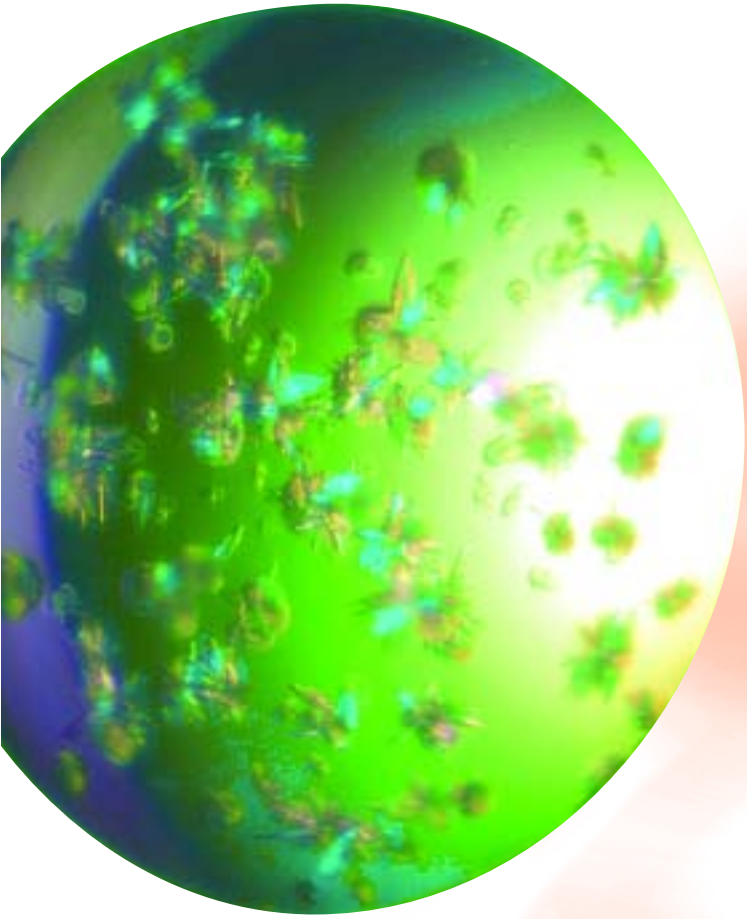
SVI
ST VINCENT'S INSTITUTE
~ continuous discovery

St Vincent's Institute
Annual Report 2004



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'Continuous Discovery'

At St Vincent's Institute we believe that medicine is constantly evolving to improve human longevity, health and well-being. Our curiosity and resources are directed towards these challenges.

SVI research is focused on exploring both disease cause and prevention, with a commitment to discovering practical and far-reaching solutions to diseases that impact on the everyday life of people around the world. SVI conducts programs of basic and clinical research into diseases that have a high impact on the community.

The Institute is a world centre of excellence for medical research in the following areas:

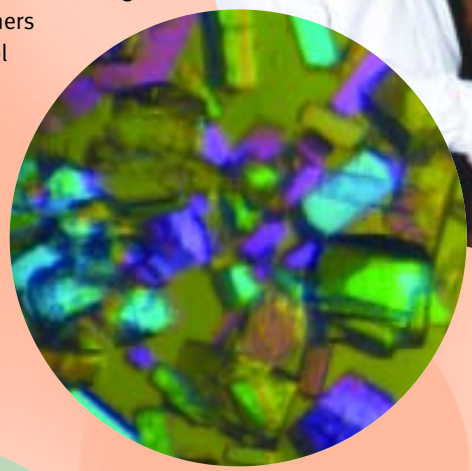
- Juvenile diabetes
- Metabolism - obesity and cardiovascular disease
- Bone diseases such as arthritis and osteoporosis
- Cancers (breast, lung and prostate) that spread to bone
- Structural Biology - 3D study of proteins at the atomic level
- Protein Chemistry - studying the end product of the cell's genetic message
- Virology - infection by AIDS and hepatitis viruses
- Neurological diseases including Alzheimer's disease and epilepsy

SVI is an independent research body, which is affiliated with St Vincent's Health and the University of Melbourne. Through these links its research programs provide a valuable service to clinical medicine, graduate education and community welfare. SVI hosts the National Serology Reference Laboratory and is a member of Bio 21, the Victorian Breast Cancer Research Consortium, St Vincent's Diabetes Centre of Excellence and the Association of Australian Medical Research Institutes. It is a member institution of Australia-wide health care facilities of the Sisters of Charity.

Major Prizes and Awards

2004 GE Healthcare Biosciences Medal

At the 2004 Australian Society of Biochemistry and Molecular Biology conference in Perth Professor Michael Parker, Head of the Institute's Biota Structural Biology Laboratory, was presented with the GE Healthcare Biosciences Medal for 2004. This award recognises Michael's achievements in solving the structures of a large number of proteins through the use of protein crystallography. His leadership has been important in the successes of the Institute in the field of structural biology and the award recognises him as being in the very top rung of protein crystallographers internationally. As part of the award, Michael will travel within Australia and New Zealand to lecture on his work.



Professor Michael Parker receiving the ASBMB GE Healthcare Bio-Sciences Award from Mr Peter Leonard.

A/Professor Matthew Gillepsie, Dr. Natalie Sims, Professor Jack Martin and A/Professor Kong Wah Ng.

NHMRC Program Grant success

The Institute's Bone, Joint and Cancer Group was one of 20 Australian research teams to receive a National Health and Medical Research Council (NHMRC) Program Grant in 2004. Chief Investigators Emeritus Professor TJ (Jack) Martin and A/Prof Matthew Gillespie, together with A/Prof Kong Wah Ng (Endocrinology and Diabetes) and Dr Natalie Sims (Department of Medicine) were awarded $5,263,070 over 5 years to study the regulation of bone resorption and formation in health and disease. This Program addresses how bone is formed and broken down, and aims to determine the hormones, growth factors and cytokines that regulate these processes. Disruption of bone formation/resorption, which is a tightly regulated process, leads to osteoporosis. Cancers of bone or those that are particularly prone to spread to bone (breast and prostate), also disrupt this process resulting in considerable morbidity and mortality. The research team aims to develop new therapies that can modify the process of bone formation, as well as therapies that can affect the growth of tumours in bone.

Clive and Vera Ramaciotti Foundation

Emeritus Professor TJ (Jack) Martin received the Clive and Vera Ramaciotti Medal for Excellence in Biomedical Research (2004). This award honours a person who has made an outstanding discovery in clinical or experimental biomedical research. The award relates principally to Jack's discovery of a protein (PTH-related protein) produced by cancers that has a powerful influence on the spread of cancers to bone. Jack also developed concepts of how osteoporosis develops, and why certain cancers spread especially to bone - particularly cancers of the breast and prostate. His discoveries have been important in generating new approaches to the prevention and treatment of these common bone cancers. Jack was awarded a medal and $20,000.

SVI Student success

It was an outstanding year for several of the students at SVI in 2004. Mr Geoffrey Kong, a PhD student in the Biota Structural Biology Laboratory received a Student Presentation Award at the 28th Annual Conference of the Australian Society for Biophysics. He presented his studies on the structure of an Alzheimer's disease protein. Geoffrey was also awarded a Ludo Frevel Crystallography Scholarship for his PhD studies. Dr Frances Milat was awarded a Medical Postgraduate Scholarship from the NHMRC and a scholarship from the Royal Australasian College of Physicians for her PhD studies in the Bone, Joint and Cancer Group. Frances was appointed as the Albert Maggs Scholar, supported by the generous bequest of Albert Maggs, a long time supporter of the Institute. A number of SVI students were also awarded presentation prizes at the Lorne Conference (Ms Carolyn McNees) and the SVH Research Week (Ms Eveline Angstetra, Ms Lorien Parker and Ms Carolyn McNees).

Mr Geoffrey Kong received a Student Presentation Award at the 28th Annual Conference of the Australian Society for Biophysics.

Research highlights

Predicting heart disease

Lowering heart disease is one of the success stories of medical research. By reducing the number who smoke, and have high blood pressure and high cholesterol, people are living longer before they develop heart disease, and are more likely to survive heart disease. However, one consequence of people surviving heart disease and living longer is that more are developing heart failure. Heart failure affects one in five people during their lifetime, usually over the age of 70. It is a lethal condition, worse than most cancers, and a major contributor to health care costs.

Research done in the Molecular Cardiology group aims to discover ways to prevent heart failure. To prevent heart failure it is important to understand why it occurs, and we embarked on a research program to discover why some develop heart failure while others do not. Essential to this research is a means to identify people who are at increased risk of heart failure, to study what is different about their hearts that leads to heart failure. In collaboration with researchers at the George Institute of International Health in Sydney, we measured chemicals in the blood of several thousand people who had had a stroke and were monitored for up to 5 years. We found that people more likely to develop heart failure had increased amounts of two different chemicals in their blood (NT-proBNP and CRP). By measuring these chemicals people at risk of heart failure can be identified up to five years before they develop heart failure. This new information will greatly assist research to discover why heart failure occurs, and the search for new strategies to prevent and treat heart failure.

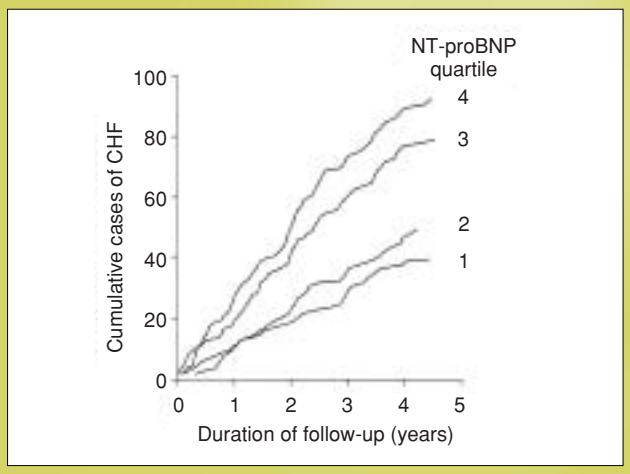


Figure. People with high blood levels of NT-proBNPwere more likely to develop heart failure (groups 3 and 4) than people with lower levels (groups 1 and 2).

New drugs to improve memory

Alzheimer's disease is the commonest cause of dementia and affects more than 15 million people world-wide. This number will increase as populations age with nearly 50% of people affected over 85 years of age. Current drug therapies are unsatisfactory since they exhibit modest efficacy, frequent side effects and do not stop the process of neurodegeneration. In addition, other causes of cognitive impairment include perinatal brain injury, cerebrovascular disease, post cardiac surgery, hypotension, anoxia, traumatic brain injury and other neurodegenerative diseases. Overall brain impairment is estimated to affect 6.5-7.9% of the US population. Our collaborators at the Howard Florey Institute (Siew Yeen Chai, Anthony Albiston and Fred Mendelsohn) have discovered a protein receptor in the brain called the AT4 receptor that plays a role in memory. Peptides that bind to AT4 receptor show a dramatic enhancement of memory and learning in rodents. These peptides, however, are not suitable for developing into drugs. The Structural Biology Laboratory has modeled the three-dimensional structure of the AT4 receptor and searched for drug-like molecules that might bind to the receptor using powerful computers. We have discovered a novel class of compounds that bind to the AT4 receptor and improve memory in rats. We are currently in discussions with Pharmaceutical companies to progress our exciting findings.

Molecular model of the catalytic site of IRAP.

New ways to replace bone when it is lost

Bone is continually being formed and broken down throughout life as a result of the activity of two main groups of cells within bone. The osteoblasts make new bone and osteoclasts remove it through a process known as resorption. Balance between these two cell types is essential to maintain the normal structure of the skeleton. If bone resorption exceeds formation, bone density decreases, resulting in osteoporosis and an increased risk of fracture. Research of the Bone, Joint and Cancer group over some years has shown that osteoblasts produce many proteins and other factors that influence the formation and activity of osteoclasts.

The new and important information from the bone research group at SVI is that active osteoclasts also produce a substance that acts directly on the osteoblastic cells to enhance bone formation. This is an important part of the mechanism by which new therapies can restore bone density in patients with severe osteoporosis. This information will also influence how treatments are chosen to inhibit bone breakdown in patients at risk of osteoporosis.

Below: High resolution 3-dimensional image of a piece of bone showing the internal structure which is regulated by osteoblasts and osteoclasts.

Combined Report from the Chair and Director of St Vincent's Institute

Highlights of the Institute's busy year in 2004 included the official opening of our new research laboratories, the launch of the St Vincent's Institute Foundation, the visit of the Federal Minister for Health and Ageing, and the award of an NHMRC Program Grant to our bone researchers. We are extremely grateful for the continuing support of the Institute's Board of Directors and the new Board of Directors of the St Vincent's Institute Foundation.

The Institute's new building was opened on April 2 2004 by the Victorian Treasurer and Minister for Innovation, the Hon John Brumby and Senator Julian McGauran and blessed by the Archbishop of Melbourne, the Very Reverend Dennis Hart. Many friends and colleagues from the Hospital, the University of Melbourne and other research institutes joined us for the opening and many later toured the building. The opening attracted extensive media coverage.

On the following day the St Vincent's Institute Foundation was launched with a gala dinner at the Park Hyatt. This was a very successful and glamorous event and being the first such function we have organised will be even better in the future. We are very grateful for the generous support from the major sponsor for the evening Deutsche Bank, and the other sponsors, Salta Properties, Zagame's, the Portsea Hotel and Dansu Constructions. The launch of the Foundation is a very significant step for the Institute and we thank all who have supported its activities. One of the Institute's main challenges is living from competitive research grants that constitute over two-thirds of our income. With the Foundation's assistance it will be possible to turn the scientific success and outstanding reputation of the Institute into greater financial stability, strength, and flexibility. Our priorities are to fund leading edge equipment and shared facilities and to support the careers of scientists, from their time as students through recruitment as laboratory heads and through occasional lean periods that are almost inevitable in the highly competitive grants system. Because of government funding we do not need to use any of the funds donated for administration. The Foundation has Directors with skills in many areas including finance, marketing and communications but most importantly has people with great passion for medical research at St Vincent's Institute and a great willingness to help. This really is a major step forward for the Institute. We are very proud to have Susan Alberti AM as Chairman of the Foundation and John Ralph AC as Patron.

Foundation activities apart from the launch have included a continuing series of Directors' Dinners, a movie night and other functions. One of the Dinners was held in conjunction with Deutsche Bank when we heard an analysis of the US Presidential Election by ex-White House staffer Dr Phillipa Malmgren. A particular initiative of the Foundation over the past year has been to support PhD students. This is an onerous period of any scientist's career and financial support for the three recipients of these funds will be very welcome indeed. SVI, the University of Melbourne Departments and the Hospital are working hard to ensure the St. Vincent's Campus is an outstanding location, attractive to PhD students.

Although unable to attend the launch of the Foundation, the Federal Minister for Health and Ageing, the Hon. Tony Abbott MP, visited soon after and was shown around our new laboratories. He was particularly interested in work being carried out to use computer-assisted drug design to identify drugs that may be able to block the effects on bone of parathyroid hormone-related protein, that is made by many cancers including breast cancers. We received a grant of $500,000 from the Federal Department of Health and Ageing to further develop this work. Other major grants in 2004 came from the Victorian Government Science Technology Innovation initiative through the Bio21 cluster.

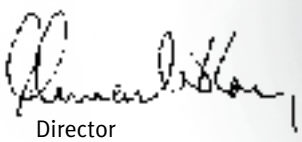
These included grants for cell therapies including pancreatic islet transplantation, protein crystallography and our new transgenic mouse facility. All of these grants were awarded to SVI in conjunction with collaborating institutes nearby and reinforce the importance of consortia in building major research facilities. The mouse facility for example is a project led by St. Vincent's Health. It is the next major part of our redevelopment following on from our new laboratories. It will house over 20,000 mice in state-of-the-art facilities designed to prevent spreading of any outbreaks of infection that can have devastating effects if unchecked.

Success in the National Health and Medical Research Council's grants remains an important benchmark. This year our major success came from the Bone, Joint and Cancer Group. The Head of the group, Matthew Gillespie, was promoted to Principal Research Fellow, a very substantial and richly deserved achievement. Matthew as well as being a leading international researcher into bone biology plays a leadership role in advocacy for Australian medical research being a past-president of the Australian Society for Medical Research and a current Director of Research Australia. The bone group as a whole received a 5 year Program Grant worth $5,263,070, which was awarded to Jack Martin, Matthew Gillespie, Natalie Sims and Kong Wah Ng as chief investigators. This takes to three the number of Programs represented in the Institute. Other noteworthy awards from NHMRC went to Dr Helen Thomas (RD Wright Career Development Award) and Peter Doherty Training Fellowships to Julian Adams, Andrew Carey and Ana Traven.

The Structural Biology Group led by Michael Parker continues to play a flagship role in our activities and it was tremendous to see external recognition of their excellence through the award of the 2004 GE Healthcare Bio-sciences Medal from the Australian Society of Biochemistry and Molecular Biology to Michael. This award includes a travelling Lectureship to present his work throughout Australia and New Zealand. Other members of the group to excel in 2004 included PhD students Geoffrey Kong and Lorien Parker who both received prizes for presentations during the year. SVI is well positioned for the "post-genome" era of medical research because of its strength in key technologies used to understand the function of proteins, particularly structural biology and protein chemistry. SVI was the first medical research institute in Australia to house protein crystallography and this technology remains at the very heart of our activities and competitive advantage. The central thrust of our scientific direction is to integrate these powerful enabling technologies with directed research into diseases that are common in our community including cancer, dementia, diabetes, osteoporosis, arthritis and others. Tackling common health problems in the community with leading-edge technology is our focus – and this was emphasized in the annual SVI Forum in 2004 when the overwhelming community problem of obesity was addressed. Bruce Kemp, Head of SVI's Protein Research Group, gave a basic science perspective while leading nutritionist Garry Egger talked from a public health perspective and athletics legend Herb Elliott gave a community based perspective. Consortia of cross-discipline approaches are a powerful way of tackling difficult problems.

While we have highlighted the Foundation's activities in 2004 there has been tremendous continuing support from the Board of the Institute and their wise counsel particularly on financial and commercial matters has been absolutely invaluable. Finally many of you will know that I have been away on sabbatical leave in Cambridge UK in the second half of 2004. This was a tremendous scientific experience in an international hub of activity in diabetes research and medical research more generally. I owe an enormous debt to Matt Gillespie, Michael Parker and all the administrative team as well as the Board of the Institute for giving me this terrific opportunity.

Chair
BM Shanahan



Director
TWH Kay

Members of the Board

Ms Brenda M Shanahan
Chair, St Vincent's Institute

Ms Shanahan has a research background in finance in Australian and overseas economies and share markets. She is Chair of St. Vincent's Health, and is a Board member of Challenger Financial Services Group and JM Financial Group Ltd. She is a former member of the Australian Stock Exchange and former Executive Director of a stockbroking firm, a fund management company and an actuarial company.

Ms Susan M Alberti AM

Ms Alberti is co-founder and Managing Director of DANSU Constructions Pty Ltd and associated companies. She has a strong commitment to fund raising and promotion of research into juvenile diabetes, and is the National President of the Juvenile Diabetes Research Foundation Australia. She is also Chair of the St Vincent's Institute Foundation.

Professor James D Best

Professor Best is Professor and Head of The University of Melbourne Department of Medicine, St. Vincent's Hospital, Melbourne. He is a Director of the SCHS Melbourne Region Board (St. Vincent's Health) and Deputy Dean of the Faculty of Medicine, Dentistry and Health Sciences at The University of Melbourne.

Sr Mary Fankhauser

Sister Fankhauser has a background in healthcare, having worked as a nurse in a wide variety of clinical and administrative positions in both the private and public sectors of St. Vincent's Health.

Mr Douglas A Wright
Deputy Chair, St Vincent's Institute

Mr Wright is a Founder and Managing Director of Wrights, an Australian-owned creative communications consultancy. He is a public affairs strategist, and has worked in the media and business in Australia and Europe. He is Chairman of the Victorian Government's Small Business Advisory Council. Mr Wright is a Member of the Public Relations Institute of Australia, the Counsellors' Academy of the Public Relations Society of America, and an Associate Member of the Australian Marketing Institute and Institute of Public Relations (UK).

Professor James A Angus

Professor Angus is Dean, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne. He is a member of the Bio21 Institute Management Committee and First Vice-President of the International Union of Pharmacology. He has extensive research experience in preclinical pharmacology in the areas of cardiovascular and antinociceptive drugs.

Mr Jeff Clifton

Mr Clifton is the Executive Chairman of Farsands Corporation Limited and Managing Director of the Clifton Coney Group, a fully owned subsidiary of Farsands Corporation. Farsands provides property solutions, environmental solutions and risk solutions to the property industry in Australia and overseas. He has over 35 years experience in the property industry.

Ms Nicole Feely

Ms Feely is the Chief Executive Officer, St. Vincent's Health and has a background in business law, politics and administration in both the private and public sectors.

Mr Charles A Griss

Mr Griss is a former Senior Executive of ANZ Banking Group Ltd and former Managing Director of Esanda Finance Corporation Ltd. He is a Director of the SCHS Melbourne Region Board (St. Vincent's Health), and Chairman of both the Quality of Safety Committee and Community Advisory Committee for the SCHS Melbourne Region Board. He is Chairman of the Audit & Compliance Committee of the Rio Tinto Staff Superannuation Fund.

Professor Thomas WH Kay

Professor Kay is Director of St Vincent's Institute. He holds a Professorial appointment within the Department of Medicine (St Vincent's Hospital), and The University of Melbourne, and is an Honorary Endocrinologist at SVHM. Professor Kay's research interests are in the area of autoimmunity, particularly of type 1 (juvenile) diabetes.

Mr Gregory Robinson

Mr Robinson joined BHP in February 2001 as Chief Financial Officer, BHP Petroleum. He was appointed Chief Finance Officer and Chief Development Officer Energy in March 2004. He is a former Director, Investment Banking Group, Merrill Lynch & Co, and Resources Research Analyst, McCaughan Dyson Limited.

Mr John Pizzey

Mr Pizzey retired in December 2003 as Executive Vice President of Alcoa Inc. (USA) and Group President, primary products. He was Chairman of the International Aluminium Institute Ltd. (UK), 2002 and 2003, and Chairman of the London Metal Exchange Ltd. (UK) in 2003. He is Director of ION Limited (in administration) appointed in October 1999 and Chairman, appointed in January 2004. He is Chairman of Range River Gold Limited, and is a Director of Amcor Limited and WMC Resources Ltd. John is also a member of the Board of Governors of Ivanhoe Grammar school.

Mr Barry J Jackson

Mr Jackson is a Director of Paperlinx Ltd, Alesco Corporation Ltd, Equity Trustees Ltd and CSR Ltd. He was formerly Managing Director of Pacifica Group Ltd (1995-2001) and has over 30 years experience in manufacturing and industrial marketing.

Ms Ruth O'Shannassy

Ms O'Shannassy worked in economic research in the finance industry in Melbourne before moving overseas. She spent seven years living and working offshore, primarily as a stockbroker in London and Asia before returning to Australia.

Mr Ian D Reid

Mr Reid comes from a manufacturing and industry background. He is a Director of Advanced Riverina Holdings and a Board Member of the Melbourne Anglican Foundation.

A brief history of SVI

- **Founded as an initiative of the Congregation of the Sisters of Charity and St. Vincent's Hospital.**
- **Established by the John Holt Medical Research Endowment - a perpetual charitable trust fund.**
- **Dr Pehr Edman, one of the world's leading biochemists, took up his appointment as the John Holt Director of Research in May 1957.**
- **Officially opened as St Vincent's School of Medical Research on 23 April 1958.**

Jack Holt

St Vincent's Institute has a long record of breakthrough discoveries with an impact on clinical medicine:

- Automating amino acid sequences, including Edman's development of the world's first automatic protein sequencer allowing the determination of the order of amino acids in proteins. This discovery laid the groundwork for the current understanding of how genes provide the code for protein synthesis, the role of protein abnormalities in causing disease, and the use of proteins like insulin, growth hormone and calcitonin as drugs. The Institute has been described as the birthplace of proteomics, one of the key components of medical research in the 21st century.
- Calcium and cancer. Emeritus Professor Jack Martin and his team discovered parathyroid hormone-related protein (PTHrP), a hormone secreted by cancers that damages the skeleton, causes excessive levels of calcium in the blood and contributes to the spread of cancer to bones. This discovery established the cause of a common complication of cancer and led to its accurate diagnosis. Anti-PTHrP drugs are now in advanced clinical trials based on the Institute's research.
- Protein kinases as drug targets. Professor Bruce Kemp has made pivotal discoveries about protein kinases, proteins that carry messages that determine many aspects of the function and behaviour of cells. Most recently Bruce has studied a protein kinase that determines how the body balances food input and use, relevant to obesity, exercise and cardiovascular disease. The pharmaceutical industry has the protein kinases as one of its three top targets for drug development.

Public Relations and Fundraising

Official opening of our new research building - 2nd April 2004

On 2 April 2004 St Vincent's Institute unveiled its new world class medical research building after a $10.5 million addition to and refurbishment of existing facilities. Following a blessing by the Most Reverend Denis J Hart, Archbishop of Melbourne, the building was officially opened by The Hon. John Brumby MP, Treasurer and Minister for Innovation, and Senator Julian McGauran, representing the Hon. Tony Abbott MP, Minister for Health and Ageing.

Gala Dinner

The SVI Foundation was officially launched at a Gala Dinner at The Park Hyatt on 3rd April 2004 with over 400 supporters and guests in attendance. The dinner was sponsored by Deutsche Bank AG (major sponsor); DANSU Corporation, Salta Properties, Portsea Hotel and Zagame's Hotels.

Sue Alberti AM, SVI Foundation Chair, and Brenda Shanahan, SVI Board Chair and Foundation Member, welcomed guests. Tom Kay, Director, presented an overview of the Institute's research and introduced Institute scientists present at the dinner. Mr John Ralph AC, Foundation Patron, talked of his tremendous admiration for the important work being undertaken at SVI. Felicity Kennett donated her services as MC and guests were treated to a stunning performance by Marina Prior.

The night proved extremely successful, raising over $320,000 and introducing 66 new members to the SVI 1000 Club. Thanks to everyone involved, particularly all those who have pledged their support to help in the journey of continuous discovery in medical research.

Deutsche Bank

SALTA DANSU Zagames

Above: Ms Sue Alberti AM, Prof Tom Kay, The Hon. Tony Abbott MP, Ms Brenda Shanahan and Mr Doug Wright

Visit by Federal Minister for Health and Ageing, The Hon. Tony Abbott MP

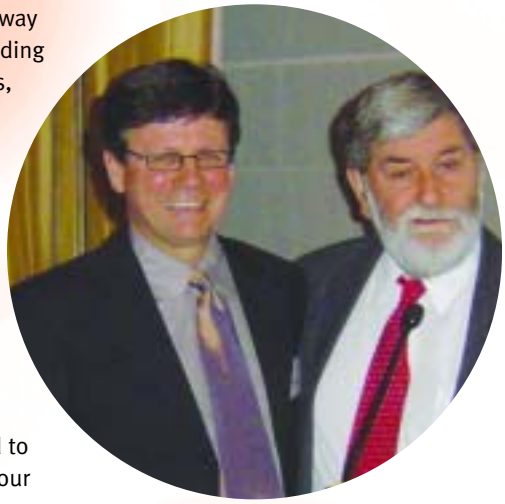
The Hon. Tony Abbott, Federal Minister for Health and Ageing, visited the Institute on 17th May, having been unable to attend the official opening in April.

Following a brief presentation, the Minister was given a guided tour of the new building and introduced to some of SVI's current research. The visit provided a great opportunity to showcase the Institute's research and discuss issues concerning medical research in Australia.

2004 Director's Dinners

The highly successful Director's Dinners series continued during 2004. These Dinners are a relaxed and informal way of introducing the work of SVI to guests as well as providing an excellent opportunity to hear distinguished speakers, including:

Joey Borensztajn, Partner, Arnold Bloch Leibler
David Smorgon OAM
The Hon Dr Barry Jones AO
Julian Burnside QC
Launa Inman, Managing Director, Officeworks
Lois Appleby, Chief Executive Officer, Tourism Victoria
The Hon Phillipa Malmgren,
President, Canonbury Group, London.
– Dinner hosted by SVI & Deutsche Bank AG



Thanks to Crown Towers for their continued support and to all our guest speakers for kindly donating their time to our cause.

PMB Committee

SVI was thrilled to receive a cheque for $120,000 from Carolyn Stubbs (President) on behalf of the women of the PMB (Private Mens' Business) Prostate Cancer Research Fundraising Committee.

These funds will enable Dr John Price and his team to evaluate the effects drugs have on the spread of prostate cancer. These experiments are fundamental in determining the potential clinical performance of a drug.

We extend our thanks to the hard working members of the PMB Committee whose commitment to the research of prostate cancer is to be highly commended.

Above:
Carolyn Stubbs
PMB President, Dr John Price *SVI*,
Christine Tarascio *PMB Vice-President & SVI Foundation Member* and Sue Alberti AM *Chair SVI Foundation.*

Palace Cinemas

Mr Antonio Zeccola, Founder and Managing Director of Palace Cinemas-Films, has become a Trustee Donor of SVI by committing to donate five Palace Films for promotion as fundraising events. The first film promotion event "SHREK 2", a DreamWorks SKG Film distributed through Palace Cinemas, was well attended with net proceeds donated to SVI.

We are grateful to Antonio and look forward to working with the team at Palace to ensure the success of this project.

SVI Support Group

The SVI Support Group, a dedicated committee led by Claire O'Callaghan, is a wonderful example of community support for medical research.

The group's fundraising dinner at the Melbourne Club in October 2004 was a great success, raising the Institute's profile throughout the wider community and much needed funds through tickets sales, a raffle and some very special donations.

The Group consistently supports Institute fundraising functions providing physical and financial assistance, and encouraging guests to attend and contribute also. The ongoing support we receive from the SVI Support Group is greatly appreciated.

YERING Station

Yering Station

Yering Station provided their outstanding wines for our Christmas Promotion for the fourth year in a row, with a very successful outcome for SVI. Yering Station has recently been awarded International Winemaker of the Year; Australian Producer of the Year; Best Pinot Noir Trophy for 2002 Yering Station Reserve Pinot Noir and a further six medals from six entries.

We were fortunate to have the Yering Station Chief Winemaker, Tom Carson, as a special guest speaker at our SVI 1000 Club Cocktail Party.

We are very grateful to everyone at Yering Station for their continued support of the Institute.

St Vincent's Institute Foundation

Report from Chair of SVI Foundation

The solitary goal of the SVI Foundation is to raise funds to provide the financial viability necessary to ensure that the Institute can sustain its record of continuous discovery at the cutting edge of medical research.

This goal can be best achieved by creating and building awareness of SVI and of the vital research conducted by the Institute. Education of the community as to the impact on us all of the diseases under study emphasizes the need for the funding of further research into disease treatment and prevention.

In spite of its enviable reputation in the global medical research community, SVI has a relatively low awareness in the Victorian and Australian community. The Foundation has tackled this issue in 2004 with abundant enthusiasm and significant inroads have been made.

Ultimately financial support and research strength lies in building and growing relationships between the SVI and its key stakeholders in the wider Australian community. The contents of the Annual Report are testimony to the width and breadth of the activities undertaken in 2004 to build such relationships.

In its first full year of operation the SVI Foundation raised $936,000 to support a future of continuous discovery by SVI. I wish to thank all those who contributed in time, effort and donation to creating a healthier Australia in the future through their support of SVI.

Ms Sue Alberti, AM
Chair, St Vincent's Institute Foundation

Mr Robin Berry
Deputy Chair, St Vincent's Institute Foundation

Mr Berry has a background in the apparel and footwear industry. He was managing director of Adidas Australia for 12 years (1991-2003), and has over 25 years experience in marketing, manufacturing and importing of branded sports and leisure products. He is a partner of a business designing and marketing branded surf apparel, footwear and hardware products.

Mr Benni Aroni
Head of SVI 1000 Club

Mr Aroni was Managing Partner of his own Legal Firm between 1982 and 1998, and has been Developers Representative of Eureka Tower from 1998 to date. He was President of JDFA Victoria between 1993 and 1997 and National Vice President from 1995. He is a Board Member on several companies, listed and unlisted.

Mrs Christine Tarascio

Mrs Tarascio's family companies are Salta Properties Ltd/Westgate Logistics. Christine has been a very active fundraiser for various causes over a long period of time.

Mr Anthony Fasso
Retired 29/12/2004

Mr Anthony Fasso is currently the CEO Asia Pacific for AXA Investment Management/AXA Rosenberg and living in Hong Kong. Past positions include Director, Private Wealth Management, Deutsche Bank AG, based in Melbourne, Managing Director and CEO, Julius Baer (Asia) Ltd, and Executive Director at Regent Financial Services. He was formerly Managing Director Asia and Executive Vice President at Bankers Trust (1984 - 2000).

Ms Brenda M Shanahan
Chair, SVI

Professor Thomas WH Kay
Director, SVI

Mr Douglas A Wright
Deputy Chair, SVI

Mrs Claire O'Callaghan

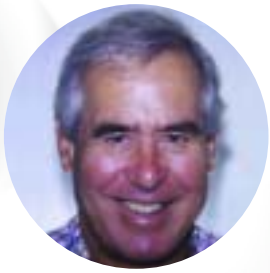
Mrs O'Callaghan, a St Vincent's trainee, returned to part time nursing once her five children were in full time education.

She has chaired a number of fund raising and educational organisations including the original Noah's Ark Toy Library for Handicapped Children.

She heads the St Vincent's Institute Support Group.

Ms Marcia Griffin

Ms Griffin was CEO of Pola Cosmetics and a former Victorian Telstra Business Woman of the Year. Current roles include Directorships of PMP Limited and National Pharmacies, as well as a position as a TEC Chair. Marcia is an author of a Business Biography "High Heeled Success". She is motivational speaker and Marketing Consultant.



Mr Martin Ralston

Mr Ralston has spent most of his working life involved with Information Technology. He worked for BHP Computer Accounting Services, then Accenture (formerly Anderson Consulting). Martin was a partner with Accenture from 1985 until 2001 when he retired. He is currently the Treasurer of the Moonee Valley Racing Club and non-Executive Chairman of Transol Corporation.

Mr Andrew Wraith
Member elect

Mr Wraith is a former senior manager of Shell Australia. He has over 20 years experience in manufacturing, supply and trading, logistics and retail operations including six years working overseas in South Africa and the Netherlands.

Ms Connie McKeage

Ms McKeage, a financial services specialist, has led a number of key financial services and charity sector projects including establishment of Etrade Australia (acting CEO); Westpac Broking; and Perpetual Funds Management. Connie has also held key executive positions at Bankers Trust Australia (BT), Rothschild Asset Management and Perpetual Funds Management. She has spent considerable time working in Asia, Canada, USA and Europe.

2003 saw Connie awarded a Centenary Medal for her contribution to Australian Society in the area of Business Leadership. Connie was CEO of Dymocks Literacy Foundation in 2003 and is currently a Councillor of Chief Executive Women (CEW).

Ms Danielle De Capele

Ms De Capele lives in Monaco where she is an organiser of international events and is on the board of various charitable organizations. She travels extensively within Europe and the USA and spends 3 months of the year in Australia.

Mr Jonathon Rowe

Mr Rowe is a founding member of Rowe Ingevics and Partners. Prior to this he was for ten years a Director of Clemenger BBDO, and is a specialist in communications strategy and effectiveness.

He holds an Economics degree, and has studied strategy planning and management in New York and London. After graduating, Jonathon studied the German language in Munich at the Goethe Institute.

Mr Sam Tarascio

Mr Tarascio gained experience with Coopers and Lybrand, then with Jones Lang Wootton before moving in 1999 to family company Salta Properties, with responsibility for management of the property investment portfolio. Currently Sam oversees the identification and purchase of new property development opportunities, project manages new developments, and assists with setting the strategic direction for the business. More recently Sam has also become involved in the family logistics business, Westgate Logistics as part of its Executive Management Committee.

SVI 1000 Club

2004 represented a year of growth and commitment by members of the SVI 1000 Club. By the end of 2004 the membership had grown to over 200 proving that it had been a breakthrough year for the SVI 1000 Club.

Every 1000 Club member becomes part of the SVI network committed to *'continuous discovery'*. The SVI Foundation is totally dedicated to meeting the challenge of sustaining research funding through our SVI 1000 Club.

The original aim of the Club was to gather 1000 people to gift $1000 each to make a million dollar leap in research. The funds generated by initial membership fees and then by the continuing involvement and support of SVI 1000 Club members are utilized to ensure SVI and its scientists can fund ongoing research, and that breakthrough discoveries are not obstructed by fiscal barriers. Specifically our aim is to encourage a sense of partnership between SVI 1000 Club members and our scientists, our research program and the ultimate clinical treatment.

Membership is tax deductible and members are invited to participate in various activities involving SVI, including guided tours of the research laboratories, information seminars, newsletters, and annual reports. SVI 1000 Club members will be presented with unique networking and information opportunities. Through the goodwill of SVI and its supporters SVI 1000 Club members will be presented with the opportunity to hear from speakers and attend venues that are rarely accessible.

It is essential that SVI 1000 Club members believe that their involvement is assisting in tangible results being achieved, and that those results will have an impact on their lives and those of many others.

St Vincent's Institute is honored and privileged to have such wonderful supporters, and looks forward to maintaining and evolving that relationship with current and future SVI 1000 Club members.

Benni Aroni
SVI Foundation Director
SVI 1000 Club

1000 Club

INDIVIDUAL MEMBERS

Abdallah, J & C
Abdallah, T & S
Alberti AM, S
Alfonso, E
Allen, J
Aroni, B
& Kaldor-Aroni, R
Barro, R
Beck, M
Beever, J
Bennett, R
Berry, R
Best, J
Bloom, B
Bloom, N
Bongiorno, A & A
Bongiorno, J & E
Bowness, WD
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Brown, SV
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Burkett, D
Bursztyn, P & J
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Caro, R
Carson, I
Carson, T & Suné, N
Casper, M & C
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Clifton, S
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Colman, J
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Curlewis, D
Dale, G
Danos, T & E
d'Apice, T & C
de Capele, D
de Gruchy, D
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Demediuk, N
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Dwyer, P & Happell, C
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Griffin, M
Griss, C
Grogan, B
Grogan, D & J
Grogan, M
Guest, A & E
Guest AM OBE, JS
Gurry, JF
Gutman Family
Hale, G
Halliday, S
Hart, L & C
Heath, WC
Hogarty, E
Hummerston, EJ & AM
Iacobucci, M
Isaac, JN
Jackson, B
Jelinek, M
Johnstone, A & J
Jolson, C
Jones, WMP
Kay, C
Kay, T
Kemp, B
Kerr, L
Kerr, M & L
Kerr, V
Kirby, R
Kopke, P & L
Kostos, K
Kozica, W
Leigh, P & G
Lempriere, J
Liberman, H
Losa, D
Lowe, D
Mahemoff AO, J
& Mahemoff, H
Mahlab, F & E
Martin, J
Martin, S
McGuire, E & C
McHale, G
McHale, J
McNamee, B
McNamee, V
McNaught, G
McPherson, J
Meadows, P
& Cross, P
Meltzer, F & W
Michelmore AO, J
Molan, M & M
Molan Family
Morlacci, P & J
Mullen Family
Niall, H & M
Nicoll, G
North, C
O'Callaghan, C
O'Callaghan SC, DJ
O'Day, J & S
O'Shannassy, M & R
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Papházy, JE
Pellicano, A
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Plant, B
Plant, K
Power, T & D
Ralph AC, J
Ralston Family
Reeve, F
Regan, J
Reid, I
Robinson, G
Rodas, M & T
Rowe, J
Rush, B
Rush, G & Menelaus, J
Russel, P & S
Russo, S
Rutman, L
Ryan, F & J
Savas, R & K
Savvides, G
Schillier, P & J
Scott, P & O
Shanahan, A
Shanahan, B
Shanahan, C
Simpson, A
Skala, L
Skala, S
Slatter, M & C
Slattery, P
Smith, C
Smith, P & T
Smorgon, D & R
Smorgon, T
Smorgon, V
Solomon, Q & E
Southwick, G & S
Spry-Bailey, P
Stapleton, M
Steven, J
Stops, W
Swaney, S
Tabak, L
Tashi, R
Thomas, C & C
Thurin, D & L
Tuckfield, PC
Turner, J
Turner, R
Verdnik, A
Watson, B & le
Maistre, E
Wellington, C
Westmore Peyton, C
Whitehead, M & M
Whiting, N & T
Wilkie, R & L
Wright, D
Xipell, J
Xipell, T
Yencken, T & M
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Young, D
Young, D
Young, H
Yu, MK

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Roslyn & David Smorgon host "an evening with Eddie McGuire"

The SVI 1000 Club was the beneficiary of a cocktail reception hosted by Roslyn and David Smorgon in their home on 4th August 2004. Special guest speaker, Eddie McGuire, spoke of community work undertaken by Football Clubs in their local areas, and the community values this instills in young players.

Roslyn and David expressed pride in the Smorgon family's contributions to a wide range of the community charities over many years. They encouraged their guests to visit St Vincent's Institute to meet the scientists doing outstanding work in the field of medical research.

SVI is indebted to David and Roslyn for opening their home and hosting such a wonderful night, and to Eddie and Carla McGuire for taking time out of their busy schedules to support the evening. We also extend a very special thanks to David and Roslyn's guests for their generosity.

SVI 1000 Club Cocktail Party

SVI 1000 Club members attended a Cocktail Party hosted by SVI Foundation Chair, Susan Alberti AM, at her home in November 2004. The Cocktail Party was held to thank members for their support and the Institute was pleased so many members were able to attend. The evening's special guest speaker, Mr Tom Carson, Chief Winemaker at Yering Station, gave guests an insight into the history of Yering Station and the current status of Australian wine worldwide.

The SVI Foundation Postgraduate Student Award was launched by Dr Robyn Starr during the evening.

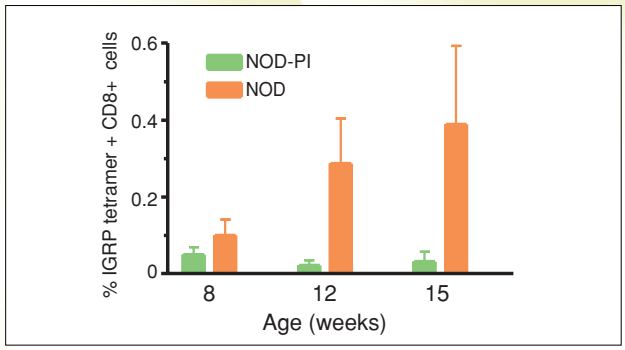
Immunology and Diabetes

People with type 1 diabetes lack insulin, the hormone that regulates the metabolism of glucose. Insulin is produced by cells in the pancreas called beta cells (β cells), which are contained within small clumps of cells called islets. In type 1 diabetes, these β cells are mistakenly attacked and destroyed by the immune system. Type 1 diabetes is a major burden because of the lifelong need for several daily insulin injections and finger prick tests to control blood glucose levels, as well as the problems of long-term complications. Approximately one in every 200 Australians has type 1 diabetes. The incidence of type 1 diabetes is increasing, especially in children less than five years of age. In the Immunology and Diabetes Group we are studying how β cells are destroyed, and we are investigating ways to protect β cells from the immune system as a potential therapy for treatment of type 1 diabetes. In particular we have been using genetically modified mice to block hormones of the immune system called cytokines, which are involved in inflammation and have been shown to damage β cells.

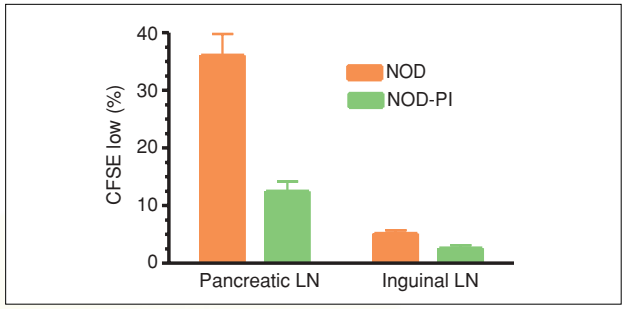
Failure of development of IGRP-specific CD8⁺ T cells in NOD mice made tolerant to proinsulin

In type 1 diabetes the immune system doesn't mistakenly recognise just one autoantigen in the β cell, it recognises several – for example proinsulin, glutamic acid decarboxylase and IA-2 in humans, proinsulin and IGRP in mice. One of the main future aims in diabetes treatment is to reverse the mistaken recognition of β-cell antigens and induce immune tolerance to the antigens. In both human and mouse trials of these therapies one antigen rather than many is generally targeted by treatment. We asked what happens to the immune response to other β-cell antigens when the immune response to one is prevented or reversed. In mice with immune tolerance to proinsulin induced by transgenic expression of proinsulin in antigen-presenting cells of NOD mice (NOD-PI mice), we have found that immune responses to IGRP are also not present. IGRP-specific CD8⁺ T cells in the blood and spleen were undetectable in NOD-PI using MHC class I tetramers that allow detection of individual antigen-specific T cells by flow cytometry. Furthermore when IGRP-specific CD8⁺ T cells were injected into NOD or NOD-PI mice they proliferated in the pancreatic lymph node of NOD but not NOD-PI recipients. Proliferation could be induced in NOD-PI mice by injection of anti-CD40 antibody, a mimic of the stimulation provided by CD4⁺ T cells.

This work suggests that immune responses to IGRP follow, or are "downstream" of responses to insulin and that it may not be necessary to separately induce tolerance to all the β-cell antigens recognised in diabetes for a therapeutic effect.



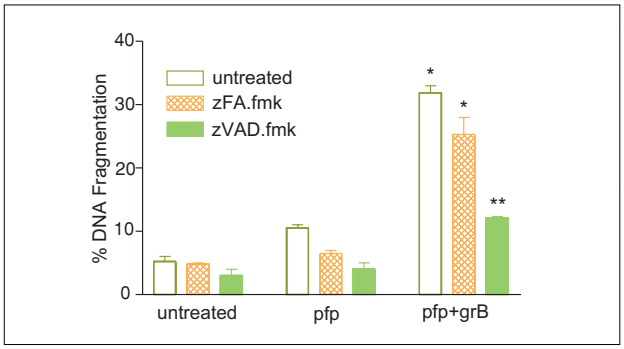
Percentage of IGRP tetramer positive CD8+ T cells in peripheral blood of NOD and NOD-PI mice at the given ages.



Proliferation of IGRP-specific cells in pancreatic lymph node (LN) of NOD-PI mice is reduced compared to in NOD.

How perforin and granzymes kill pancreatic β cells

We and others have shown that $CD8^+$ cytotoxic T lymphocytes (CTL) are the main cell that destroys pancreatic β cells in the preclinical phase of diabetes resulting in insulin deficiency. We are interested in the effector mechanisms used by CTL to kill β cells. One potential mechanism is via perforin and granzymes, the molecules contained within cytolytic granules. Some years ago it was found that NOD mice genetically prone to diabetes but in which the gene for perforin had been deleted do not develop diabetes. This suggested that CTL use perforin to kill β cells.
We have studied the direct interaction between β cells and recombinant perforin and granzyme B in vitro and have confirmed that together they can indeed kill β cells by apoptosis. Caspase inhibitors block some but not all of these effects and deficiency of the proapoptotic BH_3-only protein Bid blocks others. Professor Joe Trapani, a colleague at Peter MacCallum Cancer Institute is developing inhibitors of perforin that will be tested in our animal models of diabetes before they are tested in humans. These drugs are potentially new treatments for autoimmune diseases and aspects of transplant rejection.

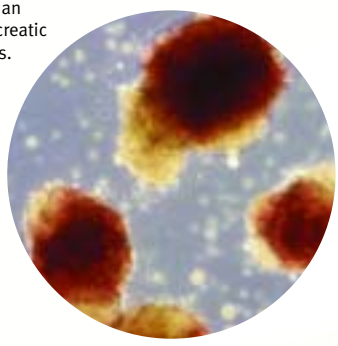


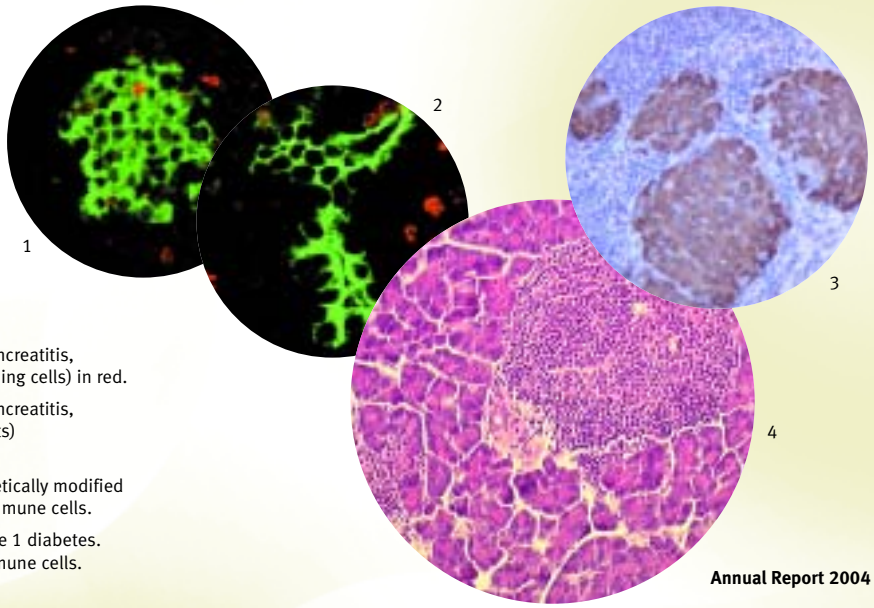
Apoptosis, as measured by DNA fragmentation, is induced by perforin (pfp) and granzyme B (grB) in pancreatic islets, and is blocked by the caspase inhibitor zVAD-fmk and not by the non-specific compound zFA-fmk.

SOCS1 deficiency enhances hepatic insulin signalling

Suppressor of cytokine signaling 1 (SOCS1) is an intracellular inhibitor of cytokine, growth factor and hormone signaling. *Socs1*$^{-/-}$ mice die before weaning from a multi-organ inflammatory disease. Neonatal *Socs1*$^{-/-}$ mice display severe hypoglycemia and hypoinsulinemia. Concurrent interferon-γ gene deletion *(Ifng*$^{-/-}$*)* prevented inflammation and corrected the hypoglycaemia. With colleagues at the University of Melbourne, hyperinsulinemic clamp studies were done and showed that *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice had enhanced hepatic insulin sensitivity demonstrated by greater suppression of endogenous glucose production compared with controls with no difference in glucose disposal. *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice had elevated liver insulin receptor substrate 2 expression (IRS-2) and IRS-2 tyrosine phosphorylation. This was associated with lower phophoenolpyruvate carboxykinase mRNA expression. These effects were not associated with elevated hepatic AMP-activated protein kinase activity. Hepatic insulin sensitivity and IRS-2 levels play central roles in the pathogenesis of type 2 diabetes. *Socs1* deficiency increases IRS-2 expression and enhances hepatic insulin sensitivity in vivo indicating that inhibition of SOCS1 may be a logical strategy in type 2 diabetes.

Human pancreatic islets.





1: Section of pancreas from a mouse with severe pancreatitis, showing insulin (beta cells) in green and BrDU (dividing cells) in red.

2: Section of pancreas from a mouse with severe pancreatitis, showing cytokeratin18 (which stains pancreatic ducts) in green and BrDU (dividing cells) in red.

3: Graft of islets (brown staining) from a mouse genetically modified to offer protection from the surrounding attacking immune cells.

4: Section of pancreas from a mouse developing type 1 diabetes. The round structure is the islet being invaded by immune cells.

Signal Transduction

Regulation of the immune system by SOCS proteins

Cytokines are important messengers that control the survival, growth, differentiation and function of cells of the immune system. Cytokines are produced in response to changes in the environment (such as infection), and act on cells to change their behaviour in response to these environmental changes. Responses to cytokines are typically transient, and unregulated responses to these potent molecules are generally harmful. Examples of cytokines include interferons, interleukins and growth factors.

Several years ago, we identified a family of proteins known as SOCS (for suppressor of cytokine signalling). These proteins function as "stop signals" to ensure that cytokine signals are turned off when they are no longer needed. To understand the roles of SOCS proteins, we have made mice that are unable to make SOCS proteins. In the absence of SOCS, mice develop immune and inflammatory disease, showing that SOCS proteins are critical for keeping the immune system in check. Drugs that enhance the expression or function of SOCS proteins may be useful in the treatment of diseases in which the immune system is defective, such as autoimmune disease.

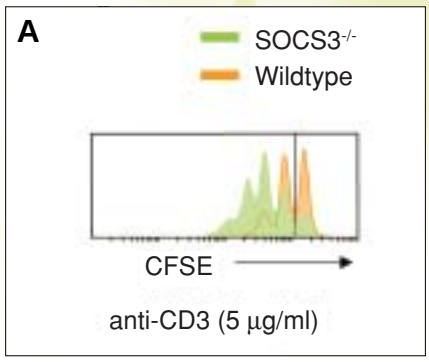
Regulation of T cell function by SOCS3

We are investigating the role of SOCS3 in the regulation of T lymphocyte function. Using mice that lack SOCS3 specifically in T cells, we have found that SOCS3 is critical for regulating the activation of T cells in response to antigen. These mice are healthy and thymic development appears normal. Lymph nodes, however, are enlarged and the number of peripheral T cells is increased. In response to an anti-CD3 stimulus, SOCS3-deficient T cells show greater IL-2 production and proliferation than wildtype cells. Co-stimulation of SOCS3-deficient T cells through CD28 ligation does not substantially augment the response, suggesting that full activation of T cells proceeds largely independently of co-stimulation when SOCS3 is absent. These data suggest that SOCS3 modulates T cell activation and may be an important regulator of T cell behaviour and homeostasis. Our current work focuses on defining the molecular mechanisms that lead to these defects in the absence of SOCS3.

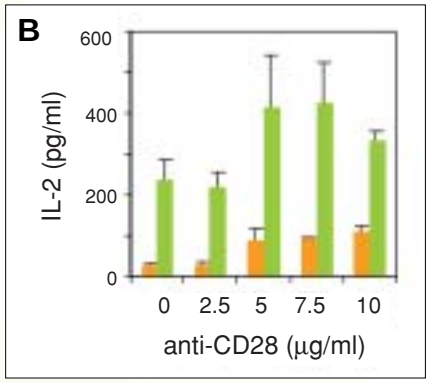
Identification of immune regulators using ENU mutagenesis

Conventional approaches to understand gene function, similar to those described above, entail the modification of target genes in mice. This 'reverse genetics' strategy enables gene function to be inferred by the spectrum of defects that occur when this gene is absent. An alternative strategy, known as 'forward genetics', begins with a biological process of interest to identify genes that contribute to that process. These phenotype-driven gene identification strategies have the advantage that they allow the isolation of genes involved in a biological process without any prior assumptions of their involvement.

We are interested in identifying genes that regulate T cell development and activity. The mutagen ENU is used to induce point mutations throughout the mouse genome, and blood samples from resulting pedigrees of mice are screened for aberrations in T cell development, number and activation state. To date, we are studying several pedigrees in which multiple members exhibit abnormalities in their immune system. We have established that these abnormalities are inherited, and are in the process of identifying the mutated genes. In addition to isolating novel genes, this approach is likely to identify known genes that were not previously known to have a role in immune regulation.



Increased proliferation of SOCS3-deficient CD8+ T cells in response to anti-CD3 alone.



Increased IL-2 production in response to anti-CD3 (10 mg/ml) in combination with anti-CD28.


NaOH

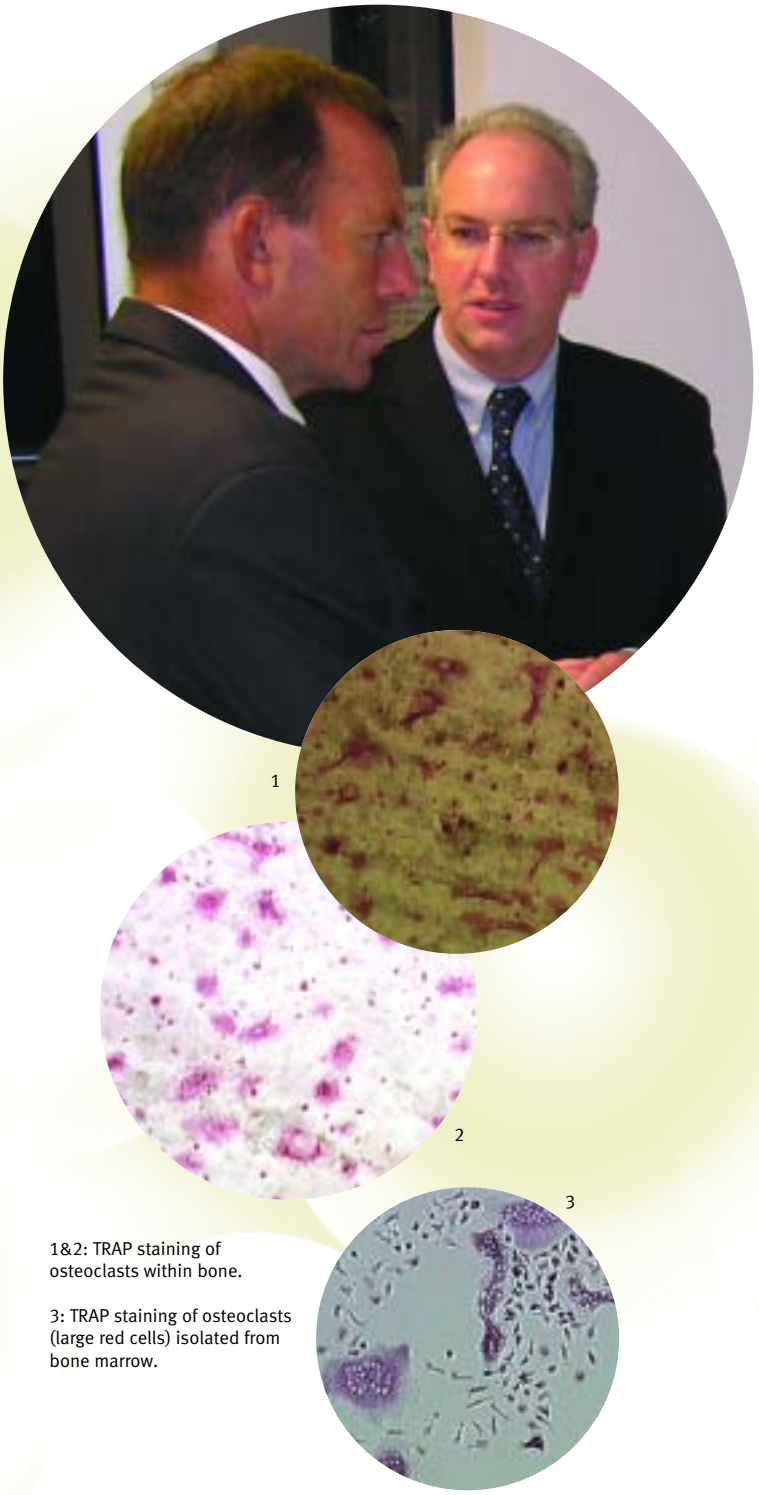
Bone, Joint and Cancer

In addition to its function as a structural support for the body, the skeleton serves several key functions in maintaining the body's immune system and blood composition. Our skeleton alters to cope with changing stresses and strains. As we age, an important change is that we lose bone mass. If we lose too much bone we can become osteoporotic, where our bones become weak and we have increased risk of fracture. More rapid bone destruction also happens in some common diseases including arthritis and some cancers that invade bone such as breast cancer. Our group is examining ways to stop the process of bone loss and find ways to build new, stronger bone. We have established several approaches to reducing bone loss and building bone in a range of clinical conditions.

Of particular note we provided the first evidence that a group of therapies currently used for treating osteoporosis called bisphosphonates, are also able to limit bone destruction in rheumatoid arthritis. Whilst these compounds did not reduce the inflammation that occurs with the onset of arthritis, they were very effective in preventing bone loss, which is a major cause of the continued joint damage, crippling and pain associated with this disease.

Secreted Frizzled-Related Protein-1

Normal bone remodelling requires osteoclasts (cells that breakdown bone) and osteoblasts (cells that make bone). Osteoclast formation in bone remodelling requires the presence of osteoblast lineage cells that express RANKL and macrophage-colony-stimulating factor (M-CSF), which interact with their cognate receptors on the osteoclast precursor. We identified secreted Frizzled-related protein-1 (sFRP-1), which is known to bind to Wnt and inhibit the Wnt signalling pathway, as an osteoblast-derived factor that impinges on osteoclast formation and activity. sFRP-1 mRNA expression was found by *in situ* hybridisation in osteoblasts and chondrocytes in murine bone, and is elevated in calvarial primary osteoblasts in response to prostaglandin E_2 or interleukin-11, factors that stimulate bone breakdown. Subsequent studies found that sFRP-1 inhibits the formation of osteoclasts *in vitro*. We also found that sFRP-1 binds to RANKL. While sFRP-1 activity might involve the blocking of endogenous Wnt signalling, our results suggest that, alternatively, it could be because of direct binding to RANKL. This study describes a new mechanism whereby osteoblasts regulate osteoclastogenesis through the expression and release of sFRP-1.



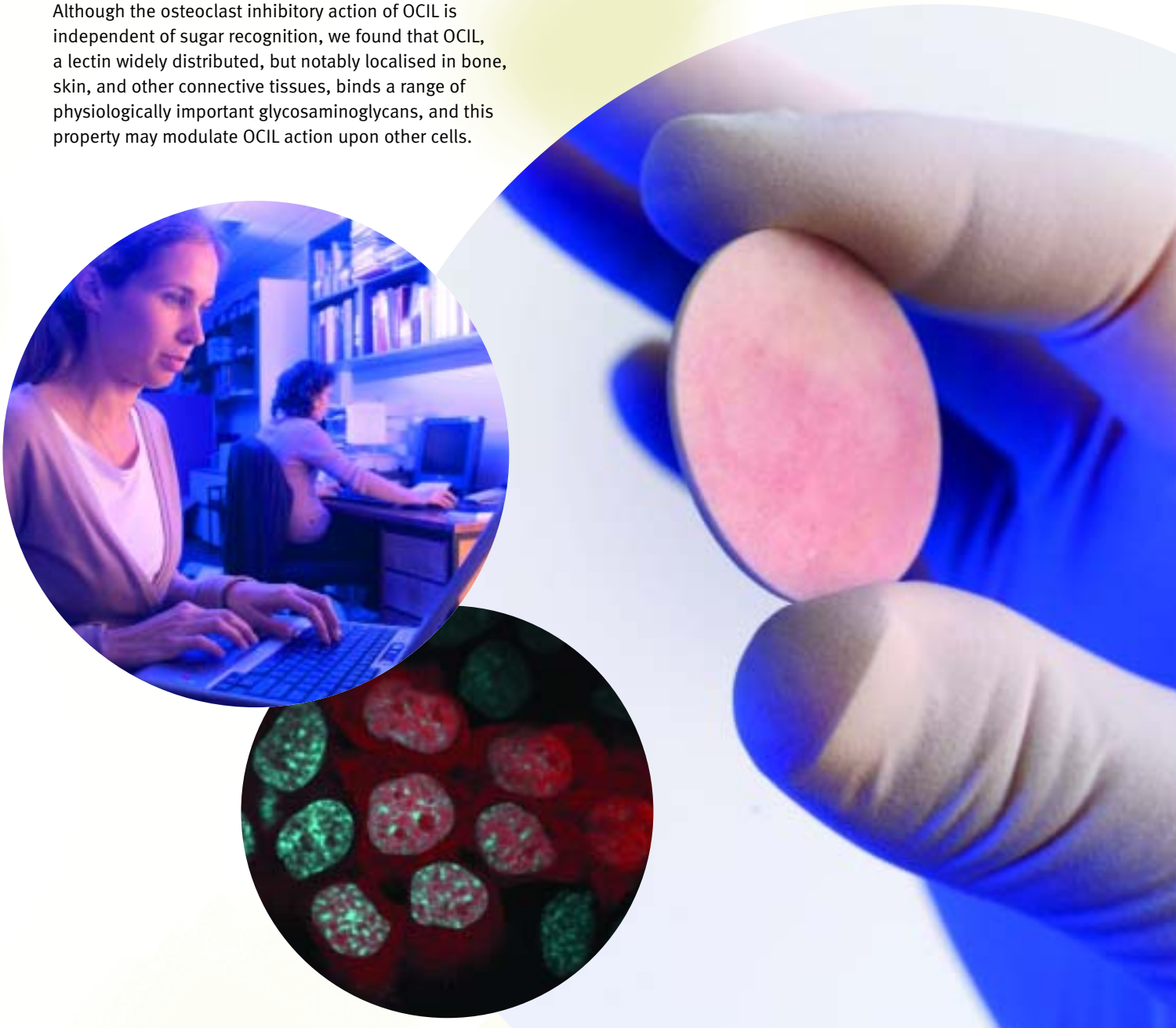
1&2: TRAP staining of osteoclasts within bone.

3: TRAP staining of osteoclasts (large red cells) isolated from bone marrow.

Osteoclast Inhibitory Lectin

Several years ago we discovered that Osteoclast Inhibitory Lectin (OCIL) is a cell membrane-bound molecule that blocks the formation of osteoclasts. We also showed that it is a member of a group of related proteins that also inhibit osteoclasts, but clearly have other functions as these proteins are present in many tissues. However, it remained unclear how OCIL works because no interacting proteins or receptors were known. Recently, research groups in the United States have not only identified a receptor, NKRP1D, but also shown that OCIL plays a role in the immune system to inhibit the cytotoxicity of natural killer cells, which are crucial for combating viral infections and cancer. We characterised the carbohydrate binding of soluble recombinant mouse and human OCIL by enzyme-linked immunosorbent assay. Although the osteoclast inhibitory action of OCIL is independent of sugar recognition, we found that OCIL, a lectin widely distributed, but notably localised in bone, skin, and other connective tissues, binds a range of physiologically important glycosaminoglycans, and this property may modulate OCIL action upon other cells.

We recently created a strain of mice that completely lack OCIL. As expected, although these mice were largely normal, they had more osteoclasts and thinner bones. Despite the thinner bones, osteoblasts were more numerous. Further investigation showed that OCIL does indeed have important effects on osteoblasts as well as osteoclasts, as well as some other cells related to osteoblasts such as adipocytes. This work has confirmed the important role that OCIL plays in controlling the cells of bone.



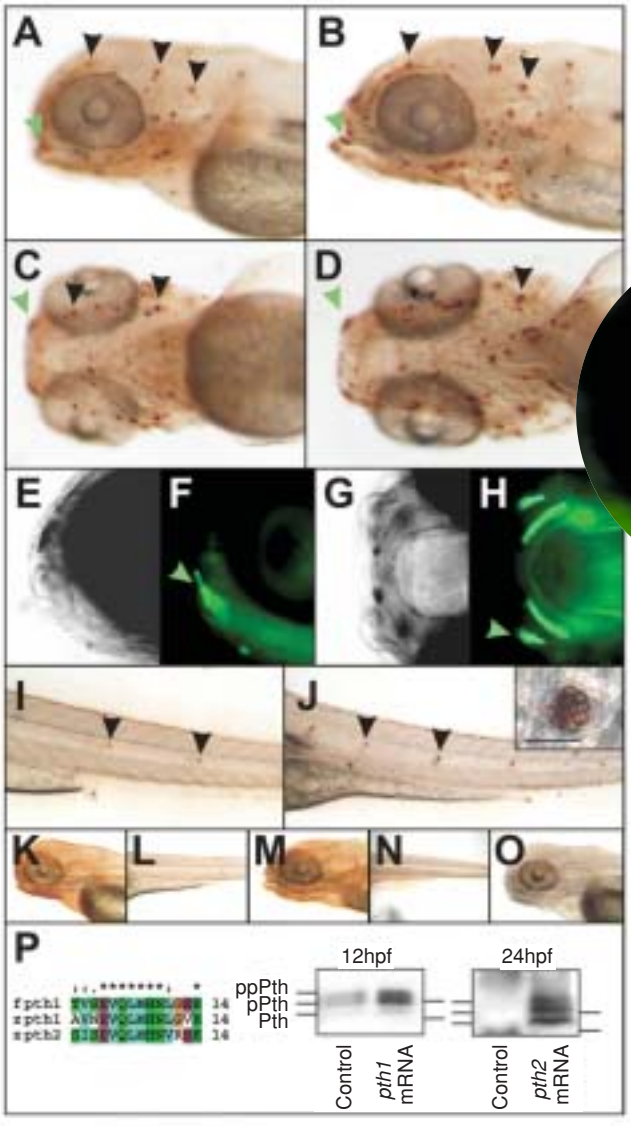
NBT-II cells

Comparative Endocrinology

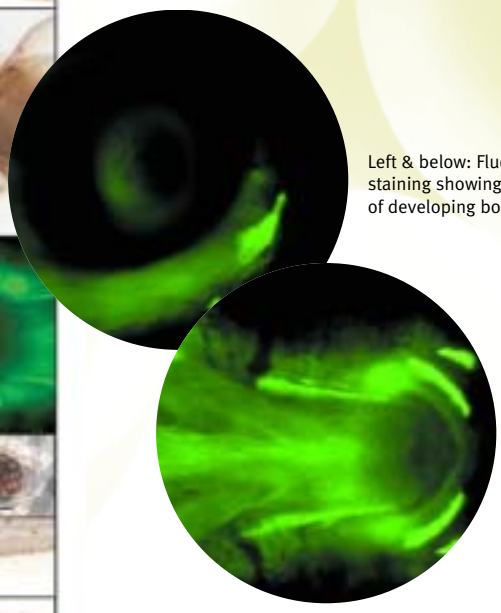
We isolated the parathyroid hormone (PTH) we isolated from the Japanese pufferfish *(Fugu rubripes)* in collaboration with Prof Jeffrey Zajac from Department of Medicine, University of Melbourne, Austin Health, two years ago. TeeleOstin Pty Ltd, a company formed by Starfish Ventures, SVI and the University of Melbourne, has funded these animal model studies. It is known that human PTH and certain molecules like human PTH are stimulators of bone growth. These factors are used clinically in the treatment of osteoporosis, and they are currently the only agents used therapeutically that stimulate bone growth. In contrast, bisphosphonates, which have dominated the osteoporosis field over the last 10 years, can only prevent bone loss. We have demonstrated that *Fugu* PTH can form new bone in rapidly growing young male rats and we were awarded a Biotechnology Innovation Fund grant in Round 6 to examine *Fugu* PTH's ability in an aged rat model that mimics post-menopausal bone loss in humans. These studies are currently underway.

Expression of PTH during embryogenesis in zebrafish

In collaboration with colleagues from the Ludwig Institute in Melbourne, we have studied PTH expression in the zebrafish embryo. In tetrapods, PTH is primarily expressed in the parathyroid glands and plays a critical role in calcium metabolism. Fish lack anatomically distinct parathyroid glands and the first animals to evolve these were the amphibians. However, fish do have PTH family ligands and receptors, which are functionally similar to their mammalian counterparts. We studied the expression patterns of duplicate zebrafish *pth* genes during embryogenesis. The gene and protein were demonstrated in the nervous system and the earliest developing bone. These temporally and anatomically restricted expression patterns imply a novel role for PTH family hormones during embryonic development of the zebrafish. These studies allow for the genetic dissection of PTH function in this model organism. We are planning to examine older zebrafish embryos to see what roles PTH plays in skeletal development in these animals and it is possible that these functions may have been conserved from fish to man.



Left: Anatomical analysis of Pth immunostaining in anterior neuromasts and the developing jaw by whole mount immunohistochemistry during zebrafish embryogenesis.



Left & below: Fluorescent image of calcein staining showing the earliest calcification of developing bone.

Tumour Cell Migration and Metastasis

The spread of cancer, rather than the growth of the primary tumour, is ultimately responsible for treatment failure, poor health and death amongst cancer patients. We currently have a limited understanding of the processes and genes that enable tumour cells to leave the primary site of growth, move throughout the body and ultimately establish tumours at other sites, a series of events commonly known as metastasis. Due to our limited understanding few therapies are currently available which directly target these types of aggressive cancer cells. Our laboratory is attempting to identify the genes within cancer cells that enable them to spread and grow at distant sites. By identifying the genes it will then be possible to isolate and produce new drugs that will be able to block their action resulting in new therapies that will halt the spread and growth of cancer cells. To identify genes involved in metastasis we have isolated cancer cells that either have a high rate or a low rate of metastasis. We have genetically profiled these cells and identified a number of genes that may be involved in enabling the cancer cells to spread and grow.

Fluorescent immunolocalisation of IGFBP-2 (red), αvβ3 (green) and their co-localization (yellow) by con-focal microscopy in MCF-7b3 xenograft tumors.

Detrimental effects of the cancer drug 17-AAG

One gene we have recently identified that may be involved in enhancing the metastasis of cancer cells is Hsp90. We have determined that Hsp90 is increased in cancer cells that have a greater ability to spread to the bone in mouse models of metastasis. There has been a great deal of interest recently in Hsp90 and its role in cancer growth and spread, so much so that drugs have been generated to block its action. These drugs are currently being tested in cancer clinics in the USA and the UK. We have used one of these drugs, 17-AAG, to test whether Hsp90 has a role in cancer metastasis to the bones of cancer patients. Using 17-AAG in mouse models of metastasis we have found that, rather than blocking the spread of cancer cells to the bone, the drug actually enhances the process. Further investigation revealed that 17-AAG enhanced the production of osteoclasts, a cell type in the bone that is responsible for bone degradation. By enhancing the number of osteoclasts in the bones, 17-AAG induced the loss of bone, making it easier for the cancer cells to establish and grow. This is the first report of a detrimental effect of a drug directed towards Hsp90 and will be important in the development of future drugs directed towards Hsp90.
We are currently using these results to aid us in the understanding of why this drug enhances the number of osteoclasts and whether the drug alters the genetic profile of cancer cells which may enhance their ability to cause bone metastasis.

A novel pathway used by cancers to enhance their ability to spread

In addition to the identification of novel genes in the metastatic process, we have also been examining the effects of one molecule, namely αvβ3, previously shown to enhance the spread of a number of cancers including prostate, brain and melanoma. This molecule is normally expressed at low levels on the surface of normal cells but is increased in cancer, allowing the cancer cell to adhere, grow and move more efficiently. We have generated a soluble form of αvβ3 allowing us to identify other molecules that interact with αvβ3. We believe that this will enable us to better understand how this molecule functions in metastasis. We have recently identified for the first time, the direct interaction of the αvβ3 molecule with the IGFBP-2 molecule. Interestingly, IGFBP-2 has also been shown to enhance the progression of prostate and brain cancers.
We are currently investigating whether the interaction between these two molecules represents a novel pathway by which cancers of the prostate and brain can enhance their ability to spread. It is hoped that these investigations will lead to the generation of novel therapeutics targeted towards inhibiting the interaction of IGFBP-2 with αvβ3 that may prove effective in combating the growth and metastasis of a number of tumour types.

Pharmacogenomics

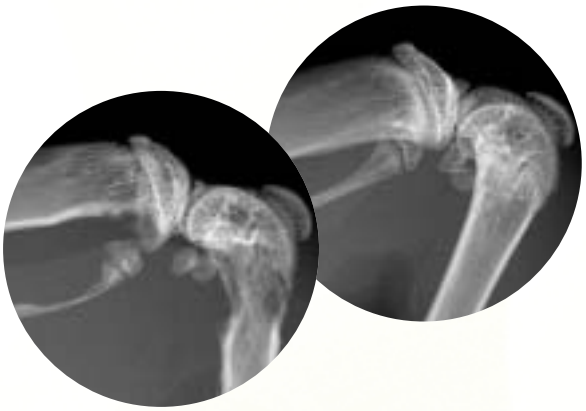
The Pharmacogenomics Laboratory is focussed on identifying the molecular processes associated with cancer and diabetes progression, and the concept of tailoring patient specific therapies to these disease processes. Achieving these goals have been greatly assisted by the recent 'mapping' of the human genome and the recent biotechnological advances that enable reading the activity level of all known genes in any tissue sample taken from a patient. We are particularly interested in identifying genes that cause cancer to spread (metastasis) and drugs which stop that process. We have also recently identified genes associated with diabetic kidney damage and are working with the Institute's Structural Biology Laboratory to design inhibitors to one of these key genes.

Identifying metastasis genes

During metastatic progression, a small population of cancer cells leave the primary tumour and disseminate to secondary organs. This is a multistep process which involves detachment of cells from the epithelium, their adhesion to the extracellular matrix (ECM), degradation of the ECM and migration. The gain of migratory and invasive properties for these cells is associated with loss of epithelial morphology and acquisition of mesenchymal characteristics; a process referred to as an epithelial-to-mesenchymal transition (EMT). In collaboration with A/Prof Erik Thompson's VBCRC laboratory at SVI, the Pharmacogenomics Laboratory has performed microarray gene expression profiling of human *in vitro* models of EMT to identify molecular mechanisms which regulate and associate with the EMT. Forty differentially expressed genes for this cell system have now been identified. This project is complemented by bioinformatic studies which utilize the ever growing tissue and disease expression databases available through international collaborations. While the established gene-fingerprint of the EMT is being refined for potential application in clinical diagnosis, the identification of functional drivers of the EMT process is being pursued by siRNA technologies to reveal potential drug targets of the metastatic cascade.

Above: Mouse mammary cell line, NMuMG, a model for epithelial to mesenchymal transition.

Right: Two-colour fluorescent microarray.



X-ray of mouse knees taken using the Faxitron. The knee on the left is damaged by cancer.

New drugs that inhibit breast-to-bone metastasis

Metastasis represents the most devastating attribute of cancer. A notable feature of this process is the variation in metastatic tissue tropism displayed for different types of cancer. Bone metastasis is a particularly frequent site of metastasis in patients with prostate carcinoma, myeloma, and for patients dying from carcinoma of the breast, approximately 85% have demonstrable metastasis to bone. Using mouse models of breast cancer, we have identified two drug molecules that are capable of inhibiting osteolytic bone damage associated with metastasis. While these drugs do not inhibit metastasis to other sites, this bone specific effect is potentially significant given that bone metastasis represents a distinct and significant clinical problem. One of the drugs is orally active and used for the systemic treatment for a variety of skin disorders clinically (predominantly in Japan & Korea). While its precise mechanism of action is not known it does have a well established safety profile and therefore could be rapidly translated into clinical use. The Pharmacogenomics Laboratory is currently further evaluating the anti-osteolytic activity of both drugs and using a variety of techniques (including gene array technology) to define the molecular basis of action in the cancer/bone environment.

VBCRC Invasion and Metastasis

The Victorian Breast Cancer Research Consortium (VBCRC) Invasion and Metastasis Group is one of five such Groups strategically placed amongst Melbourne Research Institutes, including Oestrogen Production & Regulation in Breast Cancer (Prof. Evan Simpson, PHIMR), Molecular and Developmental Biology of Breast Cancer (Dr. Jane Visvader and Dr. Geoff Lindeman, WEHI), Breast Cancer Genetics (A/Prof. Ian Campbell, PMCC), and Molecular Pathology of Breast Cancer (University of Melbourne Department of Pathology). Collectively these groups form an "Institute Without Walls" administered by the Cancer Council of Victoria, with a scientific management committee comprising the directors of most of Melbourne's premier institutions (www.vbcrc.org.au). The VBCRC was initiated by state government funding in 1995 for a period of 10 years, and has been highly successful in raising the spectrum of breast cancer research in Victoria, and indeed Australia. The SVI Invasion and Metastasis group has maintained two core streams of research in the areas targeting of matrix metalloproteinases (MMPs) - enzymes capable of degrading connective tissue structures, thus allowing the cancer cells to physically move and grow and breast cancer metastasis to bone, a favoured site for breast cancer spread which causes considerable complications in breast cancer sufferers.

Matrix metalloproteinase (MMP) in breast cancer progression

There are at least 28 MMPs and it is becoming clearer that those which are anchored on the cell surface (membrane type or MT-MMPs) are particularly instrumental in the aggressive growth and spread typical of cancer cells. We were among the first to study MT1-MMP, and have shown that it is upregulated in invasive breast cancer cells. We also found that it is further upregulated when these cells are grown in vivo. MT1-MMP is regulated by its primary substrate, collagen, and collagen structures which form around cancers (this is particularly evident in breast cancer) can regulate the tumour. We have devoted considerable effort to understanding how collagen regulates MT1-MMP, both at the transcriptional level, and perhaps more importantly for us, at the cell surface. We have found that collagen blocks the otherwise rapid internalisation of MT1-MMP in a mechanism which doesn't require the cytoplasmic tail of MT1-MMP, but does involve dynamin-mediated transport. The internalisation appears to be calveola-mediated rather than via Clathrin-coated pits. Although the most aggressive cancer cells produce MT1-MMP, it is universally upregulated by the stromal cells around all breast cancers, and may play a critical role in the accommodation and propagation of the tumour. We have obtained mice which are engineered to specifically lack MT1-MMP (so-called MT1-MMP-knock-out mice) and we will adapt these mice so we can see whether out breast cancers grow in them. We are also using gene abrogation approaches to knock-down the MT1-MMP in the cancer cells, so we can assess the relative contributions of the host/stromal MT1-MMP and the tumoural MT1-MMP. This knowledge will have important implications for MT1-MMP-directed therapies. Motivation for these studies is strengthened by observations by Mark Waltham (SVI Pharmacogenomics) that inhibitors of MMP block the growth of such tumours in mice.

Molecular mediators of bone metastasis

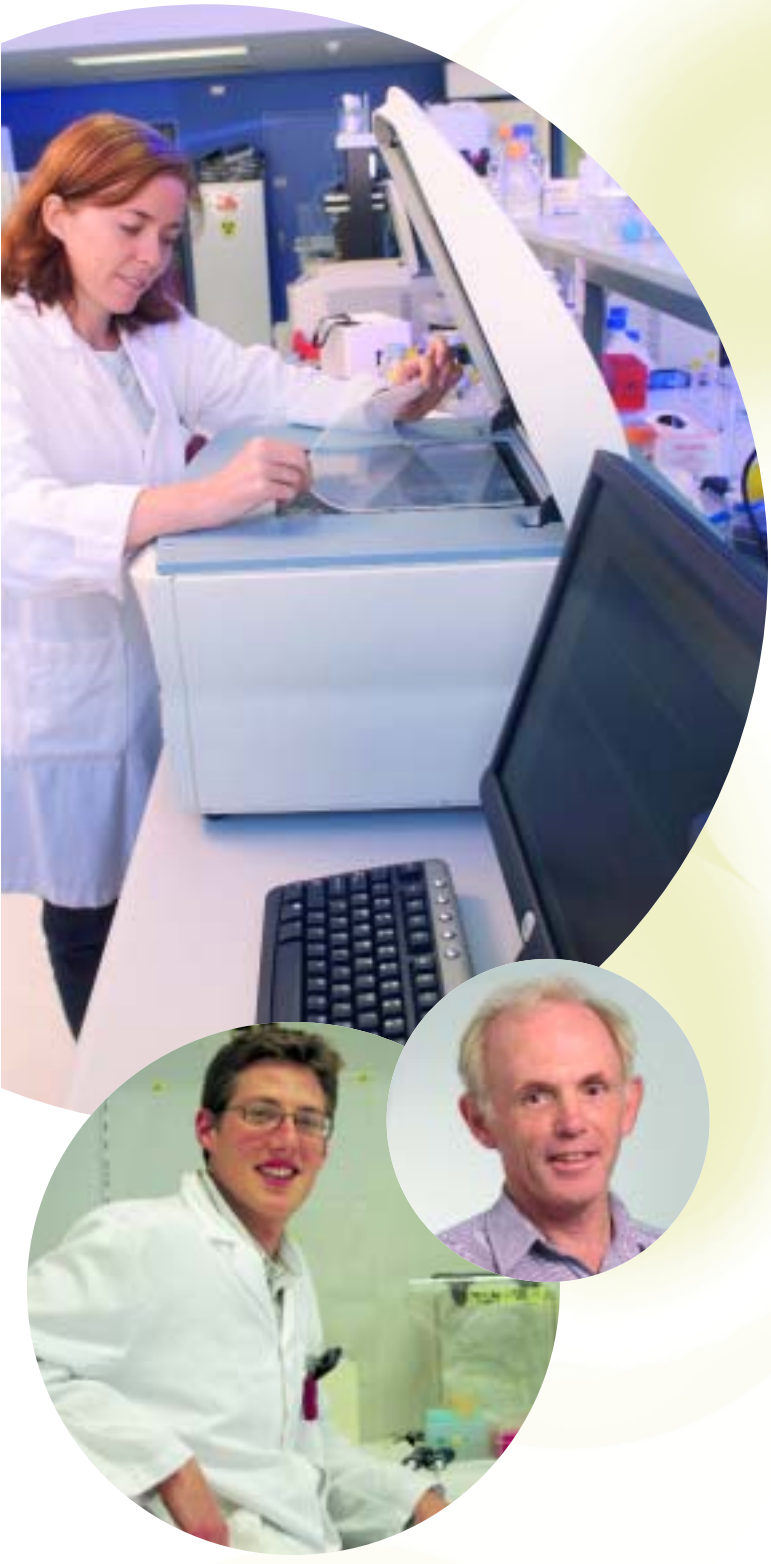
Previous studies profiling bone metastatic variants of the MDA-MB-231 breast cancer cell line identified a number of gene products which correlated with bone metastatic ability. These are under study using expression constructs and siRNA knock-down constructs. In particular, Galectin-3 is a major focus, and MDA-MB-231 cells are being engineered to overexpress and underexpress Galectin-3. These will be tested in the mouse model, and corresponding in vitro assays.

Top: MT1-MMP (green) is abundant in the MCF-7 xenograft. Red staining shows nuclei of both tumour and stromal cells. Corresponding RNA studies showed a complete lack of human (tumoural) MT1-MMP but large amounts of stromal (mouse) MT1-MMP.

Middle: Staining of the stromal protease MMP-13 (green) around a blood vessel. MMP-13 is dramatically upregulated in all human breast cancer xenograft models. Red staining shows nuclei.

Bottom: PMC42-LA breast cancer cells, stained to show cytokeratin 18 (red), vimentin (green) and nuclei (blue). The cells have undergone an epithelial to mesenchymal transition resulting in an upregulation of vimentin.

Protein Chemistry and Regulation

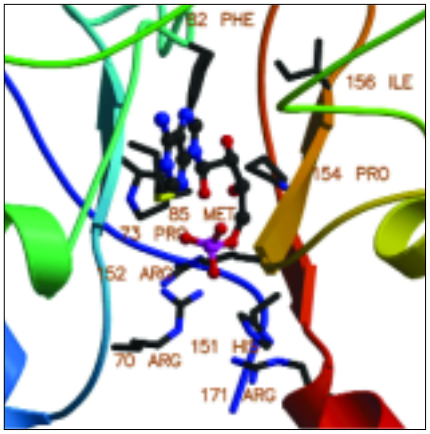


ALL activity depends on expending energy. It's a fundamental rule of nature. And it's why the research of Bruce Kemp's team at the Institute has such widespread consequences. They are unravelling the secrets of an enzyme – a protein controller of chemical reactions – that acts as the body's fuel gauge, determining its energy level. What the group is finding has relevance for treating obesity, heart disease, diabetes and cancer, for shaping exercise programs, and even for producing higher quality meat. The enzyme is known as AMP-activated protein kinase (AMPK), and in the past few years it has become the talk of the medical and pharmaceutical world. AMPK is the key to a universal energy sensing system present in all organisms. As such, it regulates the burning and storage of fats and sugars, and affects the level of sugars and cholesterol in the blood stream. The reason for its sudden notoriety is the suggestion that it may form the basis of a drug to induce the body to flare off excess fat without exercise. This opens up the almost irresistible possibility of losing weight simply by taking a "fat pill", or as it has become known, "exercise in a pill". As well as its direct impact on obesity, heart disease and diabetes through regulation of sugars and fats, AMPK can also influence the growth of cancers through control of the energy supply. Thus, AMPK is an enzyme with powerful and far reaching effects, which could play a significant role in treating conditions that cost our health system billions of dollars a year. Activation of AMPK by means of exercise leads to increased glucose uptake into muscle, and the burning of fatty acids in muscle and the liver. It is well known that exercise is beneficial to health, and that sedentary lifestyles increase the risk of obesity and type-2 diabetes developing. So, by reducing blood glucose levels and burning fats, AMPK does precisely what's required to offset the effects of obesity and diabetes. This has attracted global attention because of the epidemics of obesity and diabetes in the West and some parts of the developing world over the past 20 years. Two commonly used drugs to treat people with type-2 diabetes; metformin and rosiglitizone have been found to activate AMPK indirectly. While it is not yet proven that the effects these drugs have on AMPK are responsible for their usefulness in treating diabetes, it seems likely this will be a major component.

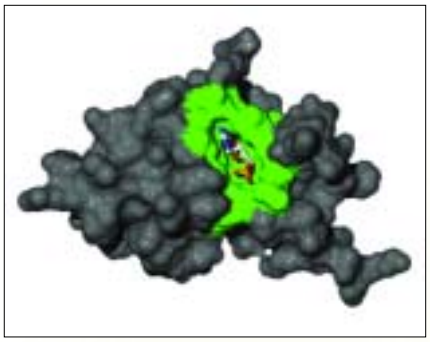
The Fat Pill

The tremendous importance of AMPK in the regulation of metabolism has raised the question as to whether more potent drugs, which act directly on AMPK, can be developed. Several laboratories and pharmaceutical companies are actively seeking to do this. But it will not be easy, because AMPK is likely to play many other roles in the body, which have not yet been discovered. This could lead to unforseen complications in the therapeutic use of AMPK-activating drugs. Nevertheless the potential benefits of research in this area are enormous. AMPK is an αβγ heterotrimer where the α catalytic subunit is controlled by the binding of AMP to the γ subunit. We have now identified the binding site for AMP on the γ subunit with the help of Michael Parker and David Stapleton's groups. Several lines of evidence suggested allosteric activation of AMP was being mediated by the γ subunits. Four CBS repeat sequences are present in the γ subunit which are related to comparable sequences found in bacterial inosine monophosphate dehydrogenase whose structure in known and this has allowed us to develop a structural model. From the model we were able to recognize the binding pocket for AMP. Mutation of the critical contact residues caused loss of AMP regulation and activation of the enzyme. As we develop our knowledge of the AMP binding pocket we hope to develop a drug that will mimic AMP's capacity to activate AMPK.

At present large numbers of Australians are treated with cholesterol-lowering drugs called "statins". They act by inhibiting the body's production of cholesterol. These drugs cost the National Pharmaceutical Benefits Plan about $500 million a year. But AMPK inhibits the production of cholesterol in the same way, and in addition switches off the production of fatty acids, triglycerides and fat cells. So drugs, which can regulate AMPK, may be more effective, having the potential to control the body's fat metabolism at multiple strategic points. Beyond the important health benefits there is also the vanity factor. Studies have already indicated that activation of the AMPK will accelerate the loss of abdominal fat.



A molecular model of the AMP binding pocket (green surface) in the AMPK γ subunit with AMP bound.



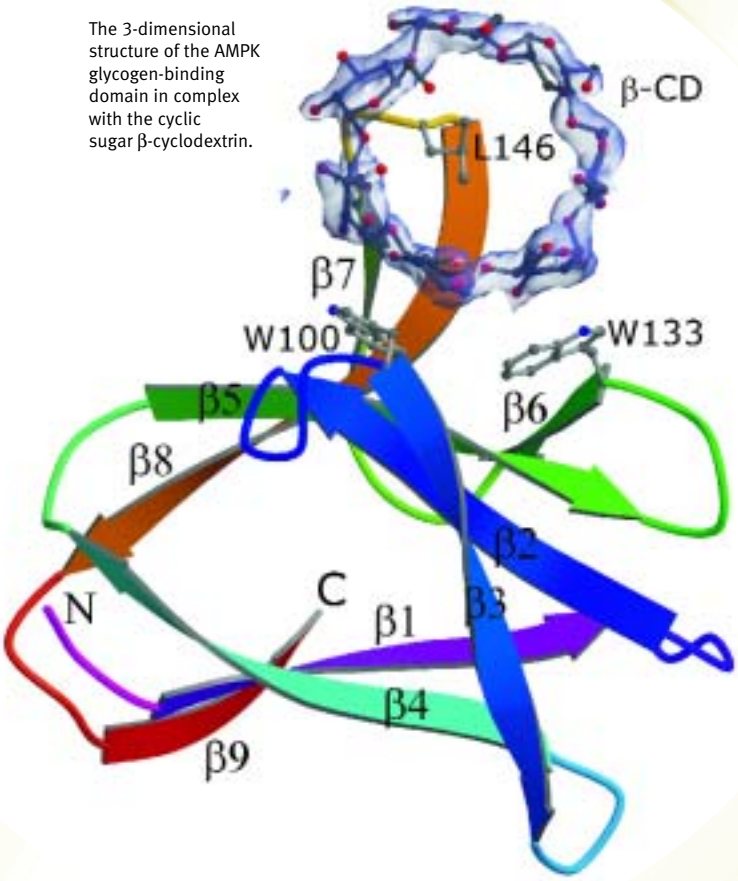
Detailed contact residues important for AMP binding.

Functional Proteomics

The AMPK comprises of three proteins that together form a functional enzyme. The laboratory focuses on discovering parts of each protein, called domains, that are important for how AMPK works, how each of the three proteins attach to each other or how AMPK moves to different parts of the cell when energy levels change. For example we have previously found that AMPK binds to a source of cellular energy called glycogen (sugar stores) via one part that we have called the glycogen-binding domain. In partnership with Prof. Michael Parker's laboratory we have obtained the three-dimensional shape of the glycogen-binding domain that is bound to a sugar molecule. Using this information we can understand how AMPK binds to glycogen. This research may lead to the identification of new molecules, similar to glycogen, that are important for AMPK regulation and may lead to the development of a new class of drugs for Type 2 Diabetes. Research into AMPK promises to dramatically increase our knowledge of how to reduce the risk of cardiovascular and neurodegenerative diseases, diabetes and obesity and provide an understanding of the reasons these diseases develop.

The 3-dimensional structure of the AMPK β glycogen-binding domain in complex with the cyclic sugar β-cyclodextrin

Several lines of evidence link AMPK with glycogen including a molecular relationship with the recent identification of a glycogen-binding domain within the AMPK β subunit. Glycogen, a branched polymer of glucose, is a cellular store of energy important for whole body glucose metabolism and is associated with an increasing number of regulatory proteins. To understand the molecular mechanism of the interaction between AMPK and glycogen we, in collaboration with Prof. Michael Parker's laboratory, have determined the 3-dimensional structure of the AMPK β glycogen-binding domain in complex with the cyclic sugar β-cyclodextrin. This is the first molecular view of this important sensor of cellular energy status. We find a unique carbohydrate-binding pocket that incorporates all known aspects of carbohydrate-binding observed in starch-binding domains into the one site, with extensive contact between several residues and five glucose units. This is in agreement with *in vitro* data showing that the five-sugar maltopentaose is the smallest oligosaccharide to prevent AMPK from binding to glycogen. β-cyclodextrin is held in a pincer-like grasp with two tryptophan residues cradling two β-cyclodextrin glucose units and a leucine residue piercing the β-cyclodextrin ring. Mutation of key β-cyclodextrin binding residues either partially or completely prevents the glycogen-binding domain from binding to glycogen. We hypothesize that this unique binding pocket enables AMPK to interact with glycogen anywhere across its helical surface.



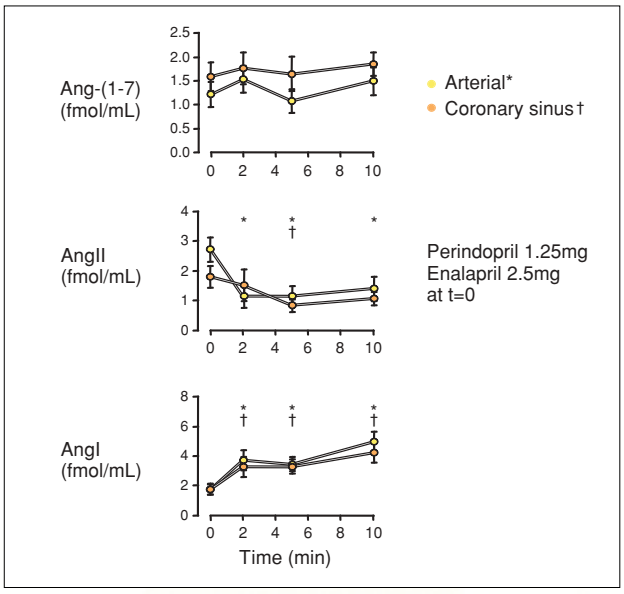
The 3-dimensional structure of the AMPK glycogen-binding domain in complex with the cyclic sugar β-cyclodextrin.

Molecular Cardiology

Cardiovascular diseases include heart attacks, strokes, and heart failure, and they are the main causes of death and sickness in our community. Our laboratory is investigating the causes of cardiovascular disease, so that we can better prevent and treat these diseases. We are particularly interested in the role of different hormones in cardiovascular disease, and the effects of drug treatments on these hormones.

The role of angiotensin converting enzyme (ACE) in angiotensin production

Angiotensin controls blood pressure by constricting blood vessels, by controlling renal excretion of salt and water, and by controlling adrenal secretion of aldosterone. High levels of angiotensin cause hypertension. High angiotensin levels cause thickening of heart muscle and thickening of the walls of blood vessels and promote inflammation in tissues. Some of the most valuable drugs we use to treat cardiovascular diseases act by reducing these effects of angiotensin. These drugs include ACE inhibitors, angiotensin receptor blockers, and beta-blockers. ACE inhibitors act by blocking an enzyme which produces angiotensin, called angiotensin converting enzyme (ACE). However, there has been a lot of debate about whether ACE is the only enzyme that produces angiotensin, and how important ACE is for angiotensin production. Other laboratories have suggested that another enzyme called chymase is more important for angiotensin production. In collaboration with our colleagues at the Howard Florey Institute, Melbourne, and Ken Bernstein at Emory University, Atlanta, Georgia, USA, we showed that ACE is the most important enzyme for angiotensin production. This is important information that helps us choose the best treatments for the prevention and treatment of cardiovascular diseases.



Angiotensin was measured in the blood from patients with heart disease. When patients were given an ACE inhibitor (perindopril or enalapril) the Ang I (inactive) levels increased and the Ang II (active) levels decreased, showing that ACE is the main enzyme that converts Ang I to Ang II. There was no change in Ang- (1-7) levels, despite the fall in Ang II levels, indicating that ACE2 does not play an important role in controlling the levels of angiotensin peptides.

The role of angiotensin converting enzyme-related carboxypeptidase (ACE2) in the control of angiotensin levels

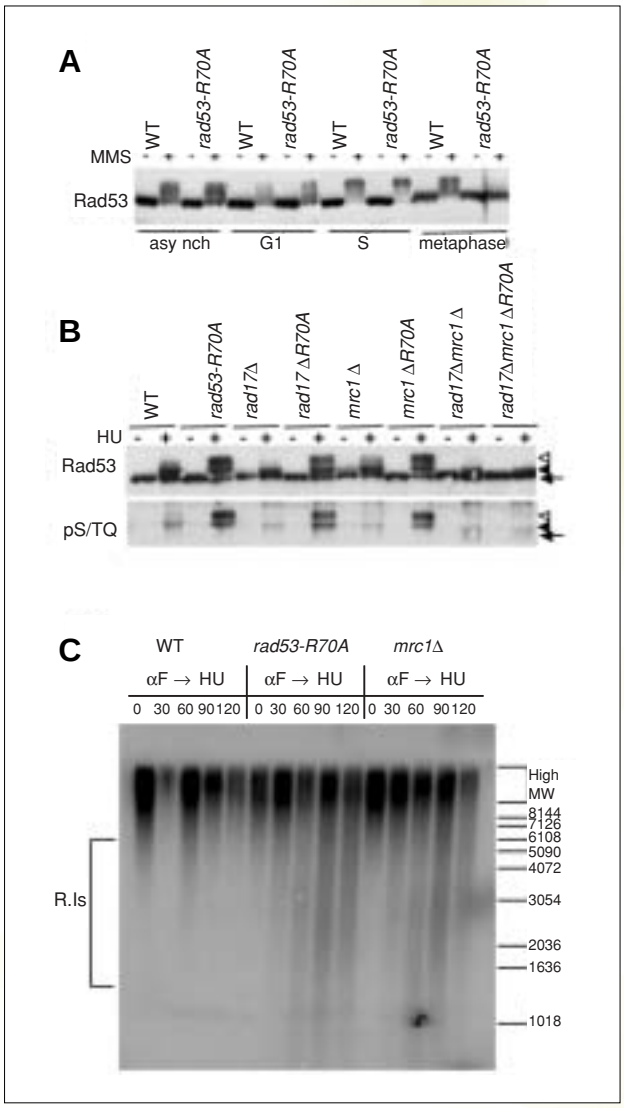
Recently, an enzyme similar to ACE was discovered called angiotensin converting enzyme-related carboxypeptidase (ACE2). It was proposed that ACE2 may be important in controlling angiotensin levels in the heart. We examined the role of ACE2 in the hearts of patients with coronary artery disease, and in patients with heart failure. We showed that ACE2 does not have a major role in the control of angiotensin levels in the heart. This is important information that reinforces the dominant role of ACE in control of angiotensin levels in the hearts of patients with heart disease. This study was performed in collaboration with Prof John Horowitz and Dr Chris Zeitz at the Queen Elizabeth Hospital, South Australia.

Angiotensin in the heart

To better understand how ACE and angiotensin cause heart disease, we collaborated with Ken Bernstein and his colleagues in the study of mice with increased ACE in their hearts. We showed that these mice also have increased angiotensin in their hearts. In addition, these mice have heart disease and die at a young age. These are important findings that demonstrate how increased amounts of ACE and angiotensin in the heart can cause heart disease. These findings reinforce the value of treatments that reduce the effects of angiotensin on the heart.

Molecular Genetics

Damage to DNA can occur spontaneously or in response to the environment. Accumulating DNA damage is one of the key factors that determine the onset and the malignancy of cancer. In addition, the vast majority of clinical cancer therapies act by causing DNA damage. Better understanding of how the cell responds to DNA damage is therefore likely to improve our knowledge of how cancer develops and could reveal new approaches to cancer therapy. It is now clear that different types of agents that can damage DNA cause a range of diverse DNA changes. Human cells contain a number of specific mechanisms to repair these DNA changes. Inappropriate repair of a particular DNA lesion by the wrong repair pathway often leads to escalating genomic changes. Our laboratory is interested in the molecular mechanisms by which cells deal with DNA damage in such a specific manner in order to prevent the onset and progression of human cancer. We have identified a novel family of DNA damage response proteins that is remarkably conserved from yeasts to human. Our hypothesis is that these proteins act by regulating the assembly of other DNA damage response proteins into complexes in the vicinity of damaged chromosomes.



Role of the conserved FHA domain in linking activated DNA damage checkpoint kinases to downstream targets

Mutations in the gene for the human CHK2 kinase are the cause of a subset of cases of the Li-Fraumeni syndrome, where patients suffer from multiple independent cancers. CHK2-like kinases are characterised by an N-terminal FHA domain, a phospho-threonine binding module involved in protein-protein interactions. CHK2-like kinases are structurally and functionally highly conserved throughout eukaryote evolution. However, the yeast CHK2 orthologue Rad53 contains a second FHA domain C-terminal of the kinase domain. We have previously reported that the two FHA domains have partially overlapping functions, where defects in one of the FHA domains can largely be compensated for by the other FHA domain. Using more detailed DNA damage response analyses in specific cell cycle stages, we have now identified two unique functions of the conserved N-terminal FHA1 domain that cannot be fulfilled by the FHA2 domain.

Rad53 in which both FHA domains have been disabled by single residue mutations in the phosho-threonine binding sites cannot be activated by DNA damage signals, leading to severely increased DNA damage sensitivity. Interestingly, we found that a single mutation in the FHA1 domain also abolishes Rad53 activation during metaphase but not other phases of the cell cycle (Fig. 1A). This result indicates that Rad53 activation during metaphase occurs by a unique mechanism that is strictly dependent on the FHA1 domain.

Surprisingly, we found that FHA1-defective Rad53 is even hyper-activated in response to DNA polymerase stalling during S phase (Fig. 1B). Despite this hyper-activation, the FHA1-defective Rad53 is unable to prevent the firing of late replication origins while early origins are stalled (Fig. 1C). These results indicate that the FHA1 domain is essential to link activated Rad53 to its targets to regulate the time-course of DNA replication during S phase.

A A single mutation in the FHA1 domain abolishes Rad53 activation during metaphase but not other phases of the cell cycle.

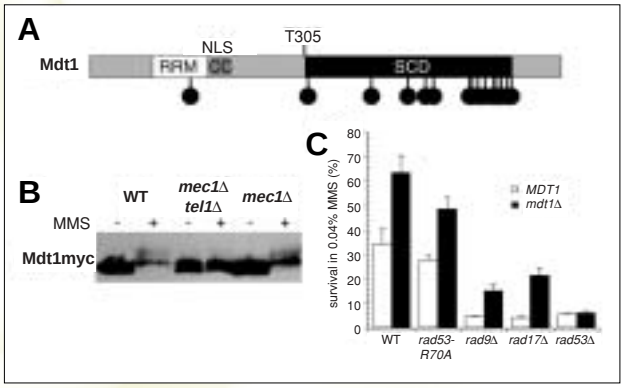
B FHA1-defective Rad53 is hyper-activated in response to DNA polymerase stalling during S phase.

C FHA1-defective Rad53 is unable to prevent the firing of late replication origins while early origins are stalled.

Mdt1 – a novel lesion-specific DNA damage response protein

By isolating Rad53 FHA1 domain-binding proteins, we have identified a novel protein termed Mdt1 (modifier of DNA damage tolerance). Mdt1 contains an SQ/TQ cluster domain (SCD) as a structural hallmark of DNA damage response proteins (Fig. 2A). The FHA1-Mdt1 interaction depends on the intact FHA1 phospho-threonine binding site, as well as a single threonine residue (T305) in Mdt1, and elevated Mdt1 protein levels are lethal in cells that lack Rad53, but not in wild-type cells. Mdt1 is hyper-phosphorylated after DNA damage in a manner that depends on the yeast kinases Mec1 and Tel1 (Fig. 2B), orthologues of the human kinases ATM and ATR that are mutated in patients suffering from ataxia-telangiectasia or Seckel syndrome, respectively.

Interestingly, while yeast cells lacking Mdt1 have increased resistance to methylating DNA damage (Fig. 2C), they are dramatically hyper-sensitive to other forms of DNA damage (unpublished). Recently, we have also isolated a human orthologue of Mdt1 that also exhibits differential responses to distinct types of DNA lesions (unpublished). We hope that future studies of these conserved proteins may shed important light on the molecular mechanisms underlying lesion-specific cellular responses to DNA damage.



A Mdt1 contains an SQ/TQ cluster domain as a structural hallmark of DNA damage response proteins.

B Mdt1 is hyper-phosphorylated after DNA damage in a manner that depends on the yeast kinases Mec1 and Tel1.

C While yeast cells lacking Mdt1 have increased resistance to methylating DNA damage, they are dramatically hypersensitive to other forms of DNA damage.

Biota Structural Biology

Knowledge of protein 3-D structure enables the intelligent design of new drugs

Protein is one of the body's essential building blocks. In addition to contributing to the structure of the body, proteins are also the "molecules of life", in that they are the molecular engines which control all functions of the body. Essential to understanding the function of proteins, we need to determine their structure. Crystallography offers the means to determine the three-dimensional (3-D) structure of proteins at the atomic level. Knowledge of protein 3-D structure enables the intelligent design of new drugs for the treatment of disease. The major areas of protein crystallography research in the group involve proteins involved in cancer, mental illness and bacterial and viral infection.

AT4 Receptor- a search for memory enhancers

Current agents available for the treatment of Alzheimer's disease (AD) have only modest efficacy and suffer from frequent side effects. Treatments that modify progression of AD pathology are extremely desirable but so far have been unsuccessful. Novel approaches to enhance cognitive function in dementia, and other causes of cognitive impairment, also need to be pursued.

Our collaborators previously discovered that a peptide called angiotensin IV (AT_4) markedly enhanced memory and learning in rodents. They subsequently identified the AT_4 receptor as the enzyme insulin-regulated aminopeptidase (IRAP). Other peptides were subsequently discovered that displayed the same effect as AT_4 and all were shown to be potent inhibitors of IRAP's aminopeptidase activity with Ki values in the high nanomolar range. Kinetic analysis and mutagenesis studies show that the peptides bind directly to the catalytic site of IRAP. Hence inhibitors of IRAP could prove useful as the basis for the development of drugs for memory loss. The known peptide inhibitors of the enzyme are unlikely to be suitable drugs because of poor oral availability, instability and failure to cross the blood brain barrier.

In the search for small molecule inhibitors of IRAP, with drug-like properties, we have generated a molecular model of its catalytic site based on the structure of an homologous enzyme. The region immediately surrounding the active site residues is well conserved with 41% amino acid identity. The predictive quality of the model was tested by the successful docking of AT_4 and other AT_4-like ligands into the active site, in conjunction with mutagenesis studies. The model of IRAP was then used as a basis for structure-based drug design. We have developed a screening procedure at SVI in which we screen virtual libraries of compounds for promising hits. We currently have assembled a library of over 4 million commercially available compounds. Inclusion of drug-like filters reduces the size of the library to about 2 million compounds. Forty compounds were selected based on predicted binding energies, purchased and assayed for the ability to inhibit the catalytic activity of recombinant IRAP. Of these, 6 were demonstrated to inhibit IRAP activity with micromolar affinities and shown not to exhibit promiscuous activity. These compounds are currently being tested in animals for affects on memory.

Our work on AT_4 receptor is a collaboration with Prof Fred Mendelsohn, Dr Siew Yeen Chai and Dr Anthony Albiston of the Howard Florey Institute in Melbourne.

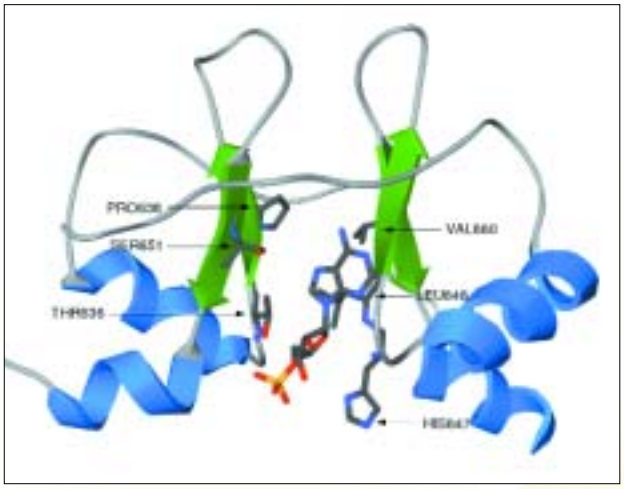
Chloride Channels – a molecular explanation for fatigue

Skeletal muscle has a high and variable demand for energy, in the form of ATP, and has elaborate systems to maintain the ATP supply. During intense exercise ATP supply may not keep up with demand and its concentration can decrease rapidly. In fast-twitch muscle fibres ATP can drop to below 25% of resting concentration within 25 seconds, a rate of ATP consumption that, if it continued, would deplete all ATP within a further 10 seconds. As the majority of ATP is consumed by the sarcoplasmic reticulum (SR) calcium ATPase pumping calcium back into the SR after each calcium-activated contraction, complete ATP depletion would lead to a rise in cytoplasmic calcium, rigor and calcium-dependent damage. This does not normally occur because force generation and ATP consumption decrease during exercise, compromising short-term function but protecting cells from complete metabolic exhaustion. This process is well known as fatigue but the factors contributing to fatigue remain controversial.

A reduction in the electrical excitation that stimulates SR calcium release is thought be a major contributor to fatigue. ClC-1 chloride channels are important regulators of skeletal muscle excitability, as highlighted by muscle hyper-excitability due to mutations in ClC-1 in congenital myotonia and aberrant splicing of ClC-1 in myotonic dystrophy. Like other ClC family members, the ClC-1 protein comprises a large membrane-embedded channel domain followed by two cytoplasmic cystathionine beta-synthase related (CBS) domains (Figure) and is thought to form homodimers with an ion conducting pore within each monomer, as revealed by the published structure of a bacterial ClC. Although the functional role of CBS domains in ClC proteins remains unclear their importance to channel function is underlined by disease causing mutations. In humans, mutations in the CBS domains of ClC-1 underlie congenital myotonia, in ClC-2 generalized idiopathic epilepsy, in ClC-5 hypercalciuric nephrolithiasis, in ClC-Kb Bartter syndrome and in ClC-7 infantile malignant osteopetrosis.

We have identified a novel mechanism linking excitability to metabolic state by showing that ClC-1 channels are modulated by ATP. The high concentration of ATP in resting muscle effectively inhibits ClC-1 activity by shifting the voltage-gating to more positive potentials. ADP and AMP have similar effects to ATP but IMP has no effect, suggesting that the inhibition of ClC-1 would only be relieved under anaerobic conditions such as intense muscle activity or ischaemia, when depleted ATP accumulates as IMP. The resulting increase in ClC-1 activity under these conditions would reduce muscle excitability, thus contributing to fatigue. We have also shown that the modulation by ATP is mediated by the CBS domains of ClC-1. This defines a function for these domains as gating-modulatory domains sensitive to intracellular ligands, such as nucleotides, a function that is likely to be conserved in other ClC proteins.

Our work on ClC channels is a collaboration with Dr Grigori Y. Rychkov, University of Adelaide.



Homology modelling of CIC-1 CBS domains. Model of CIC-1 CBS with AMP docked into the putative binding site. Residues lining the putative nucleotide binding pocket are shown as sticks coloured by atom.

Virology

Human Immunodeficiency Virus

The AIDS pandemic continues unchecked with ~ 5 million new HIV infections and ~ 3 million deaths due to AIDS in 2003. In developed countries, highly active antiretroviral therapy (HAART) can suppress viral replication and extend the life expectancy of HIV-infected people. However, HAART is often associated with severe, sometimes fatal side effects and with the emergence of drug-resistant variants. A better understanding of viral replication is essential if we are to uncover new drug targets to extend the therapeutic armoury against HIV. Our laboratory studies HIV membrane fusion, which is an early stage of the HIV replication cycle that remains incompletely understood. HIV membrane fusion is mediated by a complex of HIV proteins called gp120-gp41.

HIV membrane fusion

The membrane fusion reaction is driven by the retroviral TM glycoprotein, (gp41 of HIV and gp21 of human T cell leukemia virus [HTLV]). These proteins fold into trimers of hairpins, forcing together destabilised viral and cellular membranes, resulting in their fusion. The crystal structures of the central core region of gp41 and gp21 have been elucidated, however, we lack structural and functional information for sequences located outside the core. We have expressed the entire ectodomains of gp41 and gp21 as soluble trimers. We have uncovered a functional interaction between N- and C-terminal regions that are located outside the core. These sequences cooperate in stabilising the fusogenic conformation, driving the final, pore expansion phase of fusion. We aim to obtain 3D information for these terminal sequences in the context of complete ectodomain. We anticipate that these studies will provide a new target for antivirals.

The fusion function of retroviral TMs is activated when the surface-exposed glycoprotein (gp120 of HIV-1) binds receptors. Previously, we identified conserved residues in the disulfide-bonded region of gp41 that mediate association with gp120. We proposed that this region acts as a sensor of conformational signals that are generated when gp120 binds to CD4 and chemokine receptor, triggering the activation of gp41 fusion function. We have now found that the evolution of broad receptor-binding capacity by gp120 is associated with the coevolution of complex conformational signalling pathways in gp120-gp41. An American Foundation for AIDS Research grant is now enabling the identification of gp120 and gp41 regions that are involved in conformational signalling and their assessment as targets for the development new fusion inhibitors.

Hepatitis C Virus

HCV infects 200 million people world-wide. At present there are no vaccines to prevent infection and treatment of HCV infected people with current antiviral therapy achieves sustained responses in only 40-60% of individuals. HCV uses two proteins to bind to liver cells and mediate fusion between the viral and cellular membranes. These proteins are also recognised by antibodies made in infected people. However, there is still little information regarding the structures of these proteins and their precise role in binding and fusion.

E1 and E2 proteins in viral fusion and entry

HCV is distantly related to the Flavivirus family that includes important human pathogens such as dengue virus and tick borne encephalitis virus. The flaviviruses also encode two viral glycoproteins of which the E glycoprotein is responsible for receptor binding, and use a class II mechanism of membrane fusion. At the C-terminus of the E glycoprotein adjacent to the transmembrane domain is a highly conserved stem region that contains a hydrophobic heptad repeat referred to as the stem region. The stem region plays an essential role in E glycoprotein heterodimerization and membrane fusion.

We have examined the sequence of HCV E2 and found a similar sequence located adjacent to the transmembrane domain that is conserved in all HCV genotypes. Using site-directed mutagenesis, we found that this region is essential for heterodimerization of E1 and E2 and is also essential for viral entry. These experiments reveal that HCV uses a similar mechanism of fusion to the flaviviruses and this is the first description of the mechanism of fusion for HCV. The results of these studies also suggest that HCV glycoprotein E2 is a fusion protein and contains a fusion peptide sequence. We are currently using sequence comparisons with other class II fusion proteins and performing a mutagenesis scan of the E2 region to find amino acids that function in membrane fusion.

HCV glycoprotein E2 binds its cellular receptor CD81 through its large extracellular loop (LEL). We previously mapped the residues within the LEL of CD81 that form the receptor-binding site for HCV glycoprotein E2 to amino acids Phe186, Ile182, Asn184, and Leu162. Although these amino acids have similar effects in the context of recombinant CD81 and native CD81, we also found that a number of other mutations in CD81 did not have similar effects on E2 binding. The mutations all disrupted dimerization of recombinant CD81, but mediated their effects by distinct mechanisms. Our results suggest that native CD81 has a more robust structure in the intact tetraspanin with regions outside the LEL contributing to CD81 dimerization. The observed differences in the structure of recombinant CD81 and native CD81 need to be considered in high-throughput assays using recombinant CD81 for screening small molecule inhibitors of the E2-CD81 interaction.

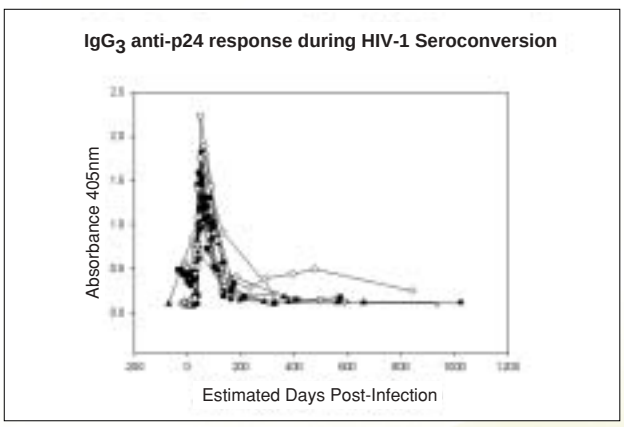
National Serology Reference Laboratory

The National Serology Reference Laboratory, Australia (NRL™) is committed to helping curb the spread of blood-borne virus and other infections by assuring and maintaining quality and confidence in laboratory results in Australia and internationally. Our objectives are achieved by providing multi-faceted quality assurance programmes, acting as an adjudicator on problematic sample results, conducting targeted research and leading training and education endeavours to secure laboratory best practice and quality. Research at the NRL focuses on the development of new and improved diagnostic tests for infectious diseases. Commercial imperatives drive the development of diagnostic tests and this can leave important issues unaddressed. Our research programme tackles such problems. An extension of this diagnostic testing includes the search for markers of disease progression relative to the hosts immune responses and viral evolution.

HIV-1 Incidence Assay

There is an urgent need to monitor the continuing spread of the HIV/AIDS pandemic. While currently available diagnostic assays can be used to determine the prevalence of infection they provide no information regarding the incidence of infection, a vital tool in understanding the spread of this disease.

We have discovered a specific marker of recent HIV-1 infection that provides the basis of a novel "incidence assay" for HIV-1. Preliminary evaluation of the assay has been performed using an ELISA format with samples obtained from individuals infected with subtype B virus. The assay relies on the detection of a transient peak of IgG3 reactivity to the HIV-1 capsid protein (p24). This peak of IgG3 occurs over an interval of 1 to 4 months following HIV-1 infection. The figure illustrates the presence of anti-p24 IgG3 antibodies detected in an ELISA in 17 HIV-1 seroconversion panels (167 samples). The results are overlayed to demonstrate the presence of this strong transient IgG3 response. This IgG3 anti-p24 assay provides a far more specific means of identifying recent infection than the current assays that depend on more variable markers such as antibody titre and affinity. The NRL's assay will provide valuable information for estimating the incidence of HIV-1 infection for epidemiological surveys as well as monitoring new infections during vaccine trials and managing treatment programmes.



The impact of early antiretroviral therapy and treatment interruption on HIV-1 viral fitness

Initiation of highly active antiretroviral therapy (HAART) early in acute HIV-1 infection can decrease the levels of virus so that the HIV-1 antigenic stimulation necessary to activate cellular and humoral immune responses does not occur. Early HAART has also been associated with impeding viral evolution, generating a viral population potentially more susceptible to neutralisation by specific antibodies. Carefully controlled or structured treatment interruptions (STI) may allow virus levels to rebound and subsequently 'boost' anti-HIV-1 immune responses.

In clinical trials to date, STIs have been shown to be the most effective in acute HIV-1 infection. The present study was designed to investigate whether early HAART, with a maximum of three STIs, resulted in eventual viral suppression in HIV-1 infected individuals. Using a primary cell-based neutralisation assay, there was an increase in neutralisation of virus for 25% of individuals over the period followed. However, there was no correlation between susceptibility to neutralisation and subsequent virus control upon STI. Lack of virus isolation or slower replication kinetics was observed for 55% of subjects with 73% of these demonstrating control of virus replication upon interruption.

Hence, while there was no correlation between virus neutralisation in vitro and virus control upon STI there was a correlation between viral replication capacity and virus control upon STI. These preliminary results work towards providing an important insight into the impact of early HAART and treatment interruption on the viral replication capacity or viral fitness, the immune response and the importance of the type of virus an individual is initially exposed to as a clinical marker for virus control.

IgG3 anti-p24 response during HIV-1 seroconversion.

Staff Members

PATRON
Gustav JV Nossal, AC CBE MBBS BSc(Med) *Syd* PhD *Melb* HonLLD *Mon* HonLLD Melb HonMD *Mainz* HonMD *Ncl* HonMD *Leeds* HonMD *UWA* HonDSc *Syd* HonDSc *Qld* HonDSc *ANU* HonDSc *UNSW* HonDSc *LaT* HonDSc *McMaster* HonDSc *Oxon* FRCP FRACP FRCPA FRACOG (Hon) FRCPath FRACGP FRSE FTSE FAA FRS

ST VINCENT'S INSTITUTE

DIRECTOR
Thomas WH Kay, BMedSci MBBS PhD *Melb* FRACP FRCPA; Professor (Medicine), The University of Melbourne

ASSOCIATE DIRECTORS
Matthew T Gillespie, BSc(Hons) PhD *Mon*; NHMRC Principal Research Fellow; Associate Professor (Medicine), The University of Melbourne

Michael W Parker, BSc(Hons) *ANU* DPhil *Oxon*; NHMRC Senior Principal Research Fellow; Professor (Biochemistry and Molecular Biology), The University of Melbourne

JOHN HOLT FELLOW
T John Martin, AO MD DSc *Melb* Hon MD *Sheffield* FRACP FRCPA FAA FRS; Emeritus Professor (Medicine), The University of Melbourne

PEHR EDMAN FELLOW
Bruce E Kemp, BAgSci(Hons) *Adel* PhD *Flinders* FAA FRS; ARC Federation Fellow; Professor (Medicine), The University of Melbourne

RESEARCH FACULTY
Duncan Campbell, BMedSci MBBS PhD *Melb* FRACP Grad Dip Epid Biostat; Associate Professor (Medicine), The University of Melbourne

Brett Cromer, BSc(Hons) PhD *ANU*

Janine Danks, BSc *LaT* MSc *Melb* PhD *Mon*; NHMRC Research Fellow; Associate Professor (Medicine), The University of Melbourne

Heidi Drummer, BSc(Hons) PhD *Melb*; Fellow (Microbiology and Immunology), The University of Melbourne

Jörg Heierhorst, MD *Hamburg*; NHMRC Senior Research Fellow; Senior Fellow (Medicine), The University of Melbourne

William McKinstry, BSc(Hons) *Tas* PhD *Melb*; NHMRC Industry Fellow; Senior Fellow (Medicine), The University of Melbourne

Belinda Michell, BSc(Hons) MBA *Mon* PhD *Melb*

Galina Polekhina, MSc(Hons) *Moscow State* PhD *Aarhus*; NHMRC RD Wright Fellow

Pantelis Poumbourios, BSc(Hons) PhD *Melb*

John Price, BSc(Hons) PhD *Aberdeen*

Julian Quinn, BSc(Hons) MSc DPhil *Oxon*

David Stapleton, BSc(Hons) *LaT* PhD *Melb*; NHMRC RD Wright Fellow; Senior Fellow (Medicine), The University of Melbourne

Robyn Starr, BSc(Hons) *Adel* PhD *Maryland*; ARC QEII Fellow; Associate Professor (Medicine), The University of Melbourne

Helen Thomas, BSc(Hons) *UWA* PhD *Melb*; JDRF Advanced Postdoctoral Fellow

Erik Thompson, BSc(Hons) PhD *Griffith*, Associate Professor (Surgery), The University of Melbourne

Mark Waltham, BSc(Hons) PhD *Qld*; Senior Fellow (Surgery), The University of Melbourne

RESEARCH SCIENTISTS
Julian Adams, BSc MSc *Cantab* PhD *Massey*

Elizabeth Allen, BSc *Otago* PhD *Melb*; Fellow (Medicine), The University of Melbourne

Steve Bouralexis, BSc *Flinders* BCompSc *Uni SA* BHealthSc(Hons) PhD *Adel*; NHMRC Peter Doherty Fellow

Christine Brender, BSc MSc PhD *Copenhagen* (from 2/04)

Zhiping Chen, BSc *Shanghai* PhD *ULP France*

Nadine Dudek, BSc(Hons) *ANU* PhD *Melb*

Susanne Feil, BSc MSc *Stockholm* PhD *Melb*

Jane Fisher, BSc(Hons) PhD *Mon*

Karl Häusler, BAppSc *PIT* MAppSc *RMIT* PhD *Melb*

Natasha Ilievska, BSc(Hons) *VUT* PhD *Melb* (until 2/04)

Ian Jennings, BSc PhD *Melb*

Vicky Kartsogiannis, BSc(Hons) PhD *Melb*

Frosa Katsis, BAppSc IIC *PIT*

Balasubramanian Krishna Murthy, MBBS *Bangalore* MD *Agra*; JDRF Postdoctoral Fellow

Marc Lafleur, BSc(Hons) *Ottawa* PhD *East Anglia*

Luke Miles, BSc(Hons) PhD *LaT*

Akira Nakamura, MD PhD *Keio Univ*

Brietta Pike, BSc(Hons) PhD *Melb*

Maria Schache, BSc(Hons) PhD *Melb*

Gregory Steinberg, BSc PhD *Uni Guelph*; NSERC Postdoctoral Fellow

Ana Traven, BSc(Hons) MSc PhD *Uni Zagreb*

Bryce Van Denderen, BSc(Hons) PhD *Melb*

TRAVELLING FELLOWS
Andrew Hammet, BSc(Hons) PhD *Melb*; NHMRC CJ Martin Fellow

Rachel Mudge, BSc(Hons) PhD *Melb*; NHMRC CJ Martin Fellow

VISITING SCIENTISTS
David Carling, PhD; Professor, Imperial College London

Lynett Danks, BSc(Hons) *Oxon*; European Calcified Tissue Society Exchange Scholar

Martin Stone, BSc MSc *Auckland* PhD *Cambridge*

Jerome Wielens, BAppSc(Hons) *Swinburne* PhD *Melb*

RESEARCH ASSISTANTS
Renae Allen, BSc(Hons) *Melb* (from 3/04)

Brett Bennetts, BSc(Hons) *Adel*

Tony Blick, BSc(Hons) *Mon*

Francene Bond, BBiomedSc(Hons) *Melb* (from 1/04 to 5/04)

Irene Boo, BBiomedSc(Hons) *Mon* (from 1/04)

Mark Chong, BSc(Hons) *Melb* (until 3/04)

Melissa Ciccomancini, BSc(Hons) *Mon* (from 1/04)

Rima Darwiche, BSc(Hons) *Melb* (until 10/04)

Susan Docherty, BSc(Hons) *LaT*

Rochelle Fernandes, BSc *Melb*

Joel Fletcher, BSc(Hons) *Melb* (from 11/04)

Ailsa Frew, BSc(Hons) *ANU* (from 1/04)

Nancy Hancock, BA *California State Fresno* MA *San Francisco State* (from 2/04)

Emma Jamieson, BSc(Hons) *Curtin*

Chi Ly, BSc(Hons) *Melb*

Anne Maerz, BAppSc *RMIT*

Lina Mariana, BSc(Hons) *Melb* (from 2/04)

Jessica Moore, BBtech(Hons) *Flinders*

Hooi-Ling Ng, BSc(Hons) *Melb*

Belinda Rizzo, BSc(Hons) *Melb*

Nora Tenis, BSc *Mon* GradDipMedLabSc *Uni SA*

Emma Walker, BSc(Hons) *Deakin*

Jade Woon, BSc(Hons) *Melb* (until 2/04)

Melisa Vazquez, BAppSc *RMIT* (from 2/04)

CHIEF TECHNICAL OFFICERS
Hannelore Diefenbach-Jagger, ChemTechCert *Augsburg* (until 4/04)

Daphne Hards, BAppSc *RMIT*

Virginia Leopold, BSc(Hons) *LaT*

SENIOR TECHNICAL OFFICERS
Jan Elliot

Patricia Ho, BSc *Mon*

Melanie Rowe, DipAppSci Animal Tech *Box Hill*

Patricia Smith, DipMedLabTech *RMIT*

TECHNICAL OFFICERS
Tara Catterall, DipAppSci Animal Tech *VUT* (from 5/04)

Catherine Li, CertLabTech *Hong Kong Polytechnic* BAppSc *RMIT* (from 10/04)

Marija Mikasinovic, DipAppSci Animal Tech *VUT* (until 11/04)

Kylie Tolley, DipAppSci Animal Tech *VUT*

LABORATORY ASSISTANTS
Rebecca Cotter (from 8/04)
Stacey Deering (from 11/04)
Sally Emini
James Katsis
Peter Rowe (from 4/04 to 7/04)

SENIOR PRINCIPAL RESEARCH ASSOCIATES
Peter Choong, MBBS MD *Melb* FRACS FAORTHA; Professor of Orthopaedics, St Vincent's Hospital and The University of Melbourne

Tony d'Apice, MBBS MD *Syd* MRACP FRACP FRCPA; Professor/Director of Clinical Immunology and the Immunology Research Centre, St Vincent's Hospital and The University of Melbourne

Jane Moseley, BSc PhD *Lond*; Associate Professor (Medicine), The University of Melbourne

Brendan Murphy, MBBS PhD *Melb* FRACP FAICD; Chief Medical Officer St Vincent's Health, Professor (Medicine), The University of Melbourne

Kong Wah Ng, MBBS (Hons) *Mon* MD *Melb* FRACP FRCP *Edin*; Associate Professor (Medicine), The University of Melbourne

PRINCIPAL RESEARCH ASSOCIATES
Michael Henderson, MBBS FRACS, Associate Professor (Surgery), St Vincent's Hospital and The University of Melbourne

John Slavin, MBBS FRACPA; Department of Pathology, St Vincent's Hospital

SENIOR ASSOCIATES
Craig Morton, BSc(Hons) PhD *Melb*; Biota Structural Biology Laboratory

Harshal Nandurkar, MBBS *Bombay* PhD *Melb* FRACP FRCPA; Staff Haematologist, St Vincent's Hospital

Evange Romas, MBBS PhD *Melb* FRACP; Senior Lecturer (Medicine), The University of Melbourne; Department of Rheumatology, St Vincent's Hospital

Natalie Sims, BSc(Hons) PhD *Adel*; NHMRC RD Wright Fellow; Department of Medicine, The University of Melbourne

ASSOCIATES
Sue Rogers, BSc(Hons) PhD *Lond*; Department of Medicine, The University of Melbourne

BUSINESS MANAGER
David Rees, BBus *RMIT* CPA ACIS Grad Dip CSP

LABORATORY AND TECHNICAL SERVICES MANAGER
David Murfitt, HNC AppBiol *Cambridge* CAT

DEVELOPMENT MANAGER
Clare Lacey

DIABETES PROGRAM MANAGER
Anne Thorburn, BSc(Hons) PhD *Syd*

EXECUTIVE OFFICER POLICY AND PROJECTS
Claire Tanswell, GCertBusAdmin *Swinburne*

PERSONNEL AND GRANTS ADMINISTRATOR
Gayle McMurray

ASSISTANT ACCOUNTANTS
Froilan Altarez
Lisnawati Wirawan-Liauw, SE *Atmajaya Katolik Uni*

ADMINISTRATIVE ASSISTANTS
Beth Castles
Leonie Loveday (from 10/04)
Kathryn O'Connell (from 2/04)
Dimitra Samaras

IT MANAGER
Peter Tonoli

IT SUPPORT OFFICER
Nazeh Calil, BSc Mech Eng *Alexandria*

National Serology Reference Laboratory

DIRECTOR
Elizabeth Dax, AM MBBS *Melb* PhD *Mon* MD *Melb*; Associate Professor (Medicine), The University of Melbourne

OPERATIONS MANAGER
Susan Best, MAppSc *RMIT*

RESEARCH COORDINATOR
Dale McPhee, BSc(Hons) PhD *Mon*; Associate Professor (Microbiology and Immunology), The University of Melbourne

QUALITY MANAGER
Roderick Chappel, BAgrSc PhD *Melb*

PROJECT MANAGER
Wayne Dimech, BAppSc *RMIT* FAIMS GDipMgt *Deakin*

SCIENTISTS
Thein Thein Aye, MBBS *Yangoon* PhD *Japan*

Hayley Croom, BSc *Melb*

Bradley Dent, BSc (Hons) *Melb* MPhil *Cantab*

Larissa Doughty, BSc (Hons) *Mon*

Barbara Francis, BSc *Melb* GdipAppSc (Health Stats) PhD *Swinburne*

Rosina Gribben, BSc *Syd*

Darren Jardine, BSc(Hons) PhD *LaT*

Marina Karakaltsas, BSc *LaT*

Sally Land, BSc(Hons) DipEd *Melb*

Lena Panagiotopoulos, BSc *LaT*

Thu-Anh Pham, BAppSc MAppSc *RMIT*

Scott Read, BSc(Hons) *Lond*

Kim Richards, BSc(Hons) *VUT*

Zoe Ryan, BAppSc *RMIT*

Joanne Schlegel, BAppSc *RMIT*

Kathy Smeh, BSc(Hons) BEdStudies MEd *Melb*

John-Paul Tung, BSc *Qld*

Sandy Walker, BSc(Hons) *LaT*

Kim Wilson, BAppSc *QIT* PhD *Melb*

DATA MANAGEMENT AND WEBSITE OFFICERS
Rosanna Fahmy
Clare Kinnear, BSc *Melb*
Clare Tomasov, BSc MSc *Mon*

LABORATORY ASSISTANT
Frank Torzillo

EXECUTIVE ASSISTANT
Linda Tracey

COMMUNICATIONS OFFICER
Romy Johnson

COMPUTER SYSTEMS MANAGER
John Tomasov, BSc(Hons) PhD *LaT* GradDipCompSc *Mon*

OFFICE MANAGER
Louie Opasinov, BSc Dip Ed *Melb*

Students and Graduates

Postgraduate education at SVI

St Vincent's Institute offers opportunities for Postgraduate training through the University of Melbourne, Department of Medicine and Department of Biochemistry. Currently, 23 students are studying for their PhD at SVI. In addition, MSc and Honours programs are offered at SVI.

Details of projects on offer can be accessed at:
www.svi.edu.au/education/phdprojects

More information about the Postgraduate programs offered by the Department of Medicine can be accessed at:
www.medstv.unimelb.edu.au/Prospective/index.cfml

St Vincent's Institute Foundation Postgraduate Award

The St Vincent's Institute Foundation offers Postgraduate Student Awards to outstanding students commencing their PhD training at SVI. A minimum of two scholarships will be awarded annually. Successful applicants will receive a $5,000 p.a. top-up stipend for 3 years.

More information about the award can be accessed at:
www.svi.edu.au/education/studentaward

or from Dr Robyn Starr, Postgraduate Student Coordinator
Tel: 9288 2480
Email: pgscholarships2005@svi.edu.au
Applications are due October 31 of each year.

UROP

St Vincent's Institute participates in the Undergraduate Research Opportunities Program (UROP), administered by Bio21. This Program gives undergraduate students the opportunity to undertake their own project in a research lab, in order to introduce them to a research environment and encourage them to pursue careers in science. Currently there are 4 UROP students at SVI.

More information about UROP can be accessed at:
www.bio21.com.au/urop.asp

or from Dr Robyn Starr, Postgraduate Student Coordinator,
Tel: 9288 2480
Email: pgscholarships2005@svi.edu.au

Applications are open in April and September of each year, for mid- and end of year intakes, respectively.

St Vincent's Student Society

This society is run by students and organises both social and career development events throughout the year. An offsite educational Student Retreat is held annually, which provides a great opportunity for socialising with other students.

Students

POSTGRADUATE SCHOLARS-DOCTOR OF PHILOSOPHY

Angela Arvanitis, Bsc(Hons) *Melb*
'Characterisation of an in vitro model of epithelial to mesenchymal transition'

Eveline Angstetra, BSc(Hons) *Melb*
'Mechanisms of immune destruction of pancreatic beta cells'

Alicia Arnott, BSc(Hons) *Deakin*
'Control of HIV-1 replication after early HAART: the role of viral phenotype and antibody responses'

Barry Dixon, MBBS *Syd* FRACP
'Characterisation of systemic inflammation following cardiopulmonary bypass'

Michelle Dunstone, BSc(Hons) *Melb*
"Structural studies of plasma pathway proteins"

Nicholas Dzamko, BSc(Hons) *Flinders*
'Hormonal activation of AMP activated protein kinase'

Eugene Estella, MBBS *Qld* FRACP
'Mechanism of β-cell destruction'

Abhilasha Gupta, Bsc(Hons) *Melb*
'The nuclear localisation of AMP-activated protein kinase'

Tristan Iseli, Bsc(Hons) *Melb*
'Structure and function of the glycogen binding AMP-activated protein kinase β-subunit'

Geoffrey K-W Kong, BSc(Hons) *Melb*
'Structural studies of Alzheimer's disease amyloid precursor protein'

Tali Lang, BSc LaT BSc(Hons) *Mon*
'Wnt signalling in breast cancer'

Chan-Sien Lay, Bsc(Hons) *RMIT*
'Structural and functional features of retroviral envelope glycoproteins'

Lisa McCarthy, BSc(Hons) *Deakin* PhD *Melb*
'Investigation of cancer cell inhibition by a novel extract of shark cartilage'

Mark McKenzie, BSc(Hons) *Melb*
'Protection of pancreatic beta cells from perforin-mediated cell death'

Carolyn McNees, Bsc(Hons) *Melb*
'ASCIZ is required for lesion-specific Rad51 foci formation and DNA damage survival'

Danijela Mirosa, BSc(Hons) *LaT*
'Lymphocyte-derived factors affecting osteoclastogenesis'

Lorien J Parker, Bsc(Hons) *Melb*
'Structural studies of glutathione transferases'

Joseph Pereira, BSc(Hons) *LaT*
'Biology of the αvβ3 integrin in breast cancer'

Matthew Pereira, BSc *LaT* BSc(Hons) *Melb*
'The role of IFIT1 in tumour cell growth, progression and metastasis'

Ruby Platt, BSc(Hons) *Virginia*
'Novel application of Tranilast for the treatment of acute myeloid leukaemia'

Erin Verity, BSc(Hons) *Swinburne*
'The importance of neutralizing antibodies in any potential vaccine against HIV-1'

Kelly Waldeck, BSc(Hons) *UWA*
'The role of FKBP52 in tumour progression and metastasis'

Mark Walter, Bsc(Hons) *LaT* BEc *Adel*
'Structure and function of the γ-subunit of AMP-activated protein kinases'

POSTGRADUATE SCHOLAR-DOCTOR OF SCIENCE

Frances Milat, MBBS *Mon* FRACP
'The PTH and Wnt pathway as anabolic targets in bone'

POSTGRADUATE SCHOLAR-MASTER OF SCIENCE

Emma Jamieson, BSc(Hons) *Curtin*
'Destruction of beta cells in type 1 and type 2 diabetes'

UNDERGRADUATE SCHOLARS - BACHELOR OF SCIENCE (HONOURS)

Anna Middleton, BSc *Mon*
'The effect of structured treatment interruptions on the humoral immune response in individuals with acute HIV-1 infection'

Dimitra Zotos, BSc *Deakin*
'Characterisation of total immunoglobulins G and subtype G3 responses in long-term non-progressors and survivors of HIV-1 infection'

Joel Fletcher, BSc *Melb*
'Analysis of SOCS3 expression during T cell development and activation'

Michelle Kouspou, BSc *Melb*
'The role of czveolin-1 in tumour cell progression and invasion'

Julian Tang, Dip Biotech *Temasek Polytechnic* BSc *Melb*
'Structural studies of pore-forming toxins'

Kwok Soon Wun, Dip Biotech *Ngee Ann Polytechnic* BSc *Melb*
'Structural analysis of the amyloid precursor protein'

ADVANCED MEDICAL SCIENCE PROGRAM

James Ho
'Role of antiretrovirals in measurement of antibody-mediated neutralisation'

Michael Chen
'The effect of adiponectin on AMPK activation in human skeletal muscle'

James Nicholson
'Expression and purification of Ark5 in insect cells'

UNDERGRADUATE RESEARCH OPPORTUNITY PROGRAM

Junquan Huang
'Purification of the diabetes autoantigen IGRP'

Kitty McCaffrey
'Characterization of the hypervariable region of the E1E2 glycoprotein of Hepatitis C virus'

Elena Tucker
'Isolation of T cell regulatory genes using ENU mutagenesis'

Kate Warren
'Identification of ASCIZ-interacting proteins'

SUMMER VACATION RESEARCH SCHOLARS

Francene Bond

Edward Cummings

Charles Kemp

Sweet Ping Ng, *Cancer Council Victoria Studentship*

Graduations

THE FOLLOWING GRADUATED DOCTOR OF PHILOSOPHY- THE UNIVERSITY OF MELBOURNE

Natasha Ilievska, BSc(Hons) *VUT* PhD *Melb*
'Role of PTHrP in DNA repair'

Sid Murthy, BSc(Hons) PhD *Melb*
'Regulation of AMP-activated protein kinase'

THE FOLLOWING GRADUATED BACHELOR OF SCIENCE HONOURS- THE UNIVERSITY OF MELBOURNE

Francene Bond, BBiomedSc(Hons) *Melb*
'Characterization of cytokine-induced NFκB activation in pancreatic islets during diabetes progression'

Carlie DiCamillo, BSc(Hons) *Melb*
'Development of an incidence assay for Rubella infection'

Lina Mariana, BSc(Hons) *Melb*
'Characterization of perforin and granzyme expression in CD8⁺ T cells in NOD mice'

Lorien Parker, BSc(Hons) *Melb*
'Structural studies of ligand binding and the nitric oxide transport function of the gutathione S-transferase enzyme'

Victor Sam, BBiomedSc(Hons) *Melb*
'Evaluation of small molecular inhibitors to hepatitis C virus (HCV) E2 glycoprotein and CD81 interactions'

Seminar Program

Dr David Carling
MRC Clinical Sciences Centre, London, UK
"AMP-activated protein kinase-linking metabolic disease to cancer"

Dr Jörg Heierhorst
St Vincent's Institute
"The Mdt1/ASCIZ family: roles in DNA gap repair and chromosome end protection"

Dr Nicole Horwood
Kennedy Institute, Imperial College, London, UK
"Role of Tec family tyrosine kinases in inflammatory cytokine production"

Dr Steve Bouralexis
St Vincent's Institute
"Apo2L/TRAIL-induced apoptos is in normal and malignant cells"

Dr Robert Kapsa
National Muscular Dystrophy Research Centre, Howard Florey Institute & St Vincent's Hospital
"Targeted corrective gene conversion and stem cell therapy for hereditary muscle disease"

Dr Anita Quigley
National Muscular Dystrophy Research Centre, Howard Florey Institute & St Vincent's Hospital
"In vivo and in vitro gene correction for neuromuscular disorders"

Dr Robyn Starr
St Vincent's Institute
"Regulation of the immune system by SOCS proteins"

Ms Angela Arvanitis
Final PhD Presentation
St Vincent's Institute
"Characterisation of an in vitro model of epithelial-to-mesenchymal transition in breast cancer"

Dr Craig Morton
St Vincent's Institute
"Membrane fusion in the paramyxoviridae - insights from molecular modelling"

Dr Heidi Drummer
St Vincent's Institute
"Structural and functional studies of the hepatitis C virus glycoproteins E1 and E2"

Dr John Price
St Vincent's Institute
"Tumour cell metastasis and growth - novel targets and insights"

Dr Julie Lucas
University of Massachusetts Medical School, Worcester, MA
"Altered T cell development in the absence of the Tec family kinase, Itk"

Dr Galina Polekhina
St Vincent's Institute
"Everything you wanted to know about crystallography but could not be bothered to ask"

Dr Helen Thomas
St Vincent's Institute
"Fas expression on pancreatic beta cells - what is its role in development of type 1 diabetes?"

Dr Luke Miles
St Vincent's Institute
"Development of cell-free methods for preparing integral membrane proteins for structural studies"

Dr Duncan Campbell
St Vincent's Institute
"Prediction of heart failure"

Dr Janine Danks
St Vincent's Institute
"PTH or PTHrP - Which came first the chicken or the fish?"

Professor TJ Martin
St Vincent's Institute
"Regulation of the osteoprotegerin gene: a pathway to drug development"

Dr Walter Thomas
Head of Molecular Endocrinology, Baker Heart Research Institute
"EGF receptor transactivation in cardiac hypertrophy"

Dr Brett Bennetts
St Vincent's Institute
"Regulation of ClC-1 skeletal-muscle chloride channel by nucleotide binding to CBS domains"

Dr Lance McCauley
CSIRO Health Sciences & Nutrition, Parkville
"Insulin regulated trafficking of glucose transporters"

Professor John Furness
Department of Anatomy, University of Melbourne
"Channels and kinases that control excitability of intestinal sensory neurons and why they are important"

Professor Colin Masters
Department of Pathology, The University of Melbourne
"Testing the amyloid theory of Alzheimer's disease"

Dr Alejandro Villarino
Department of Pathobiology, University of Pennsylvania, Philadelphia, PA
"IL-27 inhibits effector T cell responses during infection"

Mr Drew Dudley
Final PhD Presentation - Department of Medicine, St Vincent's Hospital
"Potential role of a VEGF/JAK2/STAT5 axis in mediating endothelial cell survival during hypoxia"

Dr Nicole Stupka
Department of Physiology, University of Melbourne
"Calcineurin signal transduction pathways in skeletal muscle regeneration and dystrophy"

Dr Mark Febbraio
RMIT University
"IL-6 and insulin resistance: friend or foe?"

Dr Robyn Anderson
Peter MacCallum Cancer Institute
"Genetic regulation of breast cancer metastasis"

Dr Peter Cowan
Department of Clinical Immunology, St Vincent's Hospital
"Pig-to-human transplantation: is it just around the corner?"

Ms Caroline McNees
Final PhD Seminar
St Vincent's Institute
"ASCIZ your way out of trouble - a novel repair pathway for alkylating DNA damage"

Ms Emma Jamieson
Final Master's Seminar
St Vincent's Institute
"Regulation of glucose and insulin homeostasis by SOCS-1"

Dr David Belford & Dr Geoff
Regester, GroPep LTD
"A route to commercializing your drug discovery"

Dr Motoharu Seiki
Division of Cancer Cell Research, Institute of Medical Science, University of Tokyo, Japan
"Regulation of MTI-MMP in cancer"

Professor Barbara B Kahn
Division of Endocrinology, Diabetes & Metabolism, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA
"Tissue specific knockout of Glut4 reveals inter-tissue communication in the pathogenesis of type 2 diabetes"

Associate Professor Jennifer S Pollock
Vascular Biology Centre, Department of Pharmacology & Toxicology, Medical College of Georgia, Augusta GA
"NOS subcellular localization and NO production"

Dr Mike J Weber
Cancer Center, Weaver Professor of Oncology, University of Virginia Health System, Charlottesville, VA
"MAP Kinase signalling: specific messages from ubiquitous messengers"

Dr Richard G Caro
TangibleFuture Inc., San Francisco, USA
"Applied entrepreneuring: creating business from science"

Professor Gerard Karsenty
Molecular Genetics, Baylor College of Medicine, Houston, TX
"Leptin as a central regulator of bone mass"

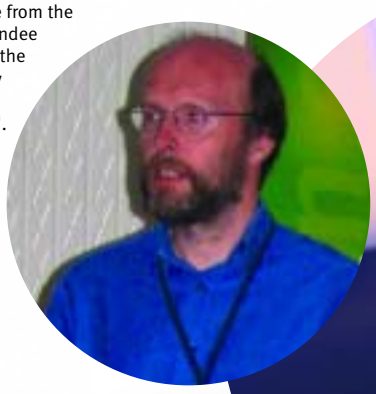
Dr Alan Munn
Institute of Molecular Biotechnology, University of Queensland
"A novel role for verprolin in regulation of the cytokinesis-specific SH3 domain protein Hoflp"

Dr Morten Karsdal
Nordic Biosciences, Copenhagen, Denmark
"Low molecular weight inhibitors of the chloride-7 channel as inhibitors of bone resorption"

3RD INTERNATIONAL SYMPOSIUM ON AMP-ACTIVATED PROTEIN KINASE

"Erskine on the Beach", Lorne, Victoria, Australia 23-26 March, 2004. AMPK 2004, held for the first time in the southern hemisphere, was the 3rd international conference in this field. Bruce Kemp, David Stapleton and Jock Campbell were co-organizers.
The conference followed the successful AMPK 2002 (Dundee, Scotland) organized by Grahame Hardie and David Carling, and the Boston meeting at the University Medical Center in December 2000, organized by Neil Ruderman. The past 4 years has seen an explosion of interest in AMPK with more papers published in that time than in the previous 25 years of research on the enzyme. There were 141 delegates (55 from Australia) from 16 countries for AMPK 2004 who enjoyed great Lorne weather and an exciting conference. Over 4 days there were 9 sessions comprising 43 oral presentations and 42 poster presentations with almost all the major research laboratories in the field represented.

AMPK 2004



Grahame Hardie from the University of Dundee Scotland giving the opening plenary lecture: "AMPK past and future".

Fellowships, Prizes and Grants

IMMUNOLOGY AND DIABETES

Fellowships and prizes

- Prof Tom Kay received the Juvenile Diabetes Research Foundation International Mary Jane Kugel Award for 2004 for service on the Medical Science Review Committee
- Dr Helen Thomas was awarded an RD Wright Career Development Award from the NHMRC
- Ms Eveline Angstetra was awarded a St Vincent's Hospital Research Week poster prize

Grants

- BK Murthy. Interactions between the autoantigens proinsulin and IGRP in the pathogenesis of diabetes in NOD mice. JDRF Postdoctoral Fellowship (2-year support)
- HE Thomas. The role of NK cells in the development of rapid-onset diabetes in the NOD mouse. Diabetes Australia Research Trust
- TWH Kay. Building Capacity for Human Cellular Diagnosis and Therapy. Bio21STI Initiative Funding
- TWH Kay. Mechanisms of pancreatic beta cell destruction in Type 1 Diabetes. Rebecca L. Cooper Medical Research Foundation Grant
- TWH Kay. Biomanufacturing costs for an islet transplant program. The Marian & EH Flack Trust
- TWH Kay. Purchase of equipment for human islet cell transplantation and research. The H & L Hecht Trust Grant
- TWH Kay. Purchase of equipment for human islet research. The Jack Brockhoff Foundation
- JDRF Summer Student Grant

SIGNAL TRANSDUCTION

Fellowships and prizes

- Dr Christine Brender received a travel award to attend Keystone Symposium "Jaks and Stats: Development to Disease" Whistler, Canada
- Dr Christine Brender received a travel award from the Danish Medical Research Council for "settling-in" to Australia for her postdoctoral studies

BONE, JOINT AND CANCER GROUP

Fellowships and prizes

- Prof TJ Martin received the Clive and Vera Ramaciotti Medal for Excellence in Biomedical Research (2004). This award honours a person who has made an outstanding discovery in clinical or experimental biomedical research
- Assoc Prof MT Gillespie was elected to the Board of Research Australia, an organization that raises public awareness of health and medical research with the view to increase government and private sector support for Australian medical research
- Assoc Prof MT Gillespie was awarded a Principal Research Fellowship of the NHMRC
- Dr Frances Milat was awarded a Medical Postgraduate Scholarship of the NHMRC and a research scholarship from the Royal Australasian College of Physicians
- Dr Frances Milat was appointed as the Albert Maggs Scholar.
- Dr Akira Nakamura won the most outstanding abstract award at the Australian and New Zealand Bone and Mineral Society Meeting held in the Hunter Valley
- Dr Jane Fisher was awarded a Senior Investigator Award at St Vincent's Hospital Research Week

Grants

- TJ Martin, MT Gillespie, KW Ng and NA Sims. NHMRC Program Grant (5-year support)
- MT Gillespie. Clive and Vera Ramaciotti Foundation equipment grant to support the purchase of an imaging system
- F Milat. Understanding the action of PTH. Eli Lilly Endocrine Research Grant
- JT Price and MT Gillespie. Live-cell imaging system. Private Men's Business, Prostate Cancer Foundation
- R Mudge. The study of interactions and mechanisms that allow nuclear fibroblast growth factor-2 to act as a survival factor in cancer metastasis. Clive and Vera Ramaciotti Foundation Establishment Gift
- NA Sims and S Rogers. Glucose transporter GLUT12: a potential target for the treatment of rheumatoid arthritis. St Vincent's Hospital, Melbourne Grant-in-aid

COMPARATIVE ENDOCRINOLOGY

Grants

- J Danks. Novel parathyroid hormone for the treatment of osteoporosis. Biotechnology Innovation Fund Round 6

TUMOUR CELL MIGRATION AND METASTASIS

Fellowships and prizes

- Dr John Price received an Outstanding Achievement Award for the best scientific abstract and oral presentation at the 9th World Congress on Advances in Oncology, and the 7th International Symposium on Molecular Medicine meeting in Hersonissos, Crete
- Ms Kelly Waldeck received a number of scholarships, including the R.J. Fletcher Scholarship, the Mable Kent Scholarship and the Randal and Louisa Alcock Scholarship
- Ms Michelle Kouspou received an Australian Postgraduate Award

Grants

- J Price. Examination of the Green Tea Catechin, EGCG, as a Novel Therapy for Bone Metastases. American Institute of Cancer Research (2-year support)
- J Price, J Quinn and MT Gillespie. The Role of HSF-1 and the Bone Microenvironment in the Enhancement of Bone Metastasis by the HSP90 Inhibitor 17-AAG. National Breast Cancer Foundation (3-year support)

PHARMACOGENOMICS

Fellowships and Prizes

- Dr Maria Schache received a St Vincent's Hospital Research Week Poster Prize

Grants

- M Waltham. The genetic basis of rapid growth vestibular schwannomas. St Vincent's Hospital Research Grant-in aid

PROTEIN CHEMISTRY

Fellowships and Prizes

- Dr Gregory Steinberg was awarded a Canadian Target Obesity Fellowship from the Heart and Stroke Foundation, the Canadian Diabetes Association and the Canadian Institutes of Health Research
- Dr Andrew Carey received a Peter Doherty Fellowship from the NHMRC
- Prof Bruce Kemp was awarded a Senior Principle Research Fellowship (Hon) from the NHMRC

Grants

- BE Kemp. Physiological effects of manipulating AMPK signalling genes, NHMRC Project grant (3-year support)
- BE Kemp, BJ Michell and GR Steinberg. Regulation of Protein Kinases and their Substrates NHMRC Project grant (3-year support)
- BE Kemp. Metabolic stress signalling in the heart. National Heart Foundation
- BE Kemp. Coordinating energy metabolism to enhance exercise capacity. ARC
- BE Kemp. Signalling detection facility. Clive and Vera Ramaciotti Foundation

MOLECULAR GENETICS

Fellowships and prizes

- Dr Ana Traven was awarded a Peter Doherty Research Fellowship from the NHMRC for post-doctoral studies within the molecular genetics group
- Dr Brietta Pike was a finalist in the Cure Cancer Australia Foundation Researcher of the Year Award
- Ms Carolyn McNees was awarded the best poster prize at the Lorne Cancer Conference
- Dr Jörg Heierhorst received the best poster prize at the Juan March Cancer Predisposition Syndromes Conference in Madrid, Spain
- Ms Carolyn McNees was awarded a Young Investigator Award at St Vincent's Hospital Research Week

Grants

- J Heierhorst. Functions of a novel conserved DNA damage response protein family in telomere stability. NHMRC Project grant (3-year support)

VIROLOGY

Fellowships and Prizes

- Mr Chan-Sien Lay received a St Vincent's Hospital Research Week Poster Prize

Grants

- P Poumbourios, HE Drummer, J Mak and M Hill. Receptor induced conformational changes in gp120: inhibitor targets? American Foundation for AIDS Research Project Grant
- P Poumbourios, HE Drummer and J Mak. Receptor-induced conformations in retroviral glycoproteins. NHMRC Project Grant (3-year support)

NRL

Fellowships and Prizes

- Ms Kim Richards received a St Vincent's Hospital Research Week Poster Prize

BIOTA STRUCTURAL BIOLOGY

Fellowships and Prizes

- Prof Michael Parker was awarded a GE Healthcare Bio-Sciences Award of the Australian Society of Biochemistry and Molecular Biology for distinguished contributions to the field of Biochemistry and Molecular Biology in Australia
- Dr Julian Adams was awarded a Peter Doherty Postdoctoral Fellowship from the NHMRC
- Mr Mark Walter received a Dora Lush Postgraduate Scholarship from the NHMRC
- Mr Geoffrey Kong received the Australian Society for Biophysics Student Presentation Prize
- Mr Geoffrey Kong was awarded a Ludo Frevel Crystallography Scholarship
- Ms Lorien Parker received a Photography Award from Melbourne University in the "Under the microscope" competition
- Ms Lorien Parker received a St Vincent's Hospital Research Week Poster Prize

Grants

- WJ McKinstry. Chromatography system for purifying proteins. Perpetual Trustees Research Grant

Publications

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Campbell D.J., Woodward M., Chalmers J.P., Colman S.A., Jenkins A.J., Kemp B.E., Neal B.C., Patel A. and MacMahon S.W. Prediction of heart failure by amino terminal-pro-B-type natriuretic peptide and C-reactive protein in subjects with cerebrovascular disease. *Hypertension,* 45:69-74, 2005.

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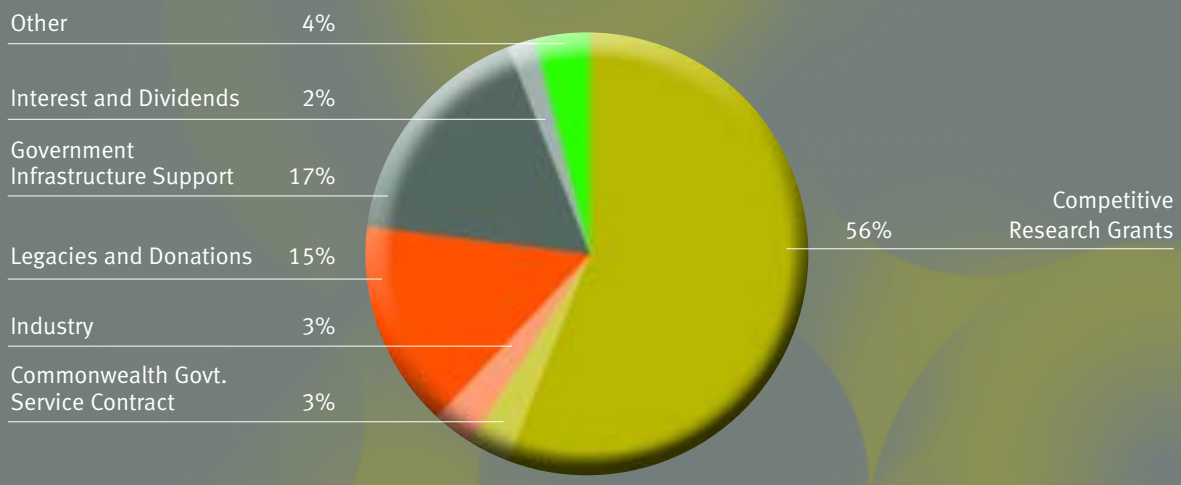
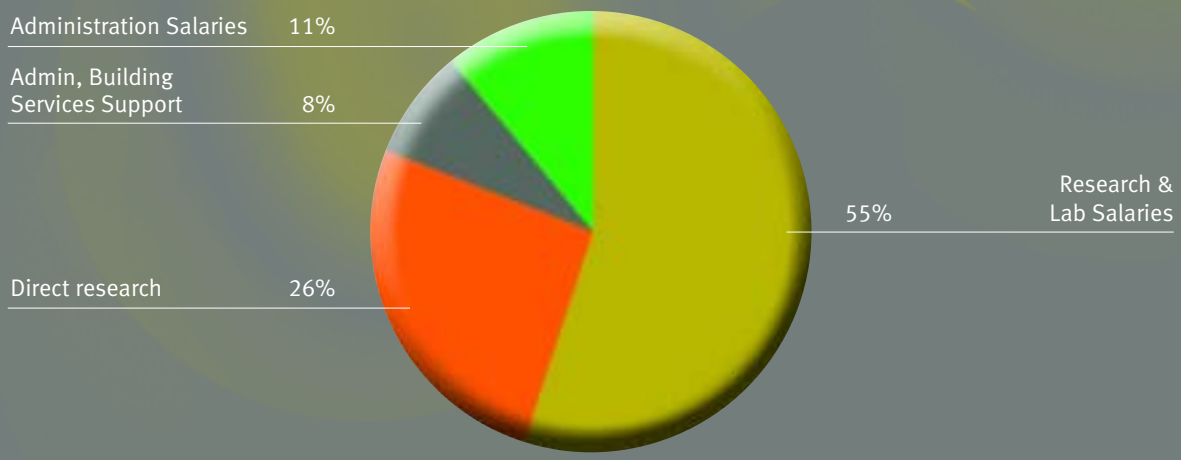
Financial Snapshot

INCOME



EXPENDITURE



DIRECTORS' REPORT

Your Directors present their report on the company for the financial year ended 31 December 2004.

1. Board of management

The names of Directors in office at any time during or since the end of the year are:

Ms Sue M Alberti
Prof James D Best
Sr Mary Fankhauser
Mr Charles A Griss
Prof Thomas WH Kay
Mr G John Pizzey (from 30 April 2004)
Mr Gregory J Robinson (from 30 April 2004)
Mr Douglas A Wright
Prof James A Angus
Mr Jeff Clifton
Ms Nicole M Feely
Mr Barry J Jackson
Ms Ruth A O'Shannassy
Mr Ian D Reid
Ms Brenda M Shanahan

Directors have been in office since the start of the financial year to the date of this report unless stated otherwise.

2. Principal activity

The principal activity of the company during the financial year was medical research. There was no significant change in the nature of the company's principal activity during the financial year.

3. Operating results

The operating surplus of the company was $468,481

4. Dividends

In accordance with the company's constitution no funds are distributed either to members of the Board or members of the company.

5. Review of operations

In 2004 the Institute focused on consolidating it's financial position after the extensive building capital works program that occurred in 2003. Competitive research grants awarded to researchers represented 66% of the total grant income of $9,577,736. In addition the company received a grant of $500,000 from the Commonwealth Government - Department of Health and Ageing for the purchase of equipment. The company continued to receive infrastructure support from the State Government through the Department of Innovation, Industry & Regional Development (DIIRD), totalling $1.46m, which was an increase of 22% on 2003. However, this year there was an overall decrease in income of $4.4 million from 2003. The decrease is due to the fact that 2003 was an exceptional year for receiving income for the building, including a donation of $750,000 and $1.95 million government funding and a change in accounting treatment that resulted in a $2.3 million building expense in 2002 being written back to capital - leasehold improvements in 2003.

Research expenditure increased by 15% on last year, reflecting a continued expansion of research activity. Administration, building and laboratory support has increased at a greater rate (31%) this year but resources have been overstretched for some years and the recent expansion of our research facilities have placed further demand on the support services. It has been timely that the infrastructure support funds from DIIRD increased by 22% in 2004, thereby making it financially possible to expand the company's research support services. The administration and building services represent 19% of the company's direct expenditure (excluding depreciation and external transfers). During the financial year the company made significant research equipment purchases, totalling $791,724.

In 2004 the number of staff and students increased to 115, a 13% increase on 2003 (102). In addition the company acts as the host institute for the National Serology Reference Laboratory (NSRL), providing administration and research support to the 31 NSRL staff.

6. Significant changes in state of affairs

The following significant change in the state of affairs of the company occurred during the financial year:

The Institute registered a public company, St Vincent's Institute Foundation, on the 12th March 2004. This company is limited by guarantee and will be the fundraising arm of the Institute with all funds raised distributed to the Institute. This change did not impact on the Institute's legal status as a company limited by guarantee and operationally should improve the Institute's financial performance.

DIRECTORS' REPORT

7. After balance date events

No matters or circumstances have arisen since the end of the financial year which significantly affected or may significantly affect the operations of the company, the results of those operations, or the state of affairs of the company in future financial years.

8. Future developments

The likely developments in the operations of the company and the expected results of the operations in future financial years are as follows:

During 2005 the Institute will continue to expand its research operations by contributing over $1.0 million towards capital works and equipment for a shared research facility with St Vincent's Hospital - Melbourne.

9. Environmental issues

The company operates predominantly within the medical research sector and is committed to conducting its business activities with respect for the environment while continuing to meet expectations of members, employees, customers and suppliers. During the period from 1 January 2004 to the date of this report, this company has complied with the requirements of the Environmental Protection Act.

10. Meetings of directors

During the financial year, 13 meetings of directors (including committees) were held. Attendees were:

	Directors' Meetings		Committee Meetings			
			Appeal (pre Foundation)		Finance	
	Number eligible to attend	Number Attended	Number eligible to attend	Number attended	Number eligible to attend	Number attended
S Alberti	6	4	2	2	-	-
JA Angus	6	5	-	-	-	-
JD Best	6	6	-	-	-	-
J Clifton	6	4	-	-	-	-
Sr M Fankhauser	6	5	-	-	-	-
NM Feely	6	3	-	-	-	-
CA Griss	6	6	-	-	5	5
BJ Jackson	6	5	-	-	-	-
TWH Kay	6	4	2	2	5	3
R O'Shannassy	6	5	-	-	5	5
GJ Pizzey	4	4	-	-	-	-
ID Reid	6	4	-	-	5	5
GJ Robinson	4	1	-	-	-	-
BM Shanahan	6	5	2	1	-	-
DA Wright	6	5	2	0	-	-

DIRECTORS' REPORT

11. Directors' and auditors' indemnification

The company has not, during or since the financial year, in respect of any person who is or has been an officer or auditor of the company or a related body corporate:

- indemnified or made any relevant agreement for indemnifying against a liability incurred as an officer, including costs and expenses in successfully defending legal proceedings;
- paid or agreed to pay a premium in respect of a contract insuring against a liability incurred as an officer for the costs or expenses to defend legal proceedings; with the exception of the following matters.

During or since the financial year the company has paid premiums to insure each of the following directors against liabilities for costs and expenses incurred by them in defending any legal proceedings arising out of their conduct while acting in the capacity of director of the company, other than conduct involving a wilful breach of duty in relation to the company:
SM Alberti, JA Angus, JD Best, J Clifton, Sr M Fankhauser, NM Feely, CA Griss, BJ Jackson, TWH Kay, RA O'Shannassy, GJ Pizzey, ID Reid, GJ Robinson, BM Shanahan, DA Wright.

12. Proceedings on behalf of company

No person has applied for leave of Court to bring proceedings on behalf of the company or intervene in any proceedings to which the company is a party for the purpose of taking responsibility on behalf of the company for all or any part of those proceedings. The company was not a party to any such proceedings during the year.

Signed in accordance with a resolution of the Board of Directors.

Director
BM Shanahan

Director
CA Griss

Dated this 18th day of April 2005, Melbourne, Australia

DISCUSSION AND ANALYSIS OF THE FINANCIAL STATEMENTS

Information on St Vincent's Institute of Medical Research Concise Financial Report
The financial statements and disclosures in the concise financial report have been derived from the 2004 Financial Report of St Vincent's Institute of Medical Research. A copy of the full financial report and auditors report will be sent to any member, free of charge, upon request.

The discussion and analysis is provided to assist members in understanding the concise financial report. The discussion and analysis is based on the company's financial statements and the information contained in the concise financial report has been derived from the full 2004 Financial Report of St Vincent's Institute of Medical Research.

Statement of Financial Performance
The net surplus from ordinary activities for the year is $6.6 million less than the results of 2003. However in 2003 the company received capital works funding of $3.7 million for the building extension project and wrote back leasehold improvements expenditure of $2.3 million. The decline in the surplus from 2003, after taking the previous factors into consideration, is $0.6 million and this is due to the increase in depreciation on leasehold improvements.

In 2004, the key sources of funds for the company were 56% from competitive granting bodies, 17% from Government for infrastructure support and 15% from donations. Expenditure on research salaries and direct research expenses represents 81% of total expenditure (excluding depreciation).

Statement of Financial Position
The total net assets increased by $468,000, representing an increase of 3.7%, due to:

- Current assets increased by $912,000 to improve the company's liquidity position after the reduction in working capital over the previous 2 years, when funds were allocated to the building extension project.
- The net value of the property and equipment decreased by $542,000 due to the increase in depreciation, brought about by a full year amortisation of the leasehold improvements.
- Total liabilities remained unchanged from 2003.

Statement of Cash Flows
At the end of 2004 the cash position increased from $1.2 million to $2.8 million. In 2004 payments to suppliers and employees increased by $0.9 million, reflecting the increased research and support activity, which was expected when the building extension project was completed. However this increase in expenditure was offset by a reduction in the building and equipment expenditure in 2004, thereby allowing the net cash position to improve.

STATEMENT OF FINANCIAL PERFORMANCE FOR THE YEAR ENDED 31 DECEMBER 2004

	Note	2004 ($)	2003 ($)
Revenues from ordinary activities	2	11,436,624	16,041,336
Employee benefits expense	3	(5,878,004)	(5,160,775)
Depreciation and amortisation expenses	3	(1,426,911)	(759,859)
Other expenses from ordinary activities		(3,663,228)	(3,047,443)
Net surplus from ordinary activities		468,481	7,073,259
Total changes in equity		**468,481**	**7,073,259**

The accompanying notes form part of this concise financial report.

STATEMENT OF FINANCIAL POSITION FOR THE YEAR ENDED 31 DECEMBER 2004

	2004 ($)	2003 ($)
CURRENT ASSETS		
Cash assets	2,823,859	1,176,245
Receivables	350,097	1,094,858
Other financial assets	10,000	-
TOTAL CURRENT ASSETS	3,183,956	2,271,103
NON-CURRENT ASSETS		
Receivables	250,000	250,000
Other financial assets	476,499	415,088
Property, plant & equipment	11,855,661	12,397,507
TOTAL NON-CURRENT ASSETS	12,582,160	13,062,595
TOTAL ASSETS	15,766,116	15,333,698
CURRENT LIABILITIES		
Payables	558,998	376,217
Funds held in trust for NSRL accrued leave	138,280	138,280
Provisions	737,012	717,467
Other	1,100,365	1,401,223
TOTAL CURRENT LIABILITIES	2,534,655	2,633,187
NON-CURRENT LIABILITIES		
Provisions	159,372	96,903
TOTAL NON-CURRENT LIABILITIES	159,372	96,903
TOTAL LIABILITIES	2,694,027	2,730,090
NET ASSETS	**13,072,089**	**12,603,608**
EQUITY		
Retained surplus	13,072,089	12,603,608
TOTAL EQUITY	**13,072,089**	**12,603,608**

The accompanying notes form part of this concise financial report.

STATEMENT OF CASH FLOWS FOR THE YEAR ENDED 31 DECEMBER 2004

	2004 ($) Inflows (Outflows)	2003 ($) Inflows (Outflows)
CASH FLOW FROM OPERATING ACTIVITIES		
Grants received	9,491,400	10,737,210
Payments to suppliers and employees	(9,498,694)	(8,544,797)
Donations, legacies and bequests	1,173,235	1,809,975
Other revenue	1,237,570	224,405
Interest received	158,951	170,848
Dividends	31,629	21,203
Leasehold improvements	-	2,305,972
Net cash provided by operating activities	**2,594,091**	**6,724,816**
CASH FLOW FROM INVESTING ACTIVITIES		
Purchase of plant and equipment	(885,066)	(1,288,441)
Leasehold improvements	-	(9,887,062)
Payments for investments	(61,411)	(56,178)
Net cash (used in) investing activities	**(946,477)**	**(11,231,681)**
Net Increase/(decrease) in cash held	1,647,614	(4,506,865)
Cash at the beginning of the year	1,176,245	5,683,110
Cash at the end of the year	**2,823,859**	**1,176,245**

The accompanying notes form part of this concise financial report.

NOTES TO THE CONCISE FINANCIAL REPORT FOR THE YEAR ENDED 31 DECEMBER 2004

The concise financial report has been prepared in accordance with Accounting Standard AASB 1039: Concise Financial Reports and the *Corporations Act 2001*.

The financial statements, specific disclosures and other information included in the concise financial report are derived from and are consistent with the full financial report of St Vincent's Institute of Medical Research. The concise financial report cannot be expected to provide as detailed an understanding of the financial performance, financial position and financing and investing activities of St Vincent's Institute of Medical Research as the full financial report.

The accounting policies have been consistently applied by the company and are consistent with those of the previous year.

Note 2: Revenue

	Note	2004 ($)	2003 ($)
Operating activities			
- grants	4-6	9,577,736	11,419,368
- contract services		295,853	269,207
- legacies, bequests, donations		1,167,235	1,719,731
- dividends	(a)	31,629	21,203
- interest	(b)	163,933	163,400
- royalty		87,749	53,691
- profit from sale of shares		23,072	-
- write back of leasehold improvements expenditure		-	2,305,973
- other		89,417	88,763
Total revenue		**11,436,624**	**16,041,336**
(a) Dividends from:			
- other corporations		31,629	21,203
(b) Interest from:			
- other corporations		163,933	163,400

Note 3: Surplus from Ordinary Activities

	2004 ($)	2003 ($)
The company's surplus has been calculated after charging the following items:		
Expenses		
- research	2,342,097	2,034,161
- research salaries and on-costs	4,709,053	4,095,693
- infrastructure	753,282	395,953
- Admin. & Lab support salaries and on-costs	1,168,951	1,065,081
	8,973,383	**7,590,888**
Transfer of funds to external joint collaborators	**567,849**	**617,330**
Depreciation of non-current assets	**761,475**	**593,500**
Amortisation of non-current assets	**665,436**	**166,359**

NOTES TO THE CONCISE FINANCIAL REPORT FOR THE YEAR ENDED 31 DECEMBER 2004

Note 4: Grants - Commonwealth Government

	2004 ($)	2003 ($)
National Health and Medical Research Council	4,655,067	4,350,720
Australian Research Council	361,505	201,206
Department of Health and Aging	500,000	1,965,000
	5,516,572	6,516,926

Note 5: Grants - Victorian State Government

	2004 ($)	2003 ($)
Department of Innovation, Industry & Regional Development		
- infrastructure support	1,460,264	1,194,298
- capital works	-	1,000,001
Department of Human Services	-	72,000
	1,460,264	**2,266,299**

Note 6: Grants - Other

	2004 ($)	2003 ($)
Australian Centre for HIV & Hepatitis		
Virology Research	93,332	-
Avexa Limited	12,500	-
Biota Holdings Ltd	78,506	79,618
Chugai Pharmaceuticals Co	126,261	172,898
Cortical Pty Ltd	34,000	-
Diabetes Australia Research Trust	71,150	-
Eli Lilly Australia	30,000	-
Juvenile Diabetes Research Foundation	385,832	341,726
Kidney Foundation Australia	-	5,366
Max Planck Research Award	-	54,716
Metabolic Pharmaceuticals Ltd	9,776	-
National Breast Cancer Foundation	47,291	53,217
National Heart Foundation of Australia	133,236	121,655
National Heart, Lung & Blood Institute	69,684	203,626
National Institutes of Health	351,496	263,220
Novatis Pharma AG	14,500	-
St. Vincent's Hospital, Melbourne	69,523	15,218
Susan G. Komen Cancer Foundation	32,348	244,201
The Cancer Council of Victoria	60,000	61,015
University of Melbourne	370,895	244,594
US Army Medical Research Command	109,450	48,663
Victorian Breast Cancer Research Consortium	357,500	400,000
Victoria Department of Education	-	9,607
Transfer from other Institutes	28,750	153,049
Other	114,870	163,754
	2,600,900	**2,636,143**

Note 7: Segment Reporting

The company operates in the medical research sector where it undertakes basic and clinical research in Australia.

DIRECTORS' DECLARATION

The directors of the company declare that the concise financial report of St. Vincent's Institute of Medical Research for the financial year ended 31 December 2004, as set out on pages 53 to 60:

a) complies with Accounting Standard AASB 1039: Concise Financial Reports; and

b) has been derived from and is consistent with the full financial report of St. Vincent's Institute of Medical Research.

This declaration is made in accordance with a resolution of the Board of Directors.

Director
BM Shanahan

Director
CA Griss

Dated this 18th day of April 2005, Melbourne, Australia

INDEPENDENT AUDIT REPORT TO THE MEMBERS OF ST VINCENT'S INSTITUTE OF MEDICAL RESEARCH

Scope

We have audited the concise financial report of St Vincent's Institute of Medical Research for the financial year ended 31 December 2004 comprising the Statement of Financial Performance, Statement of Financial Position, Statement of Cash Flows, Notes to the concise financial report and Directors' Declaration in order to express an opinion on it to the members of the company. The company's directors are responsible for the concise financial report.

Our audit has been conducted in accordance with Australian Auditing Standards to provide reasonable assurance whether the concise financial report is free of material misstatement. We have also performed an independent audit of the full financial report of St Vincent's Institute of Medical Research for the year ended 31 December 2004. Our audit report on the full financial report was signed on 18 April 2005 and was not subject to any qualification.

Our procedures in respect of the audit of the concise financial report included testing that the information in the concise financial report is consistent with the full financial report, and examination on a test basis, of evidence supporting the amounts, discussion and analysis, and other disclosures which were not directly derived from the full financial report. These procedures have been undertaken to form an opinion whether, in all material respects, the concise financial report is presented fairly in accordance with Accounting Standard AASB 1039: Concise Financial Reports.

The audit opinion expressed in this report has been formed on the above basis.

Audit Opinion

In our opinion, the financial report of St Vincent's Institute of Medical Research complies with Accounting Standard AASB 1039: Concise Financial Reports.

WEBB CALLAWAY PATON
Chartered Accountants

AP MARKS

Melbourne: 18 April 2005

St Vincent's Institute of Medical Research ABN 52 004 705 640
DONATIONS AND BEQUESTS

BEQUESTS & DONATIONS FROM ESTATES & CHARITABLE TRUSTS

Private Mens' Business, supporting Prostate Cancer Foundation	120,000
Helen Macpherson Smith Trust	100,000
Equity Trustees - Arthur A Thomas Trust	90,000
Perpetual - Ramaciotti Foundation	59,769
The Marian & EH Flack Trust	50,000
The Sarah & Baillieu Myer Family Foundation	50,000
Perpetual - H & L Hecht Trust	50,000
Perpetual - K & A Bongiorno Research Endowment	39,058
Perpetual - The Mary Jane Polinelli Foundation	37,401
Perpetual - The Ronald Geoffrey Arnott Foundation	20,132
George Castan Family Charitable Trust	15,000
Trust Company of Australia Ltd - Frederick & Winifred Grassick Memorial Fund	10,000
The Michael & Andrew Buxton Foundation	7,000
The Breast Cancer Research Trust Fund	3,855

LIST OF DONORS

$50,000 plus
Alberti AM, S
Yu, MK

$15,000 - $19,999
Anonymous

$10,000 - $14,999
McHale, JJ
O'Shannassy, M & R
Watson, B

$5,000 - $,9999
Jackson, B
Otter, G
Palace Cinemas
Robinson, G
Tabak, L
Tattersall's Holdings Pty Ltd
Vermont Cancer Research Group
Worldcom Inc & Wright Business Marketing

$2,000 - $4,999
Campbell Tuckfield, P
Cole, M
Dwyer, M
Golden Point Management Pty Ltd
Kerr , L
Lowe, D
Mayo Consulting Pty Ltd
McKeage, C
Michelmore AO, J
Molan, C & F
Power, T & D
Vamsun Pty Ltd
Westpac matching gifts program
Wilkie, R & L
Xipell, T

$1,000 - $1,999
Abdallah, J & C
Abdallah, T & S
Alfonso, E
Allen, J
Almslock Pty Ltd
ANZ Matching funds program
Beck, M
Beever, J & T
Bloom, B
Bloom, N & A
Bongiorno , J & E
Bowness, B
Brown, RV
Brown, SV
Burgess, A & L
Bursztyn, P & J
Carson, T
Carson, I
Chojna, H
Ciconte, A & L
Clancy, W & C
Clifton, S
Commins, H
Conn, B & J
Danos, T & E
d'Apice, T & C
de Capele, D
Demediuk, F
Dwyer, P
Elliott, M & P
Evans, D
Florenini, O
Fowler, M
Fried, T
Fried, E
Frost, R
Gill, P & M
Gillespie, M
Goldbloom, L & Y
Griss, C
Grogan, D & J
Grogan, B
Guest, A & E
Guest AM OBE, J
Gurry, J
Hummerston, T & A
Iacobucci, M
Isaac, J
Jelinek, M
Johnstone, A & J
Jolson, C
Jones, WMP
Kay, T
Kerr, M & L
Kerr, V
Kopke, P & L
Kostos, K
Kozica, W
Leigh, P & G
Lempriere, J
Liberman, B & H
Mahemoff AO, J & H
Marne Development Pty Ltd
Martin, S
Martin AO, TJ
McGuire, E & C
McNamee, B
McNamee, V
Meadows, P
Meltzer, F & W
Molan, M & M
Morlacci, P & J
Mullen, KJ & JA
Niall, H & M
North, C
O'Callaghan SC, D
Pellicano, N & A
Phapazy, J
Pizzey, J & B
Plant, B
Plant, K
Ralph AC, J
Reeve, F
Reidl
Rodas, T & M
Rowe, J
Rush/Menelaus, G/J
Russel, P & S
Russo, S
Rutman, L
Ryan, F & J
Sapphire One Pty Ltd
Savas, R & K
Savvides, G
Sax International Pty Ltd
Scott, P & O
Simpson, A & G
Skala, S
Skala, L
Slatter, M & C
Smorgon OAM, D & R
Smorgon, V
Smorgon, T
Solomon, Q & E
Southwick, G & S
Spry-Bailey, P
Steven, J
Stops, W
Tashi, R
Thurin, D & L
Turner, R
Turner, J
UBS Bank matching gifts program
Wellington, C
Whitehead, M & M
Whiting, N & T
Yencken, T & M
Young, D
Young, C
Young, D
Young, H

$200 - $999
Bloch, F & S
Casper, M & C
Castan, G & F
Dax AM, L
Emerson, J
Gehrig, R & H
Hall, J
Killen, JA
Little, G
Masel, L & S
McPherson, J
Mullaly, C
Nicoll, G
Noonan, G
Pappas, J & G
Ripper, GH
Ritchies Store Pty Ltd
Rowe, W
Santamaria, RB
Schillier, P & J

Under $199
Bell, B & S
Bergin, J & P
Cator, H & K
Connor, D
Cookes, C
Croagh, M & G
Demediuk, P
Douez, E
Dowell, NR
Fasso, A & J
Gill, J & A
Gray, M
Hale, G
Hamersfeld, M & B
Henderson, JK
Hien To, J
Kemp, B
Lacey, C
Mackay, B & D
Mar, V & J
May, KL & NE
McCarthy, B
McKelvie, P
McKinstry, B
O'Bryan, NM
O'Connor, J
Pack, J & V
Papas, D
Pennington, D
Rees, R
Regan, S
Renouf, S
Robertson, J
Rutman, S
Salta Property Logistics/Westgarth Logistics Pty Ltd
Townshend, P
Waldeck, W & D

In Memorial Donations
Gifts in remembrance have been made in honour of the following:

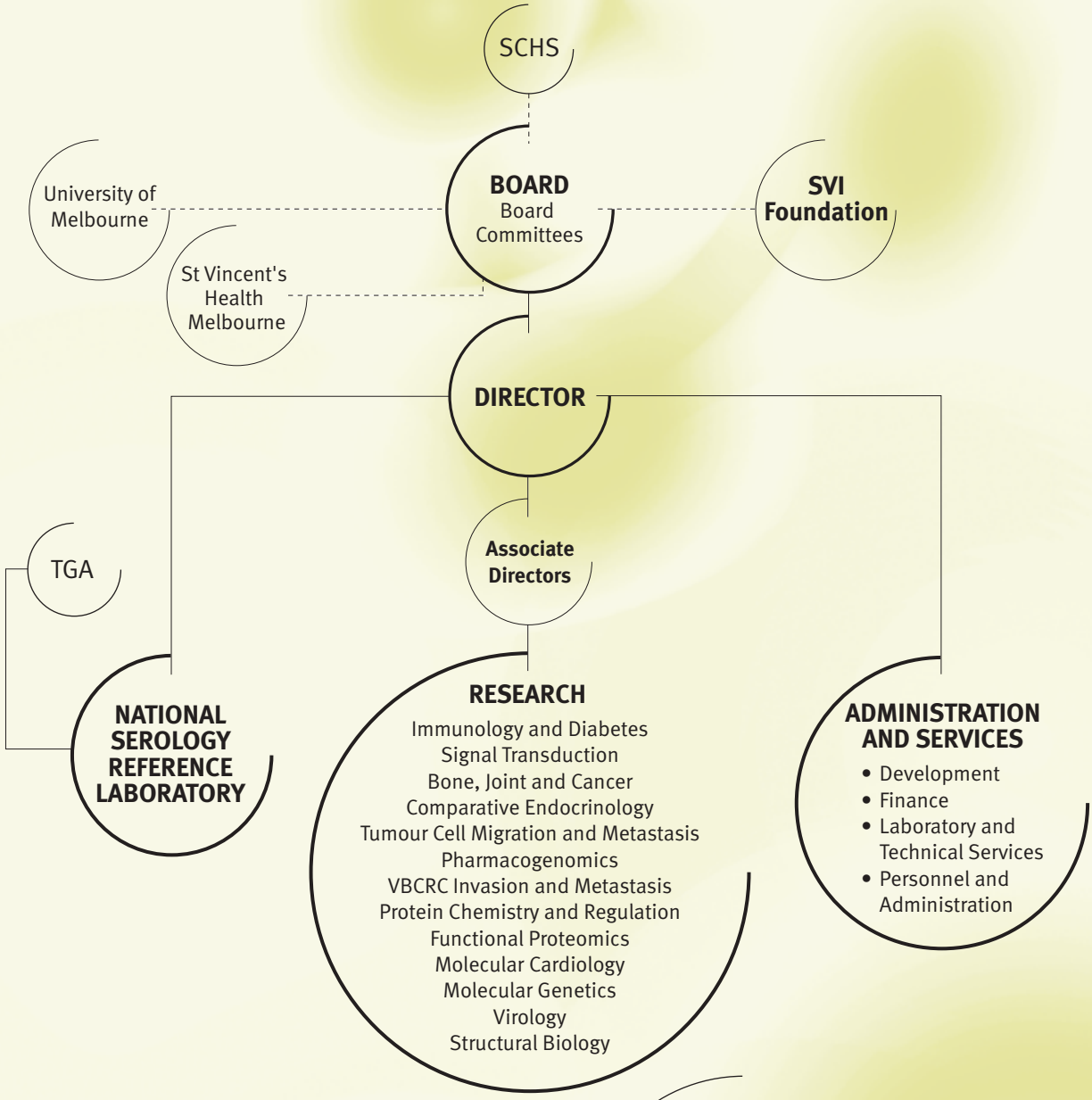
George M Carson
Anthony Molan
Gerald Morton

Permanent Invested Funds

The following permanent funds are included in the company's pool of invested funds with income being directed to the Institute's medical research programs:

The Mary Potter Research Grant	90,797
Diane B Jones Endowment	970
Lorna M Miller Endowment	208,651
Albert H Maggs Endowment	100,000

St Vincent's Institute Organisation Chart 2004



PARTICIPANT IN

Bio 21

Victorian Breast Cancer Research Consortium

St Vincent's Diabetes Centre of Excellence

DISEASE FOCUSSED RESEARCH

Diabetes

Bone Diseases

– cancers (breast, lung and prostate) that spread to bone, osteoporosis, arthritis and other joint diseases

Cardiovascular Diseases

– including metabolism and obesity

Viral diseases

Neurological diseases

St Vincent's Institute
DONATIONS AND BEQUESTS

How can you make a difference?

The scientific research of the Institute is aimed at the treatment and cure of diseases that touch the lives of people in our community. Your financial support can have a direct effect on the success of the Institute's research.

There are many ways in which you can help. These include joining the SVI 1000 Club; making single, annual or more frequent gifts; making a donation either personally or from a Prescribed Private Fund (PPF); making bequests via a Will; or making a donation in memory of a loved one or esteemed person. Your business or organisation may also be interested in workplace giving. Information about all these can be obtained from SVI. Enquiries will be welcomed by the Director of the Institute on (03) 9288 2480.

St Vincent's Institute is an endorsed deductible gift recipient and income exempt charity. Contributions are used directly in research, not on administrative or fundraising costs.

However, the Institute will be pleased to use capital or income arising from a bequest for a specific purpose or area of research according to the donor's wishes. It may be advisable to obtain professional assistance in making such a provision.

Suggested wording for bequests:

"I _____, bequeath unto St Vincent's Institute, 9 princes Street, Fitzroy, 3065 in the State of Victoria for it's general purposes (indicate the amount and/or item and/or address of property) free of all succession, estate and other death duties and declare that the receipt of the Director or other proper officer of the Institute shall be sufficient discharge to my Executors in respect thereof."

Join us in the voyage of continuous discovery and share in the rewards our research will provide.

SVI
ST VINCENT'S INSTITUTE
~ continuous discovery

St Vincent's Institute ABN 52 004 705 640
Postal: 41 Victoria Parade, Fitzroy Victoria 3065
Located: 9 Princes Street, Fitzroy Victoria 3065
Telephone: +61 3 9288 2480 **Facsimile:** +61 3 9416 2676
Email: enquiries@svi.edu.au **Web:** www.svi.edu.au

Donation Form

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Type of Membership:

◯ New ◯ Continuing

◯ Corporate ◯ Individual

SVI 1000 Club Member ($1,000 per annum)

$ _____

◯ 1yr ◯ 2yrs ◯ 3yrs ◯ 3yrs+

OTHER DONATION

◯ Donation $ _____

All gifts over $1000 will automatically qualify you as a member of the SVI 1000 Club. SVI respects your privacy. If you do not wish to receive some or all of our supporter information, please contact our office on (03) 9288 2480.

Thank you for your support.
All amounts of $2 and over are tax deductible.

SVIMR ABN 52 004 705 6400

Postal address:
41 Victoria Parade,
Fitzroy Vic 3065

◯ Mr ◯ Mrs ◯ Ms ◯ Miss ◯ Other _____

First name _____ Surname _____

Position _____ Company _____

Address _____

Suburb _____ P/Code _____ State _____

Ph Work _____ Fax _____

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PAYMENT DETAILS

◯ Cheque (please make cheque payable to St Vincent's Institute)

◯ Credit Card (please tick one of the following cards to complete details.)

◯ Diners ◯ Visa ◯ Mastercard ◯ Bankcard ◯ Amex Expiry Date ____/____

☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Amount being paid $ _____ Signature _____

OPTIONS

Please email/mail me ◯ All correspondence ◯ Newsletter ◯ Annual Report ◯ Promotions

◯ SVI 1000 Club events ◯ Forum Invitation ◯ **Yes, I would like to take a tour of St Vincent's Institute**

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Helen Thomas

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