HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR INNATE IMMUNITY AND INFECTIOUS DISEASES

2020 Student Research Projects

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

Contents

Welcome to Hudson Institute

Hudson Institute specialises in discoveries in four areas of medical need

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

Our impact is on precision medicine, stem cell therapies, women's health, hormone disorders, fertility, infection, chronic disease and child development.

Our 475 scientists and students focus on laboratory discovery science, plus translational research – taking discoveries to patients and industry for real world impact.

Students at a glance 2018

We educate and train nearly 180 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

- Get exposure to university, institute and hospital research
- Attend national and international conferences
- Publish their research (74 student first author publications in 2018)
- Are mentored by leading supervisors and their teams
- Regularly win prestigious prizes and awards
- Have continuous opportunities for networking, learning and development

All work and no play …

Hudson Institute is not all about work. Our students have the opportunity to join in a range of student networking and social events organised by the Hudson Institute Student Society (HISS).

Our precinct

Hudson Institute is a partner in the Monash Health Translation Precinct (MHTP), a major medical and scientific research hub at Monash Medical Centre in Clayton.

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

With our precinct partners, Monash University and Monash Health, our site brings together world-leading scientists, clinicians and educators to collaborate on innovative discoveries that advance human health.

Our Translational Research Facility (TRF) is connected to Monash Health via a walkway and provides a crucial link between our scientific discoveries and medical treatments.

The facility houses laboratories alongside nine state of the art technology platforms and an eight-bed, 21-chair Clinical Trials Centre supporting the transition of discoveries from initial Phase I testing to Phase IV primary health trials.

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 Head: Prof Paul Hertzog

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,* 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

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

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

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

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

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

Microbiota and Systems Biology
Dr Sam Forster
sam.forster@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 leader: 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

Improving recovery from acute exacerbations of COPD

Suitability: Honours, PhD/Doctorate, Masters by Research

Project leader: Dr Christian Osadnik, Prof Phil Bardin

e: christian.osadnik@monash.edu, philip.bardin@monash.edu

Project description: We are currently undertaking a structured suite of projects targeting improvements in recovery from acute exacerbations of chronic obstructive pulmonary disease. These projects are led by Dr Osadnik in close collaboration with a team of medical and allied health clinicians and researchers with an interest in the field of respiratory medicine. This includes Prof. Philip Bardin, Director of Respiratory Medicine at Monash Lung and Sleep, and Prof. Terry Haines, Head of Monash University's School of Primary and Allied Health Care.

Individual projects range from small to large scale, with tailoring available to suit rapid publications or PhD candidature. Most projects relate to gaining insight into the ways we can optimise care models to enhance recovery from acute exacerbations of COPD. This currently takes the form of specific cohort studies, clinical trials, systematic reviews, and instrument (outcome tool) validation. We have large data sets suitable for data-mining related to specific research questions, but am also interested in initiating new projects that build upon our team's expertise. This may include research in other chronic lung diseases such as asthma and bronchiectasis.

Data collection is based clinically at Monash Health (predominantly Monash Medical Centre, Clayton), but includes other sites as required. Our team also extends into the basic science laboratory, allowing for human and/or animal tissue sampling to assist scientific research and translation from 'bench to bedside'. We have access to administrative support, IT software and data analysis packages via Monash University, patients via Monash Health, clinical equipment such as lung function testing and exercise testing equipment via Monash Health, and a range of physical activity and muscle testing equipment via the Mobile Movement and Activity Monitoring Laboratory - an joint initiative between Monash University Department of Physiotherapy and our clinical partners.

Please don't hesitate to be in touch to see how we can cater a project to your needs. Small project funding may be possible (on an individual needs basis), subject to competitive availability.

Keywords: COPD; acute exacerbations; physiotherapy; rehabilitation; pulmonary rehabilitation; physical activity; function; phenotyping; eosinophils; personalised medicine; treatable traits; NIV; clinical care; acute; cost effectiveness; outcome measurement; instrument validation; exercise testing

Gastrointestinal Infection and Inflammation

Defining the immunomodulatory and oncogenic properties of bacterial extracellular vesicles

Suitability: Honours

Project leader: Prof Richard Ferrero, Dr Le Ying

e: richard.ferrero@hudson.org.au, le.ying@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, extracellular vesicles, exosomes

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

Suitability: Honours

Project leader: Prof Richard Ferrero, Dr Le Ying

e: richard.ferrero@hudson.org.au, le.ying@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, gastric disease, cancer, MALT lymphoma

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

Suitability: Honours

Project leader: Prof Richard Ferrero, Dr Le Ying

e: richard.ferrero@hudson.org.au, le.ying@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, signal transduction, gastric disease, cancer

Understanding how *Helicobacter pylori* regulates host immune responses through the actions of long noncoding RNAs

Suitability: Honours

Project leader: Prof Richard Ferrero

e: Richard.ferrero@hudson.org.au

Project description: A major virulence determinant of *Helicobacter pylori* is a type IV secretion system, encoded by the cag pathogenicity island (cagPAI). The H. pylori T4SS interacts intimately with host epithelial cells and delivers factors to these cells, resulting in the induction of oncogenic and pro-inflammatory signalling cascades. Studies have shown that cagPAI+ *H. pylori* strains with a functional T4SS are associated with more severe disease than cagPAI- strains. Thus, *H. pylori* strains harbouring a cagPAI are generally thought to be more virulent. We

have identified a cagPAI-encoded factor, however, that can restrict or modulate host responses, thus facilitating establishment of a chronic infection. Microarray studies on gastric biopsies from mice that had been infected with *H. pylori* wild type or bacteria lacking this factor identified the upregulation of several long non-coding RNAs (lncRNAs). The aim of the work is to confirm the regulation of these lncRNAs and thus determine the mechanisms whereby this *H. pylori* factor may dampen host immune responses. This project will involve molecular biology techniques (i.e. cloning, PCR, sequencing), cell culture and mouse infection studies, cytokine ELISA and qPCR.

Keywords: Microbiology, infectious disease, molecular biology, long non-coding RNA

Microbiota and Systems Biology

Characterization of microbiota composition in paediatric inflammatory bowel disease

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

Project leader: 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 published recently (Nature, 2016) 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.

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

Characterization of human microbiota diversity across the Australian community

Suitability: Honours, BMedSci (Hons), Masters by Research, PhD/Doctorate, Graduate Diploma, Short projects

Project leader: Dr Sam Forster

e: sam.forster@hudson.org.au

The microbial communities associated with every surface of our bodies are incredibly diverse, yet we know practically nothing about the majority of species that comprise them. Within the gastrointestinal tract, one of the most well studied sites, we estimate there are between 100 and 2000 species and numerous genetically distinct isolates. This project will collect samples from urban, rural and traditional indigenous communities across Australia to characterise the commensal bacterial genomic diversity across the Australian community. Understanding the diversity and distribution of bacterial species will provide important knowledge and insights into how these species and strains spread between individuals and contribute to health.

Keywords: microbiota, microbiology, metagenome, skin microbiota, gut microbiota, gastrointestinal microbiota, genomics, microbial genetics, computational biology, bioinformatics

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

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

Project leader: Dr Sam Forster

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

Project description: 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) 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.

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 leader: Dr Sam Forster

e: sam.forster@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. This project represents a collaboration between the Microbiota and Systems Biology Laboratory at the Hudson Institute of Medical Research, the Wellcome Sanger Institute and the European Bioinformatics Institute. Please contact Dr Sam Forster (sam.forster@hudson.org.au) for further information.

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

Nucleic Acids and Innate Immunity

Auto-immune sensing of DNA damage

Suitability: Honours, Masters by Research, PhD

Project leader: Dr 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 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: Dr 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: Dr 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

Modulating microRNA levels in inflammation

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Dr Michael Gantier

e: Michael.gantier@hudson.org.au

Project description: We have recently uncovered a critical role for microRNAs (miRNAs) in the fine-tuning of inflammation (Gantier et al., Nucleic Acids Research, 2012). Critically, our latest studies have demonstrated that miRNA length was essential in their stability upon infection (Nejad et al., RNA 2018; Pillman et al, RNA, 2019). This project proposes to study how miRNA length variations modulate immune responses in the context of infections and auto-inflammation. This project will incorporate a large component of bioinformatic analyses, and is therefore more suited to candidates with bioinformatics training.

Keywords: innate immunity, microRNAs, inflammation, gene expression, bioinformatics

Innate Immune Responses to Infection

Cell intrinsic responses to intracellular bacterial infection

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Prof Elizabeth Hartland

e: elizabeth.hartland@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 the manipulation of host cell biology. This depends on the ability of the pathogens to inject multiple virulence effector proteins into the host cell during infection. 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

Pathogen suppression of host innate immunity

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Prof Elizabeth Hartland

e: elizabeth.hartland@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

Regulation of Interferon and Innate Signalling

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 at an inappropriate time, place, duration or strength it is extremely toxic or even lethal. Therefore, it is essential to understand how positive and negative signals are controlled and balanced. This process begins at the cell surface of the responding 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 systems, ultimately in clinical studies in humans.

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

Characterisation of a novel cytokine in mucosal immune responses to infections

Suitability: Honours, PhD

Project leaders: Prof Paul Hertzog, Dr Eveline de Geus

e: paul.hertzog@hudson.org.au, eveline.degeus@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 (IFNε) 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 use of 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. Our ongoing study program 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 IFNε gene expression,
- Biochemistry – characterising the mechanism of IFNε 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 IFNε 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 IFNε in the development and progression of uterine and ovarian cancer.

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

Systems biology of innate immune signaling

Suitability: Honours, PhD

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: In the process of studying the complexities of signal transduction, we generate copious data from microarray and next generation sequencing of the transcriptome activated by pathogens and by interferons. In order to help analyse the pathways and functional gene clusters involved and how they are integrated, we have a computational biology group working on the generation of 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. These in silico studies are complemented and validated by "wet" lab experiments, including gene regulation and chromatin IP. Specific projects include:

- Analysis of IFN “signatures” in disease (infections, inflammation, autoimmunity, cancer)
- Discovery of novel signalling pathways by promoter analysis
- MicroRNA regulation of IFN-regulated genes
- Whole genome (RNA-Seq) analysis and integration of IFN signalling

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

Innate immune responses regulating breast cancer metastases

Suitability: Honours, PhD

Project leader: Prof Paul Hertzog

e: paul.hertzog@hudson.org.au

Project description: The mechanisms that regulate the process of metastases of breast cancer to distant organs such as lungs and bone are not understood and accordingly, treatments and prognosis for this disease are poor. Our studies use a murine model of breast cancer metastasis in collaboration with Dr B Parker at the Latrobe Institute of Molecular Sciences. We have compared primary and metastatic cancer cells by gene expression microarrays to determine the genes and their regulatory pathways that are activated or suppressed. This has led to the discovery of a novel epithelial innate immune pathway that is suppressed in metastases; the reversal of which reduces bone metastases significantly and increases metastases-free survival. Ongoing studies include determining the mechanisms of suppression, the effector molecules that block the metastatic process, the role of the immune response in regulating this process and clinical studies of these pathways in human samples. This research will potentially lead to new diagnostics and adjunct therapeutics and was published in Nature Medicine 2012 Aug: 18(8): 1224)

Keywords: Women's health, cancer, innate immunity, bioinformatics, signal transduction

The role of a novel cytokine in endometrial and cervical cancer

Suitability: Honours, PhD

Project leader: Prof Paul Hertzog, Dr Nicole Campbell

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

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 those 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 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 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.

Keywords: Inflammatory Bowel Disease, transition, paediatrics

Cancer and Immune Signalling

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, patttern 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

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

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

Cell Death and Inflammatory Signalling

Defining regulators of cell death and inflammasome activation

Suitability: PhD/Doctorate, Honours

Project leader: Dr Kate Lawlor

e: kate.lawlor@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 (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

Identifying mitochondrial factors that activate inflammatory signaling

Suitability: Honours, PhD/Doctor

Project leader: Dr Kate Lawlor

e: kate.lawlor@hudson.org.au

Project description: Mitochondrial (“intrinsic” BCL-2 family regulated) apoptosis has long been thought to be immunologically silent. However, using small molecule inhibitors of pro-survival BCL-2 family members, we have recently discovered that mitochondrial apoptosis can induce a cascade of events that culminate in activation of the NOD-like receptor 3 (NLRP3) inflammasome and pro-inflammatory cytokine, Interleukin-1beta (Cell Reports 2018). In this project, we will further characterise this pathway and test whether its activation alters cancer progression in vivo. 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, CRISPR Cas9 gene editing sreens, proteomics).

Keywords: Cell death, Cell signalling pathways, Inflammasomes, Innate immunity, Cancer

Mitochondrial apoptosis and inflammasome activation

Suitability: Honours, PhD/Doctorate

Project leader: Dr Kate Lawlor

e: kate.lawlor@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 which BCL-2 pro-survival family members prevent inflammatory signalling and investigate how these events 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, over-expression systems, CRISPR Cas9 gene editing).

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

The inflammasome and hyperinflammation in emerging infectious diseases

Suitability: Honours, PhD

Project leader: A/Prof Ashley Mansell

e: ashley.mansell@hudson.org.au

Project description: 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: Honours, BMedSci (Hons), PhD

Project leader: Dr Jaclyn Pearson

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 controlling *Salmonella* and other enteric infections. Research methods will include: cell culture, mouse infection model, molecular biology, protein purification, bacteriology, confocal microscopy, western blot, mass spectrometry.

Keywords: Bacterial pathogenesis, necroptosis, cell death signaling, innate immunity.

Regulation of TNF signalling in *Salmonella* infection

Suitability: Honours, PhD

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: Honours, BMedSci (Hons), Short projects, PhD/Doctorate

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

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, cell culture, molecular biology, protein purification, confocal microscopy, western blot, potential mouse infection model.

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

Identifying novel biomarkers of paediatric inflammatory bowel disease

Suitability: PhD/Doctorate, Honours

Project leader: Dr Jaclyn Pearson, Dr Edward Giles,

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

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 be 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: Dr Michelle Tate

e: michelle.tate@hudson.org.au

Project description: Fatal influenza virus infections in humans and mice are associated with hyperinflammation and there are currently no effective treatments available. While innate immune responses elicited in response to influenza viruses are important for fighting infection, 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 disease. For example, we have identified that in mice, innate immune inflammasomes play both a protective and detrimental role at different stages of infection. This project aims to examine pathways involved in the induction of inflammation using in vitro and in vivo models of influenza virus infection and a range of techniques. These studies will allow the development of novel therapeutics to treat severe influenza virus infections.

Keywords: innate immunity, viral disease, influenza, inflammation, primary human cells

Understanding the role of innate cytokine receptors in cell responses

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

Project leader: Dr Michelle Tate

e: michelle.tate@hudson.org.au

Project description: Type I interferons (IFNs) are a family of innate immune cytokines which regulate numerous biological functions in homeostasis, host defense and anti-tumorigenesis. IFNs and the receptors IFNAR1 and IFNAR2, which they bind are evolutionally highly conserved, highlighting their broad importance in maintaining health. However, the role of each IFN receptor in regulating biological cell responses such as cell survival, immunity and autophagy has not been well characterised. This project aims to better understand how IFN receptors and the biological responses they mediate are regulated, using a range of in vitro and in vivo techniques. Understanding fundamental cellular pathways forms a necessary foundation for the future development of agonists and antagonists for broad therapeutic use.

Keywords: innate immunity, cytokine, cell biology, biochemistry, immunology

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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