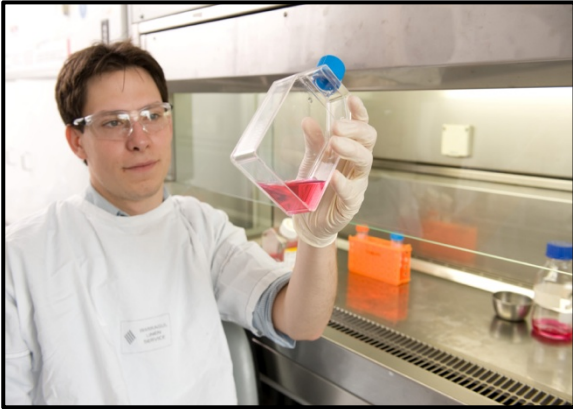


## Centre for Innate Immunity & Infectious Disease



### Centre Director: Professor Paul Hertzog

The Centre for Innate Immunity and Infectious Diseases researches the molecular regulation of the innate immune response. This early immune response determines how the body responds to infection by pathogens. It initiates the inflammatory response and can modulate the development of some cancers. By understanding the molecular pathways that regulate these processes as well as their normal, physiological roles, CIID scientists aim to contribute to the development of new approaches to the prevention, diagnosis and treatment of disease.

Staff and students working in CIID have collective multidisciplinary expertise in molecular biology, signal transduction, protein interactions, cell biology, immunology, infectious disease, functional genomics and bioinformatics and transgenic techniques for generating and characterising gene knockout and transgenic mice as models of human disease. Research within the CIID provides a multidisciplinary teaching and training environment that provides students with a strong range of skills in biomedical research that are recognised internationally for a research career. The Centre students include UROP, Hons degrees, Masters and PhD.

### Characterisation of a novel cytokine in reproductive tract immune response to infections

**Project Leader:** Prof. Paul Hertzog  
**Email:** paul.hertzog@monash.edu  
**Phone:** 9594 7206 / 9594 7236

#### Project Description:

We have recently discovered a new cytokine that is exclusively expressed in the female reproductive tract and we have demonstrated that it is essential for the optimal response to STIs such as herpes Simplex and Chlamydia. Current projects involve using gene knockouts that we have generated to characterise the mechanism whereby this new cytokine regulates the immune response in that organ. We are also characterizing the molecular mechanisms of regulation of gene expression by hormones and pathogens. We are producing and purifying the protein to characterize its activity in vitro and in vivo. We have a program to understand its potential role in vaccine development. Studies include the use of mouse models as well as clinical studies.

## Centre for Innate Immunity & Infectious Disease

### Structure-Function studies of how type I interferons interact with their receptor and transduce signals

**Project Leader:** Prof. Paul Hertzog  
**Email:** paul.hertzog@monash.edu  
**Phone:** 9594 7206 / 9594 7236

#### **Project Description:**

We utilise a variety of tools to understand how to manipulate interferon (IFN) signalling. Firstly we have a structural biology project to determine the X-ray crystal structure of ligand-receptor complexes. In addition these studies are complimented by functional studies that examine the role of the different receptors in transducing signals and activating proximal signalling pathways such as the JAK/STAT pathway. This project is a collaboration between CiiiD and Monash Biochemistry Department (Rossjohn group).

### Systems biology of innate immune signalling

**Project Leader:** Prof. Paul Hertzog  
**Email:** paul.hertzog@monash.edu  
**Phone:** 9594 7206 / 9594 7236

#### **Project Description:**

In all our project we generate copious data from microarray analyses of genes activated by pathogens and by interferons. In order to help analyse the pathways and functional gene cluster and how they are integrated, we have a bioinformatics group working on the generation of databases (e.g. INTERFEROME), whereby we can integrate our data with all published data 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. This project will move into the role of microRNAs in regulating these networks.

### The role of a novel, innate, regulatory molecule (Mul1) in influenza infections and inflammatory disease?

**Project Leader:** Dr. Ashley Mansell  
**Email:** ashley.mansell@monash.edu  
**Phone:** 9594 7215

#### **Project Description:**

We have recently discovered MUL1 as a novel negative regulator of anti-viral signalling. Deletion of MUL1 from primary cells makes them hypersensitive to infection with influenza virus and sendai virus. We have also discovered that MUL1 is a novel cysteine protease which removes ubiquitin chains from key signalling proteins RIG-I and MDA5 which provides a mechanism for negatively regulating anti-viral immune responses. There are two project associated with the further investigations into the role of MUL1 in anti-viral immune responses:

1. Characterizing the immune responses of MUL1-deficient mice to viral infections
  2. Exploring the cellular biology of MUL1 deubiquitination of anti-viral signalling pathways.
- These projects will use cellular biological techniques in conjunction with mouse models, viral infection and inflammatory gene profiling to probe the role of MUL1 in viral disease progression and potentiated inflammatory immunity.

## Centre for Innate Immunity & Infectious Disease

### A structural/functional analysis of TIR adapter proteins in pattern recognition receptor anti-pathogen signalling pathways

**Project Leader:** Dr. Ashley Mansell  
**Email:** ashley.mansell@monash.edu  
**Phone:** 9594 7215

#### **Project Description:**

Toll-like receptors (TLRs) represent the primary means by which the innate immune system recognise and respond to pathogen challenge. Our group has made significant progress in understanding how TLRs induce a signal transduction pathway from ligand recognition to initiation of the pro-inflammatory response. Critical to TLR signalling is 4 cytosolic TIR-containing adapter proteins which control downstream signalling and inflammation.

This study, in collaboration with the University of Queensland and Cambridge University, aims to solve the structure of two of these TIR-containing proteins: Mal and MyD88 both singularly and in co-crystallisation. This will be supported with structural studies of Mal and another key signalling mediator TRAF6. This project will use mutational studies in gene-deficient macrophages to probe the structural requirements for interaction between TIR-containing proteins responsible for TLR-induced inflammatory responses.

### The Role of gp130 receptor signalling in cancer and inflammation

**Project Leader:** Dr. Brendan Jenkins  
**Email:** brendan.jenkins@monash.edu  
**Phone:** 9594 7128

#### **Project Description:**

The gp130 receptor is used by all members of the interleukin-6 cytokine family to transmit intracellular signals controlling cellular functions such as proliferation, differentiation/maturation, and survival. This cytokine family plays an important role in maintaining homeostasis of various biological systems, including haemopoiesis, immunity, the lung and gastrointestinal systems. Importantly, in mice bearing a specific mutation in gp130, we have recently demonstrated the pathological consequences of uncontrolled gp130-dependent signal transduction from this cytokine family, resulting in blood disorders, chronic inflammatory responses, lung disease (emphysema and cancer) and stomach cancer. Notably, lung and stomach cancers represent the first and second most lethal forms of cancer, respectively, world-wide.

This project encompasses numerous approaches to better understand how gp130 signalling pathways are controlled, and in doing so elucidate the mechanisms by which uncontrolled signal transduction from this cytokine family leads to these disease states.

## Centre for Innate Immunity & Infectious Disease

### Gastrointestinal infection and inflammation

**Project Leader:** Dr. Richard Ferrero  
**Email:** richard.ferrero@monash.edu  
**Phone:** 9594 7221

#### Project Description:

*Helicobacter* spp colonise the gastrointestinal tracts of mammals and are associated with various types of chronic inflammatory conditions, including gastritis and colitis. In 2005, two Australian clinicians, Drs Marshall and Warren, received the Nobel Prize for their discovery of one of these bacterial species, *Helicobacter pylori*, and its role in peptic ulcer disease and gastric carcinogenesis in humans. A hallmark of *H. pylori* infection is the chronic gastritis that precedes these more severe forms of disease.

The major research theme in our laboratory concerns an understanding of how and why *H. pylori* bacteria induce inflammation. One mechanism by which *H. pylori* strains are able to accomplish this is via the actions of a type IV secretion apparatus encoded by a "pathogenicity island", the cagPAI. *H. pylori* strains harbouring a cagPAI were shown to deliver a component of the bacterial cell wall (peptidoglycan) to epithelial cells, thereby initiating a proinflammatory signalling cascade mediated by the innate immune molecule, NOD1. We are utilizing *H. pylori* interactions with NOD1 as a model to address key questions relating to the mechanisms whereby bacterial pathogens engage with the innate immune system and cause inflammation in the host.

Examples of current projects in the laboratory include, but are not restricted to:

- 1) clinical and animal model studies on the role of NOD1 in host responses to *H. pylori* *in vivo*;
- 2) microRNA regulation of NOD1 and other NOD-related protein family members;
- 3) the role of exosomes in host immune responses to *H. pylori*;
- 4) post-genomic analyses of *H. pylori* virulence factors involved in colonisation and/or pathogenesis.

- 5) development of live attenuated vaccines against infections by *H. pylori* and the related bacterium, *Campylobacter jejuni*, a major cause of gastroenteritis.

### Rhinovirus common colds and asthma

**Project Leaders:** Prof. Phil Bardin & Dr. Belinda Thomas  
**Email:** belinda.thomas@monash.edu  
**Phone:** 9594 7106 / 9594 2045

#### Project Description:

Our studies aim to understand how the common cold causes asthma attacks. Previous studies in our laboratory (Thomas et al. Am J Resp Cell Mol Biol, 2009) have demonstrated that reduced innate immune responses contribute to enhanced virus infection in asthmatic persons. Further studies using validated cell culture models are examining the mechanisms contributing to reduced host immune responses.

### Rhinovirus common colds and asthma

**Project Leaders:** Prof. Phil Bardin & Dr. Belinda Thomas  
**Email:** belinda.thomas@monash.edu  
**Phone:** 9594 7106 / 9594 2045

#### Project Description:

Our studies aim to understand how the common cold causes asthma attacks. Previous studies in our research group (Thomas et al. Am J Resp Cell Mol Biol, 2009) have demonstrated that reduced innate immune responses contribute to amplified infection in asthma. Further studies using a validated animal model will examine the mechanisms contributing to reduced host immune responses.