

RESEARCH CENTRES AND PROJECTS

CENTRE FOR FUNCTIONAL GENOMICS AND HUMAN DISEASE



CENTRE FOR FUNCTIONAL GENOMICS AND HUMAN DISEASE

The key focus of the Centre for Functional Genomics and Human Disease is to identify the role of genes in the causation of human disease. Our goals are to understand the normal functions of gene products, the molecular mechanisms by which they function and the mechanisms whereby altered gene function is involved in disease. This work will facilitate the development of markers of disease and identify targets and strategies for therapeutic intervention. The Centre, led by Associate Professor Paul Hertzog, now represents a group of about 35 scientists with a collective multidisciplinary expertise in genetics, molecular, cellular and developmental biology, pathology, neurobiology, immunology and transgenic techniques for generating gene knockout and transgenic mice.

The work at the Centre covers a number of areas including the genetics of cancer; the role of genes in inflammation; inflammatory signal transduction; innate immunity; viral immune suppression; fighting infection and developing immunity. Research within the centre provides a multidisciplinary teaching environment that provides students with a strong range of skills in biomedical research that translate internationally into a research career.

Project Heading: Genetics of producing a repertoire of Interferons in host defence

Project Leader: Prof Paul Hertzog
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Project Description:

The type I interferons (IFNs) are a family of >15 related proteins that are important in regulating physiological responses and host defence. However, little is known about their *raison d'être*. Since the biological activities of these proteins are very similar, one proposal is that the multiple subtypes exist to ensure some are produced in response to a broad range of stimuli. Some well characterized disease stimuli include viral and bacterial infection. Physiological production occurs in hemopoiesis, bone development and in response to cytokines such as TNF α . This study will determine the IFN subtypes produced by hemopoietic cells in response to physiological and pathological stimuli. Techniques include functional genomics, PCR analysis of gene expression, bioinformatics analysis of promoter elements, and gene regulation assays (e.g. reporter assays, Chromatin IP).

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Project Heading: Novel Signaling pathways in host defence

Project Leader: Prof Paul Hertzog
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Project Description:

Interferons (IFNs) are proteins produced by the body to protect against disease. They have the amazing capacity for different effects that include inhibition of viral infection, regulation of cell proliferation and activation of most effector cells of the immune system. Our goal is to understand the molecular mechanism whereby these effects are induced so that more effective disease therapies can be produced through specific activation of these pathways. This project will use typical signal transduction procedures including: immunoprecipitation, phosphorylation detection, protein-protein interactions, cells from mice with targeted gene disruptions, microarray data and bioinformatics analyses of data to discover novel signals.

Project Heading: The Role of Toll-like Receptors in Innate Immunity

Project Leader: Dr Ashley Mansell
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Project Description:

Inflammation is the body's response to infection, which in the extreme form results in sepsis. There are 18 million cases of severe sepsis worldwide per year resulting in 1400 daily deaths, killing more people than the cancers of breast, colon, pancreas and prostate combined.

Recently, the discovery of the Toll-like Receptor [TLR] family has added considerable complexity to the innate immune response to microbial pathogens. A greater understanding of the pathways and mediators of the cytosolic signalling pathway that regulates the TLR-

mediated immune response to pathogens may provide therapeutics for the control of chronic inflammatory responses such as septic shock, sepsis, and chronic inflammatory disease.

Our studies consists of several projects with a primary focus on understanding the mechanism and biological outcomes of Toll-like receptor signaling pathways, the negative regulation of these pathways and the subversion of these pathways by pathogens. A better understanding of how TLRs recognize danger, induce signal transduction pathways and are negatively regulated will give insights into better therapeutics to treat or alleviate these conditions that effect our ability to have a healthy start to life, to age well, and productively.

Project Heading: TIM TAMs: Tumour Infiltrating/ Associated Macrophages - Their Role in Anti-Tumour Immunity

Project Leader: Dr Bernadette Scott
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Project Description:

Many tumours are found to contain macrophages. Whilst macrophages can be shown to have anti-tumour effects they are often associated with progressive tumour growth. We are investigating how the loss of macrophages within the tumour environment not only affects tumour growth but also how the adaptive immune response to the tumour is altered. We will be utilizing a number of techniques including macrophage depletion, immune assays of T cell function and in vitro culture methods in this project. By understanding these interactions we may be able to formulate models of how the innate and adaptive immune responses co-ordinate to stop tumour growth.

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**Project Heading:
New gene immunotherapy
strategies for tumor therapy**

Project Leader: Dr Bernadette Scott
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Project Description:

Gene therapies have potential for combating tumors however there is often a problem with delivering the gene to the tumor site in therapeutic doses or with developing immunity to the gene-delivery vectors. Immunotherapy combining vaccination approaches with gene therapy and stem cells offers a means of using potential immunotherapeutics to induce effective anti-tumor immunity. We are interested in developing these methods to prevent tumor growth and/or tumor regression.

**Project Heading:
Gene Regulation in
inflammatory disease**

Project Leader: Dr Trevor Wilson
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Project Description:

Inflammatory diseases are a major burden on the health-care system and a significant contributor to reduced quality of life. For example Septic shock is a deadly systemic disease which accounts for 10% of admissions to intensive care units and COPD is a global health problem predicted to become the world's number 3 killer by 2020. These diseases result from hyperactivation or chronic activation of inflammatory cells respectively. In order to develop novel, more effective therapies for these diseases the mechanisms which regulate inflammatory gene activation need to be further elucidated. This project investigates the role of the gene regulators Ets1 and Ets2

in macrophages, which have a central role in the induction and regulation of inflammation. Functions of these cells include production of a variety of cytokines, phagocytosis, antigen presentation and lysis. This project will use resources such as RNA interference, conditional knockout mice and embryonic stem cells to elucidate the function of Ets2 in macrophages and disease.

**Project Heading:
The Role of gp130 receptor
signalling in cancer and
inflammation**

Project Leader: Dr Brendan Jenkins
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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 and stomach cancer. This project encompasses numerous approaches to better understand how gp130 signaling pathways are controlled, and in doing so elucidate the mechanisms by which uncontrolled signal transduction from this cytokine family leads to these disease states.