

Successful NHMRC Program Grants – to commence funding in 2005

Western Australia

Prof Fiona Stanley, A/Prof Carol Bower, Prof Nicholas de Klerk, A/Prof Deborah Lehmann, Dr Helen Leonard, Prof Sven Silburn, Prof Stephen Zubrick

University of Western Australia

\$7,725,375 over 5 years

Determinants of child health and development: populations, partnerships, pathways and prevention

There are considerable challenges to the study of complex health and developmental problems in children and young people. Despite increasing prosperity in Australia, many of these problems are not abating and some appear to be increasing. These include low birthweight, behavioural and mental health problems, autism, obesity and, in Indigenous children, infections.

This Program proposes investigating these problems with a view to prevention, thus meeting the national research priority of Promoting and Maintaining Good Health, particularly ‘a healthy start to life’ and ‘preventive health care’.

The Program is unique in that it brings together a multi-disciplinary team of researchers of international repute to investigate these complex issues. The research team comprises epidemiologists, clinicians, developmental psychologists, biostatisticians, sociologists and other social scientists. This team has a proven track record in producing research outcomes that have translated into innovative health policy and practice in areas as diverse as:

- the use of folic acid in spina bifida prevention
- understanding cerebral palsies
- suicide prevention and mental health in children and young people
- Aboriginal child health and development
- intellectual disabilities including Rett syndrome and autism
- in vitro fertilisation and birth defects.

The factors influencing how children develop into young adults include genetic inheritance, nutrition and growth, and family, socioeconomic and environmental conditions. This work demands new ways of measuring and analysing these factors in populations of children and their families.

Western Australia is one of only three sites in the world to have comprehensive linked health data on the whole of its population of children and their families. This Program comprises five overlapping themes of research planned around these unique population databases.

The five themes are:

- social, economic and psychological influences on child health and development - many paths to poor health are linked to social disadvantage. Examining these issues may explain why some childhood conditions are worsening or not improving
- pathways to wellbeing, resilience and developmental disorders, including intellectual disability, autism, birth defects and cerebral palsy
- nutrition and growth, particularly as it relates to low birthweight, childhood obesity and mental health
- infectious disease, its causes and its influence on lifelong health problems and disabilities
- Aboriginal health – whilst spanning each of the research themes above, it presents its own unique challenges and requires its own unique solutions.

This Program will investigate how children develop into young adults and will examine the influence of their families, nutrition and growth and socioeconomic and environmental conditions. It will

develop new ways of measuring and analysing these important influences in whole populations of children, their families and communities, increase our understanding of complex pathways to these difficult problems, and develop effective prevention strategies.

Northern Territory

Prof Kerin O'Dea, Prof Wendy Hoy, Dr Kevin Rowley, Prof James Best, Dr Zhiqiang Wang
Menzies School of Health Research
\$7,070,585 over 5 years

Health outcomes monitoring and evaluation: learning about activity, nutrition, diet and social factors

Diabetes, heart and kidney disease occurs in epidemic proportions among Indigenous Australians. Of particular concern is the early age of onset of conditions that are to disease of older adulthood in the broader Australian community.

While these chronic diseases are known to cause premature death and suffering in Aboriginal and Torres Strait Islander communities, there are gaps in our knowledge. For example, we know very little about how these conditions develop over time in different populations. Probably the greatest knowledge gap is the area of effective intervention - both to prevent diabetes, kidney and heart disease in young people, and to treat existing cases effectively.

The main goal of this program is to bring together a multi skilled team of researchers to better understand the development of these chronic disease across the lifespan (including differences between different populations), and to guide the development of diet, lifestyle, and clinical interventions.

Such interventions need to be simple, effective, acceptable to Indigenous people and able to be sustained over the long term. All interventions will be rigorously evaluated. The results will inform policies in areas such as quality and affordability of the food supply in remote communities; infrastructure to promote physical activity; and provision of high quality primary health care focussing on early intervention and care of people at risk of chronic disease.

Victoria

Prof Robyn O'Hehir, A/Prof Gary Anderson, Prof John Hamilton, A/Prof Jennifer Rolland
Monash University
\$4,308,220 over 5 years

The interface between innate and adaptive immunity

Allergic disorders including asthma are amongst the most prevalent diseases in Australia afflicting up to 25 per cent of the population and costing the Australian Government in excess of \$600 million annually. This program aims to understand the molecular and cellular mechanisms controlling airway inflammation, focusing on the cross-talk between scavenger cells at airway surfaces and circulating cells of the immune system. These studies will combine sophisticated mouse models of airway inflammation in the laboratory with clinical investigation and analysis of human tissue. Understanding these processes will translate into better treatments for patients suffering from life-threatening allergy and asthma.

Prof Henry Krum, Prof Richard Gilbert, A/Prof Sylviu Itescu
Monash University
\$4,634,965 over 5 years

Novel therapeutic strategies to reduce the burden of chronic heart failure

The broad aims of the Program are to develop novel strategies in the prevention and treatment of chronic heart failure.

This will involve investigating new targets for pharmacological therapies, evaluating whether common co-morbid disease states such as diabetes alter the efficacy of these therapies and investigating the role of stem-cell therapy in this setting.

The Program will also evaluate the contribution of non-heart failure drugs to the burden of heart failure, determine the impact of rurality on prescribing for this condition and explore systems of optimising delivery of best practice to the community.

This research formalises the existing collaborative efforts of a team of investigators that span all aspects of research into the therapeutics of chronic heart failure from basic laboratory research to evaluation of patients in clinical trials and public health translational aspects of this condition. The Chief Investigators and Principal Investigators have an existing successful research collaboration that will be greatly expanded via the Program.

Prof David de Kretser, Prof Gail Risbridger, Prof Milton Hearn, A/Prof Graham Jenkin, Dr Mark Hedger, A/Prof Euan Wallace, Dr Kate Loveland, Dr David Phillips, Dr Moira O'Bryan
Monash University
\$7,725,375 over 5 years

Control mechanisms of reproductive processes

This Program Grant will investigate a number of important reproductive problems that affect the fertility of men, prostate cancer and the way the mother nurtures and protects the baby during pregnancy.

The successful development of sperm requires the proper function of a number of biological processes. This grant will investigate the way in which sperm are produced, the genes that are needed to control their development, and the way sperm propel themselves and fertilise the egg.

The research will also investigate how sperm are protected during their development from infection and immunological rejection, achieved in part by a special environment within the tubes in the testis where they grow.

It appears that the general mechanisms that the body uses to combat infections are modified within the testis and the way in which this occurs may provide clues that could be applied to prevent the rejection of transplanted organs in general.

Some of the substances that control these processes appear to play an important role in the body's defence against infection. The grant will also investigate the processes that are involved in the development of prostate cancer.

These changes can occur over many years and the grant will study some substances that appear to be involved. The work will provide new knowledge that may assist in new tests to identify whether a cancer is slow or fast growing, thereby helping each man to decide the most sensible form of treatment.

The grant will investigate how a group of proteins, that also are involved in the control of processes discussed above, assist the mother in protecting her baby during pregnancy. The outcomes will assist in the management of disturbances of pregnancy that may put the foetus at risk of survival.

Prof Ross Coppel, Dr Brian Cooke, A/Prof Magdalena Plebanski, Prof Mark von Itzstein
Monash University
\$4,962,360 over 5 years

Malaria: from target identification and therapeutics

The team brings together a number of experts in various aspects of malaria, vaccines and drug design to develop new therapeutic approaches to control of one of the world's major infectious diseases.

Recent developments such as the complete sequence of every malaria gene provides an unparalleled opportunity to use a number of powerful new techniques in biology to identify vulnerabilities in the parasite that may be targeted.

Members of the team include Professor von Itzstein who was responsible for the design of the anti-flu drug 'Relenza', Professor Ross Coppel who is a pioneer in the application of molecular biology to the study of malaria, and Drs Cooke and Plebanski, exciting and talented young scientists who already have made highly significant and important contributions to our understanding of how malaria parasites function and cause disease.

Success in this research program has the capacity to save millions of lives each year by preventing the deadly toll of this important human scourge.

Prof Stephen Holdsworth, A/Prof Peter Tipping, A/Prof Eric Morand, Dr A Richard Kitching, Dr Michael Hickey
Monash University
\$5,198,635 over 5 years

Pathogenic mechanisms of inflammatory diseases

This research is directed by a team of medical and basic scientists with expertise in mechanisms of inflammation relevant to human disease. The Program will investigate the molecular and cellular events that are responsible for inflammation in the kidneys, joints and blood vessels that lead to diseases such as glomerulonephritis, arthritis and atherosclerosis. The aim of the research is to find new therapeutic targets that may be specific to certain organs or disease processes, in order to develop more effective and selective treatments of chronic inflammatory disease in humans.

A/Prof Andrew Sinclair, Prof Peter Koopman, A/Prof Vincent Harley
Murdoch Children's Research Institute
\$4,308,220 over 5 years

Molecular genetics of sex determination and gonad development

Intersex disorders - ranging in severity from hypospadias (misplacement of the urethral opening) to complete sex reversal - are surprisingly common, with estimates as high as 4 per cent of all live births. These disorders usually result in infertility, genital abnormalities, gender mis-assignment and long-term psychological trauma.

The cause of these problems is most often the failure of the delicate network of gene regulation that is responsible for proper development of testes or ovaries in the embryo. This research program will identify genes important for sex determination and development of the gonads, find out how these genes function and interact, and discover how they contribute to cases of aberrant sexual development in humans.

Australia boasts three of the foremost international researchers in sex determination. Their

contributions have been fundamental to the advancement of the field, including the identification and characterisation of the master testis determining gene and other genes critical for sex determination. They now propose to pool their expertise in human molecular genetics, mouse developmental biology and protein chemistry to bring spectacular advances in our knowledge of human sexual development and its associated disorders. This information will be used to bring improved clinical care to patients with disorders of sexual development.

Prof Thomas John Martin, Dr Matthew Gillespie, A/Prof Kong Wah Ng, Dr Natalie Sims
St Vincent's Institute of Medical Research
\$5,263,070 over 5 years

Regulation of bone resorption and formation in health and disease

Bone is continually being formed and broken down, and these two processes are critical for the maintenance of a normal skeleton. These processes are dependent upon communication between the bone building and degrading cells, and the hormones growth factors and cytokines that are present in the circulation or produced in bone. The tightly regulated processes of bone formation and degradation need to remain equal, and are essential for the achievement and maintenance of skeletal strength and form. Osteoporosis results from an excess of bone breakdown over formation, and this Program aims to identify the factors that regulate these processes, and develop new therapies that can modify them. This Program will also determine what it is about bone cell properties that make some cancers, especially those of breast and prostate, particularly prone to spread to bone.

Prof Patrick McGorry, A/Prof Christos Pantelis, Prof Ian Hickie, Prof Henry Jackson,
A/Prof Alison Yung
University of Melbourne
\$7,397,980 over 5 years

Emerging severe mental illness in young people: clinical staging, neurobiology, prediction & intervention from Vulnerabi

Mental disorders, such as psychotic and severe mood disorders, are the largest cause of disability in Australia. However, there is still little known about illness onset, relapse and progression. We have developed a clinical staging model with transition points from symptom free to subthreshold status, to threshold disorder to chronic disability. This Program will investigate neurobiological and psychosocial factors which increase the risk of progression through these stages and use this model as a basis for examining the effectiveness of interventions, for example to prevent, delay or ameliorate onset and relapse, and promote vocational recovery. Thus major clinical and public health benefits and an understanding of factors that contribute to the onset and progression of illness will result.

Dr Philip Hodgkin, Dr David Tarlinton, Dr Stephen Nutt, Dr Lynn Corcoran
Walter and Eliza Hall Institute of Medical Research
\$5,198,635 over 5 years

The regulation of antibody: A systems approach

This program brings together a team of researchers from The Walter and Eliza Hall Institute of Medical Research to study how the body regulates antibody production to fight disease.

Antibodies are made by B-cells and are essential for a functional immune system. B cells circulate in the body, searching for signs of infection. When they encounter an invader, they mature, with the help of other immune cells, into antibody-producing cells. A small proportion of the cells are set aside as “memory” cells that can rapidly become antibody-producing cells should the same infection occur again in the future. This is the basis of vaccination.

This Program aims to understand how a B cell changes into an antibody-producing cell, by studying the genes that are known to be required for the cells to form, or to do their work. They will study animals whose immune systems are under- or over-active, to find out what part of the antibody-

producing process is faulty. Using this information, we hope eventually to be able to study diseases of antibody producing cells in humans (as occur in allergy, asthma, rheumatoid arthritis and leukaemia), to be able to identify the precise cause of the problem, and to suggest a therapy. This information may also be used to improve the outcome of vaccination where an enhanced antibody response is desired.

Queensland

Prof Lawrie Powell, Dr Gregory Anderson, Dr Grant Ramm, Dr Nathan Subramaniam
Queensland Institute of Medical Research
\$3,089,760 over 5 years

Iron metabolism and liver disease

The Chief Investigators have worked as a team for 20 years as part of a successful NHMRC Program Grant that was renewed on three successive occasions and subsequently under a NHMRC Block Grant to QIMR. Their combined expertise covers the whole spectrum from the bedside to the bench with respect to clinical studies and fundamental molecular studies of iron homeostasis.

The common theme of iron homeostasis and iron overload pervades virtually all the research of the team. The team's research has led to fundamental observations of iron regulation and homeostasis and the development of guidelines for the management of, and screening for, haemochromatosis, recognised as the most common inherited disorder of Caucasian populations.

The proposed research encompasses molecular studies aimed at deciphering the mechanisms of iron absorption and transport; how these processes are regulated; and clinical studies on patients diagnosed with haemochromatosis. The findings are particularly pertinent to the diagnosis, management and prevention of clinical haemochromatosis.

Prof Ian Frazer, A/Prof Ranjeny Thomas, Dr Geoffrey Hill
University of Queensland
\$4,634,965 over 5 years

Immunological therapies for cancer and autoimmunity

The Program team comprises a group of leading scientists with a history of successful investigation into the mechanisms and treatment of diseases in which the immune system plays a role in their development. These include cancers of the cervix and blood system, and autoimmune diseases such as rheumatoid arthritis and type 1 diabetes.

Working together, the team has made discoveries that have led to testing and clinical development of new treatments for these diseases. In this Program, the team aims to discover mechanisms regulating the immune response, and to exploit this knowledge to define new ways of switching on or off, specific immune responses. They will particularly seek to develop novel vaccines for chronic infections and autoimmune diseases, and to improve the safety of bone marrow transplantation.

Dr Richard Lewis, Prof Paul Alewood, Prof David Adams, Prof MacDonald Christie
University of Queensland
\$7,161,055 over 5 years

Dissecting pain pathways with conopeptides

A major obstacle to the development of safer and more effective pain treatments is the poorly defined nature of the different pathways involved in chronic pain.

The Program team will bring together a unique set of research expertise in using neurotoxins to define, at the molecular level, how the nervous system functions. The team also shares a common interest in understanding and improving treatments for pain, especially chronic pain which continues to remain poorly managed.

Through a focus on pain research, the Program will significantly enhance the scope of existing multidisciplinary collaborations between the Chief Investigators (CIs) Lewis, Alewood, Adams and Christie, which have already made a considerable impact in the fields of pharmacology and neuroscience.

The CIs also have considerable experience in the development of pain therapeutics, having discovered two conopeptides now under commercial development with AMRAD (AM336) and Xenome Ltd (Xen2174). This Program will discover and use highly selective conopeptides such as these to dissect the pharmacology of peripheral pain pathways and their projections into the central nervous system, and to identify and characterise new targets amenable to drug intervention.

The long-term goal of the Program is to discover new targets in pain pathways and develop conopeptides that act on these targets in animal models of chronic pain. These molecules will be optimised within the Program to the point where they can be considered for pre-clinical development in collaboration with commercial partners.

South Australia

Prof Mathew Vadas, Prof Angel Lopez, Dr Jennifer Gamble, Dr Gregory Goodall
University of Adelaide
\$4,634,965 over 5 years

Leucocyte and endothelial cell biology

The foot soldiers of the immune system, the white blood cells, constantly march through the body seeking out invaders, but kept in check by the barrier of endothelial cells that lines the inside of blood vessels. When infection occurs, molecular messages are transmitted amongst the white cells and between white cells and endothelium, to activate the immune cells to pass out of the blood vessels and mount a defence. Unfortunately, the activation system sometimes goes awry, resulting in inflammatory or allergic disease, such as arthritis or asthma. This team of researchers from the Hanson Institute in Adelaide, combining expertise in molecular and cell biology, protein chemistry, structural biology and animal models, has been working together for over 10 years, investigating the molecular mechanisms involved in controlling the formation and activities of blood vessels and white blood cells. This Program seeks to further that understanding, and to develop drugs that have the potential of ameliorating the inflammatory condition.

New South Wales

Prof Perminder Sachdev, Prof Henry Brodaty, Prof Gavin Andrews
University of New South Wales
\$4,635,615 over 5 years

The prevention, early detection, & effective management of neurocognitive disorders in the elderly

The unprecedented greying of the world population is posing a major challenge to health care in meeting the needs of older individuals with cognitive disorders such as Alzheimer's disease. At the same time, drugs are being developed to prevent these disorders, or to treat them effectively.

This Program is a comprehensive attempt at dealing with the neuropsychiatric aspects of these neurocognitive disorders. The group is endeavouring to better define the early stages of these disorders, and studying methods of detecting them at an early stage, using the latest neuropsychological and neuroimaging techniques.

They will investigate new drugs for the prevention of dementia. Much of dementia is not treated early because of lack of training of primary care physicians in identifying dementia, and they are developing methods to deal with this problem.

They are also examining the role of cognitive disorders in accidents and suicides in the elderly, and the development of depression. They will determine the role of psychiatric disorders in the care of these patients, and the methods of alleviating the burden of disease. They expect that this research will make a major impact on health policy for these disorders in Australia. They also hope to make the Program the premier centre for training in geriatric neuropsychiatry.

Prof Stephen MacMahon, Prof John Chalmers, A/Prof Bruce Neal, Prof Mark Woodward, Prof Craig Anderson
University of Sydney
\$8,680,875 over 5 years

New evidence to guide decisions about the prevention and treatment of common cardiovascular diseases

The Program brings together clinicians, epidemiologists and statisticians in a unique endeavour designed to improve the prevention and treatment of heart attack and stroke. For the foreseeable future, these conditions will remain leading causes of death and disease in Australia and most other countries in the region.

While there are many established treatment and prevention strategies for these conditions there remains great potential for further advances to be made, which might avert very large numbers of premature deaths and serious disabling outcomes.

This Program of research seeks to provide new information that will give patients, doctors and policy makers innovative options for the treatment and prevention of heart attack and stroke. The Program will incorporate two main elements: observational studies and randomised controlled trials.

The observational studies will establish the precise importance of each of the main causes of cardiovascular diseases (such as diabetes, blood pressure, smoking and cholesterol) at different ages, in different ethnic groups and in different geographic regions.

Furthermore, these studies will also define the relative importance of established and novel risk factors for cardiovascular disease, providing important new information about how resources for prevention should be directed. The large-scale trials will provide evidence about the effectiveness and safety of a range of new cardiovascular disease prevention and treatment strategies. The work will

build on the team's very successful approach of evaluating the effects of established interventions in high-risk groups for whom those particular treatments are not currently indicated.

The Program will also include studies that address the critical issue of translating health research findings into practice – in terms of health policy, clinical practice and consumer behaviour. A particular focus involves the application and evaluation of novel Internet technologies for promoting best practice.

The methodologies used by the team will ensure that the evidence generated by the Program is as precise and reliable as possible, in order to provide a sound base to guide decisions about changes in health care policy and practice. The research findings will have direct relevance to the healthcare needs of millions of Australians within the next five years, and the impact of the work will be assured by the development of implementation and dissemination plans for each major component of the Program.

Prof Geoffrey Farrell, Prof Geoffrey McCaughan, A/Prof Jacob George
University of Sydney
\$4,634,965 over 5 years

Molecular and cellular pathogenesis of human liver disease

In humans, chronic liver diseases cause cirrhosis of the liver in some but not all individuals. This leads to protracted ill health, complications (fluid retention in the abdomen, confusion, bloodstream infections, kidney failure, liver cancer) resulting in hospitalisation, liver transplantation and premature death.

In Australia, cirrhosis is an important cause of death and of years of potential life lost, while liver cancer has recently doubled and is predicted to treble by 2020. The common causes are hepatitis C, fatty liver disorders, alcohol and hepatitis B; when 2 of these are present together, there is a higher risk of cirrhosis.

This Program aims to unravel the pathological processes which cause cirrhosis at the molecular and cellular levels, in order to understand why some people are at higher risk. These processes could result from genetic predisposition, other constitutional factors (age, gender) or from lifestyle factors (overnutrition, inactivity, and alcohol).

The 3 chief investigators from Westmead's Millennium Institute and the Centenary Institute of Royal Prince Alfred Hospital are international experts in hepatitis C, non-alcoholic steatohepatitis (NASH) and other fatty liver disorders, autoimmune hepatitis, liver transplantation, and scarring processes that lead to cirrhosis of the liver.

The new knowledge that will result from these studies will be used to help prevent people developing severe forms of chronic liver disease, and for treating cirrhosis if it has already occurred.

Prof Anthony Cunningham, Prof Bruce Brew, Prof Suzanne Crowe, Dr Sharon Lewin, Dr Barry Slobedman, Prof Steven Wesselingh
University of Sydney
\$6,180,170 over 5 years

Pathogenesis of Persistent Human Virus Infections of Global Significance

The study will investigate why humans cannot eradicate particular viruses (HIV/AIDS, cytomegalovirus and herpes simplex virus), the long term effects of these viruses and ways to improve control. Current treatments can only partly suppress the levels of these viruses, because they persist in certain parts of the body called reservoirs, only to resurge later causing disease.

Thus, the overall aim of the research program is to discover the mechanisms by which these viruses are able to successfully persist within reservoirs in the human body. The research program brings together a group of 6 leading scientists and clinicians located at 3 sites in 2 Australian cities.

The team is comprised of experts in the study of HIV/AIDS, cytomegalovirus and herpes simplex virus who will combine their knowledge and expertise to speed up the process of research on these viruses that are of major health importance. Studies will also utilise a number of cutting edge technologies that now make it possible to much more rapidly and precisely determine how viruses cause disease. Advances in our understanding of how viruses persist may form the basis for treatments aimed at controlling persistent infections and the serious diseases caused by these viruses.

Prof Robert Graham, Prof David Allen, Dr Diane Fatkin, Prof Michael Feneley,
Prof Richard Harvey
Victor Chang Cardiac Research Institute
\$7,724,725 over 5 years

Molecular mechanisms of cardiac function and disease

Heart disease remains the leading cause of death in our society. Almost two million Australians suffer from the debilitating effects of heart disease and it is the leading cause of premature permanent disability in our workers.

Heart defects are also the most common type of birth defect and the leading cause of deaths in infants dying from birth defects. Many of these problems can be attributed directly to defects in the development, repair and/or function of heart muscle and, at the cellular level, of heart muscle cells or cardiomyocytes.

Understanding the cardiomyocyte as well as integrated heart development, biology, physiology and function, therefore, holds great promise for major advances in the prevention and treatment of contemporary heart diseases. This Program Grant brings together a unique team of interactive researchers with expertise in cardiovascular physiology, as well as developmental, cellular and molecular biology. The outcomes anticipated from new insights into heart biology that will result from the proposed studies, are the development of novel therapeutic approaches for the prevention and treatment of heart attacks and heart failure.