

## **New South Wales**

### **Chief Investigators**

**CIA** Prof Colin Chesterman  
**CIB** Dr Michael Berndt  
**CIC** Prof Beng Chong  
**CID** Prof Philip Hogg  
**CIE** Prof Levon Khachigian  
**CIF** Prof Christopher Parish  
**CIG** Prof Roland Stocker

**Scientific Title** Vascular Biology

**Administering Institution** University of New South Wales

**Recommended Budget** \$14,516,629

### **Lay Description**

This program of research is firmly focussed on the basic mechanisms involved in normal functioning of cells and tissues, followed by a step by step process to understand the abnormal or the diseased. The disease states we are investigating involve the blood and blood vessels, and when there is malfunction it may contribute to conditions as diverse as atherosclerosis, thrombosis, inflammation and cancer. The program thus addresses the fundamentals of diseases which are responsible for most deaths in our society. We will use technology which is proven to provide precise information, the molecular and biochemical processes responsible for cell function (or malfunction). However in each individual project there will be a clear path to a clinical use, diagnostic or therapeutic. Indeed in a number of the components of the program there are already potential treatments and diagnostics in development and trial.

## **Chief Investigators**

**CIA** Prof Charles Mackay  
**CIB** Prof Jonathan Sprent  
**CIC** Prof Christopher Goodnow  
**CID** E/Pr Tony Basten  
**CIE** A/Pr Barbara Fazekas de St  
**CIF** Dr Fabienne Mackay  
**CIG** Dr Stuart Tangye  
**CIH** Dr Carola Vinuesa  
**CII** Dr Robert Brink

**Scientific Title** Molecular and cellular studies of the adaptive immune response in health and disease

**Administering Institution** Garvan Institute of Medical Research

**Recommended Budget** \$15,554,453

## **Lay Description**

Immune responses protect us against pathogens such as viruses and bacteria. However inappropriate immune responses can result in autoimmune conditions such as systemic lupus erythmatosus, multiple sclerosis, type I diabetes, asthma as well as immunodeficiencies.

The aim of our proposal is to gain a thorough understanding of how all the cells of the immune system function and interact with each other, and what goes wrong when inflammatory diseases develop. We plan to do this using state-of-of-the-art technologies, including genetically modified mice, gene microarrays, monoclonal antibodies, and flow cytometry. We have brought together Australia's leading immunologists with complimentary expertise and research interests in specific areas of immunology including cytokines, cell migration, inflammatory diseases, autoimmunity and cell-cell interactions. One aspect of the application is to understand the genetic and molecular basis of immunological diseases. However we also wish to move on from an understanding to treatment of immunological diseases through the development of novel therapeutics. We will form collaborations with biotech and pharmaceutical companies (including our own spin off companies) to advance important new therapeutics for autoimmune and allergic diseases. These conditions represent a significant health burden to Australia..

## **Queensland**

### **Chief Investigators**

**CIA** Dr Georgia Chenevix-Trench

**CIB** Prof Sunil Lakhani

**CIC** Dr Kum Kum Khanna

**Scientific Title** Beyond BRCA1 and BRCA2: pathways to breast cancer

**Administering Institution** Queensland Institute of Medical Research

**Recommended Budget** \$4,830,000

### **Lay Description**

Breast Cancer is a very common disease in women and although huge progress has been made in the last two decades, much remains to be done to improve our understanding of different types of breast cancer and its management. This program brings together the expertise of three senior researchers: 2 scientists and 1 medical scientist. Dr Trench has an interest in identifying genes involved in cancers arising in patients who have a strong family history. She will use molecular methods and cohorts of patients enrolled with Kathleen Cunningham Foundation for Research into Familial Breast and Ovarian Cancer to identify the genes responsible, assess their distribution in the population and determine whether these genes also play a role in non-familial cancers. Dr Khanna's work examines the complex array of enzymes that are responsible for maintaining the integrity of the DNA, and investigates how failure of these mechanisms leads to damage of the genetic material which ultimately results in cancer. It is known that genes involved in familial predisposition code for proteins that work as DNA repair enzymes. It is also known that different types of breast cancer exist, each with differing behaviour and response to treatment and that they are associated with specific genetic changes, including those associated with a familial predisposition. Prof Lakhani's interest lies in using microscopy and the latest molecular tools to refine the classification of these different types of breast tumour so that they can be managed appropriately by his surgical and oncological colleagues. A better understanding of the genetic changes and underlying biology of different types of breast cancer will lead to individualised and specific therapy for patients. This program brings together a unique combination, nationally and internationally, that investigates cancers at the level of genes and cells and translates the information to the clinic for the benefit of patient management.

## **Victoria**

### **Chief Investigators**

**CIA** Prof Jerry Adams  
**CIB** Dr Philippe Bouillet  
**CIC** Prof Peter Colman  
**CID** Prof Suzanne Cory  
**CIE** Dr Steve Gerondakis  
**CIF** Dr David Huang  
**CIG** A/Pr Geoffrey Lindeman  
**CIH** Dr Andreas Strasser  
**CIJ** Dr David Vaux  
**CIK** Dr Jane Visvader

**Scientific Title** Roles of Impaired Apoptosis and Differentiation in Tumourigenesis and Therapy

**Administering Institution** Walter and Eliza Hall Institute

**Recommended Budget** \$20,404,520

### **Lay Description**

The ten scientific laboratories in this program have joined forces to investigate two ways in which tumours develop. Both are of particular interest, because they suggest new ways in which cancer might be overcome. Most of our tissues are continually renewed throughout life by production of new cells. Therefore many of the old cells in each tissue must die off to maintain the proper cell numbers. To eliminate cells that are no longer needed or have become damaged, the body has developed a remarkable cell suicide process termed apoptosis. Unfortunately, however, occasionally a random accident to the genes in one of our cells prevents the machinery for apoptosis from being turned on. In that case, the cell will not die when it should and, by continually dividing, it may eventually give rise to a cancer. Since most cancer cells still retain most of the machinery for apoptosis, however, a drug that could switch on this natural cell death machinery would provide a promising new approach to cancer therapy. Identifying and developing such drugs is one major long-term goal of this program. The other focus of our program concerns stem cells. These are rare cells with the remarkable ability to generate an entire tissue. For example, one of our laboratories has identified stem cells that can generate all the cells in the breast. The almost unlimited regenerative capacity of stem cells has a built-in danger. If a stem cell acquires the ability to proliferate excessively, it can go on to form a tumour. Indeed, many cancer researchers now suspect that rare stem cells within a tumour cause its inexorable growth. If tumour growth is maintained by stem cells, it will be essential to develop new forms of therapy that target these rare cancer stem cells rather than merely the bulk of the tumour cells. This is another key long-term goal of our program.

## **Chief Investigators**

**CIA** A/Pr Richard Boyd  
**CIB** Prof Claude Bernard  
**CIC** Prof Ban-Hock Toh  
**CID** Prof Alan Trounson

**Scientific Title** Innovative stem cell-based strategies to establish immune tolerance and tissue repair

**Administering Institution** Monash University

**Recommended Budget** \$5,233,402

## **Lay Description**

Diseases such as autoimmune gastritis, multiple sclerosis and diabetes arise because a "rogue" immune system has turned inwards to attack our organs. The organ destruction follows from recognition by the immune system of specific molecules in these organs. These "autoimmune" diseases are incurable and controlled mainly by long-term administration of substances that suppress the immune system, often with serious side-effects. A rational approach is to render the rogue immune system harmless by removing the cells that recognize these particular molecules. This can be achieved by a "Trojan horse" approach in which the molecules are delivered to the immune system such that the immune cells that recognize them are removed. To deliver these molecules to the immune system we will genetically engineer bone marrow stem cells, or embryonic stem cells that generate these stem cells, because they are precursors of mature immune cells. Rejection of organ transplants arise in a similar way and also require long-term immunosuppression. A similar approach can therefore be taken to promote acceptance of foreign organ grafts. In the aged, we will combine these approaches with rejuvenation of the immune system by blockade of sex steroid production and/or by creation of a new immune organ.

## **Chief Investigators**

**CIA** Prof Geoffrey Donnan  
**CIB** Prof Stephen Davis  
**CIC** Prof Graeme Hankey  
**CID** Dr David Howells  
**CIE** Prof Michael Calford

**Scientific Title** Improving stroke outcomes: new targets and therapies

**Administering Institution** University of Melbourne

**Recommended Budget** \$6,795,000

## **Lay Description**

Previously we established a unique collaboration of researchers from the basic and clinical sciences. The main aim of this 'vertically integrated' model was to develop new therapies to improve stroke outcomes. We developed a system to identify 'off-the-shelf' compounds which protect the brain after stroke onset. This involves data assimilation (meta-analysis) in a unique way, an approach which has attracted attention internationally. We are also completing an important clinical trial using the clot dissolving agent tPA to extend the time during which the drug may be effective beyond the three-hours currently used. In the next phase of our program we plan to expand the basic science component to identify parts of brain cells (axons and dendrites) which may yield important information about new drugs to protect the brain. We will use our novel summary data technique to test drugs in animal models more appropriate to the human stroke paradigm than have been used in the past. In clinical studies we will follow our theme of identifying new targets for therapy using sophisticated PET and MRI imaging techniques, both in patients who are at great risk of stroke recurrence after a minor warning stroke and those with stroke caused by bleeding within the brain. These studies will provide information about predictors of recurrent and worsening stroke which may be modified by new therapies.

The final stage in identifying new therapies is the Phase III clinical trial. We will complete one of these in which the most appropriate drug preventing further strokes in a major new stroke subtype will be identified. Toward the end of the program, we will commence phase 3 studies of drugs we have selected as being most likely to protect the brain based on our animal experiments.

The main benefit of this unique collaborative research model is to efficiently identify new therapies to reduce the burden of stroke, currently the second most common cause of death globally.

## **Chief Investigators**

**CIA** Prof Nicos Nicola  
**CIB** Dr Warren Alexander  
**CIC** Prof Douglas Hilton  
**CID** E/Pr Donald Metcalf  
**CIE** Prof Raymond Norton  
**CIF** Dr Lorraine Robb  
**CIG** Dr Andrew Roberts  
**CIH** Dr Robyn Starr  
**CII** Dr Jian-Guo Zhang

**Scientific Title** Molecular Regulation of Blood Cell Production and Function

**Administering Institution** Walter & Eliza Hall Institute

**Recommended Budget** \$17,272,992

## **Lay Description**

The blood-forming system is an intricately controlled balance of cell proliferation, maturation and functional activity that is essential for oxygen transport throughout the body, blood clotting, and effective immune responses. Defining the genes and molecules that orchestrate blood cell production and function is crucial, not only for understanding the role of blood in health, but for establishing the bases of blood cell disorders such as autoimmunity and leukaemia, and for devising new clinical strategies for fighting these lethal diseases. This program is conducted by a large, established team of investigators that have made world-class contributions to understanding blood cell formation and function for more than 30 years. Their work established the modern era of molecular haematology via discovery and analysis of blood cell hormones (colony-stimulating factors or CSFs), their receptors and intracellular mediators, which resulted in development of treatments for millions of cancer patients. The program is a multidisciplinary, team approach to fundamental biological questions with a focus on potential clinical and commercial outcomes involving collaborations with clinical medicine and the pharmaceutical industry. Research will focus on meshing novel genetic approaches in mice with translation studies in humans to identify new validated targets for therapeutic intervention in blood cell diseases, as well as building on the team's expertise in cytokine action with emphasis on the actions of the suppressor of cytokine signalling (SOCS) molecules, a key family of proteins that controls cytokine actions.

## **Chief Investigators**

**CIA** Prof James McCluskey  
**CIB** Dr William Heath  
**CIC** A/Pr Francis Carbone  
**CID** Dr Andrew Brooks  
**CIE** Prof Jamie Rossjohn  
**CIF** Prof Ken Shortman

**Scientific Title** Antigen presentation, recognition and the immune response

**Administering Institution** University of Melbourne

**Recommended Budget** \$14,828,600

## **Lay Description**

The early events in immunity require various molecular interactions. We will examine the structural and biophysical basis for some of these interactions, including those associated with transplant rejection and autoimmunity. We will explore the impact of variation in immune response genes on immune evasion and disease susceptibility. Our basic research will determine the mechanisms by which the immune system discriminates between different self and micro-organism associated determinants. We will address the structural and biochemical basis for operation of an immune molecule called tapasin and unravel the basis for how some viruses escape the function of this molecule, thus allowing their immune evasion. We will also explore the use of modified small proteins called peptides in a humanized model of gluten hypersensitivity resembling that of Celiac disease. The molecular basis of the natural human immune system's capacity to recognise and reject grafts will be examined. This complements work aimed at improving the prediction of clinical graft rejection in transplantation. Dendritic cells play a central role in immunity, responsible for capturing material, whether from micro-organisms or self tissues, and presenting it to cells of the immune system. Our program will study the development and immunological function of the different dendritic cell subtypes. We will determine the relative contribution of each to the maintenance of immune tolerance and to the induction of immunity to several pathogens, including herpes simplex virus and malaria. Novel dendritic cell surface molecules that we have discovered will be tested for their ability to enhance the effectiveness of vaccines. Overall, this program utilises a broad array of immunological techniques designed to dissect the development and function of various immune system cell types and determine the structure/function relationships between important cell surface molecules involved in immunity.

**Chief Investigators****CIA** Prof Joseph Trapani**CIB** A/Pr Mark Smyth**CIC** Dr Ricky Johnstone**CID** Dr Dale Godfrey**CIE** Prof H. Miles Prince**Scientific Title** Immune Regulation, Effector Function and Human Therapy**Administering Institution** University of Melbourne**Recommended Budget** \$ 10,810,800**Lay Description**

The immune system plays an important role in protecting the host from viral and bacterial infections, and inhibits cancer onset and progression. Immune processes proceed through specialised cells in conjunction with soluble factors such as inteferons and interleukins. These soluble factors can regulate the activities of immune cells, and inhibit the growth and survival of aberrant (virus infected, cancer) cells. Unfortunately, the immune system can sometimes lose specificity and attack the host, resulting in autoimmune diseases such as diabetes. This research team has played a vital role in characterising the specific activities of immune cells and the associated factors. Importantly, they are deciphering the intricate communication networks of these immune components and dissecting their modes of action. By understanding these complex processes, the team aims to harness the unique therapeutic properties of our own immune system and translate their findings into the clinic. The team is developing new immune-based therapies for use, either alone or in combination with existing chemotherapies to fight debilitating human diseases such as cancer and autoimmune disease.

## **South Australia**

### **Chief Investigators**

**CIA** Prof Robert Norman  
**CIB** A/Pr Raymond Rodgers  
**CIC** Dr Sarah Robertson  
**CID** Dr Jeremy Thompson  
**CIE** Dr Michelle Lane  
**CIF** Dr Michael Davies  
**CIG** Prof Gustaaf Dekker

**Scientific Title** Periconceptual foundations for a healthy start to life.

**Administering Institution** University of Adelaide

**Recommended Budget** \$ 10,385,370

### **Lay Description**

Preconception and early pregnancy is a critical time for a women's health and that of her future child. New research suggests that a woman's genetic potential, her lifestyle and the physical and socioeconomic environment in which she lives, and her biological and social relationship with her male partner, all impact on the long term health of her baby. Abnormal events around the time of conception and in early pregnancy can predispose a newborn to later occurrence, in adult life, of conditions including heart disease, diabetes, obesity and stroke. These adverse events originate in the way that eggs and sperm develop, the uterus is prepared for implantation, the attachment of the early embryo to the lining of the uterus and subsequent growth of the placenta. This Program will study the early life events that promote or limit development of a baby's true potential for successful and healthy life. A better understanding of how lifestyle and environment interact with genes and biology to facilitate optimal growth of the fetus will underpin new preventative measures and therapeutic treatments for infertility, miscarriage and other reproductive disorders. The knowledge gained will inform health policy and clinical practise to improve reproductive health in all Australian women and promote healthy development in all Australian children. The team of researchers is a world-class group of clinicians, scientists and epidemiologists who have made major contributions to our understanding of this area. This team will interface with clinics and hospitals that engage with women prior to and during pregnancy, while having the influence to alter clinical and health practices as well as public health policies. The team will utilize the latest, most technologically advanced laboratory methods and clinical skills, including gene profiling, imaging of early pregnancy, randomised clinical trials and access to the best epidemiological and statistical assessments.

## **Western Australia**

**Scientific Title**            Developmental aspects of respiratory inflammation, allergy and asthma

**Administering Institution**    University of Western Australia

**Recommended Budget**        \$ 6,755,000

### **Chief Investigators**

**CIA**    Prof Peter Sly  
**CIB**    Prof Patrick Holt  
**CIC**    Prof Wayne Thomas  
**CID**    Prof Peter Le Souef  
**CIE**    Dr Stephen Stick  
**CIF**    Dr John Upham

### **Lay Description**

Asthma develops as a complex series of interactions between genetic susceptibility and environmental exposures occurring in early life. While many children grow out of asthma others do not and develop the chronic form of the disease that persists into adult life. Our research involves understanding why some susceptible children develop asthma and why this becomes chronic in some. We will undertake studies in children to find out how and why this occurs. A major part of our studies involve longitudinal studies in cohorts of children recruited before birth. Having the ability to study children as they grow and develop conditions such as allergies and asthma allows us to understand why these conditions occur and allow us to predict which children are likely to develop them. Our research Program also has a solid focus on Translational Research, in which we will use the findings from our basic science studies to develop and test new methods of preventing and of treating asthma. These studies will include new methods for preventing the development of allergies, preventing the damage done to the lungs by severe viral respiratory infections in early life and better methods of treating established allergic asthma by improving immunotherapy techniques. By its very nature, primary prevention of disease in young children is controversial and raises some interesting questions. As part of this Program we intend to initiate consultation and debate in public, academic, regulatory and industry circles. An important role for our Program is shifting the current emphasis away from treatment of established disease towards preventing disease occurring. This is the best way to decrease the health, social and economic burden of chronic diseases such as asthma.

## **Chief Investigators**

**CIA** Prof Dao-Yi Yu  
**CIB** A/Pr Ian McAllister  
**CIC** Dr Stephen Cringle  
**CID** Dr William Morgan

**Scientific Title** Advanced New Therapeutics and Diagnostics in Retinal Diseases and Glaucoma

**Administering Institution** University of Western Australia

**Recommended Budget** \$ 3,345,600

## **Lay Description**

This program proposal targets the most common blinding diseases in clinical ophthalmology. The applicant team includes research and clinical ophthalmologists and basic scientists. The team have an internationally established reputation in bringing basic science discoveries to the point where they can impact directly on clinical diagnosis and therapy. The proposed research includes new treatment therapies for diabetic retinopathy, age related macular degeneration, and retinal vascular diseases. A new diagnostic technique for glaucoma and new instrumentation for detecting areas of poor blood flow and oxygen supply in the eye are also to be developed. Past successes in our current program grant make us confident that we can produce clinically useful outcomes from this new proposal.