2005 ANNUAL REPORT

MONASH INSTITUTE
OF MEDICAL RESEARCH

Contents

Profile

History

Founding Director Professor David de Kretser AO established the Monash Institute of Reproduction and Development (as it was originally known) in 1991. This organisation brought together scientists and clinicians undertaking research into conception, birth and development at the Centre for Early Human Development, Monash Medical Centre, with scientists working in the field of male reproductive health at Monash University's Department of Anatomy.

With a small but highly talented team of about 70 and an annual budget around $4 million, the Institute was initially located in various laboratories throughout Monash Medical Centre, Clayton.

Over the years the Monash Institute of Reproduction and Development (or MIRD as it became known) grew into five key research centres working in a broad range of fields. In 1999 it moved into its first purpose-built facility, enabling thousands of Australians including infertile young people, parents of premature babies, and men with prostate cancer, to benefit from Institute scientists' research.

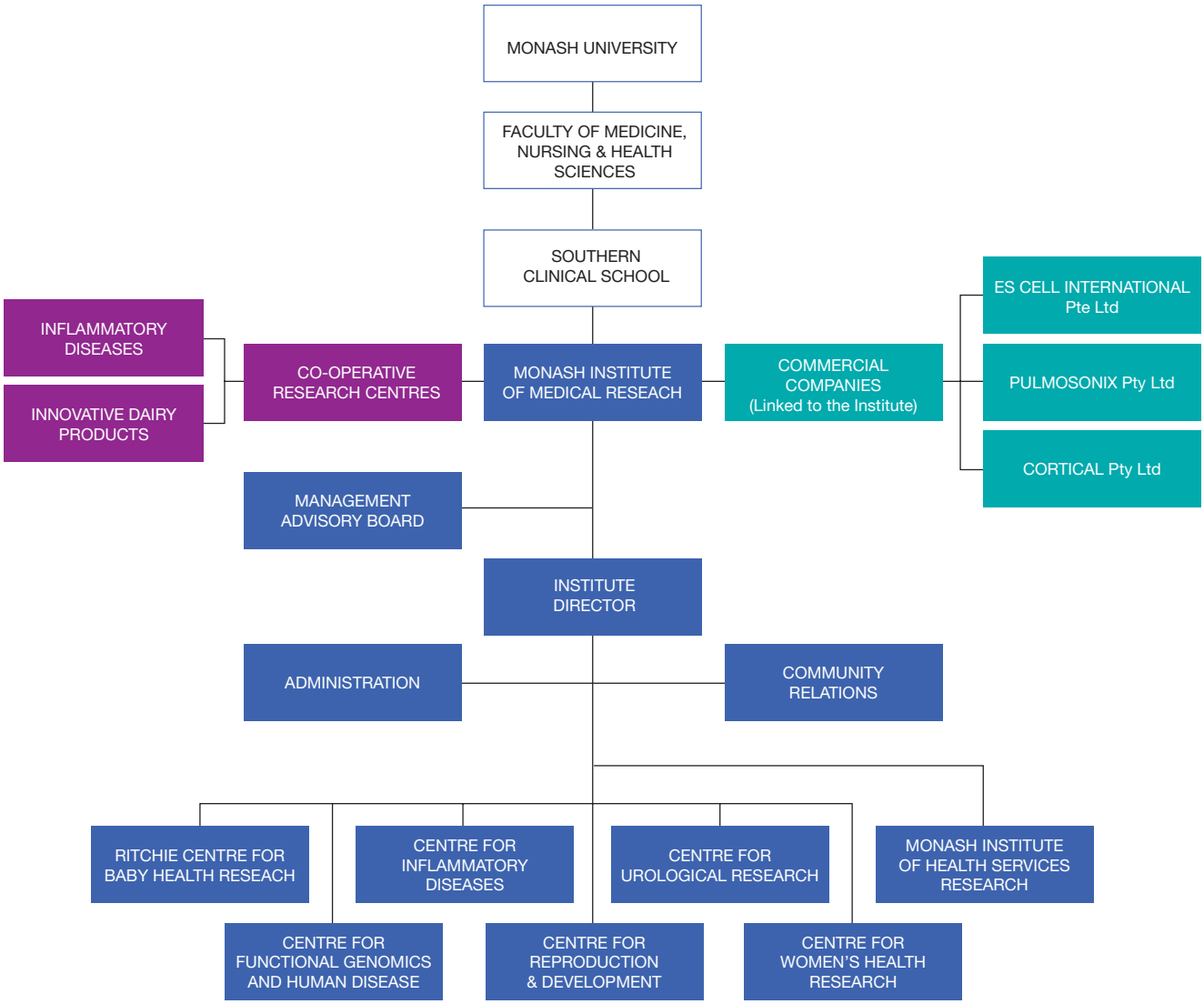
In recognition of the evolution of its research beyond reproduction and development, MIRD became Monash Institute of Medical Research (MIMR) on 1 February, 2005. Key medical research entities of Monash University and Southern Health joined forces with the existing team of researchers and clinicians to collectively take its valuable biomedical discoveries through all stages of development to commercial reality.

Today, MIMR research staff and students total more than 300 (including 100 PhD students), and continue to win international recognition for their work. Supported by a dedicated administrative team and development office, MIMR's centres have outstanding track records of scientific discovery. The Institute's commercialization team manages intellectual property, business plan development, licensing, research contract negotiation and company spin-off activities.

Throughout its relatively short but dynamic history, this Institute has enjoyed the patronage of former Australian Governor General Sir Zelman Cowen. The Director and Executive Team have also been supported by a Management Advisory Board comprising leading members of the community and representatives from the education and health sectors.

Professor Bryan Williams, one of the USA's leading cancer experts, officially commences as the new Director of MIMR on 1 January, 2006 and looks forward to leading the Institute into its next exciting phase of research achievement.

Organisational Structure



Year in Review

Year in Review

Institute Director's Report

Welcome to the Monash Institute of Medical Research.

1 February, 2005 was a landmark day for medical research in Victoria. A large audience of guests from Monash University and Southern Health, other Melbourne Institutes, government and long-term Institute supporters applauded Victorian Premier The Honorable Steve Bracks as he officially launched the new Monash Institute of Medical Research (MIMR).

Back in 1991, the establishment of the Monash Institute of Reproduction and Development (MIRD) saw key scientists working in fields related to reproductive biology combine for mutual benefit. With the remarkable growth that followed, it soon became apparent that MIRD had expertise and scientific potential well beyond its skills in reproduction. Fundamental research into reproductive biology, infertility, and fetal and neonatal physiology continued while stem cells, inflammation, the genetic basis of disease, and cancer biology became integral parts of the Institute's focus.

The creation of MIMR brought together the key medical research entities of Monash University and Southern Health at Monash Medical Centre, including MIRD, the Centre for Inflammatory Diseases and the Centre for Women's Health Research. The new partnership refined the model for developing new therapies and securing the vision for Melbourne as a world-ranking biotechnology precinct.

The newly created MIMR embodies the vision of founding Director Professor David de Kretser AO. Recognizing that translating breakthroughs from the laboratory bench into clinical benefits and commercial realities was best achieved with an integrated approach, he clearly saw the benefits of concentrating research infrastructure and expensive equipment under a single banner.

Monash University and medical science at large owes much to David, not only for the creation of MIMR but also for his years of inspirational leadership, research discoveries and teaching. Having seen the birth of MIMR, David officially stepped down as Director at the end of March 2005.

As Acting Director of our Institute through April-December 2005, I am sincerely grateful for the wholehearted dedication and support of the Institute's talented directors and administrative leaders, staff and students, and the Management Advisory Board who ensured that the momentum of the Institute was maintained.

Year in Review

In September 2005, MIMR moved into the $17.5 million Stage One research facility with collaborating partner members of the Monash Health Research Precinct. Located behind the existing MIMR building and linked by a wide bridge housing sorely needed meeting space, the four storey construction was made possible with financial assistance from Federal and State Governments, Monash University and Southern Health.

In 2005, the Chairman of our Management Advisory Board (MAB) James Murray was admitted to the degree of Doctor of Laws (honoras causa) by Monash University in recognition of his years of dedication and service to the Institute, the Monash Faculty of Medicine Nursing and Health Sciences, and the medico-legal profession. I take this opportunity to congratulate and sincerely thank James for his long-term dedication at the helm of the MAB. After almost 11 years, James retired from the position of MAB Chairman at the end of 2005.

I am delighted that Mr George Pappas has agreed to take on the role of MAB Chairman in 2006, and we look forward to working with him in the future for the continuing benefit of the institute.

In closing, I welcome Professor Bryan Williams who commences as Director of MIMR on 1 January, 2006. Since 1991, Bryan has been the Chairman of the Department of Cancer Biology at the Lerner Research Institute of the Cleveland Clinic Foundation in Ohio, USA, where he is a distinguished researcher of the highest international standing. Bryan brings a superb new dimension to our research, and he will be an exceptional leader and powerful advocate for MIMR.

At the end of 2005, MIMR is powerfully positioned at the forefront of biology, biotechnology and medical care now and in the future. We have outstanding expertise. We have key collaborative relationships. We have growing support from government, industry and the community, and we have new leadership and new facilities. The future for MIMR is bright.

Professor Adrian Walker
Acting Director

Year in Review

Management Advisory Board Chairman's Report

The opportunity to participate in medical history is a privilege which I and all other members of the Management Advisory Board (MAB) of Monash Institute of Medical Research (MIMR) cherish. It is an honour to be asked to share our skills and experience from the wider business and professional communities with an outstanding team of medical researchers and educators who practice in a wide diversification of disciplines. We are continually taken by the breadth and depth of research at MIMR, and trust our efforts and advice have helped optimize the outcomes of the Institute's activities.

Medical research is undeniably very complex, challenging and demanding. The dedicated scientists at MIMR face daily problems which do not flow from, but are related to, the complex nature of their research tasks. For example, reliability on volatile grant funding creates issues which should not follow years of education and applied research. The constant pressure to publish creates major problems of time. Rapid ongoing expansion has led to a cycle of cramped working conditions, in part alleviated by the new building. The need for hi-tech equipment to keep pace with developments around the world places additional strain on limited resources. Yet despite these formidable issues, MIMR has grown in just over a decade to be one of Australia's premier research organizations.

2005 was particularly momentous with the transition from MIRD to MIMR. This merger with other members of the Monash Health Research Precinct and Southern Clinical School is the realization of a long held goal, and the Board was delighted to assist in driving this consolidation of expertise under the one umbrella. We are confident that this new structure will position the Institute well to maintain and build its position as a leader in medical and biotechnology development.

While the ongoing growth and development of MIMR is cause for celebration, it is with some sadness, but yet great pride in his achievements, that we record the retirement of the Founding Director, Professor David de Kretser AO. A truly inspirational man, David built this organisation with his drive and dedication, with his patience and persistence, and with his passion and compassion. Not only does David retire with a world-wide reputation as a medical scientist, but he has proved himself to be an outstanding administrator and team leader. More recently he has added to his skills by becoming a fundraiser, an ambassador and political advisor on medical research. I am proud to have worked with David at MIMR and even more proud to call him a friend. On behalf of the Board I wish David all the very best for the future and look forward to his ongoing contributions to medicine, biotechnology and the wider community. He has much yet to offer in a variety of roles.

During 2005 the Board also bade farewell to two of its long-standing members, Mr Tony Rogers and Mr Grant Robertson. Both men had a long history of involvement with the Institute and Tony in particular played a major role in shaping and driving MIMR towards what it is today. I shall be forever grateful for their time and efforts. Tony held the positions of chair of the Commercialization sub-committee and Deputy Chairman of the Board for many years. I am personally very grateful for the assistance and astute advice he has provided me, stepping into the role of Board Chair on several occasions when I was away. Grant was also a long-term chair of the Fundraising sub-committee and we are grateful for his enduring advocacy for the Institute.

I congratulate and thank the chairs of our sub-committees; David Evans, who with the able assistance of the redoubtable Robert Smorgon leads the Fundraising Committee, Tony Rogers who led the Commercialization sub-committee, Bruce Parncutt his successor, and Barbara Crook who was at the helm of the Communications Committee. During the year the structure and roles of the sub-committees were further refined. These changes in name, image and organization of both the Institute and the sub-committees was a major task and the contributions from the relevant members of the Board helped to make this transition smooth and effective.

With the new formalized relationships flowing from the birth of MIMR we also welcomed Craig White to our MAB. Craig is Executive Director of Clinical Services and Chief Medical Officer at Southern Health, and joins Southern Health CEO Linda Sorrell in representing this network of hospitals. Their involvement with the MAB underlines the vital link between research and clinical practice.

In the first half of 2005 the Board continued to assist in the task of finding a new Director. A national and international search resulted in an outstanding short-list of five candidates. We on the Board are delighted that a scientist of the outstanding calibre of Professor Bryan Williams accepted the position to commence in January 2006. Bryan's arrival heralds a new and exciting era, and the Board looks forward to working closely with him and the team he leads.

On behalf of the entire Board, I wish to express profound thanks to Executive Director, Professor Adrian Walker, who undertook the weighty bridging task between the retirement of Professor David de Kretser and the arrival of Professor Bryan Williams. A man of immense talents, he never wavered under a formidable work load.

In this my last year as Chairman of the MIMR Management Advisory Board, I express my sincere gratitude and best wishes to everyone associated with this great organisation. Thank you to my fellow Board Members, Institute and Centre Directors, senior scientists and administrative staff. It has been an absolute pleasure to be part of the first decade of development of what is fast becoming a major international force in medical science. My successor George Pappas presents with a formidable range of talents, has a long history of involvement in the higher reaches of the commercial world, and will lead the Board with imagination and intelligence. I am very grateful that George has undertaken this role, Barbara Crook as his ever willing and able Deputy.

I have no doubts about the future of MIMR, which glows with promise.

James Murray
Chairman

Management Advisory Board

Professor Edward Byrne

Dean, Faculty of Medicine, Nursing and Health Sciences, Monash University

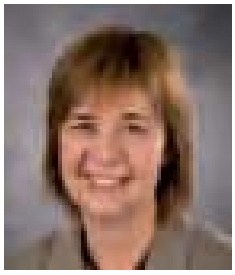
Non-Executive Board Member, Cochlear Pty Ltd

Board Member, Neurosciences Australia Pty Ltd

Deputy Chair, Neurosciences Victoria Pty Ltd

Governor, BHP Billiton Trustees

Editor-in-Chief, Internal Medicine Journal



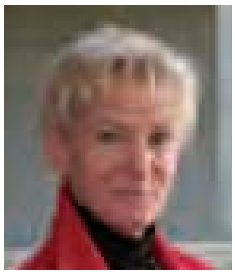
Professor Edwina Cornish

Deputy Vice Chancellor (Research), Monash University

Fellow, Australian Academy of Technology Sciences and Engineering

Director, Victorian Partnership for Advanced Computing

Former member, Prime Minister's Science and Research Council, ARC Board and CRC Committee



Ms Barbara Crook

Chief Executive Officer, Hunt and Hunt

Deputy Chair, Management Advisory Board and Executive Group

Professor David de Kretser AO
- Retired 31 March 2005

Director, Monash Institute of Medical Research

Head, Centre for Molecular Reproduction and Endocrinology, MIMR *(until 31 March 2005)*

Director, Andrology Australia (Australian Centre of Excellence in Male Reproductive Health)

Mr David Evans

Managing Director, JB Were Retail

Board Member, Goldman Sachs JB Were

Mr Michael Gorton AM

Partner, Russell Kennedy Solicitors

Deputy Chair, Infertility Treatment Authority

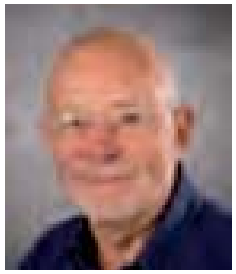
President, Health Services Review Council

Chair, Victorian Biotechnology Ethics Advisory Committee

Representative of the Minister for Health on the Management Advisory Board

Ms Anne Heyes

National Human Resources Manager, Australian Red Cross Blood Service



Mr James Murray

Consultant, Blake Dawson Waldron

Chair, Management Advisory Board and Executive Group

Mr George Pappas

Senior Advisor, The Boston Consulting Group

Chair, Committee for Melbourne

Director, Western Bulldogs Football Club

Mr Bruce Parncutt

Principal, Lion Capital

Director, Vision Systems Ltd

Council member, Melbourne Grammar School

Trustee, National Gallery of Victoria

Former Director, Australian Stock Exchange

Mr Grant Robertson
- Resigned October 2005

Executive Director, Robertson Group of Companies

Executive Director, Pegasus Aircraft Industries Group

General Counsel, Abbott Stillman & Wilson

Director, Murchison Holdings Ltd Group

Director, Quest Investments Ltd Group

Director, Environinvest Ltd

Board Member, SIDS and Kids Foundation

Mr Tony Rogers
- Resigned June 2005

Company Director

Formerly Group General Manager, ICI Australia and CEO, Smorgon/ARC

Deputy Chair, Management Advisory Board

Mr Robert Smorgon

Deputy Chair, Escor Pty Ltd

Vice Chairman, Australian Council for Children & Youth Organisations Inc

Ms Linda Sorrell

Chief Executive Officer, Southern Health, Board member

Monash Institute of Health Services Research, Board member

Prince Henry's Institute, Chair, HealthSMART Services Steering Committee, State Government of Victoria

Professor Adrian Walker

Acting Director, MIMR

Director, Ritchie Centre for Baby Health Research, MIMR

Dr Craig White

Executive Director Clinical Services and Chief Medical Officer, Southern Health

Patron

Sir Zelman Cowen AK, GCMG, GCOV

Governor General of Australia 1977 - 1982

Sub-Committee Membership

Communications Sub-Committee

Ms Barbara Crook (Chair)

Mr Michael Gorton

Ms Anne Heyes

Ms Julie Jacobs (from July 2005)

Ms Sue James

Professor Adrian Walker

Mr David Whiteside

Fundraising Sub-Committee

Mr David Evans (Chair)

Mr Robert Smorgon (Deputy Chair)

Ms Barbara Crook

Mr Michael Gorton

Ms Anne Heyes

Ms Sue James

Professor Adrian Walker

Research Commercialization Sub-Committee

Mr Bruce Parncutt (Chair)

Dr Philip Berger

Dr David Campbell

Mr Andy Gearing

Professor Paul Hertzog

Dr Michael Holland

Dr Rocco Iannello

Mr Andrew Maxwell

Dr Sally Mellor

Associate Professor Eric Morand

Professor Gail Risbridger

Associate Professor Peter Rogers

Research Centres

Ritchie Centre for Baby Health Research

The Ritchie Centre for Baby Health Research is dedicated to giving premature infants the best chance possible of long healthy lives.

Approximately 5,000 of the infants born in Australia each year require intensive care treatment. While dramatic improvements in fetal and neonatal management over the last 20 years have led to a marked increase in the number of these babies surviving, the ongoing health issues amongst these infants continues to rise.

The Ritchie Centre is a unique facility combining the talents of world-leading fetal physiologists with neonatal intensive care clinicians, engineers and sleep scientists. Nowhere else in the world does such a diverse but focused team collaborate on the care of the new born on a daily basis. Through improved understanding of the fundamentals of fetal development, real problems identified in the neonatal intensive care unit are readily addressed. Recognition is also given to the important part that sleep plays in development of the infant, with extensive study into physiological responses during sleep at different stages of early growth.

In 2005, work continued to focus on cardio-respiratory function and impaired blood and oxygen supply to the brain. Greater understanding of the risk factors associated with preterm birth was a significant step forward in understanding Sudden Infant Death Syndrome (SIDS).

Research Highlights

Understanding increased SIDS risk for preterm infants

Ritchie Centre scientists are committed to reducing the incidence of SIDS by increasing understanding about the risks through controlled clinical studies.

Autonomic dysfunction (problems with protective automatic responses) has been regarded as a possible cause of sudden infant death syndrome (SIDS). Preliminary studies by Ritchie Centre scientists in the Adamson Children's Sleep Unit at Monash Medical Centre have indicated that immature autonomic control may account for the increased risk of SIDS amongst preterm infants.

Heart rates of a small number of sleeping preterm and term infants were monitored, with particular focus on how rates changed (or failed to change) in response to small stimuli. Term babies aged 2-3 weeks were found to have a greater increase in their heart rate when aroused, compared to preterm babies at the same developmental stage or corrected postnatal age. This provides clues to the causes and risk factors for SIDS in premature infants.

For more information see Tuladhar R et al. Comparison of postnatal development of heart rate responses to trigeminal stimulation in sleeping preterm and term infants. J Sleep Res. 2005 Mar; 14(1):29-36.

PhD student Dr Flora Wong

Using sound to check lungs of unborn babies

Lung function is a critical factor in the health and survival of premature babies. For over a decade, scientists from the Ritchie Centre have provided vital insights into how lungs develop both before and after birth. These studies have helped improve the care and management of premature infants around the world. The team is now examining how sound could be used to develop new methods to assess the lungs of a fetus and newborn babies in a safe and non-invasive manner. Using laboratory models, sounds transmitted through lungs filled with different levels of air and fluid have been recorded and measured. The studies showed that both the velocity of audible sound and the degree to which high-frequency sound is attenuated relates to the degree of inflation of the lung, particularly at high lung densities. Further in vivo studies are required, but this insight may be extremely useful in the care of premature infants in the future.

For more information see Berger PJ et al. Velocity and attenuation of sound in the isolated fetal lung as it is expanded with air. J Appl Physiol. 2005 Jun;98(6):2235-41.

Professor Adrian Walker, Centre Director

How the sleeping brain regulates its blood flow and oxygen supply

Sleep has a major impact upon human health. Dreaming sleep, also known as rapid-eye-movement (REM) sleep, is the stage of sleep when children and adults are at greatest risk of sleep apnoea (stop breathing episodes) and associated problems. Remarkably, oxygen demands are greatest and brain blood flow reaches its highest level in REM (much greater than when we are awake), increasing the risk for problems such as stroke. In partnership with sleep physicians, Ritchie Centre scientists are focusing on critical factors that might impair brain blood flow in REM. In ground-breaking work, they have shown that nitric oxide is critical for keeping blood vessels widely dilated in REM; nitric oxide is low in sleep apnoea patients. In 2005, another critical feature of REM was discovered through Ritchie Centre collaboration with scientists in Italy and France: activation of constrictor nerves in the brain is also greatest in REM. Should abnormal activity in these nerves coincide with low nitric oxide release, the brain will be at heightened risk for low blood flow, poor oxygen supply, and stroke.

For further information see Loos N et al Sympathetic nervous control of the cerebral circulation during sleep. J Sleep Research 14(3):275-83.2005.

Centre for Reproduction and Development

During 2005, two of the Institute's highly successful teams, the Centre for Molecular Reproduction and Endocrinology and the Centre for Early Human Development, joined forces to become the Centre for Reproduction and Development.

Research Centres

PhD student Melissa Cooney

The Centre for Reproduction and Development (CRD) has a wealth of expertise in male and female reproductive biology, embryo development, in vitro fertilization, stem cell biology and animal biotechnology. It is envisaged that this broad platform will facilitate translation of laboratory research into the clinical setting and also into the agricultural zone.

Male infertility affects about 25% of the Australian population, and in about 40% of cases, the underlying cause remains completely unknown. Better understanding of genetic factors and the way these manifest in testicular and germ cell functions and sperm biology will improve diagnosis and treatment of infertile couples. Researchers at MIMR are not only investigating causes of infertility but may also identify factors that could lead to the development of a male contraceptive.

The Institute's expertise in hormonal function and immune responses in the male reproductive system is also helping to address problems such as liver disease, inflammatory disorders, cardiovascular disease and organ transplant rejection.

The potential of stem cell technology is widely acknowledged, but technical issues remain. This team has been a long term leader in stem cell research in Australia, and continues its work on the fundamentals of stem cells, isolating and characterizing embryonic stem cells and reprogramming somatic cells to a pluripotent state.

The growing insight in stem cell technology and other facets of reproductive biology is also being translated into agricultural biotechnology, with a view to enhancing the efficiency of cloning of elite cows and bulls for the benefit of Australian beef and dairy industries.

Dr Michael Holland, Centre Director

Research Highlights

Possible genetic cause of male infertility discovered

In an attempt to determine the origins and causes of male infertility, CRD researchers are identifying unique components of the sperm by developing mouse models of male infertility. Recent studies have focused on the final stages of sperm formation and also on the process by which sperm "mature" to become fully fertile cells. A collaborative study with the Walter and Eliza Hall Institute of Medical Research examined the important chemical modifications to the maternal and paternal DNA which occur at conception. When the gene that regulates these modifications is disrupted in some way, the packaging of DNA into chromosomes is altered. Studies showed that mice with certain changes to their DNA did not produce sperm. While scientists have hypothesized for some time that male infertility may be due to mutations in genes encoding components of sperm, identifying the genes responsible has been the challenge until now.

Webster KE et al. Meiotic and epigenetic defects in Dnmt3L-knockout mouse spermatogenesis. Proc Natl Acad Sci USA. 2005 Mar 15;102(11):4068-73

New approach to chronic liver disease

Chronic liver disease can be caused by diseases such as malaria, hepatitis, alcoholism and liver cancer. Currently the only cure is a liver transplant. However, as only about 5% of Australians in need of a new liver are able to receive one, a new treatment is urgently needed. In ground breaking laboratory research, CRD scientists working with their MIMR colleagues in the Centre for Inflammatory Diseases have shown that the reproductive hormone follistatin may halt the progression of chronic liver disease. Diseased liver cells produce a protein called activin; this contributes to the build up of thick scar tissue which inhibits blood flow through the organ. When follistatin is introduced, it binds to the activin and effectively stops scar tissue forming. The team is hopeful that after further testing and clinical trials, a safe and effective therapy based on follistatin could help thousands afflicted with chronic liver disease.

Patella S et al. Follistatin attenuates early liver fibrosis: effects on hepatic stellate cell activation and hepatocyte apoptosis. Am J Physiol Gastrointest Liver Physiol. 2006 Jan;290(1):G137-44.

Germ cell maturation

Spermatogonia are the primary stem cell type in the testis. CRD scientists have been working to identify molecular factors that begin the process of differentiation, which until now has been poorly understood. One factor involved is a family of proteins called importins, found in the membrane surrounding the cell nucleus. These factors regulate the access of various components to the cell nucleus, affecting the pattern of genes activated in the cell and thus the fate of the cell. This not only provides us with an important understanding of spermatogenesis but may ultimately assist in developing treatments for the many infertile men who suffer from arrested spermatogenesis.

Loveland KL et al. Drivers of germ cell maturation. Ann N Y Acad Sci. 2005 Dec;1061:173-82

Testes to hold the key for organ transplant patients?

The testes have a unique relationship with the male immune system. Sperm first develop during puberty, long after the body's immune system is established. When new cells are introduced, the immune system normally detects them as foreign and attacks. However, the immune system in the testes is naturally suppressed which ensures the survival of sperm, leading to the description of the testes as 'immunologically privileged.' A CRD team is seeking to identify the molecules that direct the testes to adopt a protective rather than aggressive stand towards sperm. Further appreciation of these molecules will ideally form the basis for a new targeted therapy for transplant patients.

New method to reprogram adult stem cells

Embryonic stem cells (ESC) have been acclaimed as the most promising resource in this field as they are pluripotent (have the potential to develop into any type of tissue). However, adult stem cells successfully reprogrammed so they exhibit the same characteristics of the ESC may prove to be an equally or even more viable option. Members of the CRD team have recently developed a new means of reprogramming some adult stem cells using a technique known as somatic cell nuclear transfer which involves fusing somatic cells with ESCs. This technique could have particular relevance in addressing the problem of immune rejection when transplanting the cells into patients.

Pralong D et al. A novel method for somatic cell nuclear transfer to mouse embryonic stem cells. Cloning Stem Cells. 2005;7(4):265-71.

Latest developments in cattle cloning

Early in 2005, MIMR introduced the world's first calf produced using a new cloning technique known as serial nuclear transfer (SNT). Brandy, a healthy Holstein-Friesian calf, is part of the Institute's long term work into understanding the role of gene networks in early embryo development. In addition, there is the practical application of refining and improving efficiencies in cattle cloning for possible agricultural application in the future. SNT involves two rounds of nuclear transfer before the embryo is ready for implantation into a surrogate cow. By merging the cytoplasm of a cloned embryo with that of a recently fertilized egg, the CRD team are seeking to improve the developmental potential of cloned embryos through improving the environment in which these develop. Although there are extra steps involved in SNT, this approach could improve efficiencies if a larger number of healthy offspring are produced from fewer cloned embryos.

An important factor in determining the health of cloned embryos is the success with which the donor cell nucleus can be reprogrammed into a state more closely resembling that which occurs in a normal embryo. A number of different approaches to this have been tried. CRD scientists have isolated and characterised bovine embryonic stem cells which they are using to fuse to donor cells and thus reprogram the donor nucleus. This approach has the potential to dramatically enhance the efficiency of cloning.

Preserving an endangered species – the Grey Nurse Shark

It is estimated that there are less than 500 Grey Nurse Sharks left on Australia's east coast. In conjunction with the Melbourne Aquarium, and with support from BHP Billiton, MIMR scientists have undertaken an innovative assisted reproductive program with a view to boosting the dwindling numbers of this endangered species. After two years of developing an artificial insemination process suitable for Elasmobranches (a class of fish made up of sharks, rays and skates), the first attempt to impregnate a shark at Melbourne Aquarium was undertaken in July 2005. At this stage, the technique is being tested in Broadnosed Seven-gill Sharks as they are a hardier species than the Grey Nurse. The ultimate goal of the collaborative team is to collect semen from Grey Nurse Sharks on the west coast and inseminate east coast females of species. This enhances genetic diversity which will ideally increase the odds of long term survival for these sharks.

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 human disease, determine what particular genes do and which parts of the body they affect. Genetically modified mouse models of disease and DNA microarray technologies are just some of the sophisticated techniques used to determine the impact of genetic changes.

The Centre for Functional Genomics and Human Disease (CFGHD) is establishing how and why genes function in a number of conditions including infections and immunity, inflammation and cancer as well as disorders associated with Down Syndrome such as Alzheimer's and other neurodegenerative conditions.

Greater understanding of gene content, mutations, interactions and inappropriate changes in expression will enable innovative methods of diagnosis, treatment and prevention for these debilitating and life threatening illnesses.

Once identified, disease causing genes will ideally become targets for revolutionary new therapies.

Research Highlights

Elf5 gene and breast cancer

The recent discovery that a gene known as Elf5 plays an important role in the development of the mammary gland may hold the key to future management of breast cancer. The Elf5 gene, which encodes the Ets-like Factor 5 protein, is found in the epithelial cells of many organs in the body including breast, kidney and prostate. Studies showed that Elf5 controls cell multiplication and tissue invasion that is part of normal mammary gland growth during pregnancy. Mice with drastically reduced levels of this gene did not develop any mammary glands during pregnancy and did not produce milk. As uncontrolled epithelial cell multiplication and invasion are part of the breast cancer process, this discovery is of great significance. It is anticipated that problems or irregularities with this gene could be a leading cause of breast cancer.

For further information see Zhou J et al. Elf5 is essential for early embryogenesis and mammary gland development during pregnancy and lactation. EMBO J. 2005 Feb 9; 24(3):635-44.

Revealing the immune system's genetic secrets

Suppressor of cytokine signaling 1 (SOCS1) is a critical regulator of cytokine signaling and immune responses. SOCS1-deficient mice develop severe inflammatory disease, but are very resistant to viral infections. Studies at the CFGHD have recently defined the key role that SOCS1 plays in fighting infectious diseases. It inhibits type I interferon signaling or controls when interferon, an important protein in the immune system, is blocked. Thus, SOCS1 balances the beneficial antiviral actions of the immune system against any detrimental inflammatory response. This insight into SOCS1 provides a valuable basis for future treatments for influenza, hepatitis, cancer and septic shock.

For further information see Fenner JE et al. Suppressor of cytokine signaling 1 regulates the immune response to infection by a unique inhibition of type I interferon activity. Nat Immunol. 2006 Jan;7(1):33-9. Epub 2005 Nov 27.

PhD student Yong Yu

Oxidative stress and neurodegeneration

Neurodegenerative studies at CFGHD largely focus on the cell death process called apoptosis and the role that oxidative stress plays in neuronal death. The outcome of this research has direct applications for the understanding of stroke, Alzheimer's disease, Parkinson's disease and motor neurone disease.

Injury associated with stroke is often due to oxidative stress created by cerebral ischaemia-reperfusion (the process of restoring blood flow to part of the brain). Previous CFGHD studies have highlighted the importance of Akt phosphorylation in protecting against neuronal cell death following cerebral ischaemia-reperfusion. Akt phosphorylation is the chemical modification of proteins by the addition of phosphate to the enzyme Akt or protein kinase B (PKB). Ongoing research suggests that the increased susceptibility towards some types of neuronal cell death following cerebral ischaemia-reperfusion injury can be attributed in part to diminished activation of Akt. Greater understanding of these mechanisms and others behind neuronal cell death associated with oxidative stress could lead to potential targets for new treatments for stroke and other neurodegenerative conditions, including those associated with Down Syndrome.

For more information see Taylor JM et al. Diminished Akt phosphorylation in neurons lacking glutathione peroxidase-1 (Gpx1) leads to increased susceptibility to oxidative stress-induced cell death. J Neurochem. 2005 Jan;92(2):283-93.

Professor Paul Hertzog, Centre Director

Research Centres

Centre for Inflammatory Diseases

The Centre for Inflammatory Diseases joined the Institute in 2005, bringing to MIMR a team of internationally-recognised scientists specialising in a range of inflammatory diseases.

Established in 1996 to further research efforts into inflammation of the kidney (glomerulonephritis) and the joints (arthritis), the Centre for Inflammatory Diseases (CID) has undergone considerable evolution and expansion into other aspects of inflammatory disease. It now collaborates with a range of research teams in the University and hospital and became an important part of the merged entity known as MIMR in February 2005.

CID research seeks to bridge the gap between basic experimental biology and clinical research. Through the development of a treatment which enables the body's natural defences to work properly, CID scientists are making important progress in the fight against rheumatoid arthritis. They are also developing new therapies for glomerulonephritis which often occurs in association with auto-immune diseases such as lupus. Research into new therapies for liver disease caused by viral infections such as hepatitis is also underway.

Research Highlights

New approach to chronic liver disease

CID scientists, working with colleagues in the Centre for Reproduction and Development, carried out groundbreaking research that showed a reproductive hormone, follistatin, may halt the progression of chronic liver disease. Diseased liver cells produce activin, a protein implicated in the build-up of thick scar tissue which inhibits blood flow through the organ. When follistatin is introduced, it binds to the activin and effectively stops scar tissue forming. Following further testing, this breakthrough will hopefully lead to clinical trials, after which a safe and effective therapy based on follistatin could help people worldwide afflicted with liver disease.

For further information see Patella S et al. Follistatin attenuates early liver fibrosis: effects on hepatic stellate cell activation and hepatocyte apoptosis. Am J Physiol Gastrointest Liver Physiol. 2006 Jan;290(1):G137-44.

Blocking the impact of Macrophage Migration Inhibitory Factor (MIF)

Macrophage Migration Inhibitory Factor (MIF) is a natural inflammatory protein or 'cytokine' that drives inflammation and damage in diseases like rheumatoid arthritis (RA), multiple sclerosis and lupus. Development of a MIF antagonist or mechanism to block the impact of this protein is the basis of a new treatment for inflammatory disease currently under development at CID. Levels of MIF are found to be increased by corticosteroids, a common current treatment for RA. Thus MIF limits the effectiveness of the steroids. By antagonizing MIF, the CID team is seeking to increase the effectiveness of corticosteroids and reduce the dose required to achieve a required effect (steroid-sparing). As steroid side effects are dose dependent, steroid-sparing would be of immense value to patients.

For further information see Morand EF et al. MIF: a novel cytokine link between rheumatoid arthritis and atherosclerosis. Nature Reviews Drug Discovery 5:399-411, 2006.

Furthering understanding of immune response in glomerulonephritis

Glomerulonephritis (GN) is a set of renal diseases in which an immune response triggers inflammation and proliferation of glomerular tissue in the kidney. While the disease can be moderate and short lived, it is also the major worldwide cause of chronic renal disease and kidney failure. Scientists at CID are seeking to identify the immune mechanisms which regulate the disease. T helper cell subsets Th1 and Th2 appear to influence different patterns in severity of glomerular injury in GN. Particular attention has been given to determining the part played by CD80 and CD86 costimulatory molecules. Through this insight, the team is working towards the development of more potent and selective therapeutic strategies.

For further information see Odobasic D et al. CD80 and CD86 costimulatory molecules regulate crescentic glomerulonephritis by different mechanisms. Kidney Int. 2005 Aug;68(2):584-94.

Professor Stephen Holdsworth, Centre Director

Research Centres

PhD student Dr Alberta Hoi

Evolving evidence of unique leukocyte-endothelial interactions in specific organs

Leukocyte infiltration is a key event in the development of inflammation, including arthritis, glomerulonephritis, and brain disease. Application of unique intravital microscopy techniques to these diseases has enabled a description of the cellular events involved in these processes in different tissues. Glomerular and brain leukocyte trafficking emerge as unique processes, suggesting that specific interventions may be required to control inflammation in this tissues, and potentially explaining why many immune-modulating treatments active in other parts of the body fail to control brain and kidney inflammation.

For further information see Kuligowski MP, et al. Leukocyte recruitment to the inflamed glomerulus: a critical role for platelet-derived P-selectin in the absence of rolling.J Immunol. 2006 Jun 1;176(11):6991-9) AND Lister KJ et al Immune Complexes Alter Cerebral Microvessel Permeability: Roles Of Complement And Leukocyte Adhesion. Am J Physiol Heart Circ Physiol. 2006 Mar 24.

The role of resident cells in local inflammation

A major feature of inflammatory disease is the variability between disease manifestations in different organs, even in a single systemic disease. Scientists at CID focus on individual diseases and organs but also on the factors which regulate the differences between these organs. Resident cells, or the cells present in an organ that are unique to that organ (as opposed to migrating blood leukocytes), are obvious candidates to play an important role in this regulation. New work using chimeric mice (bearing different genes in tissues compared to blood) has enabled the dissection of the relative contributions of local and migrating cells to diseases such as glomerulonephritis.

For further information Timoshanko JR et al. Resident kidney cells and their involvement in glomerulonephritis. Curr Drug Targets Inflamm Allergy. 2005 Jun;4(3):353-6.

Centre for Urological Research

The Centre for Urological Research is internationally recognised for its research into better diagnostics and treatments for both prostate cancer and benign prostate disease.

Research Centres

Scientists at the Centre for Urological Research (CURe), working with mathematicians and stem cell biologists, have a range of approaches to better understand the basic biology of the prostate gland and how it is grows normally.

In humans, the disease process is investigated with clinical colleagues from Southern Health (Department of Urology). Existing diagnostic markers of prostate cancer can be inaccurate and unreliable. Based on its understanding of prostate biology, members of CURe are identifying and validating more definitive markers that could assist the urologist to determine the best form of treatment. Patient specimens and tissues are deposited in a National Prostate Cancer Tissue Bank and used to validate and test diagnostic markers of prostate cancer or BPH.

Preclinical testing of potential therapies is conducted in collaboration with international pharmaceutical companies. The commercialization of work at Cure ensures a more effective transition from the laboratory bench to the patient's bedside.

In collaboration with colleagues at the Monash Institute of Health Services Research (MISHR), members of the CURe team are also committed to educating and informing the community about the developments in prostate research. Understanding the needs of men with prostate cancer and how to inform them is essential to enable meaningful participation in the decision making processes during the course of their disease.

Research Highlights

Measuring early origins of prostate disease

Events that occur during prostate development can lead to permanent changes in prostate structure and function, and are a factor in the onset of prostate disease in later life. In order to examine and measure these changes, CURe scientists developed a unique modelling system for use with neonatal mice. The system combines the latest imaging and computerised technology, and will underpin understanding of hormonal regulation of prostate disease.

Almahbobi G et al. Computer-based detection of neonatal changes to branching morphogenesis reveals different mechanisms of and predicts prostate enlargement in mice haplo-insufficient for bone morphogenetic protein 4.J Pathol. 2005 May;206(1):52-61.

Professor Gail Risbridger, Centre Director

Hormones and aberrant prostate growth

Hormones are critical for normal development of all parts of the reproductive system. As men age, hormone levels change and it is thought that an imbalance in hormones could be a factor in both benign and malignant prostate growth. Androgens, such as testosterone, have been known to be a factor in abnormal prostate growth; however, they do not work alone. Estrogens are also critical, and have been shown to induce proliferative or antiproliferative responses in the prostate. Recent studies have focused on the role of estrogen receptors and selective estrogen receptor modulators (SERMs) in order to understand this varying role of estrogen. CURe is currently working with industry to develop new treatments based on these discoveries, and SERMs will undoubtedly form the basis for future treatments for prostate disease.

For further information see Taylor RA et al "17beta-estradiol induces apoptosis in the developing rodent prostate independently of ERalpha or ERbeta" .Endocrinology. 2006 Jan;147(1):191-200. Epub 2005 Oct 13.

Identification of new growth factor regulator

Through increased understanding of the role that proteins, particularly Beta-C activin, play in cell growth and programmed cell death in tissues throughout the human body, CURe scientists are seeking to identify new approaches to the management of cancer and other diseases of abnormal growth such as prostate disease. This MIMR team has shown that activin C levels are increased in cancer cells in the ovaries, testes, liver, kidneys and lungs, and is currently working towards further evidence that beta-C-activin is an important growth regulator. The full extent of the importance of this protein in developmental biology and cancer is under intense review with a view to using beta-C-activin as a new therapeutic target in diseases of abnormal growth.

For further information see Gold EJ et al. " betaA- and betaC-activin, follistatin, activin receptor mRNA and betaC-activin peptide expression during rat liver regeneration." J Mol Endocrinol. 2005 Apr;34(2):505-15.

Informing men of developments in prostate cancer research

Keeping the community informed of developments in prostate cancer research is vital. Preparing the community for what lies ahead will assist with the appropriate uptake of innovative diagnostics and treatments. CURe, in conjunction with MIHSR, is committed to providing accurate and relevant information to men, and is investigating the best means of delivering this information in order to generate "informed men".

For further information see Ilic D, et al Searching the Internet for information on prostate cancer screening: an assessment of quality. Urology. 2004 Jul;64(1):112-6.

Centre for Women's Health Research

The Centre for Women's Health Research joined MIMR in 2005, formalizing the relationship between Monash University's Department of Obstetrics and Gynaecology with the Institute.

Research Centres

Research Assistant Rachel Zillwood

The creation of MIMR in February 2005 formalized this relationship and the Centre for Women's Health Research became an integral part of this expanded research institute.

Interfacing on a daily basis with staff and patients in Monash Medical Centre's Maternity and Neonatal wards, the research team has direct access to, and appreciation of, the very real and debilitating health problems impacting the quality of life of women in the local community. Doctors can approach scientists with treatment problems and issues, and scientists can undertake laboratory-based research to enhance clinicians' understanding of diseases.

Female-specific health issues under investigation include endometriosis, uterine fibroids, pelvic prolapse and ovarian and breast cancer. Maternal-fetal medicine experts are also breaking new ground in understanding miscarriages and stillbirths and the research possibilities of placental stem cells.

Associate Professor Peter Rogers, Centre Director

Research Highlights

Angiogenesis and endometriosis

Growing new blood vessels (angiogenesis) is a principal function of the female reproductive system. Endometrial cells produce and shed new blood vessels each month as part of the menstrual cycle. In endometriosis, these cells implant outside the uterus on the surface of the ovaries, bowel and bladder and bleed directly into the pelvic cavity, causing pain and infertility. Understanding and controlling angiogenic processes could hold the key to new and improved treatments for this debilitating condition and other problems in the female reproductive tract such as cancer and fibroids. Hormones appear to play an important role; both estrogen and progesterone can promote as well as inhibit endometrial angiogenesis. Recent work has also identified the hormone relaxin as a player in the regulation of endometrial angiogenesis.

For further information see Bond CP et al. Increased expression of the relaxin receptor (LGR7) in human endometrium during the secretory phase of the menstrual cycle. Ann N Y Acad Sci. 2005 May;1041:136-43.

Stem cells in the uterus

Adult stem cells are rare cells which maintain the tissue in which they reside. They have been identified in diverse tissues, including human bone marrow, breast, prostate, brain and liver. As the endometrium is a highly proliferative, cyclically regenerating tissue scientists at the CWHR hypothesised that the lining of the uterus could also be a source of adult stem cells. Over the past few years, this team has made a number of important developments in this field, initially identifying a small population of epithelial cells and stromal cells that exhibit stem/progenitor cell behaviour. These cells were reviewed at different stages of the menstrual cycle and shown not to demonstrate any variation in their clonogenic activity. This showed for the first time that inactive endometrium contains clonogenic epithelial and stromal cells, an important indicator of the presence adult stem cells. At the meeting of the European Society of Human Reproduction and Embryology (ESHRE) in Copenhagen in June 2005, the CWHR gained international attention and acclaim when they announced the identification of mesenchymal stem cells in the uterus. Publications on this will be forthcoming in 2006.

For further information see Schwab KE et al. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. Fertil Steril. 2005 Oct;84 Suppl 2:1124-30.

Fibroids

Uterine fibroids are benign tumors that cause menorrhagia, pain and infertility. Existing medications can sometimes shrink but not cure fibroids. Hysterectomy is the only absolute solution. Further understanding of this condition is urgently needed. Scientists and clinicians are working together at the CWHR to understand the various factors that influence the development of fibroids. A recent study demonstrated a significant difference in the tissue surrounding fibroids in post-menopausal women. Myometrial microvascular density increases markedly after menopause, while fibroid microvascular density did not alter. Understanding the impact of menopause on the disease has implications for treatment, and also provides valuable insight into this condition.

For further information see Weston GC et al. Differences between the pre-menopausal and post-menopausal uterine fibroid vasculature. Maturitas. 2005 Aug 16;51(4):343-8.

Reducing the chance of miscarriage

Cerebral palsy may be caused by a number of different problems arising either during pregnancy, during birth or during the early days after birth. One of the most important causes of cerebral palsy is infection. However, it is not precisely clear by what mechanisms infection causes the damage that leads to irreversible cerebral palsy. Recent CWHR studies have investigated the function of a pathway (the kynurenine pathway) in the placenta that metabolizes tryptophan to form neuroactive substances such as quinolinic acid. These neuroactive metabolites have been previously implicated in neuro-inflammatory disorders such as AIDS, dementia and Alzheimer's disease. The research undertaken at CWHR has shown that in pregnancy infection switches on the pathway in the placenta, releasing quinolinic acid and other metabolites into the fetal circulation. Further research is underway to explore whether these heightended levels of metabolites then cause cerebral damage leading to cerebral palsy and may lead to the development of new neuroprotective therapies.

Manuelpillai U et al. Identification of kynurenine pathway enzyme mRNAs and metabolites in human placentae: Up-regulation by inflammatory stimuli and with clinical infection. Am J Obstet Gynecol. 2005; 192: 280-8.

Research Centres

Monash Institute of Health Services Research

During 2005, MIMR entered into a formal agreement with the Monash Institute of Health Services Research for a closer working relationship.

The Monash Institute of Health Services Research (MIHSR) undertakes research, education and advocacy in the areas of clinical management, health services delivery and health policy. Six centres form MIHSR:

- The Australasian Cochrane Centre, part of the renowned Cochrane Collaboration, undertakes systematic reviews of the effects of health care interventions, as an authoritative information resource for researchers and clinicians.
- The Centre for Clinical Effectiveness (CCE) seeks to identify best practice and facilitate positive practice change. It systematically appraises and prepares reports on research evidence relevant to clinical questions.
- Health Informatics conducts courses to assist health professionals use and maximise information to enhance healthcare delivery.
- Monash Ageing Research Centre (MONARC) encompasses Southern Health's aged care program and Monash University's research into ageing.
- Jean Hailes Research Centre is part of the Jean Hailes Foundation working towards meeting the healthcare needs of women.
- The Centre for Gender in Medicine provides a unique gender-based perspective throughout Monash University's medical curriculum.

Research Highlights

Informed choice on whether to screen for prostate cancer

The pros and cons of using prostate cancer screening have been heavily debated in medical circles, so how can the average man make an informed choice as to whether he should have a PSA blood test? In conjunction with MIMR's CURe team, MIHSR have trialed a number of resources with volunteers to determine what type of information is preferred and how it affects decision making ability. This study followed on from earlier work which found that information on this topic on the internet was of variable quality and reflected the lack of clear consensus on this subject.

For further information see Ilic D, et al Searching the Internet for information on prostate cancer screening: an assessment of quality. Urology. 2004 Jul;64(1):112-6.

Cochrane Colloquium comes down under

The Australasian Cochrane Centre was proud to host the Cochrane Colloquium, annual international meeting of the Cochrane Collaboration, in October 2005. With 'corroboree' as the meeting's theme, clinicians, policy-makers, researchers and consumers with an interest in generating and using evidence to inform decision making met for three days in Melbourne. Keynote speakers from all over the world discussed how the Collaboration is responding to the challenge of producing reviews that are both relevant and widely used, and highlighted the new direction the Collaboration is exploring.

For further information visit: www.colloquium.info/2005/

Health for Kids in the South East

Health for Kids in the South East is a highly successful CCE program at MIHSR dedicated to improving health outcomes for children through the implementation of best practices determined through on evidence-based practices and partnerships. Input has been sought from a range of stakeholders with a key interest in improving children's health: the Consumer Participation Program enables parents and carers to provide a consumer perspective in the development of new services and clinical processes, and the Health for Kids Network recognizes the value of GPs involvement in developing a Children's Program protocols. A range of innovative new services and evidence based guidelines and clinical paths have been developed which aim to manage children's health in the best way possible.

For further information visit: www.mihsr.monash.org/hfk/index.html

Professor Don Campbell, Director, Monash Institute of Health Services Research