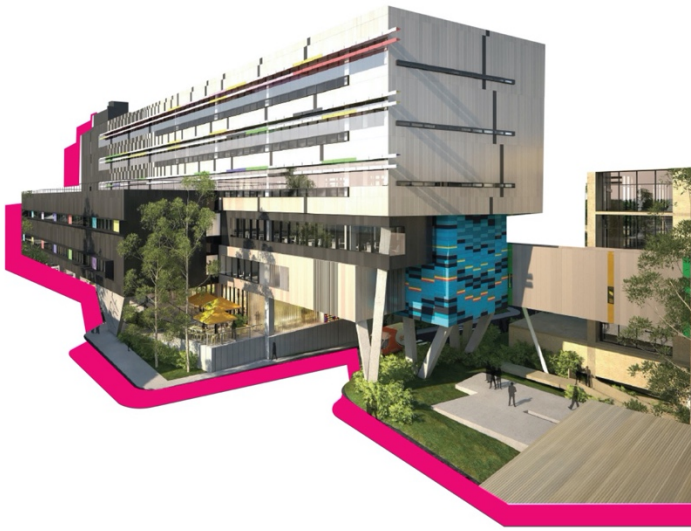
HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR INNATE IMMUNITY AND INFECTIOUS DISEASES

2022 Student Research Projects

MHTP Monash Health Translation Precinct | MONASH University | HUDSON INSTITUTE OF MEDICAL RESEARCH | MonashHealth

Contents



The Translational Research Facility is connected via a link bridge to Monash Health. The facility provides a crucial link between our scientific discoveries and medical treatments, housing nine world-leading technology platforms and an eight-bed, 21-chair Clinical Trials Centre that support the transition of discoveries from initial Phase I testing through to Phase IV primary health trials.

Welcome to Hudson Institute

Hudson Institute specialises in discoveries in five areas of medical need

- **Inflammation**
- **Reproductive health and pregnancy**
- **Infant and child health**
- **Cancer**
- **Hormones and health**

Our 443 scientists and students focus on laboratory discovery science, plus translational research – taking discoveries to patients and industry for real-world impact.

285 STAFF

158 STUDENTS

43 RESEARCH GROUPS

285 RESEARCH PUBLICATIONS

Students at a glance 2020

60 POSTGRADUATE AND HONOURS STUDENTS COMPLETED

158 STUDENTS 113 PHD 6 MASTERS 38 HONOURS

31 STUDENTS WITH MEDICAL TRAINING

We educate and train more than 150 students through our academic affiliation with Monash University. Our postgraduate training is predominantly through the School of Clinical Sciences at Monash Health, part of the Faculty of Medicine, Nursing and Health Sciences at Monash University.

Our students

- Are exposed to university, institute and hospital research
- Attend national and international conferences
- Publish their research (there were 41 student first author publications in 2020)
- Are mentored by leading supervisors and their teams
- Regularly win prestigious prizes and awards
- Take part in regular networking and learning and development programs.

All work and no play …

Our students can join in a range of student networking and social events organised by Hudson Institute Student Society (HISS), including being part of the management committee.

Our precinct

Hudson Institute is a leading Australian medical research institute recognised internationally for discovery science and translational research into inflammation, reproductive health and pregnancy, infant and child health, cancer, hormones and health.

Our Institute is home to 443 world-class scientists, who push the boundaries of scientific knowledge to answer complex questions about human disease, including prevention and treatment.

We are a founding member of the Monash Health Translation Precinct with partners Monash Health and Monash University. Our close ties with clinicians and industry enable us to translate our discoveries into new preventative approaches, therapies and devices for patients.

Our location at Monash Medical Centre means our research is informed by patient need and our discoveries are rapidly transitioned into practical treatments.

Working alongside clinicians in Melbourne hospitals for more than 50 years, our scientists pioneered IVF and stem cell discoveries and are now leading developments in cell therapies, paediatric cancer and the human microbiome. Our worldwide scientific and medical collaborations provide a foundation for transformative healthcare programs across the globe.

CENTRE FOR INNATE IMMUNITY AND INFECTIOUS DISEASES

Location: Centre for Innate Immunity and Infectious Diseases, Hudson Institute of Medical Research, Monash Medical Centre, Clayton

t: +61 3 85722739

e: rebecca.smith@hudson.org.au

w: https://hudson.org.au/research-centre/centre-for-innate-immunity-infectious-diseases/

Centre Heads:

Prof Paul Hertzog

2021

Prof Brendan Jenkins

2022

At the Centre for Innate Immunity and Infectious Diseases (CiiiD) we discover and model how the innate immune response regulates disease. We translate our findings into practical outcomes that impact on our health.

The immune response is important in every disease you'll study as a scientist or doctor. A successful early, innate immune response can resolve infectious diseases and eliminate cancer. A poorly regulated immune response causes chronic inflammatory diseases, with multi-organ impact. We:

- are world-leaders in research on the innate, or first, immune response
- perform high quality discovery research using the latest technologies
- translate our research into preventions, diagnostics and treatments
- publish in the world's top impact journals

CiiiD is one of the largest centres for innate immunity in Australia, bringing in nearly $5.1M in grant funding per annum and publishing nearly 185 peer-reviewed publications in the past three years, including works in prestigious journals such as *Nature, Science, Nature Immunology, Nature Medicine* and *Cancer Cell*.

CiiiD values its students. We offer world-class training in biomedical research and carefully help students find appropriate projects and supervisors. Students receive one-on-one training and mentoring in practical and theoretical aspects and career development.

Staff and students working in CiiiD have collective multidisciplinary expertise in molecular biology, signal transduction, protein interactions, cell biology, immunology, bacteriology, infectious disease, functional genomics and bioinformatics, as well as clinical research and transgenic techniques for generating and characterising gene knockout and transgenic mouse preclinical models of human disease.

CiiiD students are first authors on scientific papers in prestigious journals

Students were first authors on 75 of Hudson Institute's 333 research publications in 2016. Some examples from our Centre are:

- William Berry et al., Endoscopic ultrasound-guided fine-needle aspirate-derived preclinical pancreatic cancer models reveal panitumumab sensitivity in KRAS wild-type tumors. Int J Cancer. 2017; 140(10):2331-2343.
- Martin MacDonald et al., Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease. Lancet Respir Med. 2016; 4(2):138-48.
- Ka Yee Fung et al., Interferon-ε protects the female reproductive tract from viral and bacterial infection. Science. 2013; 339(6123):1088-92.

CiiiD students win prestigious prizes and awards

- Winner Faculty of Medicine, Nursing and Health Sciences '3 Minute Thesis' Competition – Zoe Marks
- Travel scholarship from the US National Institute of Allergy and Infectious Disease (NIAID) – Jesse Balic
- Travel scholarship from the Australian Thoracic Society – Sultan Alhayyani
- Travel grant from the Science Mobilisation Program of the Embassy of France in Australia – Kimberley D'Costa
- Winner, PhD Student Prize, Victorian Infection and Immunity Network Young Investigator Symposium – Charlotte Nejad

What we study

Infectious diseases (influenza, HIV, *Helicobacter pylori,* malaria, diarrhoeal diseases, Legionnaire's disease, *Shigella*, Respiratory syncytial virus and others)

Cancer (stomach, lung, pancreas, ovary, breast and others)

Inflammatory diseases (inflammatory bowel disease, sepsis, lupus, gastritis, diabetes, COPD)

Research Groups Heads

Regulation of Interferon and Innate Signalling
Prof Paul Hertzog
paul.hertzog@hudson.org.au

Innate Immune Responses to Infection
Professor Elizabeth Hartland
elizabeth.hartland@hudson.org.au

Cancer and Immune Signalling
Professor Brendan Jenkins
brendan.jenkins@hudson.org.au

Respiratory and Lung Disease
Professor Phil Bardin

Gastrointestinal Infection and Inflammation
Professor Richard Ferrero
richard.ferrero@hudson.org.au

Pattern Recognition Receptors and Inflammation
Associate Professor Ashley Mansell
ashley.mansell@hudson.org.au

Viral Immunity and Immunopathology
Associate Professor Michelle Tate
michelle.tate@hudson.org.au

Nucleic Acids and Innate Immunity
Associate Professor Michael Gantier
michael.gantier@hudson.org.au

Cell Death and Inflammatory Signalling
Dr Kate Lawlor
kate.lawlor@hudson.org.au

Host-Pathogen Interactions
Dr Jaclyn Pearson
jaclyn.pearson@hudson.org.au

Molecular Immunity
Dr Tony Sadler
anthony.sadler@hudson.org.au

Microbiota and Systems Biology
Dr Sam Forster
sam.forster@hudson.org.au

Structural Biology of Inflammation and Cancer
Dr Wilson Wong
wilson.wong@hudson.org.au

Respiratory and Lung Disease

Characterisation of innate immune responses during exacerbation of asthma and COPD

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leaders: Dr Belinda Thomas, Prof Phil Bardin

e: belinda.thomas@monash.edu, philip.bardin@monash.edu

Project description: Our research is focussed on understanding how viruses and bacteria cause exacerbations of inflammatory lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Previous studies in our laboratory have demonstrated that reduced innate immune responses contribute to enhanced virus infection in asthmatic persons and in a mouse model of influenza A infection. We have also demonstrated the detrimental effect of glucocorticosteroids on viral infection in these diseases (Thomas et al., Am J Resp Cell Mol Biol, 2009, Thomas et al., Sci Rep, 2014). Further studies using validated primary cell culture models and various mouse models of viral and bacterial infection are examining the mechanisms contributing to reduced host immune responses and potential therapeutic strategies to counter these adverse effects.

Keywords: asthma, virus, bacteria, innate immunity, mouse models, infection

Inflammasome in lung diseases

Suitability: PhD/Doctorate, Honours

Project leaders: Dr Saleela Ruwanpura, Prof Phil Bardin

e: saleela.ruwanpura@hudson.org.aumonash.edu, philip.bardin@monash.edu

Project description: Growing evidence indicates that the inflammasome (an intracellular protein complex that regulates the maturation and release of proinflammatory cytokines of the IL-1 family in response to pathogens and endogenous danger signals) play a key role in the pathogenesis of lung diseases, such as chronic obstructive pulmonary disease (COPD), a condition predicted to be the third-leading cause of death worldwide by 2020. Using novel cell/molecular biology methodologies, gene-deficient mouse models and human clinical biopsies/serums, we will understand the mechanism of inflammasome signaling in COPD pathophysiology, and this will lead to new therapeutic approaches. This project offers the opportunity to interact with our collaborators in the University of Melbourne.

Keywords: inflammasomes, lung diseases, signal transduction, biomarkers

Gastrointestinal Infection and Inflammation

Characterisation of the immunomodulatory and oncogenic properties of bacterial extracellular vesicles

Suitability: PhD/Doctorate, Masters by research, Honours, BMedSc(Hons)

Project leader: Prof Richard Ferrero

e: richard.ferrero@hudson.org.au,

Project description: 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. The overall aim of the project is to investigate the immunomodulatory and oncogenic properties of bacterial-derived EVs. For this, we will use cell culture and mouse models to elucidate EV interactions with host cells and to characterise the responses induced by these EVs. This project will involve a variety of techniques, including cell culture, mouse models, proteomics, molecular biology, fluorescence imaging, flow cytometry, cytokine ELISA and qPCR.

Keywords: Innate immunity, infection, immune regulation, extracellular vesicles, exosomes

Defining the role of a novel NLR protein in stomach B cell lymphoma associated with chronic *Helicobacter* infection

Suitability: PhD/Doctorate, Masters by research, Honours, BMedSc(Hons)

Project leader: Prof Richard Ferrero

e: richard.ferrero@hudson.org.au,

Project description: Our laboratory has for the first time identified a new NOD-like receptor (NLR) protein in the regulation of inflammation in response 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. The overall aims of the project are to investigate 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. These questions will be addressed in 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.

Keywords: Innate immunity, infection, signal transduction, gastrointestinal disease, cancer, MALT lymphoma

Development of a vaccine to prevent stomach cancer using genetically modified bacterial membrane vesicles

Suitability: PhD/Doctorate, Masters by research, Honours, BMedSc(Hons)

Project leader: Prof Richard Ferrero

e: richard.ferrero@hudson.org.au,

Project description: 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. It was suggested that 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 *H. pylori* vaccine based on membrane vesicles (MVs) that bud off growing bacteria. These nano-sized particles are non-infectious, non-replicative and contain many components of the live bacteria from which they originate. This project will involve a variety of techniques, such as cell culture, mouse models, proteomics, molecular biology, bacterial mutagenesis, fluorescence imaging, flow cytometry, cytokine ELISA and qPCR.

Keywords: cancer, extracellular vesicles, genetic engineering, infection, innate immunity, outer membrane vesicles, vaccine

The role of the innate immune system in preventing stomach cancer during chronic *Helicobacter pylori* infection

Suitability: Honours, BMedSc(Hons)

Project leader: Prof Richard Ferrero

e: richard.ferrero@hudson.org.au,

Project description: During cell division, bacteria remodel their cell walls, resulting in the release of low molecular weight fragments of peptidoglycan, known as muropeptides. The muropeptides from Gram-negative bacteria are recognised by host cells via the actions of the innate immune molecule, NOD1, resulting in the induction of a pro-inflammatory signalling cascade. Preliminary data suggest that *Helicobacter pylori*

exploits the NOD1 signalling pathway to maintain tissue homeostasis during chronic infection. This project will test the hypothesis that *H. pylori* can alter its muropeptide composition to actively engage the NOD1 pathway thereby preventing pre-cancerous changes in the stomach and thus favouring its survival in vivo. This project will involve a variety of techniques, including primary cell culture, mouse infection, histology, cytokine ELISA and qPCR.

Keywords: innate immunity, infection, inflammasome, signal transduction, gastrointestinal disease, cancer

Microbiota and Systems Biology

Characterization of microbiota composition in paediatric inflammatory bowel disease

Suitability: PhD/Doctorate, Honours, BMedSc(Hons)

Project leaders: Dr Sam Forster, Dr Ed Giles

e: sam.forster@hudson.org.au, edward.giles@monashhealth.org

Project description: The gastrointestinal microbiota, mediated by complex interactions between the patient's immune system and environment, is now associated with diseases as diverse as infections, inflammatory bowel diseases and cancers. Paediatric Inflammatory bowel disease (PIBD) is a chronic incurable condition, affecting children and teenagers, that is increasing in incidence. Changes in the microbiota reflect the development of IBD and are a potential target for therapy or even cure. This project combines expertise in the culturing and phenotypic analysis of the human gastrointestinal microbiota (Nature, 2016; Nature Biotech, 2019) to discover and characterize the bacterial community present in PIBD. These insights will lead to identification of novel biomarkers and predict potential clinical interventions for further experimental validation and therapeutic validation. The project represents a close collaboration between clinical and experimental elements with sample collection (ethics already established), world-leading in-vitro culturing, bacterial whole genome sequencing, phylogenetic analysis and metagenomic sequencing. Students interested in experimental or computational biology are welcome to take the opportunity to develop skills in both areas. The Centre for Innate Immunity and Infectious Diseases is a world leader in infection and inflammation with a strong record of student training and development. Please feel free to contact Dr Sam Forster (sam.forster@hudson.org.au) or Dr Ed Giles (edward.giles@monashhealth.org) for further information.

Keywords: microbiota, microbiome, paediatric, inflammatory bowel disease, microbiology, IBD, UC, ulcerative colitis

Novel bacteriotherapeutics in paediatric inflammatory bowel disease

Suitability: PhD/Doctorate, Honours, BMedSc(Hons)

Project leaders: Dr Ed Giles, Dr Sam Forster

e: edward.giles@monashhealth.org, sam.forster@hudson.org.au

Project description: Inflammatory Bowel Disease (IBD), predominantly Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic inflammatory condition of unknown aetiology. It is caused by an aberrant immune response to the environment, including the microbiota. IBD is incurable, with debilitating albeit hidden symptoms and an increasing incidence worldwide. The cost to the Australian economy was $2.7 billion in 20123. IBD affects 1 in 250 Australians aged 5-40. Over the last decade, an explosion in microbiome research in IBD has not yet affected diagnostic algorithms or treatments. I have developed a program at Hudson Institute to isolate and mechanistically characterise bacteria while simultaneously measuring host immune response to form a more complete understanding of the host-microbiome in IBD. My preliminary work has shown several exciting novel candidates for bacterial therapeutics and new targets for therapy. The exceptional technical resources and infrastructure that I have established in a world-leading environment will ensure transformational changes from this program, including a clinical trial of bacteriotherapy. I am seeking students to progress this working into Phase I clinical trials.

Keywords: IBD, microbiota, Crohn, colitis, mucosal immunology, clinical trial

Discovery of antibiotic resistance gene dispersal networks in the human gastrointestinal microbiota

Suitability: PhD/Doctorate, Honours, BMedSc(Hons)

Project leaders: Dr Sam Forster, Dr Emily Gulliver

e: sam.forster@hudson.org.au, emily.gulliver@hudson.org.au

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 optimise 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 recently development methods to culture the vast majority of the human gastrointestinal microbiota (Nature, 2016; Nature Biotech, 2019) providing an important resource to undertake these studies. This project will combine detailed genomic and metagenomic sequence analysis with in-vitro microbiology techniques 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. The Centre for Innate Immunity and Infectious Diseases is a world leader in infection and inflammation with a strong record

of student training and development. Please feel free to contact Dr Sam Forster (sam.forster@hudson.org.au) or Dr Emily Gulliver (emily.gulliver@hudson.org.au) for further information.

Keywords: Antibiotic Resistance, Antibiotic, Antimicrobial Resistance, AMR, Microbiology, Microbiota, Bioinformatics, Genomics, Microbiome, Computational Biology

High Resolution Computational Analysis of the Gastrointestinal Microbiota

Suitability: PhD/Doctorate, Honours, BMedSc(Hons)

Project leaders: Dr Sam Forster, Dr Vanessa Marcelino

e: sam.forster@hudson.org.au, vanessa.Marcelino@hudson.org.au

Project description: For over 100 years the need to understand particular disease causing, bacterial isolates to treat disease has been clearly understood. Importantly, combining genomics and traditional microbiology, it is now clear that different bacterial lineages and even individual isolates may induce vastly different disease outcomes for patients. While these principles are well established for pathogenic organisms it is now evident that the vast majority of bacterial species with which we are associated likely provide beneficial functions. Similar strain and isolate level understanding are limited by our ability to identify, classify and investigate these species. In the human gastrointestinal tract alone, there are 100 trillion bacteria, representing more than 500 species, that are intimately associated with our daily lives. We have recently development methods to culture the vast majority of the human gastrointestinal microbiota (Nature. 2016) that has unlocked high resolution, whole genome shotgun metagenomics sequencing for detailed analysis. This project will focus on analysis of over 13,000 shotgun metagenomics samples to identify key bacterial species and co-existence networks required for maintenance and reestablishment of health after microbiota perturbation. Please contact Dr Sam Forster (sam.forster@hudson.org.au) or Dr Vanessa Marcelino (vanessa.marcelino@hudson.org.au) for further information.

Keywords: computational biology, bioinformatics, metagenomics, microbiota, machine learning, statistics, genomics, phylogeny, ecology, microbiome

Modulating gastrointestinal microbiota stimulation of the innate immune system

Suitability: PhD/Doctorate, Honours, BMedSc(Hons)

Project leaders: Dr Sam Forster, Dr Michelle Chonwerawong, Dr Vanessa Marcelino

e: sam.forster@hudson.org.au, michelle.chonwerawong@hudson.org.au, Vanessa.Marcelino@hudson.org.au

Project description: 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 maintaining health and causing or exacerbating disease. We recently developed novel methods to grow for the first time, the vast majority of bacteria from the gastrointestinal microbiota (Nature, 2016) resulting in the discovery of hundreds of novel species which 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. The Centre for Innate Immunity and Infectious Diseases is a world leader in infection and inflammation with a strong record of student training and development. Please contact Dr Sam Forster (sam.forster@hudson.org.au) or Dr Michelle Chonwerawong (michelle.chonwerawong@hudson.org.au) for experimental projects or Dr Vanessa Marcelino (vanessa.marcelino@hudson.org.au) for computational projects.

Keywords: innate immune response, gastrointestinal microbiota, immunology, microbiology, bioinformatics, genomics, microbiome, metagenomics, microbiota

Identifying the bacteria in our food and how they might be used to improve health

Suitability: PhD/Doctorate

Project leaders: Dr Marina Iacovou, Dr Sam Forster, Dr Nicole Kellow

e: marina.iacovou@hudson.org.au, sam.forster@hudson.org.au

Project description: While considerable effort has been devoted to minimising contamination of the food supply by pathogenic bacteria, little is known about the health-promoting microbes present in our food. Previous work has demonstrated that live bacterial loads in many common foods exceed 100,000 CFU/gram, and we now plan to determine how successfully they are able to colonise the human gut and whether they can be used as a future therapy to prevent or treat disease. This project aims to understand the association between food-based micro-organisms and gastrointestinal bacteria, and how we can apply this knowledge to develop microbiome-based therapies. This project will involve several components, which we are happy to discuss with potential applicants. Tasks may include development of a bacterial composition database for a range of commonly consumed foods and identifying how different food processing methods effect microbial survival, exploration of dietary components which

promote or inhibit the growth of specific bacterial species, and co-ordination of a human clinical trial to determine colonisation efficiency of food-derived microbes. A strong nutrition and/or dietetic background is recommended, and an in-depth knowledge of foods typically consumed in Australia, both in mainstream and culturally diverse communities.

Keywords: food microbes, bacteria, diet, nutrition, microbiota, gastrointestinal, gut, human health, clinical-trial

Nucleic Acids and Innate Immunity

Auto-Immune sensing of DNA damage

Suitability: PhD/Doctorate, Masters by research, Honours

Project leader: A/Prof Michael Gantier

e: michael.gantier@hudson.org.au

Project description: We and others have recently discovered that DNA damage can promote inflammation through recruitment of the cGAS-STING pathway (Pepin et al., Nucleic Acids Research 2016 and 2017). In this project we propose to investigate how cGAS activation is propagated by immune cells, and how this may play a pivotal role in auto-immune sensing of DNA for instance seen in Cutaneous Lupus Erythematosus. The successful candidate will gain cutting edge practical knowledge in molecular, cellular and animal biology, working on a project with a strong translational angle.

Keywords: immunology, inflammation, DNA, Lupus

Creating a new generation of adjuvants for vaccine and cancer immunotherapy

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons)

Project leader: A/Prof Michael Gantier

e: Michael.gantier@hudson.org.au

Project description: Our laboratory has recently discovered that select Toll like receptor agonists could be modified to present novel adjuvant properties - with broad implications in vaccine development and cancer treatments. This project will advance our knowledge of the therapeutic applications of our discovery using cutting age disease models to study immune responses - with a combination of in vitro and in vivo experiments. It has the potential to revolutionise adjuvants (for instance leading to less frequent vaccinations in children), and reignite immune responses against cancer cells within the tumor microenvironment. Importantly, the successful candidate is guaranteed to publish peer-reviewed works related to their studies upon joining our laboratory (with a possible Thesis by publication stream for PhD students).

Keywords: innate immunity, adjuvants, immune responses, cancer immunotherapy

Defining the side-effects of CRISPR-Cas9 gene editing on immune responses

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons)

Project leader: A/Prof Michael Gantier

e: michael.gantier@hudson.org.au

Project description: CRISPR-Cas9 gene editing has revolutionised our vision of the genome, which can now be edited to correct mutations, or silence aberrant genes. The technology already has widespread applications, but a detailed understanding of its off-target effects on immune responses is lacking. This needs to be defined as unintended immune responses could cause severe effects in patients, as previously seen with first in human RNA interference technologies. Our laboratory has discovered that CRISPR-Cas9 gene editing had the potential to instigate immune activation, which this project will further define. Building on unique resources present on the Hudson precinct, along with our international collaborations, this project will characterise how to best minimise off-target effects of CRISPR-Cas9 gene editing, using cutting edge in vitro and in vivo models. This project is directly pertinent to students with a keen interest in functional genetics, cancer/cell biology and immunology.

Keywords: CRISPR-Cas9, immune responses, gene editing, treatment

Innate Immune Responses to Infection

Intracellular bacterial pathogens and cell intrinsic immunity

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leaders: Prof Elizabeth Hartland, Dr Garrett Ng, Dr Raissa Wibawa

e: elizabeth.hartland@hudson.org.au, Garrett.Ng@hudson.org.au, Raissa.Wibawa@hudson.org.au

Project description: Many bacterial pathogens have acquired the capacity to replicate inside human cells by avoiding cell intrinsic innate immune pathways. Pathogens such as *Legionella* and *Burkholderia* are environmental organisms that cause the life-threatening opportunistic infections known as Legionnaire's Disease and melioidosis respectively. A feature of both pathogens is the capacity of the bacteria to replicate within human cells through effector-mediated manipulation of host cell biology. Our goal is to identify and characterize effectors that interact with cell intrinsic innate immune pathways. Ultimately this will allow us to understand the molecular mechanisms by which intracellular bacteria cause disease.

Keywords: microbiology, *Legionella*, *Burkholderia*, innate immunity, cell biology, melioidosis, Legionnaires' Disease

Translocated effector proteins of bacterial pathogens

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leaders: Prof Elizabeth Hartland, Dr Kitty McCaffrey, Dr Cristina Giogha

e: elizabeth.hartland@hudson.org.au, kathleen.mccaffrey@hudson.org.au, cristina.giogha@hudson.org.au

Project description: The subversion of host cell processes by microbial pathogens is an intrinsic part of the host-pathogen interaction. Many bacterial pathogens have the ability to transport virulence proteins, termed effector proteins, into host cells via specialized protein secretion systems. We work on a range of effectors from pathogenic *E. coli*, *Shigella* and *Salmonella* that interfere with host innate immune signaling pathways and block inflammation and cell death. The aim of this work is to investigate the manipulation of host cell signaling by effector protein families to understand their influence on host cell function, inflammatory signaling and the innate immune response.

Keywords: microbiology, inflammation, cellular biology, innate immunity, bacterial diseases, infant diarrhoea, dysentery

Innate immune responses to the human microbiota

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons)

Project leaders: Prof Elizabeth Hartland, Dr Sam Forster, Dr Cristina Giogha

e: elizabeth.hartland@hudson.org.au, sam.forster@hudson.org.au, cristina.giogha@hudson.org.au

Project description: The study of host-pathogen interactions has significantly advanced our understanding of bacterial virulence, infection and the host immune response. However, until recently these studies have largely ignored the role of the resident microbiome. Although the commensal microbiome is known to provide some protection against infection by mucosal pathogens, we know little about the interactions between pathogens, the specific elements of the microbiome and the innate immune response at mucosal surfaces. Classical bacterial pathogens have evolved specific virulence factors to compete with resident commensals as well as subvert host immune responses. In addition, many bacterial infections are treated with antibiotics causing further disruption to the microbiome. To understand how the mucosa and microbiome communities respond to disruption by pathogen infection and antibiotic treatment, we will use an iPSC-derived tissue systems and defined human microbiome communities to map the mechanisms underlying infection resistance, tissue repair and ongoing inflammation, as well as identify potentially protective human microbiome communities and isolates.

Keywords: microbiome, innate immunity, commensal bacteria, intestinal microbiota, mucosal immune responses

Regulation of Interferon and Innate Signalling

Characterisation of a novel cytokine in mucosal immune responses to infections

Suitability: PhD/Doctorate, Honours

Project leaders: Dr Eveline de Geus, Prof Paul Hertzog

e: eveline.degeus@hudson.org.au, paul.hertzog@hudson.org.au,

Project description: We have discovered a new cytokine exclusively expressed in the female reproductive tract, which is essential for the optimal response to Sexually Transmitted Infections such as Herpes Simplex Virus (HSV) and Chlamydia and possibly HIV. It is unique for several reasons: unlike conventional cytokines, IFN epsilon (IFNe) is constitutively expressed, especially in the female reproductive tract, is not regulated by pathogens, but is regulated by hormones. This work was recently published in the prestigious journal, Science. 2013 Mar 1;339 (6123):1088-92. Current projects involve our unique repertoire of reagents including gene knockout mouse models of the female reproductive tract, as well as recombinant cytokines, antibodies, clinical patient cohorts and primary cell cultures for an ongoing study program that includes the following specific areas to characterise the mechanisms whereby this new cytokine regulates the immune response:

- Molecular Biology – determining the mechanism of regulation of IFNe gene expression,
- Biochemistry – characterising the mechanism of IFNe interaction with receptors and activation of novel signalling pathways,
- Immunology – determining how and which immune cells are regulated in the FRT mucosa during infections and other disease,
- Infectious Diseases (clinical and animal models) – determining whether hormonal regulation of IFNe makes women more susceptible to infection at certain times with pathogens such as HIV, HSV and Chlamydia, and
- Cancer Biology and immunology – characterising the role of IFNe in the development and progression of uterine and ovarian cancer progression of uterine and ovarian cancer.

Keywords: Women's health, reproductive / sexual health, innate immunity, infectious diseases

Systems biology of innate immune signaling

Suitability: PhD/Doctorate, Masters by research, Honours, BMedSc(Hons), Short projects

Project leader: Prof Paul Hertzog, Dr Jamie Gearing, Dr Sam Forster

e: paul.hertzog@hudson.org.au, jamie.gearing@hudson.org.au, sam.forster@hudson.org.au

Project description: This project studies the complex regulation of cell signalling in the innate immune response to infection and inflammation. This is performed at the genome, transcriptome, proteome and sometimes metabolome level. The objective is to understand how this immune response is balanced to achieve a protective response, rather than a disease-causing inappropriate response. The systems biology team use a combination of computational and "wet lab" approaches to discover regulatory factors, networks and molecular control pathways involved in disease pathogenesis. in order to help analyse the pathways and how they are integrated, we have a computational biology group working on the generation of methods and databases (e.g. INTERFEROME), whereby we can integrate our data with all published information on this topic. We are developing tools to predict pathways and regulatory networks, including transcription factor binding sites in gene promoters. Specific projects include:

- Analysis of innate immune or inflammatory "signatures" in disease (infections, inflammation, autoimmunity, cancer)
- Discovery of novel signalling pathways by computational predictions and practical experimentation
- Transcriptional regulation of gene expression
- Post-transcriptional regulation of gene expression
- Whole transcriptome (RNA-seq) analysis and integration of interferon signalling across multiple datasets

Keywords: signal transduction, innate immunity, bioinformatics, microRNAs, infectious diseases

Structure-function studies of interferon signalling

Suitability: Honours, PhD, Short projects

Project leaders: Dr Nicole De Weerd, Dr San Lim, Prof Paul Hertzog

e: nicole.deweerd@hudson.org.au, san.lim@hudson.org.au, paul.hertzog@hudson.org.au

Project description: The type I interferons (IFNs) are important in regulating host defence against cancer infectious and inflammatory disease. However, if signaling occurs an an inappropriate time, place, duration or strength it is extremely toxic or even lethal. Therefore, it is essential to understand how positive and

negative signalis are controlled and balanced. This process begins at the cell surface of the respinding cell when the IFNs interact with two receptor components that ultimately transmit a signal into the cell. We use structural biology, biochemistry and sophisticated imaging to examine this process. Importantly we also correlate results from these studies with sophisticated, systems biology assessments of signaling, biological responses in cells and model systms, ultimately in clinical studies in humans.

Keywords: structural biology, biochemistry, protein chemistry, signal transduction, imaging

The role of a novel cytokine in endometrial and cervical cancer

Suitability: Honours, PhD

Project leader: Dr Nicole Campbell, Prof Paul Hertzog

e: nicole.Campbell@hudson.org.au, paul.hertzog@hudson.org.au,

Project description: Cervical and endometrial cancers are major human diseases with unmet medical needs. We have recently discovered a new interferon designated interferon epsilon (IFNε) which is highly expressed constitutively in the female reproductive tract and regulated by hormones. IFNε belongs to a cytokine family that regulates the development of cancers by direct effects on cell proliferation, survival and migration as well as by indirect effects of activating innate and adaptive anti-tumour immunity. Aspects of this project will utilize preclinical models of these diseases, in vitro cell biology and molecular genetics approaches to examine the effects of IFNε in the development and/or therapy of endometrial and cervical cancers.

Keywords: Cancer, immunity, novel therapeutics, reproductive health, anti-tumour response, ovarian cancer, tumour immunology, immunotherapy

Investigation of a novel cytokine in female reproductive tract infections

Suitability: Honours, PhD

Project leader: Prof Paul Hertzog

e: paul.hertzog@hudson.org.au,

Project description: We have discovered a new cytokine, interferon epsilon (IFNe) that is exclusively expressed in the female reproductive tract, which is essential for the optimal response to Sexually Transmitted Infections such as Herpes Simplex Virus and Chlamydia and possibly HIV. IFNe is expressed most abundantly by epithelial cells in the female reproductive tract. Epithelial cells that are the first line of defence against infections and not only provide a protective physical barrier against infections but they also have direct antigen presenting and anti-microbial functions to restrict and block infections with commensals and pathogens. The aim of this project is to understand for the first time the role of IFNe in the modulation of epithelial cell functions in the female reproductive tract. Techniques to be used include in vitro infection studies, primary cell culture and cell line culture, cell proliferations and migration assays, co-culture studies, realtime PCR, cytokine quantification assays.

Keywords: women's health, reproductive / sexual health, immunology, innate immunity, infectious diseases.

The role of MDA5 in orchestrating the response to viral infection

Suitability: Masters by Research, Honours, BMedSc(Hons), Short projects

Project leaders: Dr Natalia Sampaio, Prof Paul Hertzog

e: natalia.sampaio@hudson.org.au, paul.hertzog@hudson.org.au,

Project description: The innate immune system is the body's first line of defence against infection, and is necessary for our survival. Our cells have evolved specialized mechanisms of sensing infection by a virus in order to mount an immune response. Sensors of aberrant nucleic acids play a central role in detection of viral infections. MDA5 is one of these sensors, and can detect a wide array of viruses, including SARS-CoV2. MDA5 binds the unusual double-stranded RNA form to induce an antiviral response in cells. This double-stranded RNA is normally absent in uninfected cells. However, the exact mechanisms involved in regulation of this process are poorly understood. We have performed a proteomics-based screen and identified several potential new binding partners of MDA5. This project will characterize leading candidates from this screen to determine their role in the antiviral state of cells, and MDA5 activation and downstream signalling. A broad range of experimental techniques will be applied, including viral infection models, protein-based molecular biology, immune activation assays, RNA-seq, and CRISPR/Cas9 gene knockout technology.

Keywords: viral infection, innate immunity, RNA, MDA5

Interferon-epsilon: a novel interferon in endometrial function

Suitability: PhD/Doctorate, Masters by research

Project leaders: Dr Fiona Cousins, Prof Paul Hertzog,

e: fiona.cousins@hudson.org.au, paul.hertzog@hudson.org.au,

Project description: In the female reproductive tract (FRT), homeostasis is maintained to enable embryo implantation and development in parallel with priming of the immune system, which protects against localised infection. Interferon epsilon (IFNε) is a new protein of the Type I Interferon family that are important in the protection of the body from infections. Our group have shown that IFNε is most abundantly expressed in the FRT, in the endometrium, where it has an important role in protection against sexually transmitted infections. However, it is not well understood how IFNε protects the FRT from infections or what endometrial and immune

factors regulate its expression. We do know that the levels of IFNε are constantly changing during the menstrual cycle, during which the endometrium is undergoing cycles of breakdown and regeneration. Importantly, factors in menstrual fluid have been shown to influence the repair of the endometrium following menses and we hypothesise that these factors also regulate IFNε expression. Endometrial epithelial cell lines will be treated with menstrual fluid or patient matched peripheral blood plasma and the impact of these fluids in IFNε gene expression determined. Similarly, supernatants from treated cell cultures will be examined for secretion of interferon-epsilon. Cell lines will be treated with IFNε at the same time as treatment with the above fluids to determine how IFNε affects the immune response induced by these fluids. Finally, expression of IFNε within immediately pre-menstrual, menstrual and repair phase human endometrium will be determined.

Keywords: Female reproductive tract, FRT, interferon, endometrium, endometriosis.

A new model of transition to adult care in paediatric inflammatory bowel disease

Suitability: Masters by Research, Honours, BMedSc(Hons), Short projects

Project leader: Dr Edward Giles

e: edward.giles@monashhealth.org

Project description: Inflammatory Bowel Disease is an incurable disease that affects approximately 1 in 200 young Australians, with increasing incidence worldwide. Up to 25% of patients are diagnosed <20 years of age, many in the paediatric services. Transition to adult care is a complex and high risk time for all patients with chronic diseases, and IBD is no exception. Monash has recently established a dedicated young adult IBD clinic under Dr Ed Giles. This unique service in Australia is based on limited overseas models, however the evidence for the success of such clinics remains limited. This project would involve a combined approach of assessing the outcome of the establishment of this service through audit and prospective evaluation of patient outcomes, as well as patient satisfaction data. Please do not hesitate to contact me should you wish further information or preliminary data for this project.

Keywords: Inflammatory Bowel Disease, transition, paediatrics

Mucosal Immunology in Paediatric Inflammatory Bowel Disease

Suitability: PhD/Doctorate, Honours, BMedSc(Hons)

Project leader: Dr Edward Giles

e: edward.giles@monashhealth.org

Project description: This project would involve working in the Centre for Innate Immunity and Infectious Disease, an internationally recognised centre with a very successful publication record. This project involves the translation of findings from mouse models of inflammatory bowel disease (IBD) to human patients, both with IBD and healthy controls. This project explores novel targets for treatment in IBD, as well as exploring possible causes for IBD. By focusing on paediatric patients, we aim to better understand the development of the mucosal immune system and its relationship with the microbiota in early life, and how this can be disrupted in IBD. Currently there are two mouse models of colitis (IBD) with significant results supporting important new pathways for disease in IBD. The project (s) will therefore focus on identifying the importance of these pathways in human patient samples.
This project will involve the handling of human samples (ethics already approved and some samples stored), and the use of such techniques as immunohistochemistry, flow cytometry and quantitative real-time PCR, as well as novel microbiome culturing and analysis. The lab has a strong record of training and supporting students regardless of previous laboratory experience.

Keywords: paediatric, IBD, immunology, interferon

A novel protein regulator of host-bacterial interactions in the gut in health and disease

Suitability: PhD/Doctorate, Masters by research, Honours, BMedSc(Hons), Joint PhD/Exchange Program

Project leaders: Dr Edward Giles, Dr Eveline de Geus

e: edward.giles@monashhealth.org, eveline.degeus@hudson.org.au

Project description: The healthy intestine maintains a homeostatic equilibrium between epithelial integrity, a resident immune system and a symbiotic microbiome. Intestinal infections temporarily disrupt this balance, and inflammatory bowel disease (IBD) can be defined as permanent disruption of this homeostasis. Enteric infections are a significant cause of childhood mortality worldwide, and remain a major cause of GP and hospital presentations in Australia. IBD affects 1/200 young Australians, with increasing worldwide incidence. IBD is a life-long disease that often presents in childhood. Treatments are expensive, have serious side effects and lose efficacy over time. There is an urgent need for new therapies for IBD that are effective without systemic immunosuppression. Type I interferons (T1IFN) are a family of cytokines with a single receptor and pleiotropic functions. Constitutive T1IFN is critical in maintaining intestinal homeostasis and limiting inflammation after infection or injury. We have recently identified IFNε, a novel T1IFN, in mouse and human intestinal epithelium. We propose it plays a crucial role in regulating intestinal immune responses to the microbiome. We have compelling preliminary data to support this idea, as IFNε was protective in a mouse model of IBD and limited in vitro infection with Salmonella Typhimurium. Other T1IFNs have been used in both IBD patients and models of infection with conflicting results about their protective effects. We now hypothesise that IFNε, expressed in the human intestinal epithelium, is an important regulator of

responses to the microbiome. To move these findings from murine models to the clinic, we have recently developed a creative technique to simultaneously analyse both host immune responses from patient intestinal biopsies and the bacteria from the same sample. This allows concurrent host-microbiome analysis to tease apart their interactions. From our paediatric (P)IBD cohort (n=150), we have shown a dysregulated T1IFN response in IBD. By using cutting edge bioinformatic analysis of this extremely large dataset (>3000 bacterial isolates), we have identified a candidate Lactobacillus species associated with this T1IFN response. From this same cohort we have grown small intestinal organoids (mini-guts). These will allow us to analyse ex vivo epithelial-microbe interactions in health and IBD with both pathogens and putative commensal organisms. This patient cohort, combined with unique access to in-house IFNε reagents, will allow us to understand the role of this critical cytokine in human intestinal health and disease. We are seeking enthusiast students to student this novel protein-microbiome interaction with the aim of developing new therapies for gut diseases in children and adults around the world.

Keywords: Interferon, microbiota, IBD, colitis, gastroenteritis, mucosal immunology

Synergy Program

Innate Mucosal Sensing and Shaping of the Human Microbiome

Suitability: Honours, PhD, Short projects

Project leaders: Prof Liz Hartland, Prof Paul Hertzog, Dr Sam Forster, Prof Christine Wells

e: elizabeth.hartland@hudson.org.au, paul.hertzog@hudson.org.au, sam.forster@hudson.org.au

Project description: The reciprocal interactions between mucosal epithelium, innate immune cells and commensal microbial communities across sites including the gastrointestinal and urogenital tract, play an essential role in health and disease. The commensal organisms sculpt the nature and the responses of the local epithelial and immune cells. Conversely, the status of these front-line innate cells influence the composition of the commensal microbiome. However, a deep understanding of these reciprocal interactions is lacking despite it being an important problem that defines the healthy state, modulates the pathogenesis of disease in mucosal sites and potentially in distant organs.
This program offers student projects in multidisciplinary areas including innate immune signaling, commensal and pathogenic microbiology, systems biology and bio-engineering with complementary aims to uncover interactions enabling understanding of the microbe-host interactions that regulate mucosal immunity, define the healthy state and determine disease outcomes. This important problem will be addressed with integrated projects under the umbrella of the three following themes:

1. Characterising the impact of microbiome components on the innate response.

2. How does the host innate immune system influence the microbiome community

3. Model discovery systems for interrogation, biomarker and diagnostic discovery and *in vivo* sensor and delivery.

One example approach will be to use iPSC-derived tissue systems and defined human microbiome communities to map the mechanisms underlying infection resistance, tissue repair and ongoing inflammation, as well as identify potentially protective human microbiome communities and isolates.
The outcomes will be in knowledge gain: to define the microbiome community composition and the host response in the intestine, compared with other sites, to identify organ-specific factors; to distinguish commensal from pathogen and why can an organism can be a symbiont at one sites pathogen at another. This will lead to the development of next generation diagnostics and therapeutics.

Keywords: signal transduction, innate immunity, bioinformatics, infectious diseases, microbiology, inflammation, cellular biology, microbiome

Cancer and Immune Signalling

Precision medicine for innate immune pattern recognition receptors in pancreatic cancer

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons)

Project leader: Prof Brendan Jenkins, Dr Daniel Croagh

e: brendan.jenkins@hudson.org.au

Project description: Pattern recognition receptors (PRRs) are key molecules of the innate immune system that recognise microbial- and/or host-derived products to trigger the inflammatory response. Recently, however, we and others have identified that PRRs, such as toll-like receptors (TLRs) can be involved in non-immune responses, such as driving tumour cell survival and proliferation. In this regard, this project aims to understand the molecular basis by which specific PRRs promote pancreatic cancer, which is one of the most lethal and aggressive cancers in the world that is strongly linked with a dysregulated immune response (albeit ill defined). This research is intimately linked with the use of preclinical genetically engineered and xenograft (including patient-derived) mouse models, as well as translational studies using our large collection of biobanked pancreatic cancer patient samples. Such research will ultimately assist in identifying genes that could be used as biomarkers for screening/early detection of pancreatic cancer, and also targets for the design of therapeutic treatment strategies in the context of precision medicine/targeted therapy.

Keywords: cancer, pancreatic cancer, innate immunity, patient samples, mouse models, translational studies, biomarkers

Identification of immune system regulators as therapeutic targets in lung cancer

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons)

Project leader: Prof Brendan Jenkins

e: brendan.jenkins@hudson.org.au

Project description: The cytokine Interleukin-6 (IL-6) has been implicated as a causative factor in lung cancer, the most lethal cancer worldwide, albeit by unknown mechanisms. Since IL-6 is also important for immune system homeostasis, the development of anti-IL-6 therapies requires an intimate knowledge of pathological versus physiological IL-6 signalling pathways. To address this, we are studying the role of the ADAM family of proteases as key upstream oncogenic regulators of pathological IL-6 signalling in the lung. This project aims for the first time to fully elucidate the mechanistic basis by which ADAM family proteases can influence lung carcinogenesis, and in doing so also identify how they potentially impact on innate immune responses triggered by pattern recognition receptors. This project employs a combination of in vivo lung cancer mouse models (genetically engineered, xenograft - including patient-derived), CRISPR gene editing and clinical biopsies to foster translation, as well as a vast range of molecular and cellular biological techniques.

Keywords: cancer, lung cancer, ADAM proteases, innate immunity, pattern recognition receptors, cytokines, signal transduction

Identification of novel immune regulators in stomach (gastric) cancer

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons)

Project leader: Prof Brendan Jenkins

e: brendan.jenkins@hudson.org.au

Project description: Stomach (gastric) cancer is among the most common cancers worldwide, and is strongly linked with a deregulated immune response, leading to chronic inflammation. However, the identity of regulators of the immune system, in particular those of innate immunity, with oncogenic potential in the stomach remains largely unknown. Using preclinical genetically engineered and xenograft mouse models for gastric cancer, our aim is to identify and understand how novel immune regulators (e.g. pattern recognition receptors, inflammasomes, cytokine signal transducers such as STAT3) in the stomach trigger chronic inflammatory and oncogenic responses that lead to gastric cancer. This project encompasses a wide range of molecular and cell biological and genetic approaches (including CRISPR/Cas9).

Keywords: cancer, gastric carcinogenesis, pattern recognition receptors, cytokines, signal transduction, innate immunity

Cell Death and Inflammatory Signalling

Defining regulators of cell death and inflammasome activation

Suitability: PhD/Doctorate, Honours

Project leaders: Dr Kate Lawlor, Dr Mary Speir

e: kate.lawlor@hudson.org.au, mary.speir@hudson.org.au

Project description: Pattern recognition receptors, including Toll-like receptors (TLRs) and NOD-like receptors (NLRs), are key components of the innate immune response. They sense microbial, host derived and environmental danger molecules, and induce inflammatory signalling responses via inflammasomes and other molecular complexes. We recently defined how deficiency in the cell death inhibitory protein XIAP sensitises innate immune cells to TLR-induced NLRP3 inflammasome activation, which may explain why XIAP-deficient patients suffer from autoinflammation (Lawlor KE et al. Nature Comms 2015, Lawlor KE* et al. Cell Reports 2017). The aim of this project is to further define molecules, like XIAP, that regulate this alternative inflammasome pathway. This project offers the opportunity to be trained in a variety of techniques, including cell culture, Western blotting/immunoprecipitation, proteomics, overexpression/CRISPR Cas9 gene editing, flow cytometry, ELISA and qPCR.

Keywords: Cell death, Inflammasomes, Innate immunity, infection, type I IFN, signal transduction

Mitochondrial apoptosis and inflammasome activation

Suitability: PhD/Doctorate, Honours

Project leaders: Dr Kate Lawlor, Dr Mary Speir

e: kate.lawlor@hudson.org.au, mary.speir@hudson.org.au

Project description: Macrophages are innate immune cells that detect environmental, pathogen or host cellular danger molecules, and initiate appropriate immune responses. We have recently discovered that targeting pro-survival proteins BCL-XL and MCL-1 in macrophages induces apoptosis to clear microbial infection (Speir M et al. Nature Microbiology 2016) and also triggers inflammation via activation of the NOD-like receptor 3 (NLRP3) inflammasome and Interleukin-1beta (Cell Reports 2018). This project aims to define novel regulators of this pathway and investigate how these proteins alter pathogen clearance. This project will use our novel gene knockout macrophages and specific targeted drugs, as well as a range of cell biology and biochemical/molecular approaches (e.g. inflammasome/cell death assays, ELISA, Western blotting, Q-PCR, over-expression systems, CRISPR Cas9 gene editing, infectious preclinical models).

Keywords: Cell death, Cell signalling pathways, Inflammasomes, Innate immunity, Infectious Diseases

Pattern Recognition Receptors and Inflammation

Innate Immune immunometabolism: the intersection between metabolism and immunology

Suitability: Honours, PhD

Project leader: A/Prof Ashley Mansell

e: ashley.mansell@hudson.org.au

Project description: Recent discoveries have positioned mitochondrial reprogramming by Toll-like receptors (TLRs), at the centre of innate immune inflammation. Immunometabolism describes the interplay between immunological and metabolic processes which are not only critical to the immediate innate immune response to infection, but also the new paradigm of innate memory or training, the concept that myeloid lineage cells can respond more strongly to future challenge via epigenetic reprogramming. We have discovered a role for STAT3 in immunometabolism and how this regulates inflammatory gene induction, mitochondrial health, and metabolism. This project offers the opportunity to explore the molecular dynamics and mechanisms of TLR-induced mitochondrial metabolism, and the temporal influence on transcriptional and epigenetic remodelling using advanced genetic sequencing and metabolomic approaches, in conjunction with novel mouse models of dysfunctional STAT3 signalling and inflammatory disease.

Keywords: Innate immunity, inflammation Toll-like receptors, Pattern Recognition Receptors, cell biology, mitochondria, metabolism

Inflammasomes and how to drug them to treat emerging pandemic viruses

Suitability: Honours, PhD

Project leader: A/Prof Ashley Mansell

e: ashley.mansell@hudson.org.au

Project description: The recent and deadly emergence of SARS CoV 2 (COVID-19) has illustrated how unprepared we are for an emerging infectious disease.There is a desperate need to identify and target how these pathogens induce severe and lethal inflammation during infection.
We recently identified and characterised aggregated viral proteins as a novel class of inflammasome activators that induce hyperinflammation characteristic of infections such as avian influenza. We have now identified several proteins that show aggregating potential and inflammasome activation in viruses characterised by excessive inflammation, such as Ebola virus, SARS-coronavirus, dengue virus and picornaviruses. Using novel cell biology methodologies, cell lines, microimaging and gene-deficient mouse models, we will explore the capacity of peptides based on these viral proteins to examine inflammasome activation. This project offers the opportunity to interact with virologists and our collaborators in Bonn, Germany.

Keywords: innate immunity, inflammation, emerging infectious diseases, inflammasome, infectious disease

Host-Pathogen Interactions

Host cell death signaling and susceptibility to *Salmonella* infection

Suitability: PhD/Doctorate, Masters by research, Honours, BMedSc(Hons), Joint PhD/Exchange Program

Project leader: Dr Jaclyn Pearson, Prof John Silke

e: Jaclyn.pearson@hudson.org.au

Project description: Enteric bacterial pathogens such as *Salmonella* spp. and enteropathogenic *E. coli* deliver "effector" proteins directly into host cells via specialised secretion systems which exert specific enzymatic activity on host proteins to subvert host responses and prolong infection. Our recent work characterised an effector protein from pathogenic *E. coli* as a cysteine protease that cleaves and inactivates all mammalian RIP homotypic interaction motif (RHIM) proteins including RIPK1, RIPK3, TRIF and DAI. RHIM proteins are key immune signaling factors that mediate inflammation, apoptosis and necroptosis. Dysregulated immune responses and cell death form the basis of much human disease pathogenesis. This study aims to understand the role of RHIM proteins, in particular RIPK1 and RIPK3, in controlling *Salmonella* and other enteric infections. Research methods will include: cell culture, mouse infection model, molecular biology, protein purification, bacteriology, confocal microscopy, western blot, proteomics and transcriptomics.

Keywords: Bacterial pathogenesis, necroptosis, RIPK1, inflammation, cell death signaling, innate immunity

Regulation of TNF signalling in *Salmonella* infection

Suitability: PhD/Doctorate, Honours

Project leader: Dr Jaclyn Pearson, Dr Kate Lawlor

e: jaclyn.pearson@hudson.org.au, kate.lawlor@hudson.org.au

Project description: The regulation of host immune and cell death signaling is central to the pathogenesis of many human diseases. We have recently gained some exciting new preliminary data that suggests *Salmonella enterica* serovar Typhimurium induces the degradation of host proteins that regulate tumour necrosis factor receptor (TNFR1) signaling, thus regulate cell death and innate immune responses. This project aims to understand how the bacterium, *Salmonella* mediates degradation of these critical immune signaling factors and what the implications are for pathogen survival within the host and disease outcomes for the host. Research methods include: molecular biology, protein purification, bacteriology, cell culture, confocal microscopy, western blot, potential mouse experimental work.

Keywords: Innate immunity, bacterial pathogenesis, host-pathogen interaction, cell signaling pathways

Understanding the biochemical mechanisms of *Salmonella* virulence proteins

Suitability: PhD/Doctorate, Honours, BMedSc(Hons), Short projects

Project leader: Dr Jaclyn Pearson, Prof Elizabeth Hartland

e: Jaclyn.pearson@hudson.org.au, Elizabeth.hartland@hudson.org.au

Project description: Pathogenic serovars of *Salmonella* are the causative agents of a spectrum of disease states, including typhoid fever, self-limiting gastroenteritis, and invasive bacteremia. Australia has one of the highest incidences of Salmonellosis in the developed world. Pathogenesis is dependent on the activity of two distinct type III secretion systems (T3SS), encoded by genetic regions termed Salmonella pathogenicity islands (SPI). The SPI-1 T3SS is associated with bacterial invasion as well as activation of innate immune signaling, and the SPI-2 T3SS is associated with intracellular survival in immune and epithelial cells, replication and systemic infection. While the importance of the SPI-1 T3SS to *Salmonella* pathogenesis is well established, the function of many SPI-2 encoded effectors remains unknown. This project aims to investigate the role of a subset of relatively uncharacterised SPI-2 effectors in *Salmonella* virulence. Overall this project will provide critical insights into the pathogenic mechanisms of an important public health issue and provide the basis for potential future therapeutic development. Research methods will include: molecular biology, protein purification, bacteriology, cell culture, confocal microscopy, western blot, mass spectrometry, protein-protein interactions.

Keywords: Bacterial pathogenesis, *Salmonella,* type III effector proteins, innate immunity, cell signaling pathways.

Understanding the molecular basis of virulence in invasive *Salmonella* lineages

Suitability: PhD/Doctorate, Masters by Research, Honours, BMedSc(Hons), Short projects

Project leader: Dr Jaclyn Pearson, Prof Deborah Williamson

e: Jaclyn.pearson@hudson.org.au

Project description: Pathogenic enteric bacteria often occupy distinct ecological niches, and have evolved specific genomic characteristics that enable host and environmental adaptation, with resulting changes in virulence (manifested by clinical disease severity) and transmissibility. For example, *Salmonella* is an example of a genus in which there is a genomic signature for either a gastrointestinal or an extra-intestinal lifestyle, whereby functions required for promoting growth in the gastrointestinal tract are lost when the lineage becomes invasive. This project aims to integrate epidemiological,

genomic and molecular microbiological data to understand the host and pathogen factors that result in invasive salmonellosis. This information will inform our understanding of the evolutionary pressures that lead to the emergence of highly adapted clones that persist in the food chain. Using a combination of molecular genetics, cell biology approaches and established infection models, we will test the role of these evolving factors in the initiation of infection and progression of disease. Research methods include: bacteriology, bacterial genomics, bioinformatics, cell culture, molecular biology, protein purification, confocal microscopy, western blot, potential mouse infection model.

Keywords: Salmonellosis, food borne, invasive bacteria, inflammation, molecular biology, genomics, bioinformatics, antimicrobial resistance, epidemiology.

Identifying novel biomarkers of paediatric inflammatory bowel disease

Suitability: PhD/Doctorate, Masters by research, Honours, BMedSc(Hons), Joint PhD/Exchange Program

Project leader: Dr Jaclyn Pearson, Dr Edward Giles,

e: Jaclyn.pearson@hudson.org.au, edward.giles@monash.edu

Project description: Inflammatory bowel disease (IBD) is an incurable lifelong disease for one in 200 Australians, including more than 10,000 children, that causes severe inflammation of the gut. It's often so severe that sufferers need to be hospitalised and may require surgery.

Currently IBD is kept under control using drugs that suppress the immune system, but these become less effective over time and can have significant side effects, leaving patients with an increased risk of colorectal cancer. The ongoing and chronic nature of IBD impacts a young patient's emotional, physical and social wellbeing, causing severe embarrassment and disruption to their education, employment and relationships. Overall, a better understanding of the true causes of IBD are needed to develop new and more effective treatments.

We have strong evidence that disruptions in 'programmed cell death' in the gut plays a major role in the development of IBD. In collaboration with paediatric gastroenterologist, Edward Giles, we aim to specifically identify these cellular disruptions in a cohort of 200 young IBD patients from the IBD clinic at the Monash Medical Centre in Melbourne. This study will providing a new and specific target for IBD treatments that we hope will be more effective with less side effects.

Keywords: Inflammatory Bowel Disease, cell death, microbiome, inflammation

Molecular Immunity

Control of inflammation in colitis

Suitability: Honours, Masters by Research, PhD

Project leader: Dr Anthony Sadler

e: anthony.sadler@hudson.org.au

Project description: Inflammatory bowel disease (IBD) is a debilitating, relapsing condition that is considered to be a consequence of the loss of immune tolerance against gut microbiota. Although immunologically mediated, the precise mechanisms of how this disorder manifests remain to be established. There is no cure and current anti-inflammatory and immunosuppressive treatments provide only temporary relief and are not effective in a subpopulation of patients. A project exists to test a therapeutic cytokine strategy to treat IBD. The project will establish the efficacy cytokine treatment to induce protective physiological responses to prevent the development of colitis and to ameliorate existing colitis to restore gut homeostasis in preclinical murine models of IBD.

Keywords: Inflammatory bowel disease, colitis, inflammation, cytokine signalling

Investigating antiviral responses that induce type I diabetes

Suitability: Honours, Masters by Research

Project leader: Dr Anthony Sadler

e: anthony.sadler@hudson.org.au

Project description: A project exists to investigate the development of one of the most common childhood chronic diseases, type I diabetes. This condition results from progressive autoimmune destruction of insulin-producing pancreatic β-cells. The trigger that causes autoreactive cells is unknown and there is no cure or prevention, and so there is an imperative to identify drivers of the condition. This project will investigate a promising lead in type I diabetes, identified from population genetic studies and demonstrated by us to drive immune pathology in the pancreas. We will investigate the function of this pathway in order to understanding of how these immune processes are controlled to identify strategies to intervene in the progression of type I diabetes.

Keywords: Autoimmunity, inflammation, type I diabetes, antiviral response

Targeting cytokine signalling in systemic lupus eryhematosus

Suitability: Honours, Masters by Research, PhD

Project leader: Dr Anthony Sadler

e: anthony.sadler@hudson.org.au

Project description: Lupus is a multisystem autoimmune disease affecting 5 million people worldwide and 1 in 1000 in Australia. These patients suffer chronic immune-mediated inflammatory damage in multiple organs, resulting in morbidity and a marked reduction in life expectancy. Lupus is strongly associated with dysregulated cytokine production, characterised by an interferon-stimulated gene (ISG) signature that is believed to contribute to disease development and/or progression. We have identified two transcription factors that we propose are key to the progression of lupus. A project exists to determine how these factors contribute to pathology in lupus, thereby identifying a route for therapeutic treatment of this complex disease.

Keywords: Lupus, autoimmunity, immune pathology, gene expression, inflammation

Viral Immunity and Immunopathology

The role of innate immune responses in modulating disease during in influenza virus infections

Suitability: PhD/Doctorate, Honours, BMedSc(Hons)

Project leader: A/Prof Michelle Tate

e: michelle.tate@hudson.org.au

Project description: Without effective drugs we are currently ill-prepared for the next viral pandemic. During severe and fatal influenza virus infections our immune response system overreacts, causing life-threatening damage to the lung. While innate immune responses elicited in response to influenza viruses are important for limiting and resolving the infection, host responses need to be tightly regulated to limit tissue damage and the development of disease. Understanding how the innate immune system responds to different strains of influenza virus is of great importance and may provide insight into the mechanisms involved in the development of severe disease. For example, we have identified that the NLRP3 inflammasome plays an early protective role but subsequently promotes the development of hyperinflammation. This project aims to characterise the pathways involved in the induction of hyperinflammation using in vitro and in vivo models of influenza virus infection, identify new therapeutic targets and develop new treatment strategies for severe respiratory viral infections.

Keywords: respiratory virus, innate immunity, viral disease, influenza, inflammation

Structural Biology of Inflammation and Cancer

Structural Biology of Infection, Inflammation and Cancer

Suitability: PhD, Honours

Project leaders: Dr Wilson Wong

e: Wilson.wong@hudson.org.au

Project description: My laboratory utilises cryo-electron microscopy (cryo-EM) to investigate the structure and function of protein and protein-nucleic acid complexes important in Infection, inflammation and cancer. Cryo-EM enables visualisation of macro-molecular complexes to atomic resolution without the need for crystallisation and is revolutionising the field of structural biology. Students undertaking a PhD project will obtain expertise in protein chemistry, biochemistry and structural biology using single particle cryo-EM.

Genome maintenance in normal and cancer cells

The human genome is subjected to numerous genetic alterations throughout the lifespan of an individual as a consequence of exposure to environmental mutagens, such as UV-sun irradiation, cigarette smoke, as well as DNA damages induced by endogenous sources, eg, reactive oxygen species. These DNA damages are constantly monitored by genome surveillance mechanisms to ensure genome integrity is maintained. Malfunction of these surveillance and maintenance mechanisms predispose the genome to oncogenic changes, which ultimately led to the development of cancers. Furthermore, cancer cells have adapted specific genome maintenance mechanisms to ensure the appropriate genetic information are passed to the daughter cells during cell division, as well as the need to utilise DNA repair mechanisms in response to cancer chemotherapies. It is important to understand the molecular details on genome maintenance mechanisms to understand how normal cells maintain the heathy state, and how cancer cells develop.

Our research is focusing on protein-nucleic acid complexes that monitor and maintain the genome integrity of normal and cancer cells. Cells have sophisticated molecular machines that detect and repair these DNA alterations. We use cryo-electron microscopy (cryo-EM) and biochemical methods to characterise the mechanisms of these molecular machines to understand how genome integrity is maintained. The ultimate goal is to apply these knowledges to develop therapeutics that can offer new ways to treat disorders or cancers associated with genome instability.

Malaria parasite invasion

Our research also focuses on understanding the mechanisms by which malaria parasite invade human red blood cells. Malaria is an infectious disease of global significance causing close to 0.5 million deaths annually. We study the biology of blood stage infection because infection of red blood cells by malaria parasites is responsible for the clinical symptoms of malaria. Blood stage malaria antigens are important target for drug and vaccine development.

To invade red blood cells, the parasite utilises secretion machinery to display molecular “keys”, called invasion ligands that recognise specific receptors on the surface of red blood cells. These parasite ligand-host receptor interactions mediate signalling events in an orderly sequential manner to enable the parasite to move into red blood cells in a short space of 60 seconds. We aim to characterise these molecular ligand-receptor interactions by cryo-EM, as well as how these parasite ligands could be blocked by invasion inhibitory antibodies. This information will be fundamental for designing a potential malaria vaccine to mount effective immune responses to protect against malaria infection.

Selected publications

Wong W*, Huang R*, Menant S, Hong C, Sandow JJ, Birkinshaw RW, Healer J, Hodder AN, Kanjee U, Tonkin CJ, Heckmann D, Soroka V, Sogaard TMM, Jorgensen T, Duraisingh MT, Czabotar PE, Jongh WAd, Tham WH, Webb AI, Yu Z, Cowman AF. (2019) Structure of Plasmodium falciparum Rh5-CyRPA-Ripr invasion complex, Nature. 565: 118-121. *co-first author

Wong W*, Bai XC*, Sleeb BE*, Triglia T*, Brown A, Thompson JK, Jackson KE, Hanssen E, Marapana DS, Fernandez IS, Ralph SA, Cowman AF, Scheres SHW, Baum J. (2017) Mefloquine targets the Plasmodium falciparum 80S ribosome to inhibit protein synthesis. Nature Microbiology 2 Article number: 17031. *co-first author

Wong W*, Bai XC*, Brown A*, Fernandez IS, Hanssen E, Condron M, Tan YH, Baum J, Scheres SH. (2014) Cryo-EM structure of the Plasmodium falciparum 80S ribosome bound to the anti-protozoan drug emetine eLife 3 – P12695994, *co-first author

Wong W, Skau CT, Marapana DS, Hanssen E, Taylor NL, Riglar DT, Zuccala ES, Angrisano F, Lewis H, Catimel B, Clarke OB, Kershaw NJ, Perugini MA, Kovar DR, Gulbis JM, Baum J. (2011) Minimal requirements for actin filament disassembly revealed by structural analysis of malaria parasite Actin Depolymerizing Factor 1, PNAS 108(24):9869-74.

Keywords: Cryo-EM, Structural biology, Biochemistry, Genome Maintenance, CryoEM, Cryo-electron microscopy

Top-up scholarship available: Year 1: $5000, Year 2: $5000, Year 3: $5000, Year 4: $5000

Contact our supervisors

Students are encouraged to contact supervisors to discuss projects, arrange a time to visit the lab and view our facilities. Simply email the supervisor to arrange a time.

STEP 1: Find a project you are interested in.

STEP 2: Email the supervisor, *"I am interested in your student project. Could I please arrange a time to visit you in your lab?"*

All the information you need to enrol is on our website, or your supervisor can help you.

w: hudson.org.au/students/courses-available/

Keep up-to-date with our research news. Sign up for our e-newsletter at hudson.org.au/news/newsletters

HUDSON INSTITUTE OF MEDICAL RESEARCH

27-31 Wright Street
Monash Medical Centre
Clayton VIC 3168
Australia
t: +61 3 8572 2700
e: info@hudson.org.au
w: hudson.org.au