improving CDI diagnostic criteria to ameliorate the clinical outcomes of patients.

Investigating how Circadian Rhythms influence *Clostridioides difficile* infection

Prof Dena Lyras, Dr Steven Mileto, Dr Lena Le, Dr Desirel Ng

The brain, intestinal functions and gut microbiota communicate through bidirectional signalling pathways known as the gut-microbiota-brain axis. The brain also regulates circadian rhythms which optimise physiological processes according to natural 24-hour light cycles. Modern artificial lighting has disrupted these rhythms, increasing the risk of metabolic, mood and neurologic disorders. However, its impact on infectious gut disease is less understood, despite a link between the gut and brain which controls these rhythms. *Clostridioides difficile* infection (CDI) is the leading cause of diarrhoea in hospitals, where irregular lighting disrupts circadian rhythms. CDI causes toxin-mediated gut damage but has recently been found to alter brain metabolism, suggesting interactions with the gut-brain axis. As the gut-brain axis is bidirectional, brain-related processes such as circadian rhythms may play an unrecognised role in CDI pathogenesis. Our current results have found that circadian rhythm disruption alters the severity of CDI; however, the exact mechanism that drives this is still unknown. This project will use our novel mouse model of CDI and lightinduced circadian rhythm disruption to determine if these changes in disease severity are driven by the host or by changes within the microbiome and *C. difficile.* This work will aid in determining if host-pathogen interactions rely on normal circadian rhythms for normal disease progression, and if changes in hospital-based lighting may impact disease outcomes.



Understanding the role of bacterial surface structures in horizontal gene transfer amongst enteric pathogens

Prof Dena Lyras, Dr Yogitha Srikhanta, Dr Sarah Revitt-Mills, Dr Galain Williams, Dr Irene Alevizos

The widespread emergence of antimicrobial resistance amongst bacterial pathogens is a serious challenge to global healthcare systems. Of particular concern is the spread of antibiotic resistance genes through horizontal gene transfer, which allows resistance to develop at a rate much faster than would otherwise occur. One of the mechanisms underpinning this is bacterial conjugation, which involves the transfer of plasmid DNA between bacterial cells via conjugative pili. Alarmingly, conjugation occurs at high frequencies in the communities where bacteria naturally reside, such as in the human gut, yet our understanding of conjugation within these communities is limited. In this project, we will examine the factors that govern conjugation amongst Gram-negative enteric pathogens, with a specific focus on the role played by bacterial cell surface structures. You will develop skills in traditional microbiology and genetic techniques, and gain exposure to bioinformatics and live-cell microscopy. Students with a strong interest in bacteriology but who are not yet confident in molecular biology or genetics are still encouraged to apply. The findings from this project may lead to the identification of new therapeutic targets and strategies through which the spread of antibiotic resistance can be inhibited.

Understanding how the gut environment shapes antibiotic susceptibility during infection

Prof Dena Lyras, Dr Melanie Hutton, Dr Milena Awad, Dr Houdaii Khalil

One in three people worldwide use antibiotics each year, however ~17% of infections no longer respond to standard first line treatments, and antimicrobial resistance (AMR) continues to rise and spread among bacteria. AMR is driven in part by the off-target impact of antibiotics on the gut microbiome, which creates broad selection pressure that accelerates the emergence of resistant bacteria and the spread of AMR genes. Therefore, finding ways to protect the gut microbiome from the off-target effects of antibiotics without impacting drug efficacy is an exciting approach to combating AMR. This project will examine how to protect gut bacteria from the effects of a range of clinically used antibiotics. Using a combination of in vitro assays and mouse models, this project will investigate strategies to counteract the detrimental effects of antibiotics on the microbiome, while retaining antibiotic efficacy against pathogens. This work will lead to a new discovery program that could mitigate microbiome disruption and resistance emergence during antibiotic therapy.

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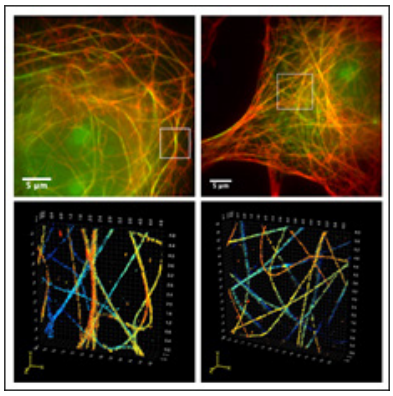

Immunofluorescence microscopy (upper panel) and 3D dSTORM super-resolution imaging (lower panel) of the cellular microtubule cytoskeleton associated with viral protein reveals significant differences between proteins of lethal (left) and non-lethal (right) viral strains.

Viruses pose one of the grand challenges to human and animal health globally and within Australia. Viral disease progression is critically dependent on the formation of specific interaction networks between viral proteins and host cell factors, which enable viral subversion of important cellular processes such as antiviral immunity and cell survival.

We use advanced cellular/molecular biology approaches including quantitative proteomics, structural biology, functional genomics, immune signalling assays, and live-cell/super-resolution imaging to elucidate these interactions at the molecular and cellular level, and viral reverse genetics and *in vivo* infection models to define their functions in disease.

Our major focus is on highly lethal human viruses including rabies/lyssaviruses, Nipah, Hendra, SARS-CoV-2 and Ebola virus, as well as a number of agriculturally significant and potentially zoonotic animal viruses. The overarching aim of the research is to identify new strategies for the development of novel vaccines and therapeutics for currently incurable diseases. Beyond disease, we also research the biology of so-called “Giant Viruses” that straddle the boundary between living cells and “non-living” viruses, to better understand this potential fourth domain of life.

The research involves extensive collaborations within Monash University and other leading national (e.g. University of Melbourne, CSIRO-ACDP high-containment facility) and international institutes (e.g. Pasteur Institute, Paris; Gifu and Hokkaido Universities, Japan; IITB, Mumbai, India), enabling access to unique resources and technologies including novel and highly pathogenic viruses.

Elucidating the Rabies Virus P Protein Axis

A/Prof Greg Moseley, Dr Stephen Rawlinson, Ms Cassandra David

Rabies is a currently incurable disease that has the highest fatality rate of known infectious diseases. The etiological agents of rabies are lyssaviruses, such as rabies virus and Australian bat lyssavirus. Despite a very limited genomic capacity these viruses are able to mediate replication, assembly and budding, while simultaneously arresting potent control over the infected cell and host immunity. Central to this are multifunctional proteins including P protein, which resides at the core of the virus-host interface, forming a myriad of interactions with viral and host proteins. We showed that by inhibiting such interactions, we can prevent otherwise invariably lethal disease, identifying the P protein ‘axis’ as a therapeutic target. However, the molecular/structural mechanisms by which this small protein coordinates/regulates its diverse interactions remain unresolved, leaving major gaps in knowledge concerning fundamental processes in a lethal human disease.

The project will seek to define the specific molecular surfaces mediating key interactions of P protein, and to analyse their function using mutagenesis. This will contribute to the elucidation of the structural organisation and regulatory mechanisms of the virus-host interface and help to define novel mechanisms by which viruses efficiently co-regulate host cell subversion and replication. These findings have the potential to redefine our understanding of the virus-host relationship and to provide critical tools and data for the development of new vaccines and antivirals.

Viral Reprogramming of Host Cell Signalling

A/Prof Greg Moseley, Dr Stephen Rawlinson, Ms Cassandra David

Central to the spread of pathogenic viruses is their capacity to interfere with host immunity, in particular the antiviral system mediated by cytokines such as the interferons. It is well known that many viruses target interferon signalling to shut down the expression of antiviral genes. However, our recent work indicates that the interaction of viruses with cytokine signalling pathways is much more complex and intricate, involving interaction with multiple cytokine signalling pathways through a number of mechanisms including the remodelling of cellular structures of the cytoskeleton and nucleus. Importantly, mutagenic analysis and viral reverse genetics, indicates that altering viral targeting of these pathways profoundly inhibits pathogenesis *in vivo*, indicative of critical roles in disease. We are currently seeking to delineate the precise mechanisms by which viruses, such as rabies, SARS-CoV-2 and Ebola interfere with and modulate cellular pathways, not only to inhibit antiviral signalling, but also to reprogram specific signalling pathways toward 'pro-viral' responses, a novel concept in viral biology.

Can Rabies Cure Alzheimer's?

A/Prof Greg Moseley, Dr Stephen Rawlinson, Ms Cassandra David

Neuroinflammation is a major factor in human pathologies such as stroke, Alzheimer's disease (AD), and traumatic brain injury (TBI). Viruses such as rabies/lyssaviruses, paramyxoviruses Nipah, Hendra, measles, coronaviruses, and Ebola virus, have evolved powerful mechanisms to shut down inflammatory signalling for immune evasion. We aim to discover the molecular 'tricks' used by viruses to subvert host immunity, and to harness these mechanisms to develop new methods to prevent inappropriate responses underlying neuroinflammatory disorders and other diseases including cancers.

Are Giant Viruses alive, and how do they interact with other microbes?

A/Prof Greg Moseley, Ms Cassandra David

The recently discovered giant viruses inhabit a unique evolutionary space, somewhere between living biological organisms and non-living microbes. The evolutionary history and fundamental biological nature of giant viruses remain poorly defined, including such fundamental questions as whether giant viruses are 'alive' and what these viruses mean for our understanding of life. We recently initiated new studies of giant viruses in collaboration with the Indian Institute of Technology Bombay (IITB) using techniques including super-resolution imaging and proteomics to understand the life cycle of these viruses and their structure and to define whether giant viruses have evidence for a biochemical 'spark of life'. We are also examining how giant viruses interact with other microbes, and the implications for their biology and evolution.

Super-Resolution Analysis of the Virus-Host Interface

A/Prof Greg Moseley, Dr Toby Bell

Viruses are experts at remodelling the infected cell, and can fundamentally alter cellular biology to transform host cells into efficient virus factories. Although molecular/biochemical evidence indicates that certain viral proteins can functionally modify structures such as the mitochondria, cell membranes, the nucleus and cytoskeleton, understanding of the physical effects on these structures is limited due to the poor resolving power of standard cell imaging approaches. Using single molecule localization techniques to surpass the physical diffraction limit of visible light, we have developed methods to observe and quantify the effects of viral proteins on cellular structures at super-resolution, enabling us to directly measure viral remodelling of the subcellular environment. Using this approach, we demonstrated that virus protein targeting of the cytoskeleton correlates with the capacity to cause lethal disease *in vivo*. The project will apply state-of-the-art single molecule localization techniques such as 3D dSTORM to define viral effects on cellular structures in unprecedented detail; this will provide new insights into the ways that viruses co-opt cellular function to cause disease.

Why do Cytoplasmic RNA Viruses Target the Nucleolus?

A/Prof Greg Moseley, Dr Stephen Rawlinson

Many diverse viral proteins have evolved independently to target the nucleolus but this phenomenon had been largely overlooked, particularly for RNA viruses that replicate within the cytoplasm. Following the development of advanced 'systems-biology' approaches to analyse nucleolar biology, it has become clear that the nucleolus is complex, dynamic, and highly multifunctional machine that coordinates many critical cellular processes including immunity and cell survival. This has redefined our understanding of the nucleolus and suggests that the virus:nucleolar interface might represent a central hub for viral hijacking of cellular processes, important to viral replication and pathogenesis.

Using highly pathogenic RNA viruses, including rabies and Hendra virus, we are investigating the mechanisms by which viruses can reprogram the nucleolus to alter cellular biology. These studies are identifying for the first time specific nucleolar functions for RNA virus proteins. The project will utilize techniques including molecular biology, proteomics, super-resolution microscopy, virus replication and gene expression assays, and gene knockout approaches to delineate the precise events underlying cellular dysfunction caused by virus-nucleolus interaction.

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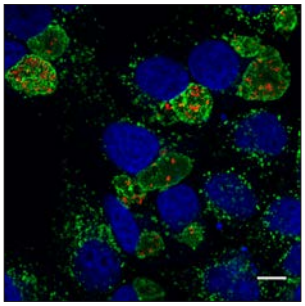

Coxiella (red) replicates in a spacious lysosome-derived vacuole (green = lysosomal membrane protein).

Our laboratory aims to create new knowledge in hostpathogen interactions driven by intracellular bacterial pathogens. We are fascinated by *Coxiella burnetii,* the causative agent of Q fever, and Legionella species, the causative agents of Legionnaires' disease, which both replicate inside human cells in a manner that requires the Dot/Icm type IV secretion system. This multi- protein apparatus delivers a huge number of novel effector proteins into human host cells, manipulating many aspects of human cell biology, to facilitate intracellular replication of the pathogen. However, very little is known about how individual effectors influence pathogen success.

Defining the mechanisms of lysosome survival by *Coxiella burnetii*

Prof Hayley Newton, Dr David Thomas

The Dot/Icm type IV secretion system is central to the ability to establish a replicative niche within mammalian lysosomes. We have identified several *C. burnetii* effector proteins that support replication of *Coxiella* by manipulating lysosome function. This project aims to functionally characterise these effectors to provide insight into both *Coxiella* pathogenesis and lysosome biology.

Techniques used in this project will include genetic manipulation of *C. burnetii,* cell culture infection and transfection, immunofluorescence confocal microscopy, protein biochemistry, mass spectrometry and molecular biology.

Characterisation of effector proteins that perturb host cell signalling

Prof Hayley Newton, Dr Sarah Garnish

Coxiella burnetii employs a cohort of Dot/Icm effector proteins to block human host cell death allowing the pathogen to slowly replicate to large numbers intracellularly. We have preliminary data supporting a role in preventing host cell death for several novel *C. burnetii* effector proteins, but we do not yet understand their mechanism of action. This project will characterise one of these cell death blocking effectors by:

i) determining changes to infection dynamics associated with the absence of this effector

ii) examining the protection this protein offers human cells from different cell death stimuli

iii identifying and characterising interactions between this effector and its host cell targets

This project will involve immunofluorescence confocal microscopy, protein biochemistry, mass spectrometry, molecular biology and the use of cell culture for infections, cell death assays and transfections.

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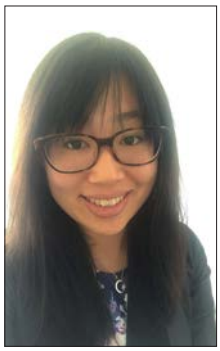
TWO VACANCIES


Professor Anton Peleg


Dr Margaret Lam


Dr Faye Morris


Dr Xenia Kostoulias


Dr Jhih-Hang Jiang


Dr Jackie Cheung

MECHANISMS OF PATHOGENESIS OF HOSPITAL-ACQUIRED ORGANISMS

Impact of Antibiotic Resistance on Immune Recognition of *Staphylococcus aureus*

Dr Jhih-Hang Jiang, Prof Anton Y. Peleg

S. aureus is one of the most common human bacterial pathogens, and is able to cause a wide range of life-threatening infections in the community and hospital setting. As a consequence of the rising rates of methicillin-resistant *S. aureus* (MRSA), agents such as vancomycin and daptomycin have been increasingly relied upon. Unfortunately, reduced susceptibility to these agents has now emerged. By using large-scale, whole-genome sequencing of clinical *S. aureus* isolates, whereby the first isolate is susceptible and the paired isolate is non-susceptible, we have been able to describe the genetic evolution of antibiotic resistance in patients. Interestingly, we have also identified, using both mammalian and non-mammalian model systems that these resistant strains have altered host-pathogen interactions, and appear to be more persistent.

Project 1

The aim of this project is to characterise the mechanisms of MRSA adaptation and evasion to antibiotic and host innate immune attack. The work will comprehensively identify genetic mutations that confer a survival advantage to MRSA under daptomycin pressure in the context of an immune response. This will be achieved by exposing clinically relevant MRSA strains to both antibiotic and host immune selection pressure, and apply a novel sequencing approach to characterise the full repertoire of mutations in specific phospholipid biosynthesis genes known to be important for antibiotic resistance. The significance of the identified mutations will be assessed by making independent mutants using our well-developed targeted mutagenesis system. The impact of individual mutations on antibiotic resistance, staphylococcal virulence, bacterial membrane biogenesis and host immune responses, will be assessed. As a proof of concept, we will target these identified resistance mechanisms using genetic inhibition and small-molecule inhibitors to enhance antibiotic bactericidal activity and prevent resistance. This project will combine exciting bacterial genetic techniques and advanced biochemical approaches together with novel infection model systems.

Project 2

In collaboration with Prof Meredith O'Keeffe (Dept. of Biochemistry)

The aim of this project is to characterise the activation of pathogen recognition receptors by our paired susceptible and resistant clinical isolates. This will be achieved by studying one of the key first responders of our immune system; dendritic cells. Different dendritic cell types differ in their expression of pattern recognition receptors and hence the types of pathogens that they recognise. They also differ markedly in their subsequent innate response to pathogens, with discrete dendritic cell subsets specialised in the production of different cytokines and interferons. This project will focus on the differences in pathogen recognition and the subsequent immune activation between clinically important and drug-resistant *S. aureus* strains. Using established *S. aureus* mutants, we will also determine the impact of changes in bacterial surface characteristics on activation of pathogen recognition receptors.

Characterising Novel Virulence Mechanisms in the Emerging Hospital-Acquired Pathogen; *Acinetobacter baumannii*

Prof John Boyce, Dr Faye Morris, Dr Xenia Kostoulias, Dr Jackie Cheung, Prof Anton Peleg

Despite the significance of *Acinetobacter baumannii* in nosocomial environments, we currently have a very limited understanding of the connections between gene regulation, metabolic capacity and virulence. Our lab has previously identified numerous metabolic pathways, individual genes and small RNA (sRNA) molecules, important for *in vivo* fitness. We have generated an assortment of sRNA and individual gene mutants, and in this project we will characterise the genetic regulation, mechanisms of action and specific pathways through which these components contribute to the success of this pathogen.

By comparing our repertoire of strains (ie mutants, complements and overexpression strains) using high-throughput proteomics and RNA sequencing we will aim to identify and confirm the specific targets and pathways impacted, and validate these observations using a range of virulence-associated phenotypes (growth in human serum, biofilm formation, neutrophil chemotaxis and mouse infection models, etc). Where inactivation of particular pathways affects virulence, we will design and construct inhibitors and test these as novel antimicrobials.

Note: Working with animals is not compulsory for any of the advertised projects.

How does plasmid transmission drive antibacterial resistance and virulence in the clinic and the environment?

Dr Margaret Lam, Prof Anton Peleg

Plasmid transmission between bacteria of the same or different species is an important driver of genetic diversity, bacterial adaptation and evolution. In the clinical setting, the transmission of plasmids between hospital pathogens such as *K. pneumoniae* plays a critical role in the dissemination of virulence and antimicrobial resistance (AMR) genes that can subsequently imbue strains with the ability to cause invasive and untreatable infections. Outside of the clinical setting, bacterial samples from animal and environmental sources are also enriched with plasmids, and alongside the occasional detection of AMR genes, also encode other lifestyle-enhancing traits such as heavy metal resistance or virulence.

Differences in plasmid distributions across the bacterial population and within different sampling niches highlight complexities in both the transmission dynamics of different plasmids and the varying ability of bacterial strains to uptake and maintain plasmids. For example, the AMR plasmids are detected at higher frequencies in the bacterial populations that circulate and cause outbreaks in hospitals. While comparative genomics and experimental evolution experiments have so far provided some insights into both bacterial and plasmid mechanisms responsible for this variation in transmission, many questions remain unanswered.

This project will use techniques within the comparative genomics space to examine how plasmid loads and types vary across *Klebsiella* strains from different sampling origins (i.e. clinical vs non-clinical) and genetically distinct lineages. These insights will be important for identifying 'high risk' species, lineages or plasmids that have higher plasmid transmission/maintenance rates, and therefore may be important targets in genomic surveillance or transmission intervention strategies.

This project will largely utilise techniques in the genomics space including, but not limited to, *de novo* genome assembly and annotation, DNA sequence alignments, building phylogenetic trees and BLAST. The work is therefore suitable for students with an interest in computational biology and its application in studying bacterial pathogens.

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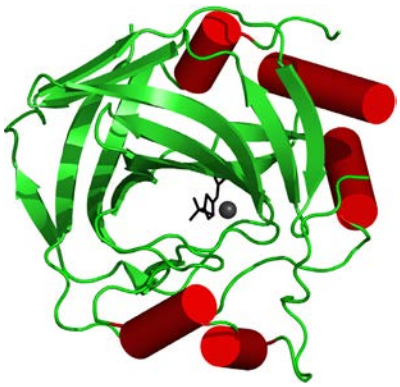
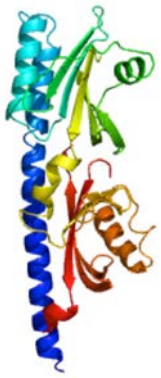


H. pylori CA-inhibitor complex



Chemoreceptor sensory domain

Antibiotic resistance: discovery of new antimicrobial targets

Helicobacter pylori is a pathogenic bacterium that infects the stomachs of half the world's population, causing chronic gastritis, ulcers, and even stomach cancer. While current treatments combine antibiotics with acid-reducing drugs, their effectiveness has declined due to increasing antibiotic resistance.

This project aims to identify and validate novel targets for developing alternative therapies against *H. pylori* infections. To validate the candidate microbial enzymes as viable drug targets, we will:

1 Determine the antimicrobial activity of their inhibitors (substances that block their function).

2 Test the efficacy of the inhibitors against a panel of clinical isolates to ensure broad-spectrum activity.

3 Test their ability to inhibit biofilm formation.

4 Study the structure-activity relationship (how chemical structure affects biological activity) of these inhibitors.

5 Assess the likelihood of *H. pylori* developing resistance to these inhibitors.

6 Use the mouse model to test the effect of enzyme inhibition on infection outcomes.

By exploring the new targets, we hope to pave the way for more effective and sustainable treatments against this widespread bacterial infection, which, if left untreated, can lead to the development of stomach cancer.

Dissecting the Structure of the Bacterial Motor

The bacterial flagellar motor is a remarkable nanoscale molecular engine. *H. pylori* evolved to be highly motile in the very viscous mucous layer of the stomach, and its flagellar motor is specialised for locomotion in viscous liquids – it produces a significantly higher torque (turning force) than, for example, enteric bacteria. Preliminary cryo-electron tomography reconstruction of this motor revealed a unique protein cage that supports a wider power-generating ring allowing it to sustain the larger torque. Our aim is to unravel the make-up of this cage and the structural basis for its ability to recruit more force-generating units.

Chemotaxis as a new antimicrobial resistance mechanism

Most bacteria display active movement by means of surface appendages. This movement is termed chemotaxis because it can be controlled by external chemical signals. It is well understood that nutrients are perceived as attractants, so that bacteria move towards sources of food. The aim of this project is to investigate a less well understood phenomenon - that bacteria are able to sense antimicrobial compounds and swim away from them. In the context of antimicrobial peptides produced by the innate immune system of the gut, this is a new mechanism of antimicrobial resistance.

Applications are welcome from students with a strong interest in structural biology, X-ray crystallography, the biology of *H. pylori*, or protein biochemistry.

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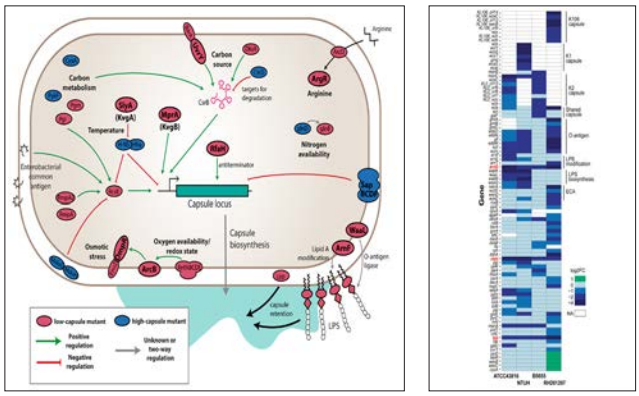
Dr Rhys Dunstan

A/Professor Kelly Wyres (Alfred Hospital)



(Left) Capsule regulation network of hypervirulent *Klebsiella pneumoniae*, constructed from high-throughput mutant profiling (Right) Strain-dependence of serum resistance in diverse *K. pneumoniae* isolates

In our lab we are fascinated by how Gram-negative "superbugs" survive outside the host. Antimicrobial resistance (AMR) is a defining public health challenge of our time, yet many of the most devastating pathogens of this crisis are not truly human-adapted but are widely-distributed microbes able to survive in diverse environments. Non-host environments provide a means for these pathogens to reach and colonise new hosts, equip them with beneficial genes through horizontal gene transfer, and select for new clinically-relevant traits. We use a combination of genomics and molecular microbiology to understand environmental survival, in order to develop new interventions. All projects in my lab offer training in both bioinformatics and "wet lab" microbiology.

Capsule as an anti-starvation strategy in *Klebsiella pneumoniae*

Dr Francesca Short, Dr Rhys Dunstan

Klebsiella pneumoniae is a serious public health threat, and its thick polysaccharide capsule is its primary virulence factor. *K. pneumoniae* capsule is highly diverse – over 100 different types have been described. Capsule has roles during infection that include protecting from antimicrobial peptides and blocking phagocytosis, and increased capsule production is connected with hypervirulence. We have recently discovered that capsule is the dominant factor enabling *K. pneumoniae* to survive and persist in natural waterways, because the bacterium can avoid starvation by using its own capsule as a carbon source. This is a new role for capsule and shows how essential virulence factors can also be selected outside the host. This project will characterise the enzyme involved in capsule catabolism, determine how widespread this ability is in diverse *K. pneumoniae* strains, and explore whether the capacity to "eat" capsule is also important in the human host. The project will include a range of microbiological and biochemical laboratory methods, as well as introductory genomics.

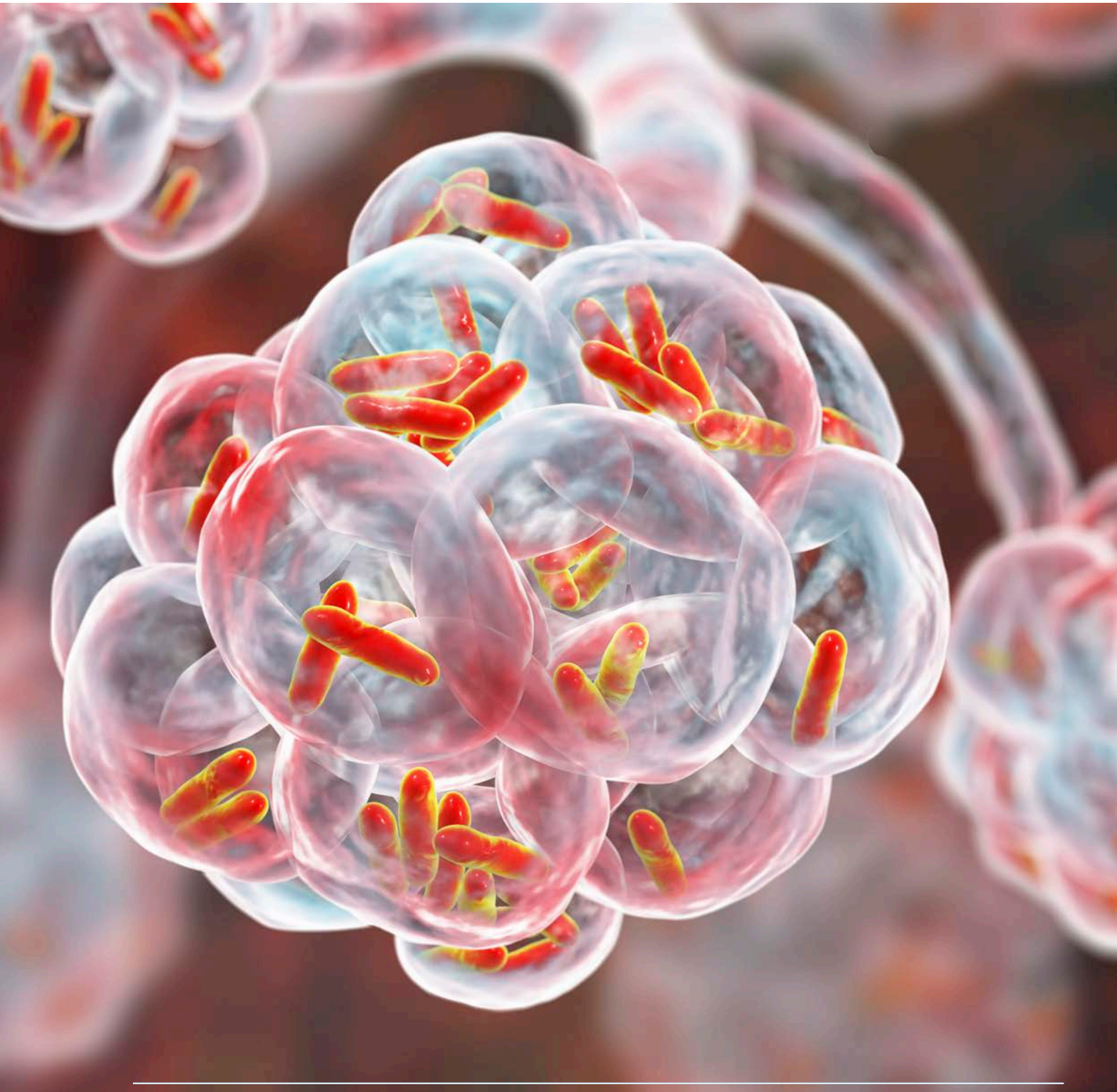
Eat to compete: Comparative and functional genomics to explore metabolism and competition between *Klebsiella* species

Dr Francesca Short, A/Prof Kelly Wyres (Alfred Hospital)

Klebsiella species are major healthcare-associated pathogens, and among the World Health Organization's critical priority antimicrobial resistant organisms. However, *Klebsiella* are also asymptomatic human gut colonisers, estimated to be carried by 15-70% of healthy populations. Metabolism is a major driver of colonisation and competition with the commensal gut flora, which likely impacts the risk of subsequent *Klebsiella* infection. Interestingly, it has been shown that *Klebsiella oxytoca* can competitively inhibit its close relative, *Klebsiella pneumoniae.*

Genome-scale metabolic modelling is a powerful approach for exploring bacterial metabolism and predicting growth substrate usage at a scale that cannot be tested in the laboratory. The current generation of *K. pneumoniae* metabolic models are highly accurate (95.4% accurate for aerobic growth predictions, 78.8% for anaerobic growth predictions), and have shown high metabolic diversity between strains within the same species, which we hypothesise drives differences in competitive success. We are now developing similar models for *K. oxytoca,* to understand its metabolic diversity and which metabolic traits drive competitive interactions with *K. pneumoniae.*

In this project you will use a state-of-the-art functional genomics (transposon mutant library screening, transcriptomics) and genome-scale metabolic modelling approaches to explore metabolism in *K. oxytoca* and how this compares to *K. pneumoniae.* The project is best suited for students who wish to learn both laboratory and computational analyses, including highly transferable skills in command-line computing and basic computer programming. No prior experience in programming is required as full training will be provided.



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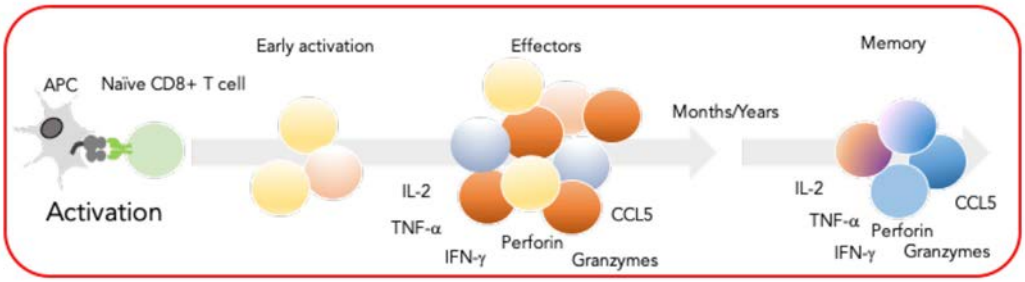
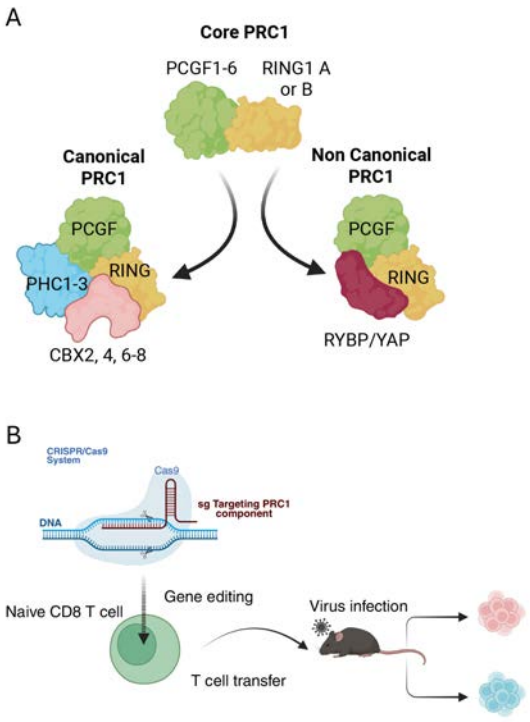


Assessing how chromatin modifying enzymes regulate virus-specific CD8+ T cell responses

Prof Stephen Turner

Virus infection triggers large-scale changes in the phenotype and function of CD8+ killer T cells and are critical for effective immune function (top figure) While it is appreciated the changes in gene transcription that occur upon T cell differentiation are associated with remodeling of genome regulatory elements, the mechanisms that mediate these changes are not fully elucidated. Polycomb Repressive complexes (PRC) are chromatin remodeling complexes implicated in silencing genes encoding crucial developmental regulators. Prior work in the Turner lab has implicated a role for components of the PRC1 complex in regulating T cell differentiation (Figure 1A); however, the mechanisms of action are still unclear. This project will use a combination of virology, cellular immunity, advanced molecular biology (eg CRISPR/ Cas9 targeting), genomics (CUT&TAG), cellular immunity and biochemistry to assess the impact of PRC1 subunit deficiency on influenza A virus-specific killer T cell function and establishment of immunological memory.



(A) Polycomb respressive complex 1 (PRC1) comprises a core of PCGF proteins (one of 6 subunits) paired with either one of two ubiquitin ligase subunits (RING1A or B). The canonical PRC1 complex (cPRC1) is formed by the addition of a pplyhomeochromatic (PHC) subunit (PHC1-3) and one of 7 chromobox proteins (CBX2, 4, 6-8). In contrast the noncanonical PRC1 (ncPRC1) is comprised of PCGF/RING1 proteins paired with either RYBP or YAP proteins. (B) This project will use CRISPR/CAS9 targeting to delete cPRC1 or ncPRC1 components from the genome of naive CD8+ T cells, that can then be transferred into recipient mice. Mice will be infected with influenza A virus and the subsequent impact of PRC1 deletion on T cell responses measured.

Projects Based at Affiliated Institutions

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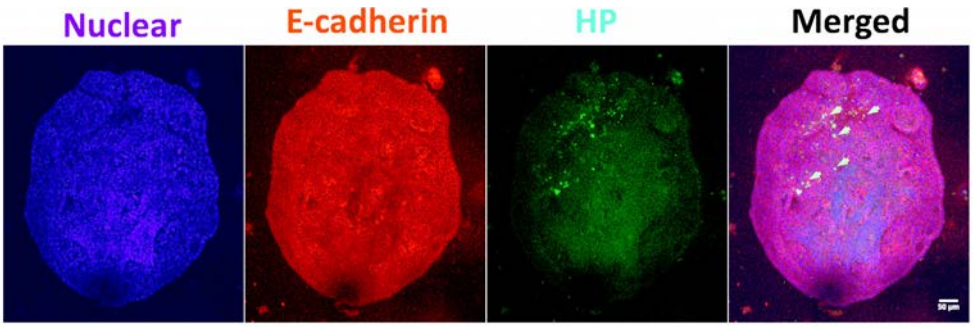


H. pylori bacteria (green) within a gastric organoid. (Images courtesy of L. S. Tran and G. Kerr)

Defining the Role of a Novel NLR Protein in Stomach B Cell Lymphoma Associated with Chronic *Helicobacter* Infection

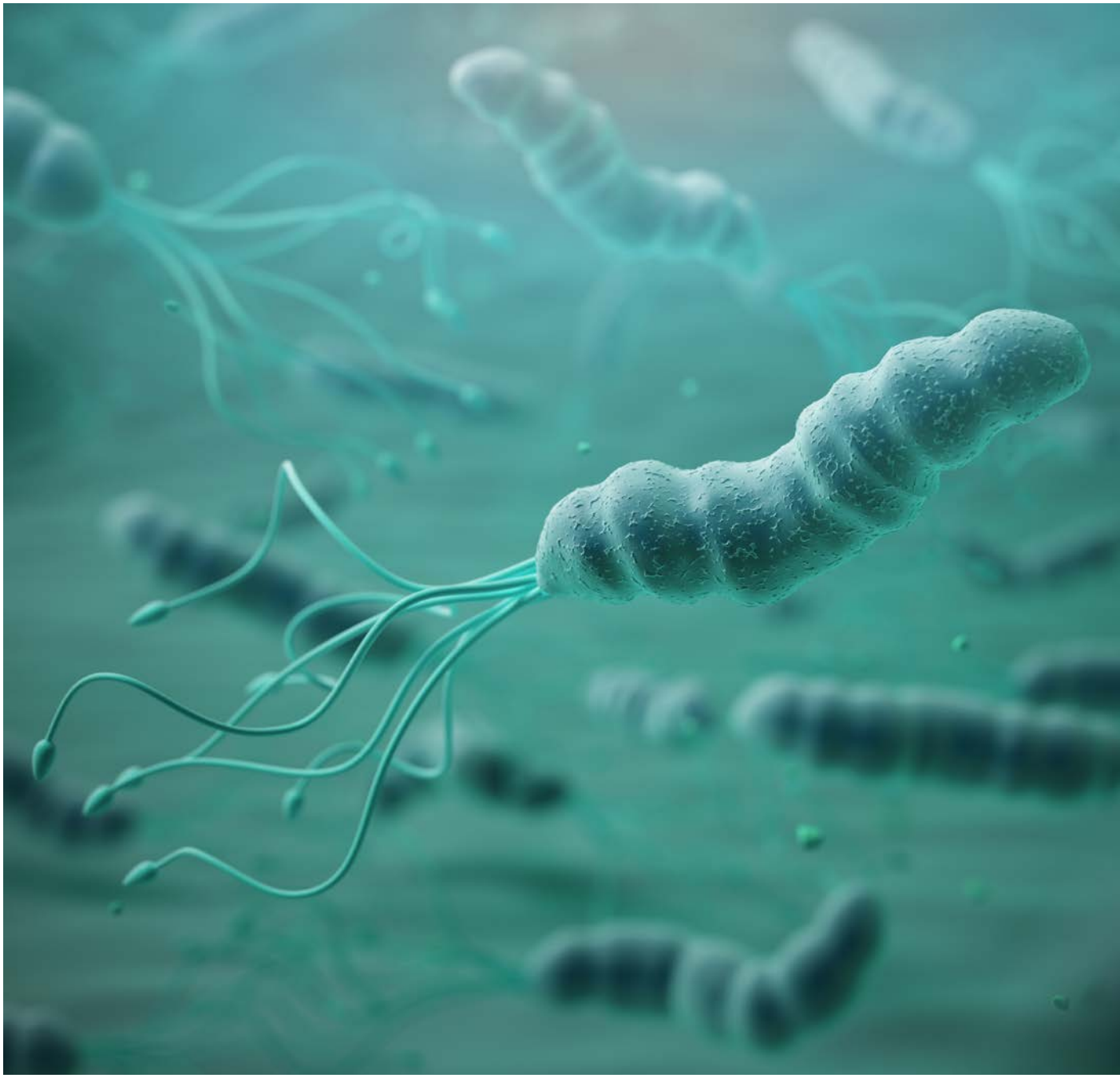
Prof Richard Ferrero

Our laboratory has identified a new NOD-like receptor (NLR) protein in the regulation of inflammation in responses to chronic *Helicobacter pylori* infection. Specifically, we have shown that conditional knockout mice lacking this NLR exhibit an accelerated formation of gastric B cell mucosa-associated lymphoid tissue (MALT), consistent with the early stages of MALT lymphoma, in response to chronic *Helicobacter* infection. We are now investigating how this novel NLR prevents B cell lymphomagenesis induced by chronic infection and whether this protein may play much broader functions in the host immune system. A particular focus of current studies is the role of NLRC5 in regulating anti-tumour immune responses. These studies will be undertaken using both *in vitro* and in *vivo* models, including conditional knockout mice. The project will involve various techniques, such as primary cell culture, mouse infection, immunohistochemistry, flow cytometry, cytokine ELISA and qPCR.

Characterisation of the Immunomodulatory and Oncogenic Properties of Bacterial Extracellular Vesicles

Prof Richard Ferrero

The release of extracellular vesicles (EVs) is a property that has been conserved by both multi- and unicellular organisms during evolution. One of the major functions of these EVs is to facilitate intercellular communication and transport of molecules. The release of EVs by prokaryotes was first described over 50 years ago, yet the biological significance of these structures is only beginning to be appreciated. We have shown that bacterial EVs are potent modulators of host immune responses. Several projects are available to investigate how bacterial-derived EVs target the nucleus, interfere with host cell functions and even promote oncogenesis. These projects will involve cell culture and, potentially, mouse models to elucidate EV interactions with host cells and to characterise the responses induced by EVs. A variety of techniques will be used, including cell culture, mouse models, proteomics, molecular biology, fluorescence imaging, flow cytometry, cytokine ELISA and qPCR.



Development of a Vaccine to Prevent Stomach Cancer using Bacterial Vesicles

Prof Richard Ferrero

It is estimated that half of the world's population have *Helicobacter pylori* infection. This bacterium lives in the stomach where it causes inflammation of the mucosa. Most individuals, however, do not know that they are infected. As a consequence; stomach cancer is often diagnosed once the disease is already advanced. Although antibiotic therapies are available to eliminate *H. pylori* infection, these are not always effective. Therefore, new approaches are needed to better manage the infection and associated disease.

A vaccine against *H. pylori* infection would be the most cost-effective means of preventing stomach cancer. Although vaccine trials in animals reported promising results, subsequent findings from clinical studies have generally been disappointing. The proposed project is directed at developing an entirely new type of vaccine based on bacterial vesicles. This project will involve a variety of techniques, such as molecular biology, bacterial mutagenesis, cell culture, mouse models, proteomics, fluorescence imaging, flow cytometry, cytokine ELISA and qPCR.

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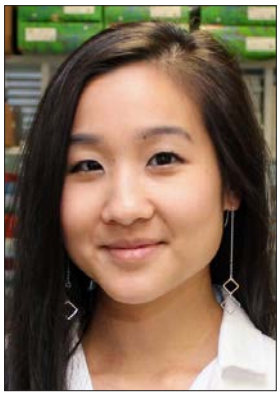
Dr Emily Gulliver



Dr Michelle Chonwerawong

Human Gastrointestinal Bacteria

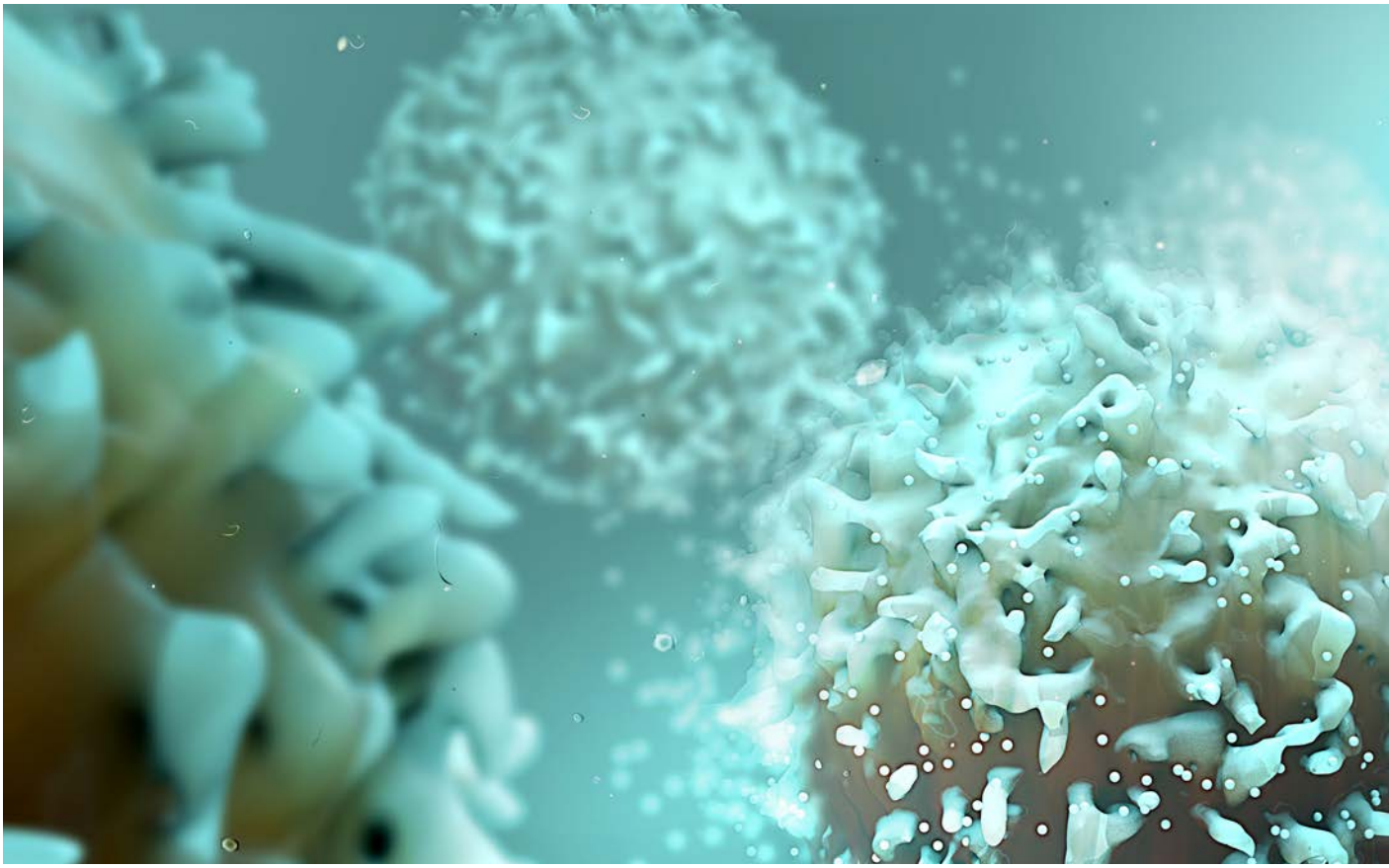
Understanding Microbiome Interactions with the Innate Immune System

Dr Michelle Chonwerawong, A/Prof Sam Forster

The innate immune system is capable of intricately detailed detection, differentiation and elimination of pathogenic bacteria. However, the vast majority of bacteria encountered by our innate immune system are beneficial to health. Indeed, over 500 species of these commensal bacteria, containing approximately 10,000-fold more genes than the human genome, exist in the human gastrointestinal tract alone.

Emerging research is demonstrating the importance of these bacterial communities in both maintaining health and causing or exacerbating disease. We have recently developed novel methods to grow the vast majority of bacteria from the gastrointestinal microbiota. This research has resulted in the discovery of hundreds of novel species that require further investigation. Combined with the established experimental and computational expertise in the analysis of innate immune signalling pathways, this project will include cutting-edge microbial culturing techniques, cell culture assays and advanced computational analysis to identify pro- and anti-inflammatory bacterial species.

Students interested in experimental or computational elements, will have the opportunity provided to develop skills in both areas.



Discovery of Antibiotic Resistance Gene Dispersal in the Human Microbiome

Dr Emily Gulliver, A/Prof Sam Forster

Antimicrobial resistance (AMR) is emerging at an alarming level, rendering some bacterial infections untreatable and increasing dependence on last-line antibiotics. There is an urgent need to provide clinicians with the data to inform antibiotic selection that will optimize treatment success, while minimizing the spread of resistance-containing species and dispersal of antibiotic resistance genes.

Despite the bacterial diversity within our microbiota, current understanding of the genetic factors that confer resistance is almost exclusively limited to pathogenic or opportunistically pathogenic organisms. For example, in the human gastrointestinal tract, there are 100 trillion bacteria, representing more than 500 species, which are exposed to selection for antibiotic resistance during oral antibiotic treatment. The resistance mechanisms in these commensal bacteria remain largely undefined, despite representing a significant, hidden source of antibiotic resistance genes that could be transferred to pathogenic or other commensal bacterial species.

We have developed methods to culture the vast majority of the human gastrointestinal microbiota (Nature, 2016; Nature Biotechnology, 2019), which will provide an important resource to undertake these studies. This project will combine detailed genomic and metagenomic sequence analysis with *in vitro* microbiology to understand and monitor the diversity and distribution of antibiotic resistance within the human gastrointestinal microbiota. The opportunity also exists to focus the project to experimental or computational biology.

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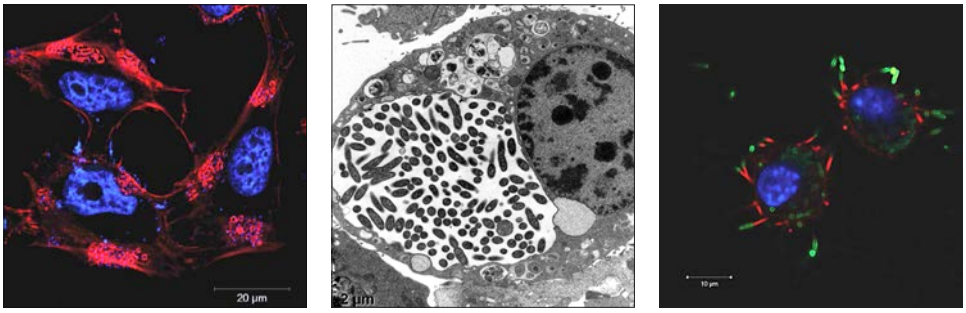


Left to right, Enteropathogenic *E. coli* adhering to epithelial cells and causing the rearrangement of actin (red) underneath the adherent bacteria. Cell nucleus (blue). Electron micrograph showing the replicative vacuole of the Legionnaire's pathogen, *Legionella pneumophila*. Actin tail formation (red) by the intracellular bacterium, *Burkholderia thailandensis* (green). Cell nucleus (blue).

Cell intrinsic and Innate Reponses to Bacterial Infection

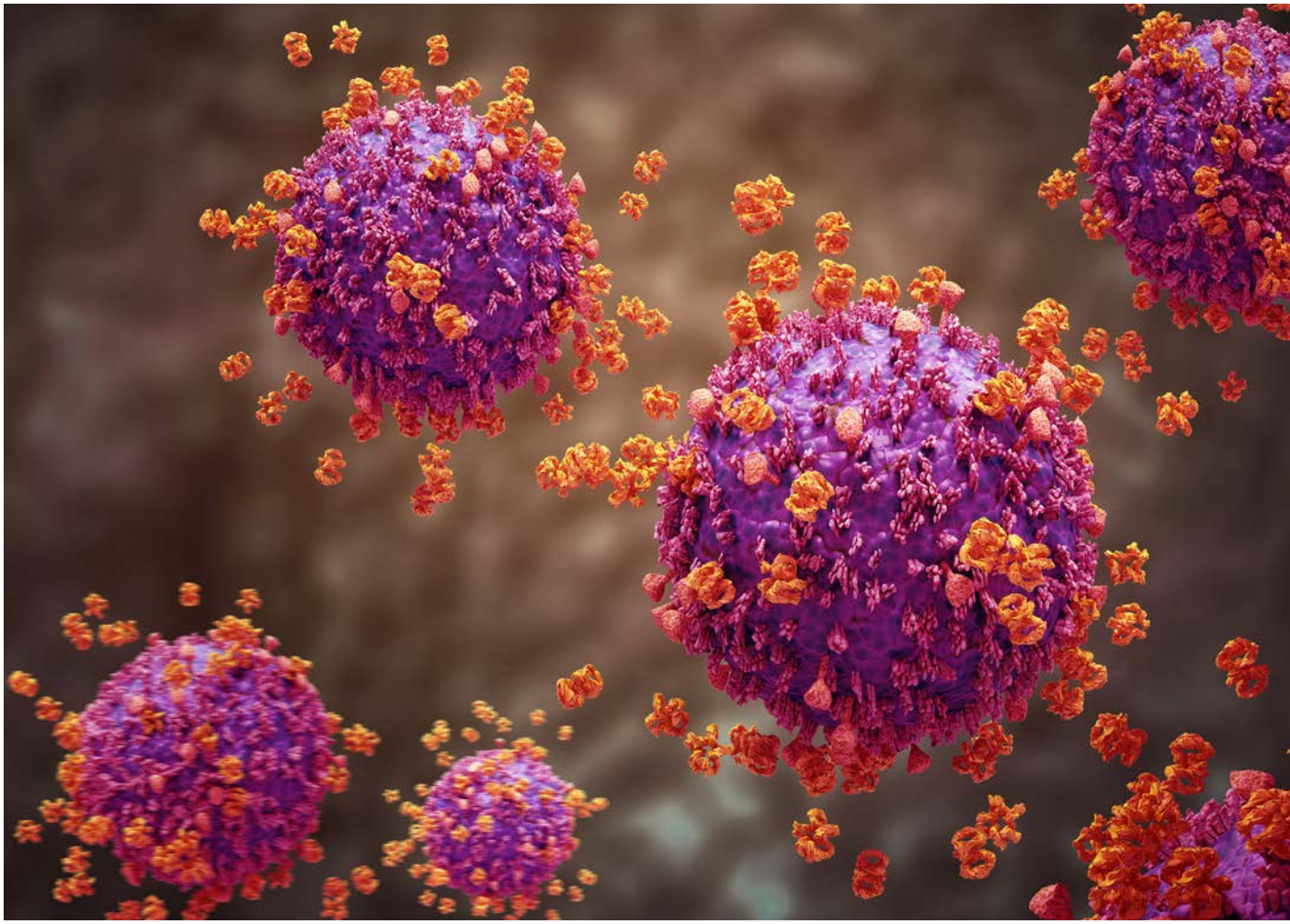
Cell intrinsic immunity is an innate immune, cellular defence system that directly restricts the replication of intracellular pathogens thereby safeguarding cell and tissue integrity. Upon pathogen invasion, cell intrinsic immunity may be induced by different cell stress pathways, resulting in an antimicrobial environment that is less permissive for pathogen replication. Cell stress responses have been also linked to inflammatory signalling and immunometabolism, providing a direct connection to the broader innate immune response. We and others have discovered that the intracellular bacterial pathogens *Legionella, Burkholderia* and *Shigella* species interact with diverse host cell stress pathways during infection.

Targetting host RNA interactions in bacterial infection

Prof E. Hartland, Dr K. McCaffrey

Legionella pneumophila translocates more than 300 effector proteins into the infected macrophage that manipulate a range of host cell processes. We have discovered that one effector protein induces the degradation of mRNAs encoding enzymes involved in immunometabolism. This project will investigate the modification of host messenger RNA (mRNA) by effector proteins during *Legionella pneumophila* infection.

Using bacterial genetics, you will generate gene-knockout bacterial strains to characterise the role of host mRNA interactions in bacterial replication as well as host responses to infection. As part of this project, you will gain experience in molecular microbiology techniques as well real-time quantitative PCR, Western blotting and confocal microscopy methods.



Understanding the role of virulence effector proteins in bacterial infection

Prof E. Hartland, Dr G. Ng

This project will investigate the role of effector proteins from the intracellular pathogens, *Burkholderia* and *Legionella*, in host cell stress, inflammatory and cell death signalling. Based on preliminary discoveries in our lab, we have identified effector proteins that block cytokine secretion, cell death and cell stress. Here these will be biochemically characterised to determine their host targets and activities during infection. Ultimately this will allow us to understand the molecular mechanisms by which *Burkholderia* and *Legionella* facilitate their intracellular replication and cause disease. This project will employ techniques such as bacteriology, mass spectrometry, high-throughput screening, genetic modification of bacterial pathogens, cell culture, protein expression and purification, molecular biology, western blot, and confocal microscopy.

Innate immune signalling in intestinal stem cells during infection

Prof E Hartland, Dr E Chan, Dr C Giogha

Tissue resident epithelial stem cells maintain epithelial homeostasis and mediate epithelial regeneration. However, how infection affects epithelial repair and regeneration by the stem cells is poorly understood. Here we will utilise human intestinal organoid models of epithelial responses and regeneration to examine the role of certain innate immune factors in gut repair following bacterial infection. Gut commensal bacteria as part of the human microbiome also contribute to intestinal maintenance and repair. We will also explore how microbial factors produced by defined microbiome communities influence damage and repair pathways following infection and inflammation. This project will employ techniques such as bacteriology, organoid culture, transcriptomics, molecular biology, western blot, and confocal microscopy.

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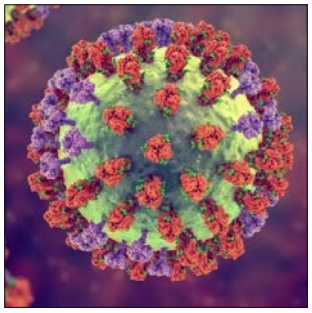

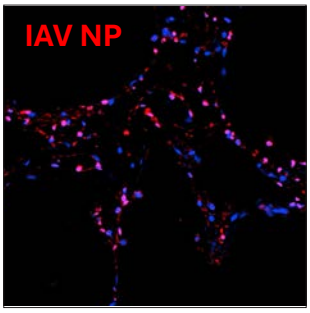

Left: Influenza virus.
Right: Human lung slice infected with influenza A virus (IAV) with NP protein shown in red. Nuclei shown in blue.

Viral Immunity and Immunopathology Laboratory

Severe viral infections can trigger uncontrolled inflammation and tissue injury, leading to life-threatening disease. Our laboratory investigates the molecular and cellular mechanisms underlying viral pathogenesis, with a particular focus on how innate immune responses contribute to tissue damage and disease severity.

We aim to uncover novel host-directed therapeutic strategies that dampen harmful inflammation and cell death while limiting viral dissemination. By mapping the pathways that drive pathogenic responses, we are identifying new drug targets and developing treatments that improve patient outcomes in severe viral disease.

Our research uses cutting-edge *in vitro, ex vivo,* and *in vivo* models of infection, combined with advanced immunological and imaging techniques, making this an excellent environment for students who want hands-on experience at the interface of virology, innate immunity, and translational medicine.

Understanding How Influenza Viruses Drive Lung Immunopathology

Prof Michelle Tate

Influenza remains one of the most significant respiratory pathogens globally, and experts warn that another pandemic is not a matter of if, but when.

Paradoxically, the severity of influenza disease is driven not only by the virus itself, but by the host's own inflammatory response. Excessive and dysregulated innate immune activation in the lung leads to immunopathology, tissue destruction, oedema, and respiratory failure, hallmarks of fatal infection.

Current antiviral drugs target the virus directly and have limited efficacy, particularly once inflammation is established. There is an urgent and unmet need for host-directed therapies that can protect the lung from damaging immune responses without compromising viral clearance. This project will investigate the cellular and molecular drivers of lung inflammation during influenza A virus (IAV) infection.

Using a combination of in vitro, ex vivo, and in vivo preclinical infection models, you will:

- Characterise the innate immune cell populations and signalling pathways responsible for immunopathology and viral dissemination in the infected lung
- Investigate the temporal dynamics and strain-specific inflammatory responses
- Uncover and evaluate potential host-directed therapeutic candidates

Models include: animal models, human primary and immortalised cells, and ex vivo lung tissue slice infection models.

Techniques include: tissue culture, flow cytometry, confocal microscopy, histology, western blot, ELISA, cytokine bead array, and viral plaque assays.

This project is ideally suited to students with an interest in the interplay between virology and immunology.

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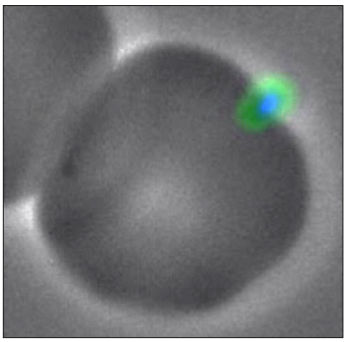
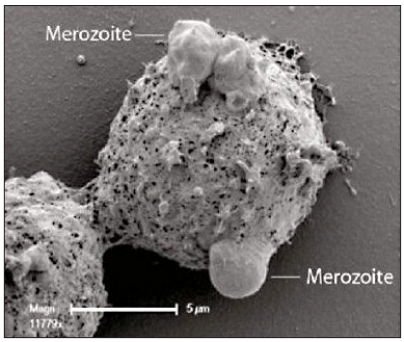
ONE VACANCY

Professor James Beeson



Immunofluorescence microscopy showing invasion of a human red blood cell by a malaria merozoite (green)



Phagocytosis of malaria merozoites by a human monocyte, an important mechanism of immunity, visualized using electron microscopy

Developing Vaccines Against Malaria

Malaria is one of the world's leading causes of death and illness, particularly among young children. There remains a strong need for highly effective vaccines to reduce the burden of malaria and progress towards eventual malaria elimination. To date, most vaccines have achieved only modest levels of efficacy, emphasising the need for novel approaches in vaccine design that can induce potent immune responses.

This project will focus on identifying key antigens and specific epitopes that are targets of protective immunity against malaria and understanding the mechanisms mediating immunity, which includes antibodies and cell-mediated responses.

This knowledge is crucial for the development of effective vaccines against malaria. The project will also involve using knowledge of immunity to malaria for informing vaccine design, and the expression and testing of novel vaccine candidates. These studies will use novel approaches in molecular biology, cell biology and immunology to address these aims, and will build on recent major advances generated from our malaria vaccine program.

The project will primarily involve laboratory-based research, including western blotting, imaging, standard immunoassays, functional immunoassays (e.g neutralisation assays, cell-mediated immunity), flow cytometry, cell culture and protein expression. The project links with our malaria vaccine developoment work using mRNA, protein, and peptide-based vaccine platforms. The project could also include bioinformatics, structural modelling of vaccine antigens, or modelling vaccine impact depending on the student's interest. The specific activities and focus of the project will be refined to suit the interests and training background of the student and align with our research group's priorities. Interested students should contact Chrissie Collins, chrissie.collins@burnet.edu.au

Discovering the Mechanisms and Targets of Immunity Against Malaria

Antibodies are an important component of acquired immunity against malaria, as demonstrated in pivotal studies in which immunoglobulin G (IgG) from immune adults was transferred to malaria-infected children and resulted in clearance of infection. In recent studies, we have begun to uncover important roles for antibodies that can directly inhibit host-cell infection, interact with immune cells to kill and clear malaria, or recruit complement to neutralise infection.

The aims of this project include identifying the key targets of specific mechanisms mediating immunity. The project may combine detailed studies of immune responses with clinical and population studies in Africa, Asia, and Papua New Guinea. It will examine how immune responses protect children from malaria or protect pregnant women and their developing babies from the devastating consequences of malaria in pregnancy.

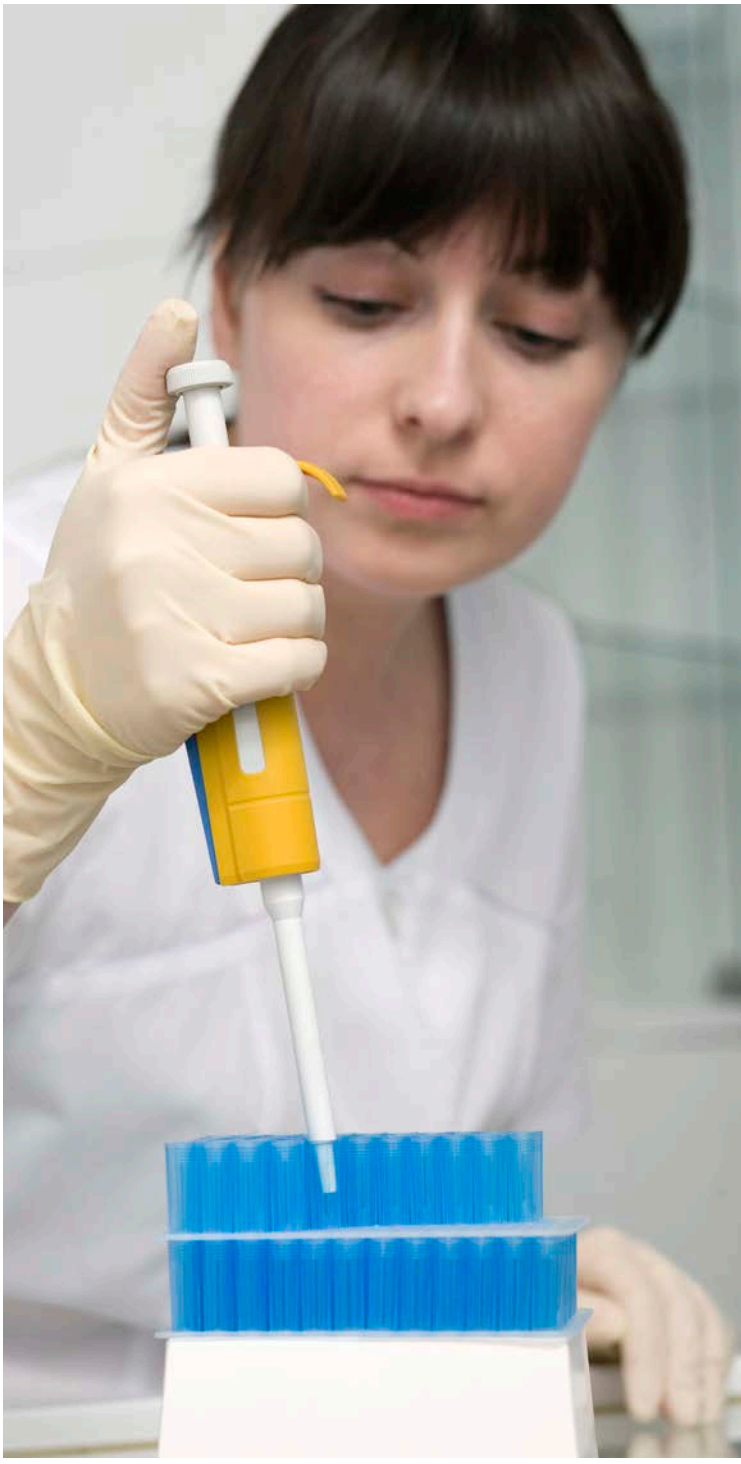
The studies would particularly focus on using innovative approaches to understand how antibodies neutralise and clear malaria parasites in the blood, including interactions with monocytes/macrophages and dendritic cells, and identifying specific epitopes targeted by protective antibodies. Skills may involve assays of functional immunity, cell culture, isolation and analysis of immune cells, flow cytometry, western blotting, ELISA, and epitope mapping. The project will be tailored to best match the student's interests and training background and research priorities of the group. Interested students should contact Chrissie Collins, chrissie.collins@burnet.edu.au

Interactions between SARS-CoV-2, malaria, and other infections that impact vaccine immunity in Africa

Major infectious diseases including malaria, COVID-19, and other respiratory infections have a major health impact in African populations, in part because of the moderate efficacy of vaccines being implemented in many countries, waning immunity and incomplete vaccine coverage. The protective efficacy and longevity of immune responses induced by SARS-CoV-2 and other vaccines vary markedly between individuals and populations. Knowledge on vaccine immunity in African populations, and factors that impact immunity, is limited but is important for controlling and preventing major infectious diseases such as COVID-19 and malaria.

Repeated exposure to malaria, intestinal parasites, and respiratory viruses, as well as specific nutritional deficiencies, are common in sub-Saharan Africa, and can impact innate and adaptive immunity to influence the magnitude and longevity of vaccine-induced immunity.

As part of an international collaborative program, this project will investigate immunity in cohorts of naturally infected and vaccinated individuals in Malawi (central Africa) and address important knowledge gaps. The project will involve laboratory-based studies in Melbourne that assess the acquisition and longevity of immunity generated by vaccines and natural infections and determine how parasite infections, undernutrition, and anemia impact on immunity. We will use a comprehensive range of immunoassays including quantification of antibody magnitude (subclasses and isotypes), neutralizing antibodies to different variants, avidity and antibody-dependent cellular cytotoxicity. Additionally, studies will profile specific epitopes targeted by immunity and their relationship to immune escape by virus variants. The overall objective of this work is informing strategies to improve protection from COVID-19, and identifying those most at risk, by understanding key gaps in natural and vaccine induced immunity. Interested students should contact Chrissie Collins, chrissie.collins@burnet.edu.au



Dr Johanna Fraser

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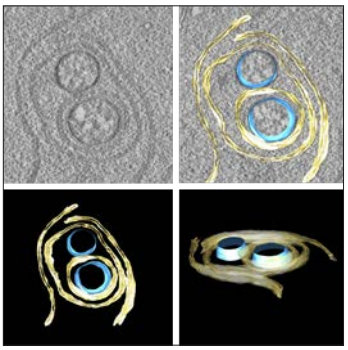
TWO VACANCIES

Dr Johanna Fraser

Wolbachia-infected mosquitoes are being released in dengue-prone regions by Monash-based World Mosquito Program to reduce the burden of dengue in communities.



Wolbachia (blue) resides inside mosquito host cells and associates with ER membranes (yellow).

Defining the mechanisms of *Wolbachia*-mediated virus inhibition

Dr Johanna Fraser

Wolbachia is an endosymbiotic bacterium found in nearly 60% of insect species. It is not naturally found in *Aedes aegypti*, the mosquito vector responsible for transmitting significant human pathogenic viruses such as dengue and Zika. Work over the last decade has shown that *Wolbachia* can be introduced into *Ae. aegypti*, and interestingly, it can impart a potent antiviral state in these mosquitoes. An overwhelming body of evidence has now demonstrated the efficacy of *Wolbachia* as a biocontrol tool, including significantly reducing dengue disease in regions where these mosquitoes are established in the field. However, the detailed mechanisms by which virus inhibition occurs are yet to be fully elucidated. This project will utilize a range of molecular techniques to examine hypotheses such as nutritional parasitism and host cell organelle disruption that may contribute to the antiviral impacts of *Wolbachia*.

Viral resistance towards *Wolbachia*

Dr Johanna Fraser

As this *Wolbachia* biocontrol system ages in the field, there comes an increased risk of viral resistance developing towards *Wolbachia*. We have established a novel viral passaging technique to study how virus populations evolve towards *Wolbachia*. This project aims to characterize the ability of *Wolbachia*-adapted viral variants to infect mosquito and human hosts by using molecular and classical virology methods.

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TWO VACANCIES

Dr Jane Hawkey

A/Professor Kelly Wyres

In our lab, we are interested in uncovering the dynamics of the evolution and transmission of antimicrobial resistant bacterial pathogens. Our research primarily focuses on high-priority Gram-negative pathogens which pose threats to vulnerable communities and hospital settings. We use computational approaches to develop new knowledge and methods that are frequently implemented in public health or hospital workflows.

No prior command-line or programming knowledge is required to undertake these projects. You will gain hands-on experience in navigating command-line programs, handling large datasets, and analysing data in R using existing pipelines – skills which will be broadly applicable across research projects or industries. Genomic skills that will be developed include phylogenetic analysis, *de novo* genome assembly, annotation, and reference-based variant detection.

Understanding the evolution and global dissemination of *Shigella* using genomics

Dr Jane Hawkey, Dr Danielle Ingle (University of Melbourne)

Shigella is WHO priority pathogen that causes severe diarrhoea and dysentery. In low-and-middle-income countries, it drives significant mortality in children under the age of five. In high-income countries, it primarily impacts returned travellers and the gay, bisexual and men-who-havesex-with-men (GBMSM) communities. Compounding this public health threat is a rise in extremely drug-resistant infections, which leaves clinicians with few or no treatment options available.

Understanding the evolutionary history of *Shigella* and establishing standardised, global surveillance frameworks are key for controlling outbreaks, informing vaccine development, and improving our knowledge about this important pathogen.

We have two projects available in this space, which are primarily computational. However, there is scope for the student to undertake some genomic sequencing.

Investigating convergent evolution and gene loss in *Shigella* and enteroinvasive *E. coli*

Despite the fact that they are named differently, *Shigella* species and enteroinvasive *E. coli* (EIEC) belong within the broader *Escherichia coli* group. Each *Shigella* serogroup and EIEC lineage have independently evolved the same disease phenotype via convergent evolution. A hallmark of this adaptation is the acquisition of a virulence plasmid, gene loss, and as a result, loss of various metabolic pathways. Within *Shigella* and EIEC, gene loss is often mediated by insertion sequences (IS) which are small, transposable elements that are ubiquitous in *Shigella* and EIEC genomes.

Using an existing comparative genomics framework, you would investigate the precise role of IS elements and their role in gene loss and metabolic pathway loss in different *Shigella* and EIEC lineages, comparing the lineages to one another and to the broader *E. coli* group. The outcomes of this project will improve our understanding of the less wellstudied *Shigella* and EIEC lineages.

Expanding the global genotyping framework for *Shigella sonnei*

S. sonnei has emerged as one of the dominant agents of shigellosis globally. To track its international transmission and the spread of critical antimicrobial resistance determinants, public health laboratories rely on robust genomic classification. Our group previously developed a globally recognized, SNP-based genotyping scheme for *S. sonnei,* which has been implemented by public health laboratories in Australia, the UK, and France. In this project, you will use new data that has been generated since the original scheme was published to improve this genotyping scheme, and compare it to novel typing approaches that have since been developed for *E. coli*. This work will be conducted in collaboration with the *Shigella* Genomics Working Group (an international consortium) where you will help develop the standards and rules for expanding the scheme. Your findings will directly contribute to this unified global nomenclature which is used by public health agencies worldwide.

Advancing detection of complex antimicrobial resistance mechanisms in bacterial pathogens

Dr Jane Hawkey, A/Prof Kelly Wyres

The burgeoning pandemic of antimicrobial resistant (AMR) bacterial pathogens poses a major threat to global health. In Australia alone, 6.5 deaths per 100,000 population are caused by AMR bacteria and these infections often occur in vulnerable patients in hospital settings. Much of this AMR burden is hidden to clinicians as current phenotypic methods for diagnosing resistance are slow and do not reveal its mechanism or mode of acquisition: pieces of information that are vital for managing and preventing AMR infections and outbreaks in the long term. Whole-genome sequencing (WGS) is becoming routine for surveillance of AMR bacterial pathogens and there is an urgent need to predict AMR phenotypes using genomic data. We have two projects available in this space, which are primarily computational. However, if desired, there is also scope for the student to undertake some wet-lab work including genomic sequencing, qPCR, broth microdilution or other antimicrobial susceptibility testing approaches.

Deciphering complex resistance mechanisms in Gramnegative pathogens

Extended-spectrum beta-lactamase (ESBL) and carbapenemase producing Enterobacteriaceae are priority-1 organisms. Resistance to beta-lactam antibiotics is mostly due to the production of beta-lactamases, and drugs comprising a combination of beta-lactamase inhibitor and a beta-lactam antibiotic are used to negate the effect of some beta-lactamases. Prediction of resistance to beta-lactams using genomic data is more difficult than most other drug classes, as the specific gene allele and expression levels can influence the observed phenotype – e.g., bacteria that over-express betalactamases are able to escape treatment with more sophisticated beta-lactams and beta-lactam/inhibitor combinations. Gene duplication is one way a bacterial isolate can over-express beta-lactamases. Current tools used to detect AMR-encoding genes typically only identify the presence or absence of a specific gene, but not whether the gene is duplicated. In this project, you will investigate clinical genome data to identify genomes with duplicated beta-lactamase genes and compare them to phenotypic resistance profiles. New genomic methods will be developed to better characterise gene duplication from genome data.

Capturing organism-specific knowledge on AMR for neglected pathogens

Most genomic tools treat AMR genomic data with a “one-size-fits-all” approach, which often leads to incorrect interpretations about the impact of genetic resistance determinants on the phenotype of a particular bacterial species. For example, the *oqxABR* operon is core to the *Klebsiella pneumoniae* chromosome, where its expression is typically regulated to a level below the clinical breakpoint for fluoroquinolone resistance. However, *oqxABR* can be mobilised from the *K. pneumoniae* chromosome into other species, where expression is regulated differently. Therefore, the presence of *oqxAB* in non-*K. pneumoniae* species typically results in clinical resistance to fluoroquinolones, and so the functional implications of *oqxAB* detection are species-specific. In this project, you will select a bacterial species for which AMR is of significant concern (e.g. species of *Stenotrophomonas, Klebsiella oxytoca, Klebsiella aerogenes*). In collaboration with the AMRrules Consortium (https://esgem-amr.amrrules.org/), we have developed a framework for organism-specific rules relating to functional interpretation of genetic resistance determinants. You would develop and test a rule-set for interpreting AMR genomic data from that organism.

Professor Gilda Tachedjian

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UP TO TWO VACANCIES

Top: Lactobacilli attached to a vaginal epithelial cell. Bottom: Cell infected with HIV (green dots). Right: An Australian black flying fox (Pteropus alecto).

Bat Viruses and Antiviral Defences

Prof Gilda Tachedjian, Dr Joshua Hayward, Dr Paula Ellenberg

Bats are a major reservoir of viruses such as Hendra virus, Ebola virus, and coronaviruses that are pathogenic in humans but not in bats. The reasons why bats can coexist with these viral pathogens are not fully understood. However, one explanation is that the coevolution of bats and their viruses has resulted in a 'peace treaty', a biological equilibrium in which viral replication is regulated in such a way that both host and virus can co-exist without undue antagonism. The role of the host's immune system is to control infections and antiviral restriction factors are at the front line of the innate immune response that targets viruses. These antiviral restriction factors were originally discovered to restrict retroviruses from other mammalian species, such as HIV [Hayward et al 2018 *Mol Biol Evol* 35(7)], and some of these factors e.g. tetherin, can additionally restrict paramyxoviruses, coronaviruses and filoviruses. Bats have recently been found to be an important reservoir of retroviruses from the genus Gammaretrovirus and are involved in transmission of retroviruses between mammalian species [Hayward & Tachedjian et al 2020 *PNAS* 117(17); Hayward, Tian and Tachedjian 2024 *Virus Evol* 10(1)].

The genomic fossil record of endogenous retroviral sequences, which are present as a critical part of eukaryotic genomes, also indicates that bats have a long history of infection with gammaretroviruses and betaretroviruses indicating that retroviruses have circulated in bats throughout their evolutionary history. How the innate immune system of bats has adapted to tolerate or combat infection with retroviruses remains largely unexplored, and this project seeks to further characterise the interactions between bat restriction factors and newly discovered bat retroviruses including the Hervey pteropid gammaretrovirus (HPG), the first extant retrovirus discovered in bats [Hayward & Tachedjian et al. 2020 *PNAS* 117(17)]. This is a joint project between the Tachedjian Lab and CSIRO Australian Animal Health Laboratory.

Vaginal Microbiota and HIV/STI Susceptibility

Prof Gilda Tachedjian, Dr David Jose Delgado-Diaz Dr Paula Ellenberg, Dr Joshua Hayward

The composition of the vaginal microbiota can influence the transmission of pathogens such as HIV. Women colonised with optimal vaginal bacterial communities, typically dominated by beneficial *Lactobacillus* spp., have a decreased risk of acquiring and transmitting HIV compared to women colonised with non-optimal microbiota. A non-optimal vaginal microbiota is characterised by a depletion of beneficial *Lactobacillus* spp. and high relative abundance of non-beneficial bacterial species, as exemplified by bacterial vaginosis (BV), which is a common form of vaginal dysbiosis in women of reproductive age that occurs in up to 55% of women in sub-Saharan Africa where HIV predominates (McKinnon *et al* 2019 *AIDS Res Hum Retroviruses* 25(3)). Non-optimal vaginal microbiota increase local pro-inflammatory cytokines, recruit activated HIV target cells and disrupt cervicovaginal epithelial barrier integrity that together drive increased risk of HIV acquisition. While studies have described the association between the vaginal microbiota and increased susceptibility to HIV and sexually transmitted infections (STIs), relatively little is known about how the microbiota and its metabolites act on the epithelium to mediate this effect.

Major distinguishing features of women colonised with optimal vaginal microbiota compared to women with BV is a dramatic increase in the levels of lactic acid and depletion of short chain fatty acids (SCFAs) suggesting a role for these metabolites as effector molecules of vaginal bacteria. Projects are available to determine the direct anti-HIV and bactericidal mechanisms of vaginal microbiota metabolites, their immune modulatory and barrier promoting effects on cervicovaginal epithelial cells (Delgado-Diaz *et al* 2020 *Front Cell Infect Microbiol* 9:446). These studies are underpinning an exciting program at the Burnet to advance strategies to treat and prevent genital inflammation and consequently susceptibility to HIV, other STIs as well adverse reproductive health outcomes.

Discovery of a New Drug Class for HIV Treatment and Prevention

Prof Gilda Tachedjian, Dr Paula Ellenberg, Dr David Chalmers

There is a real threat that drug resistance, toxicity and intolerance will eventually lead to exhaustion of antiretroviral drug options for both HIV treatment and prevention, especially since there is little in the way of new drug classes in the pipeline. We have initiated a drug discovery program targeting HIV-1 reverse transcriptase (RT) to identify compounds that inhibit this essential enzyme. We are using an innovative and validated paradigm for drug discovery called fragment-based drug design (FBDD) that uses very small compounds called 'fragments' to find inhibitors with novel mechanisms of action against HIV-1 RT. Using FBDD means screening far fewer compounds than conventional drug screens since fragments are so small, and can be developed into more potent drugs. Two screens have identified promising fragments that inhibit HIV-1 RT. We have discovered fragments with mechanisms that are distinct from other drugs that inhibit HIV-1 RT in the clinic (La *et al* 2015 *PNAS* 112:6979) and some of these have been progressed to molecules that have low micromolar activity against wild-type and drug-resistant RT. The aim of this study is to progress fragment hits into more potent RT inhibitors or drug leads. Compounds that are structurally related to the fragment hit will be evaluated for their ability to bind and inhibit wild-type and drug-resistant RT, as well as inhibit HIV-1 replication. This study will identify leads for the development of a novel class of RT inhibitor for use in HIV treatment and prevention.

This is a joint project between the Tachedjian Lab and Monash Institute of Pharmaceutical Sciences.

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TWO VACANCIES


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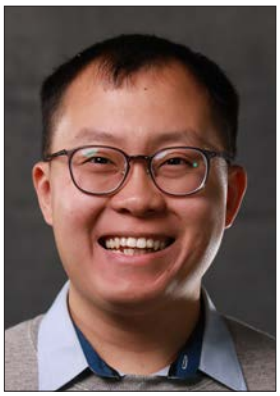
Dr Timothy Lim


Dr Fiona Lynch


Dr Rasmika Dewi

The One Water Laboratory

The One Water Laboratory is a collaborative space bringing together researchers from The School of Public Health and Preventive Medicine and Department of Civil Engineering to make positive global impact across the field of health-related water microbiology. Our research encompasses traditional culture, molecular assays, genomics and computational analysis offering broad learning opportunities to students with an interest in applied microbiology.

Preserving the Evidence: Making the Most of Environmental Samples for Pathogen Detection

Dr Rebekah Henry (School of Public Health), Dr Rasmika Dewi (School of Public Health and Preventive Medicine), Dr Fiona Lynch, Prof John Boyce (Dept. Microbiology)

Rapid molecular methods are increasingly used for monitoring microbial contamination in environmental systems, including water environments. To facilitate sample transport and storage, environmental samples are often preserved using nucleic acid stabilisation reagents that inactivate microorganisms while preserving DNA and RNA for downstream molecular analyses. Such approaches offer substantial practical advantages by reducing reliance on cold-chain transport, enabling sampling in remote locations, supporting retrospective investigations, and allowing archived samples to be reanalysed as new molecular methods emerge. However, little is known about how these preservation methods influence immunomagnetic separation (IMS), a technique that relies on antibody binding to microbial surface antigens for pathogen concentration and detection. Because IMS targets cell surface structures rather than nucleic acids, preservation-induced damage to cellular membranes may reduce capture efficiency and compromise subsequent molecular analyses.

This honours project will investigate the effect of DNA/RNA preservation media on the performance of IMS for the capture and detection of environmental pathogens, using Salmonella as a model organism and proof-of-concept system. Specifically, the project will evaluate IMS recovery following exposure of target organisms to preservation media, determine the impact of preservation on downstream molecular applications including qPCR sensitivity, detection limits, and potentially long-read sequencing approaches such as Oxford Nanopore sequencing, and assess whether washing or buffer exchange procedures can improve recovery from preserved samples. The findings will be used to develop recommendations for integrating sample preservation with IMS-based pathogen concentration methods and rapid molecular monitoring workflows.

Throughout the project, the student will gain experience in environmental microbiology, immunomagnetic separation techniques, quantitative PCR and molecular diagnostics, experimental design and method validation, statistical analysis and data visualisation, and scientific communication.

By addressing an important methodological gap in environmental pathogen surveillance, this project has potential applications in water utilities, public health laboratories, food safety investigations, and environmental monitoring programs that increasingly rely on molecular approaches for pathogen detection and characterisation.

Finding Wally: Merging Artificial Intelligence and Microbial Source Tracking to Combat Waterway Contamination

Dr Rebekah Henry (School of Public Health), Dr Timothy Lim, Dr Fiona Lynch, Prof Enes Makalic (Faculty of IT)

The sustainability of safe waterways is under constant pressure from urban stormwater runoff, animal waste, and unregulated sewage discharges. These unseen contamination events introduce dangerous faecal pathogens into community spaces and local waterways, risking severe gastrointestinal illnesses for recreational users. While traditional microbiology laboratory testing for faecal indicator bacteria is a crucial baseline, results can take 24 to 48 hours, making public health responses entirely reactive. Advancements in microbial source tracking can identify exactly where pollution comes from, but it cannot act as a real-time warning to stop exposure. The Finding Wally initiative aims to bridge this gap by testing a novel hypothesis: whether the automated, artificial intelligence (AI) supported analysis of animal and human activity near water can serve as a rapid proxy indicator to enhance existing hazard frameworks.

Students undertaking this project will work at the intersection of digital technology and environmental health microbiology. The project evaluates how automated, AI-supported analysis of animal and human activity acts as a rapid proxy indicator for water quality hazards. Working with two extensive, rarely matched historical datasets consisting of thousands of river time-lapse images and matching DNA-based microbial source tracking results, students will analyse data to pinpoint contamination pathways and map precisely how long it takes for a source on camera to leave a biological signal in the water. Through this work, students will gain highly valuable skills in environmental microbiology data integration, bioinformatics, and the practical application of microbial source tracking datasets. Students will also learn how to systematically evaluate machine-learning outputs against real-world biological data using strict quality control and verification frameworks.

Ultimately, this project will lay the foundation for a new generation of AI-enabled environmental health tools, transforming passive cameras into active decision-support systems for public safety. By defining the exact conditions under which visible data reliably reflects microbial risk, this work will deliver a smarter and more transparent hazardidentification framework. These outcomes will directly benefit water utilities, local councils, and environmental protection authorities by providing a low-cost, scalable asset to augment their regulatory monitoring. Beyond pure academics, students will work within a highly crossdisciplinary research environment. This collaborative setting provides firsthand experience in translating applied microbiological and DNA-based tracking data into realworld public health policies that actively prevent illness across shared water environments.

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TWO VACANCIES

Dr Yue Qu

Professor Anton Peleg

Professor David McGiffin

Project 1. Understanding the interactions between microorganisms and prosthetic heart valve causing infective endocarditis

Dr Yue Qu, Prof Anton Peleg, A/Prof Benjamin Roger (MMC), Dr Christopher Robson (VHH), Prof John Forsythe

The importance of biofilm formation in the pathogenesis of infective endocarditis has been previously proposed, particularly for those involving prosthetic valves or damaged endocardium and valve subendothelium. In patients with infective endocarditis, transesophageal echocardiogram (TEE) echocardiography often identifies large-size biofilm-like vegetations on infected valves. Whether these vegetations represent microbial biofilms for infective endocarditis remains to be clarified, as many vegetations yielded negative results on microbiological culture or a negative blood culture.

Microbial biofilms are believed to be a cause of treatment failure of infective endocarditis, due to their high resistance to conventional antibiotics used to treat the infection. Such speculation, however, is based on studies of *in vitro* biofilms grown in the over-simplified 96-well microplate cultivation system and has limited clinical relevance. A dynamic laboratory-based model that closely mimics physiologic hemodynamic of the left ventricular chamber is urgently needed. This model should produce *in vitro* biofilms that have similar characteristics as clinical biofilms encountered in infective endocarditis and can allow us to determine device-related key factors that make the prosthetic valves resistant to biofilm formation and infections, such as the design and surface characterise of the valves.

We will modify the pulsatile two-chamber circulation model by Lauten *et al.* (2021) to allow the growth of microbial biofilms on prosthetic valves; these biofilms should retain their resistance to antibiotics and should be morphologically like clinical biofilms grown on explanted materials. Mueller Hinton Broth or RPMI-1640 +10% bovine serum that has a similar chemical composition as human serum will be used as the biofilm growth medium. The impact of platelets in the growth medium on biofilm growth on prosthetic valves will also be assessed.

This study will be carried out using the developed *in vitro* biofilm model. Prosthetic valve materials with different surface characteristics and designs will be assessed for their capabilities to support biofilm formation by above-mentioned model microorganisms. Cell enumeration and high-resolution scanning electron microscopy will be used to assess biofilm formation quantitatively and qualitatively on prosthetic valves. Surface chemistry of the prosthetic valves will be examined using X-ray photoelectron spectroscopy. Elementary composition and the presence of specific function groups on the device surface have been reported to be the key

factors regulating biofilm formation. Surface roughness and hydrophobicity, two factors that are known to influence microbial biofilm formation will also be evaluated. This section will determine the key factor(s) of the prosthetic valve that may be utilized to prevent infective endocarditis associated with the implanted prosthetic valve. We will also use the developed biofilm model to screen various biomaterials that are used for pacemaker leads (including silicone, Pellethane and Carbothane) to understand differences in the anti-biofilm performance and durability of these materials.

Project 2. Developing antimicrobial hydrogels for biofilm-associated ventricular assist device driveline infections

Dr Yue Qu, Prof Anton Peleg, Prof David McGiffin (Alfred), Prof John Forsythe (MIME), A/Prof Tim Scott (MIME)

Ventricular assist device (VAD) implantation is an advanced therapy for heart failure that temporarily or permanently replaces a heart transplant. The driveline is an important percutaneous tube, consisting of smooth tube and velour sections and connecting the internal pump and the extracorporeal controller unit and batteries. Driveline infection is a major complication of VAD therapy that is difficult to treat and is associated with 8-20% of death of VAD patients.

We have published experimental and clinical evidence to support the importance of biofilm formation and migration in the occurrence and recurrence of driveline infections. Systemic antibiotics are recommended by the International Society of Heart and Lung transplantation (ISHLT) and are however suboptimal in treating driveline infections.

Local antibiotics using STIMULAN beads as vehicles have been used in orthopedics for implant-related infections, by eradicating microbial biofilms grown on the implant surface and often achieved satisfying patient outcomes. Cardiothoracic surgeons have also used antibiotic beads for deep driveline infections and reported cases of successful treatment. We have recently elucidated key parameters that determine the efficacy of antibiotic beads in eradicating biofilms. The keys are the class of antibiotics selected for the beads and their release dynamics in the subcutaneous tissue tunnel.

In our clinical study, we have demonstrated the presence of micro-gaps at the driveline-tissue interface as a shelter for microbial pathogens, particularly in the driveline velour section (Figure 1). STIMULANS beads as an antibiotic vehicle does not have the flexibility to get into these micro-gaps and can't be used topically.

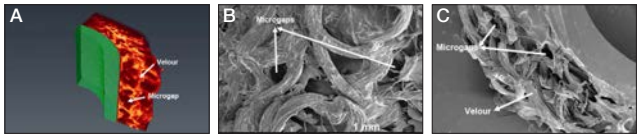

Figure 1. The presence of microgaps in the driveline tissue tunnel.

The proposed project aims to develop antimicrobial hydrogels that contain biofilm-active antimicrobial agents with an ideal release dynamic. Such a system will be able to effectively kill biofilm cells, including the stubborn persister cells. This system can be used to completely cure the trouble driveline infections and other surgical site infections that involve microbial biofilms. The project also aims to translate the developed antimicrobial hydrogens from *in vitro* to *in vivo*, using a small animal model of subcutaneous implant infection.

Project 3: Fabricating nanowire arrays with tunable geometries as an anti-infective weapon: From *in vitro* to the preclinical stages

Dr Yue Qu, Prof Anton Peleg, Prof David McGiffin (Alfred), Prof Nicolas Voeckler (MCN), A/Prof Roey Elnathan (MIPS)

Heart failure is a growing public health issue affecting at least 26 million people worldwide. VADs have emerged as an advanced therapy for heart failure, either as a "bridge to transplantation" for those awaiting a donor heart, or as "destination therapy" for patients who are ineligible for a heart transplant. The driveline is an important percutaneous tube connecting the internal pump and the extracorporeal controller unit and batteries, conducting telemetric data and power (Fig. 2). Driveline infections remain an Achilles heel of VAD therapy (Fig. 1A). These infections often spread along the driveline tissue tunnel and cause other major infections such as pump infections or bloodstream infections and have also been implicated in other major complications such as thrombotic and haemorrhagic stroke, causing death in 8-20% of VAD patients. Despite the introduction of various anti-infective strategies in the last decade, such as using drivelines with velour (Fig. 2) or using systemic and/or local prophylactic antimicrobials, driveline infections still occur at a high rate of 10-20% annually. Although the future of VADs will be a transcutaneous energy transfer system, this is many years away. *There is a pressing need to develop more effective strategies to mitigate driveline infections.*

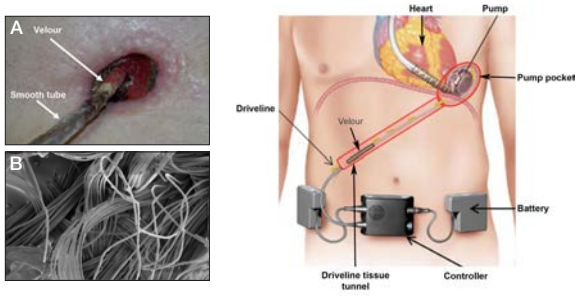

Figure 2: VAD and driveline infections.
A) A driveline exit site infection and
B) Ultrastructure of the driveline velour.

In vitro and animal studies suggest that the formation of biofilms, a microbial self-protective growth mode, characterised by high-cell-density growth and the presence of an extracellular polymeric substance (EPS) matrix, is the major cause of local driveline infections at the skin exit site. *Staphylococcus* species are model biofilm-producing microorganisms and account for over 50% of driveline infections. Once a microbial biofilm is established, the embedded microorganisms may become extremely resistant to antimicrobials and the human immune system. Furthermore, migration of biofilms along the tissue tunnel may enable deep-tissue access to the pathogens resulting in severe infections. Clinical evidence directly supporting the importance of microbial biofilms in driveline infections, and detailed analyses of clinical biofilms, were recently published by our group.

Our team has made considerable progress in leveraging our understanding of how driveline infections begin and further progress. Based on our understanding of the pathogenesis of driveline infections, we have explored the concept of surface modification by incorporating novel anti-infective nanowire arrays to prevent deadly device-related infections. Highly effective nanowire arrays were recently developed by our collaborative team. These nanowire arrays have been proven safe for human red blood cells and fibroblast cells, and effective in killing pathogenic bacteria with low risks of inducing antimicrobial resistance (Fig. 3). Our *in vitro* study showed that the developed nanowires with specific geometries were more effective than the well-known “black silicon” in killing *Staphylococcus* cells attached to the surfaces of biomaterials. With the support from the recently announced Artificial Heart Frontier Program (AHFP), the collaborative team is now seeking to further optimize nanowire arrays for better anti-infective efficacies and biocompatibilities, to translate our research findings from *in vitro* to *in vivo* using a small animal model that has been established in my lab, and to understand molecular mechanisms that underpin bacterial lyses induced by nanowires.

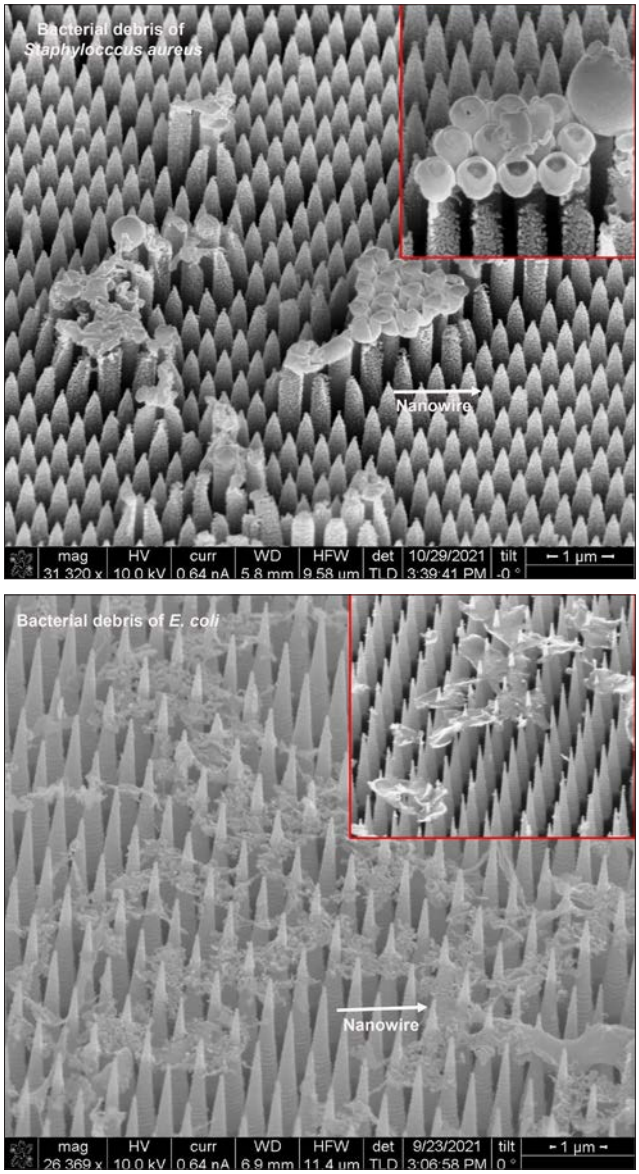

Figure 3. Anti-infective nanowire arrays developed by our collaborative team.

Notes

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