SVIMR
MOLECULES TO MEDICINE

Annual Report 2001 | St.Vincent's Institute of Medical Research

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SVIMR
MOLECULES TO MEDICINE

SVIMR | molecules to medicine

MISSION STATEMENT

St. Vincent's Institute of Medical Research is a centre of excellence in medical research. Its mission is to take molecules to medicine thereby promoting human well-being through the prevention and treatment of diseases. Its programs of basic and clinical research are applied to the study of certain diseases that are of great cost to the Australian community. These include osteoporosis and other bone diseases, cancers (breast, lung and prostate) that spread to bone, and also diseases of the heart and blood vessels.

The Institute is an independent one, founded in 1955 as an initiative of the Congregation of the Sisters of Charity and St. Vincent's Hospital. It is a member institution of Australia-wide health care facilities of the Sisters of Charity, and is sponsored and supported by the Congregation in many ways.

The contribution made by the research of the Institute to advancement of health care in Australia is an important one, and is conducted in close co-operation with a major teaching hospital, St. Vincent's Hospital Melbourne, and with The University of Melbourne. Through these links its research programs provide a valuable service to clinical medicine, graduate education and community welfare.

Image: Recent PhD graduate Andrew Hammet

CHAIRMAN'S 2001 REPORT

The new development will allow us to provide for existing staff and technologies as well as providing for the opportunities that come out of the exciting research of the Institute

Institute Governance

It is my pleasure to report that 2001 was a busy and productive year that will stand as a turning point in the Institute's history. We not only had an excellent year in research achievements but we also commenced our delayed building program. In October the Victorian Government announced a grant to the Institute of $2 million under its Strategic Technology Initiative Program for Infrastructure. Together with $0.75 million from the Sisters of Charity Health Service and with other supplementary funds, this allowed us to match the $3.5 million that had been awarded in early 2000 by the Commonwealth Government as part of their Capital Works Program for medical research institutes in Australia. We have appointed project managers, architects and other consultants with extensive experience for the planned expansion of the Institute. The plan is to double the size of the existing building, which is necessary because the number of researchers at the Institute is now more than twice that planned for the current building when it was opened in 1987. The new development will allow us to provide for existing staff and technologies as well as providing for the opportunities that come out of the exciting research of the Institute in protein structure and function, cancer and bone biology. The Board sees this as a vitally important task of the next two to three years, ensuring that we do all that is necessary to bring this project to its successful completion.

The Development and Marketing Committee, headed by Board member Brenda Shanahan, recently changed its role to that of an Appeal Committee and is embarking in earnest on a plan to raise funds for major equipment needed in the new development and upgrading of the old. The Committee was very active throughout the year, with its activities helped greatly by the appointment of Diane Losa as Development Manager, which was made possible by a generous donation. We had a number of "Director's Dinners" throughout the year, each of which featured a talk by a distinguished community leader – notable examples were our patron Sir Gustav Nossal, and former Olympian and now philanthropist, Ron Clarke. We appreciate the courtesy of Bryan Hiscock of Crown Limited, who generously sponsored these evenings at which visitors were also told something of the Institute's research and history.

Late in the year, encouraged by the marketing energy within this Board subcommittee and with the generous help of the Yering Station vineyard and Elaine Hogarty of Origin Design, the Institute promoted a special "Jack Holt" vintage as a novel and successful fund-raising venture. A particular event that gave us cause to celebrate was the induction of John Holt into the Racing Hall of Fame at a function held by the Racing Museum in July. Jack Holt, the highly successful racehorse trainer known as the "Wizard of Mordialloc", died in 1951 and it was his bequest that established the Institute. Wonderfully good at selecting great thoroughbreds and training them, he was a remarkably generous and kind man throughout his life, and we have always been aware of our debt to him. His photograph is displayed prominently in the Institute and we strive to do credit to his vision, expressed in his last will and testament, "to facilitate the establishment ... of a Medical Science Research Institute at the said St. Vincent's Hospital".

The Board recognizes that the success of the Institute is dependent on a strong partnership with the community, and we are striving to increase community awareness of the scientific success of the Institute and its implications for the health of the community.

Important though the preceding activities have been, the most crucial task for the Board has been to appoint a new Executive Director. Professor Jack Martin wishes to step down after a long and distinguished term to pursue other challenges. Although finalization of the

appointment did not take place until shortly after the end of the year, it is appropriate that it be announced in this Annual Report. In February 2002 Dr. Thomas Kay accepted the position and will have assumed the post by the time of this Annual General Meeting. He comes to us from The Walter and Eliza Hall Institute and has an outstanding record in diabetes research. We look forward to an exciting future under his leadership.

I am also delighted to report that in the Australia Day 2002 Honours our past Chairman, Tony Sallman, was made an Officer of the Order of Australia (AO). We congratulate him and thank him for his many years of devoted work on behalf of the Institute and the Hospital.

Finally, I wish to thank all Board members for their willing and generous support and, in many cases, for the great deal of extra work that they have taken on in this last year. I also want to congratulate the scientific staff for their continuing high quality research and the recognition that they achieve for it and to thank the administrative staff of the Institute for all their splendid work. It is the enthusiastic contribution of every member that helps the Institute live up to the vision of our original benefactor.

Ian Reid
Chairman

Board Members: *(left to right)*: Brenda Shanahan, Ian Reid, Charles Griss, Kerrie Cross, James Best, Douglas Wright

MEMBERS OF THE BOARD

Professor James Best
MD, BS, FRACP, FRC Path.

Professor Best is Professor and Head of The University of Melbourne Department of Medicine, St. Vincent's Hospital, Melbourne. He is the Co-Head of St. Vincent's Hospital's Department of General Internal Medicine, and is a Member of the Board of Directors of Eastern Health.

Mr John Gurry
Retired 28th May 2001
MBBS, FRCS, FRACS, FACS.

Mr Gurry is Director of Vascular Surgery, St. Vincent's Hospital (Melbourne) and a Senior Associate within The University of Melbourne's Department of Surgery. He is a Member of the International Society for Cardiovascular Surgery, European Society for Vascular Surgery and International Endovascular Society.

James Best | Laurence Clemens | Kerrie Cross | Marcia Griffin | Charles Griss | Sister Kathleen Higgs

Dr Laurence Clemens
MBBS,FRACP.

Dr Clemens is Director of The Department of Rheumatology, St Vincent's Hospital, Melbourne and Chairman of the Division of Medicine at St Vincent's Hospital Melbourne. He is the immediate past president of the Australian Rheumatology Association and a member of the British Society for Rheumatology.

Ms Kerrie Cross
BA, BSW, MHA.

Ms Cross is the Chief Executive Officer of the SCHS Service Melbourne. Prior to her current role, Ms Cross was a Regional Director with the Department of Human Services, a public hospital CEO and a Network Clinical Director. She is a member of the Boards of the SCHS Melbourne Region, Eastern Palliative Care, St. Vincent's Hospital (Launceston) Ltd, Wesley Mission Melbourne and the Brotherhood of St. Laurence.

Ms Marcia Griffin
BA, DipEd. B. Com.

Ms Griffin is a Board Member of PMP Communications Ltd, National Pharmacies, the Queen Victoria Market and the 2002 World Masters Games. She is on the Advisory Board for the Carr Design Group.

Mr Charles Griss
FCPA, FCA, FAICD.

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, and Chairman of both the Quality of Audit Committee and Community Advisory Committee for the SCHS Melbourne Region Board

Sr Kathleen Higgs
RSC, RN, BA, Grad. Dip. Health Services Management.

Sr Higgs is currently missioned to the role of Clinical Risk Manager, St. Vincent's Hospital Melbourne (SVHM). She has a broad background in health care having worked extensively in both clinical and administrative areas, including Administrator of St. Vincent's Hospital Launceston, and Director of Nursing at St. Vincent's Private Hospital, Sydney. She is a Member of the SVHM Foundation Board and the Melbourne Neuromuscular Institute Research Board.

Mr Terrence Power
FCPA, FAICD.

Mr Power was responsible for Business Development, Marketing and Client Services in the Funds Management Division of the BT Financial Group until January 2000. He is a non-executive Director of BT Funds Management Ltd, is Chairman of the Investor Group (a listed public company) and is an Industry Member of the Financial Industry Complaints Services Ltd Panel. He is an Associate Fellow of the Australian Marketing Institute and an Executive Member of the American Marketing Association.

The Board recognizes that the success of the Institute is dependent on a strong partnership with the community, and we are striving to increase community awareness of the scientific success of the Institute and its implications for the health of the community.

Professor Richard G Larkins
MDBS, PhD, FRACP, FRCP.

Professor Larkins is Dean of the Faculty of Medicine, Dentistry and Health Sciences and Head of the School of Medicine at The University of Melbourne. Posts he has held in the past include Chair of NHMRC, President of the Endocrine Society of Australia and Chair of the Accreditation Committee of the Australian Medical Council. He has clinical and research interests in diabetes and endocrinology. He is currently President of the Royal Australasian College of Physicians.

Ms Brenda Shanahan
BEc, BCom.

Ms Shanahan has a research background in finance in Australian and overseas economies and sharemarkets. She is a Non-Executive Director of AWB Ltd and AWB International Ltd, BT Financial Group, and a Director of the SCHS Melbourne Region Board. 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.

Richard Larkins | Terrence Power | Ian Reid | Graham Rogers | Brenda Shanahan | Douglas Wright

Mr Ian D Reid
BE (Chem), ASA, FIEAust, MAICD.

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

Mr Graham Rogers
FIA, FIAA, ASA.

Mr Rogers is Chairman of SMF Funds Management and serves on the Boards of RACV Financial Services, the Private Health Insurance Administrative Council, and the Victorian College of the Arts Foundation. He is Chairman of the University of Melbourne Actuarial Foundation and is Principal of the Offley House Group. His background includes more than 25 years as a chief executive in the financial services industry including Colonial Investment Management, Jacques Martin Group and Equitable Life.

Mr Douglas Wright
FAICD.

Mr Wright is a Founder and Managing Director of Wright Business Marketing, 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 a Member of the Victorian Government's Small Business Advisory Committee. 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).

MEMBERS OF THE INSTITUTE

Current Institute Members

The following is a list of current Members:

The Memorandum and Articles of Association provides for appointment of Members of the Institute. They comprise some members of the Hospital Senior Medical Staff, and others from business, the professions and academic life, who are interested in the Institute and wish to promote its activities. Members are kept informed of Institute activities, and are represented on the Institute Board.

Dr FP Alford
Professor JD Best
Dr KJ Breen
Dr DH Campbell
Mr JC Chappell
Mr WJ Clancy
Dr LE Clemens
Sr Maryann Confoy
Ms KL Cross
Dr JJ Griffin
Ms M Griffin
Mr CA Griss
Mr J Gutman
Mr JF Gurry
Sr Kathleen Higgs
Dr DJ Hillis
Mr BJ Jackson
Ms MA Jackson
Professor ED Janus
Professor BE Kemp
Professor RG Larkins
Mr Justice A McDonald
Dr IG McDonald
Professor TJ Martin
Mr HJ Nicholas
Professor DG Penington
Sr Paulina Pilkington
Mr T Power
Mr ID Reid
Mr GEN Rogers
Professor GB Ryan
Mr PJ Ryan
Mr AF Sallmann
Ms B Shanahan
Mr C Smith
Mr P Spry-Bailey
Mr MJ Walsh
Mr D Wright

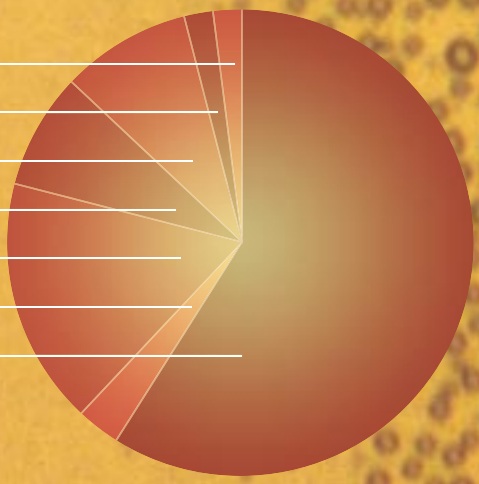
Institute Members

Image: Laboratory chemicals

Financial Snapshot

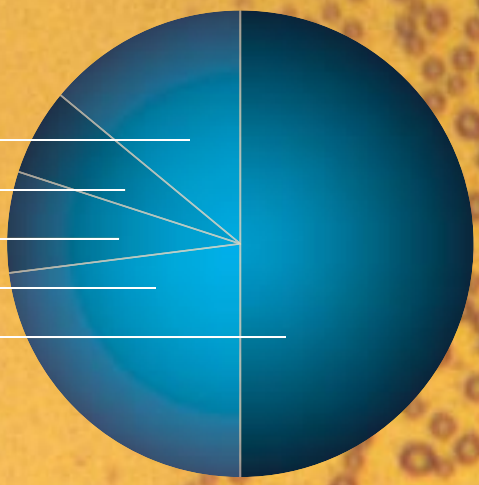
Income

Interest and Dividends	2%
Other	2%
Victorian Govt Infrastructure	9%
Legacies and Donations	8%
Industry	17%
Commonwealth Govt Service Contract	3%
Competitive Grants	59%



Expenditure

Infrastructure - Admin & Tech Support Salaries	14%
Infrastructure - General	6%
Depreciation	7%
Research Consumables	23%
Research Salaries	50%



AWARDS AND FELLOWSHIPS

Our major goals are to support high quality staff with the best possible facilities, working together and with outside collaborators to achieve at a high level in science – with that science contributing to understanding of important diseases and, where possible, capable of some commercial application.

MAJOR AWARDS

Associate Professor Elizabeth Dax

Elizabeth Dax was appointed Member of the Order of Australia in the General Division (AM) in the Queen's Birthday Honours 2001. This award recognises Professor Dax's services to medical research, particularly in the fields of public health, HIV/AIDS, and drug addiction.

Professor Michael Parker

Michael Parker was appointed a Professorial Fellow and Professor within the Department of Biochemistry and Molecular Biology, The University of Melbourne. This appointment recognises Professor Parker's pivotal contribution in the field of structural biology of medically important proteins.

Major Awards

Associate Professor Matthew Gillespie

Matthew Gillespie was appointed Associate Professor within the Department of Medicine, The University of Melbourne, in recognition of his contribution to medical research, particularly in the field of bone cell biology and for services to the medical research community through his role as President of the Australian Society for Medical Research.

Professor TJ Martin

The Director received the China Healthstar Osteoporosis Medical Award (HOMA), presented by the Deputy Minister of Health (China), at a ceremony in Beijing in October.

FELLOWSHIPS and PRIZES

Michael Parker

NHMRC Senior Principal Research Fellowship. This prestigious fellowship will support Michael's research over the next five years.

Jörg Heierhorst

Jörg was appointed an NHMRC Senior Research Fellow. In addition Jörg was awarded the Kendro Prize and AMRAD Senior Investigator Award, for his presentation during St. Vincent's Hospital Research Week

David Stapleton

Australian Academy of Science and NHMRC Career Development Award recognises David's research into protein/protein interactions that are important for AMP kinase regulation. David was also successful in obtaining a Ramaciotti Award for Biomedical Research for the purchase of a centrifuge.

Andrew Hammet

The Anti-Cancer Council of Victoria Post-Doctoral Fellowship will allow Andrew to continue on with his research arising from his PhD studies on DNA damage repair mechanisms at SVIMR.

Rachel Thomas

Rachel was awarded a Fellowship from the Association pour la Recherche sur le Cancer, France. This will support her research into breast cancer within Professor Jean-Paul Thiery's group at the Institut Curie in Paris.

Joe Pereira

Joe was awarded the Denis Lowther Student Poster Prize at the Matrix Biology Society of Australia and New Zealand, and received a high commendation for his poster at the Australian Society of Biochemistry and Molecular Biology ComBio 2001 meeting in Canberra. Joe was also awarded the RJ Fletcher Research Scholarship, the Sir Thomas Naughten Fitzgerald Scholarship and the Randal and Louisa Alcock Scholarship from the Faculty of Medicine, The University of Melbourne.

Karl Häusler

Karl was awarded a Young Investigator Award at the 23rd Annual Meeting of the American Society for Bone and Mineral Research, Phoenix, AZ, USA.

Chan-Sien Lay

Chan was awarded a highly competitive Dora Lush Scholarship from the NHMRC to allow him to undertake PhD studies investigating the structural and functional features of retroviral envelope glycoproteins.

Geoffrey Kong and Carolyn McNees

Both Geoffrey and Carolyn were successful in obtaining Australian Postgraduate Research Awards for pursuing studies of Alzheimer's disease amyloid precursor protein and novel tumour suppressor genes respectively.

MAJOR ACHIEVEMENTS

These discoveries will help us design new treatments for osteoporosis, rheumatoid arthritis and cancer-induced bone loss.

Discovery of proteins that regulate bone formation and destruction.
We discovered proteins that prevent bone from being destroyed. These discoveries will help us design new treatments for osteoporosis, rheumatoid arthritis and cancer-induced bone loss. *(see page 14)*

A new action for a not-so-new protein.
Parathyroid hormone related protein (PTHrP) plays an important role in promoting bone destruction by cancers. It had previously been assumed that PTHrP changes cell behaviour by acting like a key in a lock on the cell surface. We now know that PTHrP can get through the cell membrane into the cell nucleus where it may influence cell behaviour by turning genes on or off. *(see page 16)*

New understanding why cancers spread.
Cancers in one part of the body usually kill by spreading to other parts of the body. The spread of cancers is due in part to the cancer making proteins that break down tissue barriers. We have devised new methods to study how cancers spread that will help us develop new treatments to prevent this complication of cancer. *(see pages 17 and 18)*

A new mechanism of control of the heart and blood vessels.
Nitric oxide is a chemical that increases blood flow to heart muscle and reduces the tendency for blood to clot. Our studies have revealed how nitric oxide production in the heart is regulated. These studies suggest new ways to protect the heart from heart disease. *(see page 20)*

From bacterial toxin to treatment.
The bacterial toxin perfringolysin O kills cells by making holes in the cell membrane. Our elucidation of the shape of this toxin by protein crystallography indicates new strategies to prevent the injury caused by this toxin. *(see page 26)*

New insights into the immune response.
We used protein crystallography to show the shape of a protein that plays a key role in the body's recognition of the Ebstein Bar virus, a virus that causes glandular fever and can also, in some patients, cause cancer. *(see page 28)*

Getting better results from treatment of heart failure.
Some of the treatments we use for heart failure act by reducing the blood levels of a small protein called angiotensin. We showed that combination of different treatments produces more efficient reduction of blood angiotensin levels and explains why these combined treatments produce more benefit to patients. *(see page 22)*

What gives the heart its power.
We showed that a particular protein in the heart makes an important contribution to the efficiency of the heart as a pump. This discovery gives us new understanding of conditions where the heart is inefficient, such as in heart failure. *(see page 24)*

Major achievements

Discovery how viruses cause infection.
Using protein crystallography we discovered the shape of a protein on the surface of the human T cell leukaemia virus that is responsible for infection by this virus. Knowing the shape of this protein helps us understand how the virus causes infection and indicates new ways to prevent infection by this and other viruses. *(see page 24)*

Revealing the shape of a protein with an important role in the regulation of cell behaviour.
By revealing the shape of the Siah protein, protein crystallography has given us new understanding how this protein may play a role in cancer. *(see page 26)*

New understanding of heart disease.
The protein AMP-activated kinase plays an important role in the regulation of energy production in the heart and other cells. Recently it was shown that abnormalities of this protein cause enlarged hearts and irregular heart beat. Our own investigations revealed the basis of this abnormality and help explain its effects on the heart. *(see page 20)*

JACK MARTIN THE SCIENTIST

"Jack Martin combined the ordinary with the extraordinary in a very humble way

Sr Anthea Groves, RSC, former Sister Administrator of St. Vincent's Hospital, Melbourne.

"Jack joined us at the Department of Pathophysiology in Bern for part of his sabbatical. It was a wonderful time for the whole group who profited a great deal from his presence. This stay was also a milestone in Jack's career, since we could convince him to use a computer, an activity he had absolutely loathed beforehand and now greatly enjoys."

Professor Herbert Fleisch, Lausanne, Switzlerland.

"He taught me that science is not about who is right or wrong, it is about what's true or false"

"In the eyes of his colleagues he has been a beacon who continuously guided us to new scientific challenges and I feel extremely privileged to be one of his collaborators and friends"

Gideon Rodan, Research Vice President, Department of Bone Biology/Osteoporosis Merck & Co Inc., Pennsylvania, USA.

Farewell to TJ Martin

When Jack Martin became the Director of SVIMR he brought with him his vast knowledge and expertise of calcium regulating hormones, for which he had a well-deserved international reputation. Subsequently, Jack has been the recipient of numerous international awards for his research achievements, including the highest award of The American Society for Bone and Mineral Research, the William F. Neuman Award. Recognition of his work over the years at SVIMR and his contribution to medicine has culminated in the award of The Order of Australia in 1996 and his appointment as a Fellow of the Royal Society (London) in 2000.

Together with the late Roger Melick, his earliest mentor, Jack became foundation father of bone and mineral research in this country. He was the inaugural President of The Australian and New Zealand Bone and Mineral Society, which today has a membership of more than 300. Its Annual Scientific Meeting attracts leading scientists and clinicians from all corners of the globe, testament to the high scientific standards that Jack has promoted amongst the society's membership. Almost without exception the leading experts in bone and mineral research in this country spawned their passion for research under Jack's supervision. They continue to seek his mentorship today. Three University of Melbourne Professors of Medicine trained in his research group and many of his former students, now spread around the world, have achieved significant recognition for their own work.

Anyone who has attended international meetings, to which Jack is regularly invited to speak cannot fail to be highly aware of the enormous respect for him throughout the international research community. This results not only from the standard and breadth of his research but also from his reputation as "a jolly good bloke" who is more than willing to share his wealth of experience in discussions with younger members of the research community. As a result, his laboratories have attracted a large number of international visitors from Europe, USA and Japan. These have included students wishing to study for higher degrees, postdoctoral fellows, collaborators and research institute directors and professors on sabbatical leave. Requests to join the group inevitably escalated when word spread of his hospitality both inside and outside the laboratory.

Apart from his work on calcitonin early in his career, a major achievement occurred when his group were first to isolate and clone a new regulator of cell growth (parathyroid hormone-related protein or PTHrP) in 1987. Produced by certain cancers, this protein causes widespread complications, including hypercalcaemia in cancer patients and it came as something of a surprise

"He has built the Institute into a formidable palace of highest quality medical research both through the excellence of his own work and his sponsorship and support of first class colleagues across a wide spectrum of disciplines"

Professor Emeritus Sir Gustav Nossal, Melbourne.

"Jack Martin has a special status in his chosen field of bone cell biology. He is equally as admired for his scientific contributions as he is valued as a friend by a host of colleagues around the world"

Hugh Niall, CEO, Biota Holdings Ltd, Melbourne.

"He has been remarkably successful in establishing fruitful collaborations with Japan, Europe and the USA, was President of the International Bone and Mineral Society, and gave Australia great visibility in a very competitive scientific field"

Gregory R Mundy, SBC Chair in Cancer Research, Director, Institute for Drug Development, Cancer Therapy & Research Center, USA.

"It is overwhelming to see what Jack Martin produced in so many areas of skeletal biology over the past four decades"

Stephen Krane, Professor of Medicine, Harvard Medical School, USA.

"Jack, I want to tell you that you have been one of the most popular foreign scientists in the Japanese community of bone biology"

Tatsuo Suda, Vice Director and Professor, Research Center for Genomic Medicine, Saitama Medical School, Japan.

"the atmosphere at the School (Royal Postgraduate Medical School, Hammersmith) encouraged by young doctors and scientists to question and even refute their seniors' view, openly and without authoritarian criticism. This delightful atmosphere was a joy to young people like me and Jack"

Professor Iain MacIntyre, FRS.

History in the making: The discovery of PTHrP, February 1987
(back row left to right): Janine Danks, Bruce Kemp, Jack Martin, Jane Moseley, Christine Rodda.
(front row left to right): Peter Ebeling, Valdo Michelangeli, Hanne Diefenbach-Jagger.

THE HERALD THURSDAY SEPTEMBER

Melbourne team hits the jackpot

A Melbourne research team is believed to be the first in the world to identify a protein hormone commonly produced by certain cancers.

The discovery, which has attracted worldwide interest, could have major implications for the early diagnosis of lung and skin cancer, kidney disease and bone disorders, including osteoporosis.

The hormone, described in the latest issue of the US journal Science, was unrecognised until recently. It is central to the critical bodily process of calcium metabolism and is abundant in the cells in deep layers of the skin.

The head of the research team, Prof. Jack Martin of the department of medicine at the University of Melbourne, said it was suspected the hormone was present in healthy and unhealthy people.

"We don't yet know its normal function but we know it is overproduced by certain cancers.

"It also has a profound effect on bones which had not been recognised."

Prof. Martin, who is collaborating with LaTrobe University biochemist Dr Richard Wettenhall, the CSIRO and the UK biotechnology company, Genentech, on the project, said it was believed the hormone could be important in calcium regulation of the foetus before birth.

when the team from "down under" first presented the work to the international community. Subsequently, PTHrP was found to have roles in many normal tissues and is now recognised to be important for specific functions in several different organs. This work was a fine example of how addressing one problem can lead to understanding many others, and of Jack's insight in steering the research process to maximum benefit. PTHrP continues to attract enormous research interest as its widespread actions are revealed. In the year 2 001 alone over 200 papers on PTHrP were published from research groups world-wide.

Jack's research group has grown considerably as he has built up one of the few bone and cancer research laboratories in the world which integrates the expertise of cell biologists, molecular biologists, protein chemists, histologists and clinicians. This has meant that any challenging research question could be dissected by multidisciplinary approaches allowing full evaluation and application of the research outcomes. Thus, a problem taken from the clinic to the laboratory, to gain basic understanding, can then be translated into therapeutic strategies for the benefit of the patient. Perpetuation of this valuable strategic approach has left a tangible expression of Jack's breadth of vision.

The research staff wish Jack well in his retirement and look forward to opportunities for his future mentorship in their work.

2001 IN REVIEW

This fundamental science is a great resource for the Institute's efforts to apply its research to the mechanisms of common diseases, especially cancer and diseases of bone and of the heart and blood vessels.

This is my last Research Report as Director of the Institute, and above all I want to acknowledge with much gratitude the many colleagues who have worked together towards its success. Of those of us who joined in 1988, nine remain, and two are with us from the pre-1988 era. It has been a time of scientific successes and failures, happily more of the former, and one of about four-fold growth in staff and in development of great research technologies. Much of the growth has been "bottom up", in that people have been trained and careers developed *in situ* or with the intervention of a period elsewhere, but some has been with the appointment of senior, experienced scientists. Many of our graduate students and post-doctoral fellows have gone on to successful research careers elsewhere. Growth has been such that we have long since outgrown the building that was first occupied in 1987. Our plans for the Institute

Research Report

building expansion, doubling its size, are well under way now with the help of funding from the Commonwealth and State Governments and the Sisters of Charity, as well as the strong support of our Board in seeking the extra funding that is essential for the project. I had hoped that I might have been able to spend all of 2001 working on the building, to lighten the load for my successor, but the final injection of funds only became available in time for us to begin in October.

The research of the Institute continues successfully in all its areas. Our major goals are to support high quality staff with the best possible facilities, working together and with outside collaborators to achieve at a high level in science—with that science contributing to understanding of important diseases and, where possible, capable of some commercial application. We measure that success in numerous ways: the number and quality of our publications, the recognition made nationally and internationally of our scientists, the successes with granting bodies, the alliances forged with industry, contributions made to postgraduate teaching and training, and the transfer of technologies in the health system.

The research environment has changed no less in Australia than it has worldwide. Peer-reviewed research funds are progressively more difficult to obtain, and our staff have engaged this problem by seeking and obtaining overseas research funding, as well as collaborative research agreements and contracts with pharmaceutical and biotechnology companies. One of our major challenges is to keep at the forefront of the various technologies we use. This, together with the constant need to replace old equipment, makes for big capital costs, highlighted by the development of the new building. We face these next few years confidently though, with the help of the Board and with the industry and innovation of our scientists.

The following Research Report summarises highlights of the year's achievements in each of the scientific sections of the Institute. As happens in all of science, much of our accumulated wisdom comes to us step by step. There are not many huge leaps, but we move along feeling that we understand a little more than we had before, and each discernible increment is a great help. We need to distinguish between "understanding" on the one hand, and "attainment of explanation" on the other. Our regular scientific advances help us with explanations that are necessary for understanding. Real understanding comes when we can put these collections of explanations together and make real intellectual progress. Each year we have been able to lay claim to progress in understanding and 2001 is no exception.

Some of what we report here is basic science, in which the nature of biological processes is studied at a very fundamental level. In some cases this is approached by investigating the structure or chemical properties of proteins which confer upon them biological activities, in others it is how genes are controlled to govern protein production. This fundamental science is a great resource for the Institute's efforts to apply its research to the mechanisms of common diseases, especially cancer and diseases of bone and of the heart and blood vessels. Scientific language is mostly constrained by the requirements of scientific papers, and we try to escape this to some extent in the Report, but I suspect with only intermittent success.

Image: Members of the Bone Cell Biology group, *(left to right)*: Daphne Hards, TJ Martin, Janine Danks and Patricia Ho.

Contrary to most people's expectations, bone is a very dynamic tissue. Our bones are being continually dissolved and rebuilt. Bones use these processes to repair fractures.

Bone Biology and Diseases

T.J. Martin, Head

Clinical Bone Endocrinology

Kong Wah Ng, Head
Christine Gange
Yun Shan Hu
Vicky Kartsogiannis
Chi Ly
Natalie Sims
Hong Zhou

Bone Physiology

Jane Moseley, Head
Hannelore Diefenbach-Jagger
Vivian Grill
Daphne Hards
Patricia Ho
Ingrid Kriechbaum
Ginny Leopold
Pat Smith

Comparitive Endocrinology

Janine Danks, Head
Patricia Ho

Molecular Endocrinology

Matthew Gillespie, Head
Elizabeth Allan
Lindus Conlan
Jan Elliott
Jane Fisher
Karl Häusler
Natasha Ilievska
Danijela Mirosavljevic
Julian Quinn
Rachel Thomas

BONE BIOLOGY AND DISEASES

Contrary to most people's expectations, bone is a very dynamic tissue. Our bones are being continually dissolved and rebuilt. Bones use these processes to repair fractures. However, a change in the balance between the dissolving and rebuilding of bone can produce diseases such as osteoporosis and arthritis. Cancers can tip this balance when they spread to bone.

Specialised cells in bone perform the dissolving and rebuilding of bone. The cells that dissolve bone are called osteoclasts and the cells that build bone are called osteoblasts. Our research is focussed on the regulation of these two types of cells in bone. We are particularly interested in protein hormones that control the behaviour of these two types of cell and the mechanisms by which some cancers attack bone.

OSTEOCLAST AND OSTEOBLAST BIOLOGY

Inhibitors of osteoclast formation

In earlier work we showed that the proteins osteoprotegerin (OPG) and RANK ligand (RANKL) have important roles in the regulation of osteoclast function. We extended these studies by discovery of additional osteoclast regulators. The protein IL-18 prevents osteoclast formation by instructing T cells to make the protein GM-CSF, which in turn prevents osteoclast formation. T cells are an important component of the immune system and have many additional actions including the control of bone biology. We also found that another protein, IL-12, acts in a similar manner to that of IL-18, and that the combination of IL-18 and IL-12 has a much more powerful effect on osteoclasts than either agent alone.

Another inhibitor of osteoclast formation we discovered is referred to as osteoclast inhibitory lectin or OCIL. Unlike other osteoclast inhibitors, OCIL is found on the cell membranes of osteoblasts, cartilage cells (chondrocytes) and other cell types. We originally identified mouse OCIL and we have since identified human OCIL. We have also discovered that there is a whole new family of OCIL related proteins.

Other aspects of osteoclast biology

Transforming growth factor β (TGFβ) is an abundant protein in bone and has complex effects on the processes that dissolve bone. In some cases TGFβ accelerates the dissolving of bone by osteoclasts and in other cases it has the opposite effect. The different effects of TGFβ on osteoclasts are dependent on which other cells and protein hormones are present, emphasising the complexity of this fundamental process of bone biology.

In collaboration with Dr Toshio Sasaki (Tokyo) we extended these studies to the cellular mechanisms of physiological root resorption in human deciduous teeth, and showed that in several respects the cellular mechanisms of physiological root resorption appear to be quite similar to the way osteoclasts dissolve bone.

Parathyroid hormone (PTH) action

Parathyroid hormone (PTH) is a protein made by the parathyroid gland that plays an essential role in the regulation of the concentration of calcium in blood. PTH performs this function in part by promoting the dissolving of bone, so that calcium is released from bone into the blood. Paradoxically, PTH can have the opposite effect and stimulate bone formation when it is administered by intermittent injection. Understanding these actions would be of great benefit to patients with fragile bones such as those with osteoporosis. In a collaborative study with Dr Jude Onyia and Dr Linda Ma (Indianapolis, USA) we showed that PTH has different effects on osteoclasts and osteoblasts depending on whether it is administered as a constant infusion or as intermittent injections. We are performing further studies to obtain an additional understanding of these processes.

PARATHYROID HORMONE RELATED PROTEIN (PTHRP) - MOLECULAR, PHYSIOLOGICAL AND PATHOLOGICAL ASPECTS

Molecular aspects of PTHrP action

Produced by various types of solid tumours, parathyroid hormone related protein (PTHrP) causes elevated levels of calcium in blood, a condition known as humoral hypercalcaemia of malignancy. PTHrP also influences the ability of breast cancers to spread to bone, a process known as metastasis.

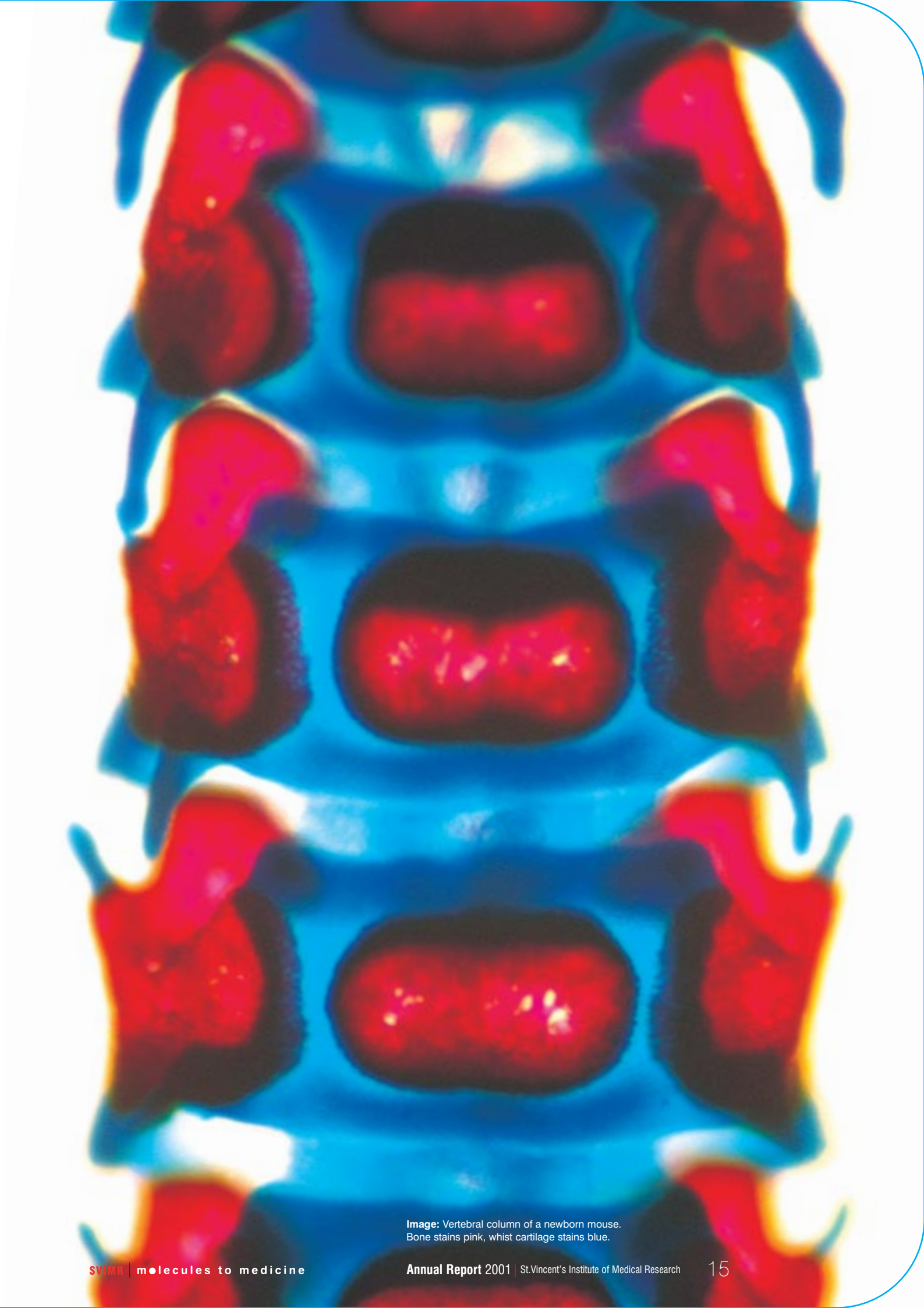


Image: Vertebral column of a newborn mouse.
Bone stains pink, whist cartilage stains blue.

The implication of these findings is that production of PTHrP by breast cancer cells confers upon them a less malignant phenotype, one that is less invasive and less likely to result in metastasis.

It had previously been assumed that PTHrP changed cell behaviour by acting like a key in a lock on the cell surface. Our recent studies show that PTHrP can pass through the cell membrane and enter the cell nucleus where it may influence gene expression. In collaborative work with Dr David Jans (John Curtin School of Medical Research) and Dr Mark Lam (Monash University), we identified the mechanism by which PTHrP is imported into the cell nucleus by a special import protein called importin β. Further, in association with Gino Cingolani (Scripps Institute, USA), we determined the crystal structure of importin β attached to PTHrP.

Physiology of PTHrP

Studies of the role of PTHrP in normal physiology comprise an important part of our work. We previously showed that PTHrP is a foetal hormone responsible for promoting the transport of calcium across the placenta, making it available for the growing foetal skeleton. Both the foetal parathyroid glands and the placenta produce PTHrP. In collaboration with Dr Chris Kovacs (Nova Scotia, Canada) we showed that the foetal parathyroid glands are not essential for the maintenance of placental calcium transport.

Other physiological roles, especially in vascular control and pregnancy, continue to be of major interest, and some of these areas have been pursued in collaboration with Dr Mary Wlodek (University of Melbourne). Intrauterine PTHrP concentrations are reduced in association with growth restriction in the spontaneously hypertensive rat (SHR) compared to the normotensive control Wistar Kyoto (WKY) rat, implicating PTHrP as a pivotal foetal growth factor. Using embryo cross-transplantation between SHR and WKY we showed that the SHR foetus is growth restricted and has suppressed amniotic fluid PTHrP, outcomes that are largely determined by the foetus and are independent of maternal hypertension or maternal PTHrP. This leads us to suggest that the low SHR amniotic fluid PTHrP may play a role in the growth restriction of SHR, and this is being studied further.

Processing of PTHrP

PTHrP is a complicated protein and different sections of the protein have different functions. One part of PTHrP (the N-terminus) stimulates the dissolving of bone, whereas another part (the C-terminus) has the opposite effect. Moreover, once it is made, PTHrP may be chopped into smaller proteins with different actions, so that the overall effect depends on the actions of these smaller fragments. Since breast and prostate cancers produce PTHrP, we are investigating whether these cancers chop PTHrP into fragments and we are identifying the fragments these cells produce. These studies will help us understand better the effects of these cancers on bone.

Image: The physiological role of PTHrP was studied in young sharks.

COMPARATIVE ENDOCRINOLOGY OF PTHrP

An important approach to understanding the role of a hormone is to study whether it is produced in earlier life forms. We are using this approach in our investigation of PTHrP in fish. The concentration of PTHrP in fish blood is much higher than in mammals. Our studies suggest that PTHrP may have an important role in regulating the water and salt composition of blood of fish.

PTHrP AND CANCER

Our previous studies indicated that PTHrP not only has direct effects on bone but also influences whether cancers spread to bone. In collaboration with Mr Michael Henderson (Department of Surgery, St. Vincent's Hospital) we showed that women with breast cancers that produce PTHrP have better survival than women with breast cancers that do not produce PTHrP. In addition, breast cancers that produce PTHrP are less likely to

Our focus is the processes cancers use to spread to other parts of the body, a process called metastasis.

spread to other sites including bone. The implication of these findings is that production of PTHrP by breast cancer cells confers upon them a less malignant phenotype, one that is less invasive and less likely to result in metastasis. This clinical study also suggests that breast cancers that do not produce PTHrP may be more likely to spread to other parts of the body. In collaboration with Dr Robin Anderson (Peter MacCallum Institute) we are investigating how PTHrP production by cancer cells influences their ability to metastasise.

VVBCRC INVASION AND METASTASIS UNIT

SVIMR is a member of the Victorian Breast Cancer Research Consortium (VBCRC) and host of the VBCRC Breast Cancer Invasion and Metastasis Unit, headed by Rik Thompson. Our focus is the processes cancers use to spread to other parts of the body, a process called metastasis. One process that cancers use to metastasise is epithelio-mesenchymal transition (EMT), a process whereby cancer cells dramatically change the way they behave. We were the first to describe EMT in human breast cancer cells, and have now characterised a breast cancer cell system where EMT can be induced by the addition of a single growth factor protein, called epidermal growth factor (EGF). With this system we can now study exactly how EMT occurs. Collaborative studies with Dr Robin Anderson, from the Peter MacCallum Cancer Institute showed evidence of EMT in mouse mammary carcinoma cells with elevated metastatic potential, and studies with Dr Elizabeth Williams *(see Prostate Cancer Group,following page)* found a similar association among human prostate cancer cell lines.

Image: Bioinformatic analysis of genes expressed in cancer.

Another mechanism cancers use to metastasise is to make enzymes that break down tissue barriers. Matrix metalloproteinase-2 (MMP-2), an enzyme that degrades basement membranes and thus allows cancer cells to escape from the primary tumour mass, continues to be a major focus of our research. This enzyme is usually produced in an inactive form by normal cells around the tumour and is activated by breast and prostate cancer cells that have undergone EMT. Our study of how MMP-2 is activated will allow for the design of new treatments to block this process, and complement ongoing studies with inhibitors of MMP's already in clinical trial (see Pharmacogenomics group below).

Work supported by the Thomaïy Breast Cancer Research Fellowship has focussed on the role of bone sialoprotein (BSP) in breast cancer metastasis. BSP stimulates the migration and proliferation of breast cancer cells. When we introduced the BSP gene into breast cancer cells we found increased migration of these cells in culture and increased growth of the cancer cells in mice. We are very grateful for the support of the Thomaïy Breast Cancer Research Fund that makes this work possible.

Our work on cancer metastasis to bone has been very productive. We are using a gene discovery approach using gene arrays to identify molecules that may participate in this process. These studies attracted major funding from the USA and enabled the establishment of a new cell migration and bone metastasis group headed by John Price *(see following page).*

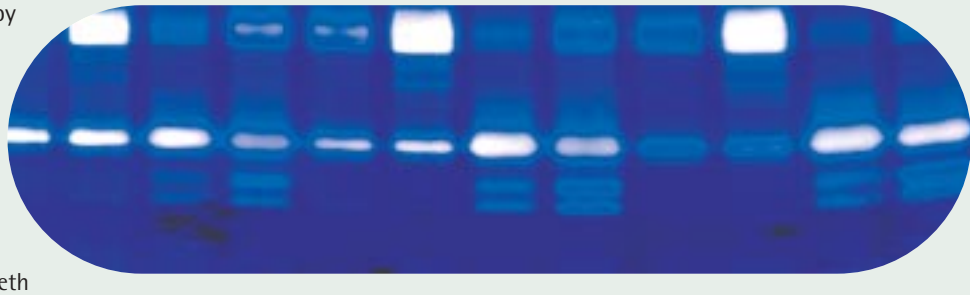


Image: Zymogram used to analyse matrix metalloproteinases.

VBCRC Invasion and Metastasis Unit

Erik (Rik) Thompson, Head
Margaret Bills
Nirada Dhanesuan
Masha Fridman
Nicolle Gibson
Annet Hammacher
Toni Harris
Ingrid Kreichbaum
Marc Lafleur
Neeracha Ruangpanit
Julie Sharp

We are examining gene expression profiles of cells that have an increased ability to migrate in response to stimulation by growth factors.

Cell Migration and Bone Metastasis

John Price, Head
Tony Blick
Joe Pereira

Pharmacogenomics

Mark Waltham, Head
Angela Arvanitis
Tony Blick
Emma Walker

Prostate Cancer

Elizabeth Williams, Head
Susan Docherty

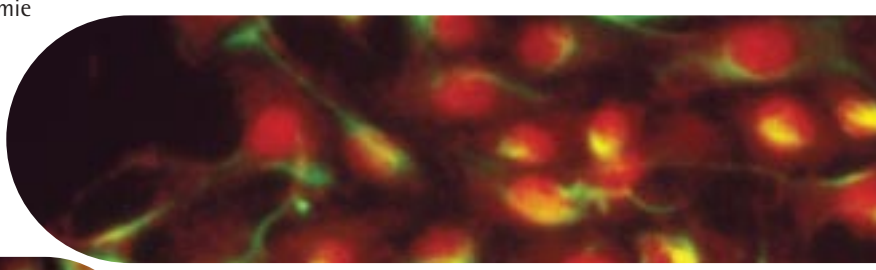
CELL MIGRATION AND BONE METSTASIS

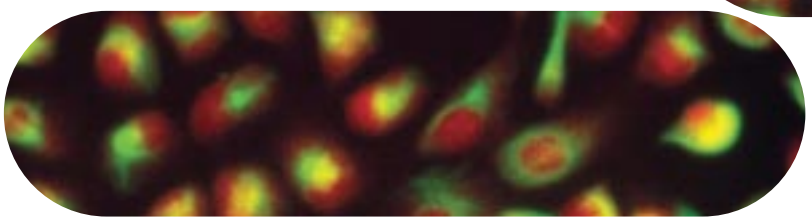
Cancer cells differ in their ability to metastasise to bone. By comparing cells that do or do not metastasise to bone, and in particular the genes expressed, we can identify how these cells metastasise. An exciting finding is that a drug directed towards one of our candidate genes is currently in Phase I clinical trials in the USA and the UK. We are currently examining whether this drug may also prevent cancer spreading to bone.

A major component of tumour cell metastasis is cell migration. We are examining gene expression profiles of cells that have an increased ability to migrate in response to stimulation by growth factors. We hope to identify novel molecules that are involved in this process so that new therapies can be designed for the prevention of metastasis. A protein implicated in tumour cell migration as well as cancer progression is the integrin $\alpha v\beta 3$. In collaboration with Dr Jamie Rossjohn we are investigating the structure of this protein to better understand its role in breast cancer migration and metastasis.

that could account for the observed anti-tumour effect. Our data and understanding of this action suggest that this agent would be most effective in the early phase of tumour growth, a finding that may help guide future clinical trials for this agent and related drugs. In support of this hypothesis, our extensive trial of dose and withdrawal schedules for this drug revealed that early exposure is critical to tumour suppression by this drug.

We are also performing gene array analysis of EMT model systems described above. Candidate effector genes and pathways have been identified which may potentially serve as novel therapeutic targets to stop tumour metastasis, or as a way to diagnose the potential of a tumour to metastasise. This work is complemented by bioinformatic and data mining studies, and utilises the ever-growing tissue and disease expression databases that are available publicly and through collaboration.





Images: Fluorescently stained breast cancer cells.

PHARMACOGENOMICS

Pharmacogenomics is the study of how the genetic profile and genomic response of a target tissue (or entire organism) influences drug action. Our group is involved in a number of cancer related projects using this approach which incorporates use of technologies such as proteomics and gene expression arrays.

We are studying how different cancers respond to different drugs, including a drug currently in clinical trial. Whereas this drug has many potential actions, our analysis indicates one primary action

PROSTATE CANCER

Our major focus is to increase understanding of how prostate cancer metastasises to other tissues. Prostate cancers most commonly metastasise to bone and lymph nodes. We established two new human prostate cancer models to study the mechanism of metastasis. Our bone metastasis model produces clinically authentic osteosclerotic (bone-forming) lesions and has resulted in a collaboration with a major international pharmaceutical company to test one of their new drugs. We are working closely with our clinical collaborators Professor Tony Costello, University of Melbourne, Royal Melbourne Hospital, Urology Department and Dr John Slavin from Pathology at St. Vincent's Hospital to develop additional resources for these studies.

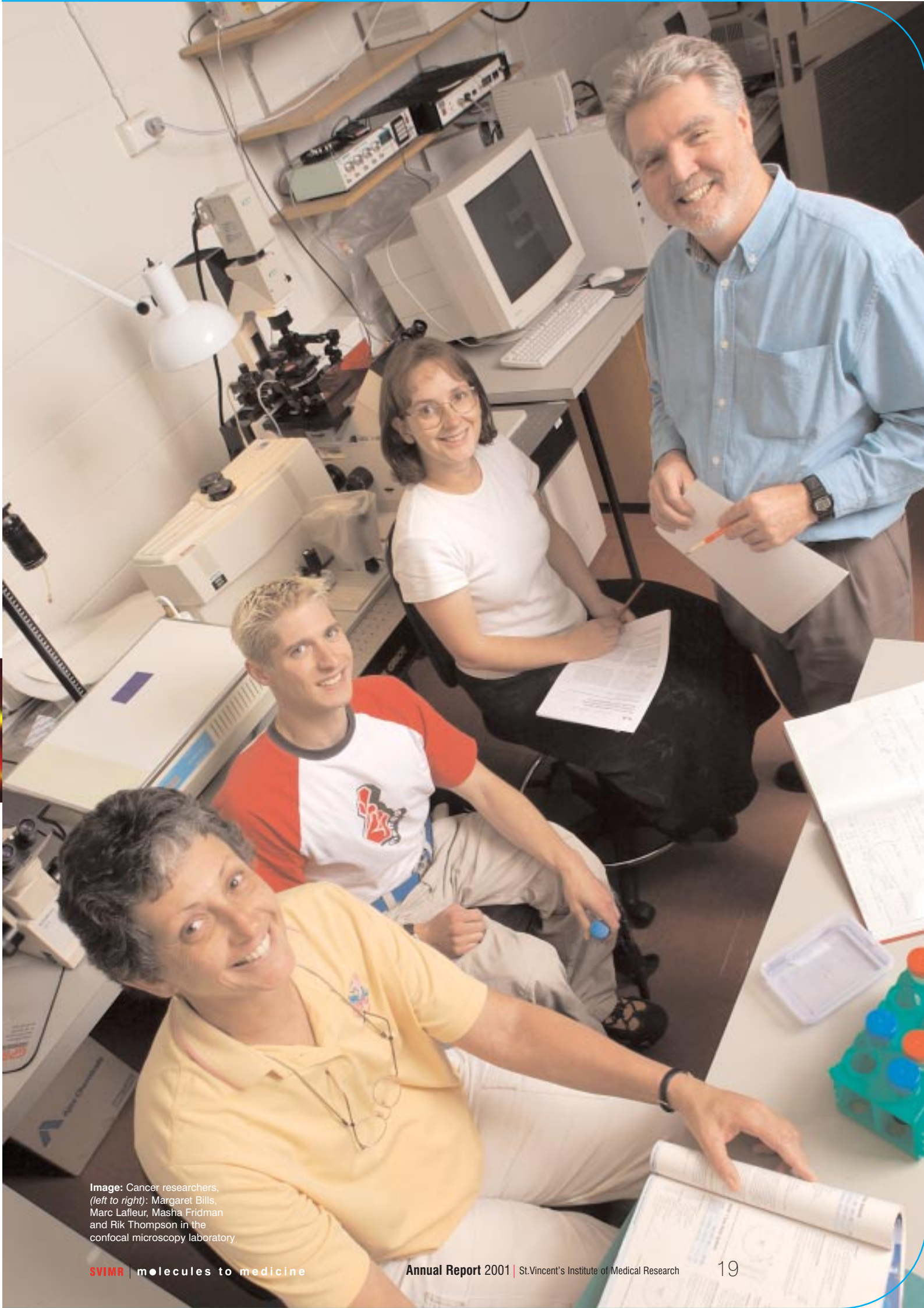


Image: Cancer researchers, *(left to right)*: Margaret Bills, Marc Lafleur, Masha Fridman and Rik Thompson in the confocal microscopy laboratory

During exercise AMPK is switched on and it accelerates the uptake of glucose by cells and increases the burning of fat.

Protein Chemistry and Regulation

Bruce Kemp, Head
Zhiping Chen
Peter Hoffmann
Ian Jennings
Frosa Katsis
Belinda Michell
Sid Murthy
Bryce van Denderen

PROTEIN CHEMISTRY AND REGULATION

It is well recognized that diet and exercise are very important for maintaining health and extending life. We are studying an enzyme called the AMP-activated protein kinase (AMPK). This protein plays an important role in regulating metabolism and gene function in response to changes in energy demand (exercise) and supply (dietary intake of calories). During exercise AMPK is switched on and it accelerates the uptake of glucose by cells and increases the burning of fat. In some tissues, including the heart, kidney, and placenta, it also accelerates the metabolism of glucose. In addition to enhancing the conversion of glucose and fat to energy, AMPK switches off the production of fatty acids, cholesterol and triglyceride in the liver. The acute effects of AMPK activation in response to metabolic stress result from it modifying (by a process called phosphorylation) key regulatory enzymes in these metabolic pathways. In addition to these acute effects, AMPK is emerging as an important regulator of gene function to adapt the body to increased energy demand or lack of supply of nutrients. Because of its key role in the control of metabolism it seems likely that AMPK will be important in metabolic diseases that include obesity, maturity-onset diabetes, and cardiovascular disease.

AMPK is a complex enzyme with 3 different proteins working together, the α, β, and γ subunits. It was recently shown that mutations in the γ subunit can cause hereditary heart disease characterised by an enlarged heart and predisposition to rapid heart rate (Wolf-Parkinson-White syndrome). In collaboration with Dr Lee Witters at the Dartmouth Medical College in New Hampshire, USA, we showed that the mutation responsible for this condition causes AMPK to be persistently activated in the heart. This new understanding of the cause allows the design of treatments for this condition.

We previously found that AMPK controls the production of nitric oxide in the heart. Nitric Oxide (NO) is a chemical that increases blood flow to heart muscle and reduces the tendency for blood to clot. AMPK activates the enzyme that makes NO, endothelial NO synthase. We have now identified a number of other proteins that regulate endothelial NO synthase. These studies will help us design treatments to improve blood supply to heart muscle after a heart attack.

As mentioned above, AMPK stimulates the breakdown of fat to provide energy for exercise. In collaboration with Dr Glenn McConell at Monash University we showed AMPK accelerates fat breakdown in exercising human muscle by inhibiting an enzyme called acetyl CoA carboxylase. Even moderate exercise is sufficient to activate the AMPK and block acetyl CoA carboxylase, so it seems likely that AMPK contributes to the beneficial effects of exercise on health.

The importance of AMPK in metabolic regulation has been further highlighted by the recent discovery that metformin, a major drug used in the treatment of maturity-onset diabetes, causes activation of AMPK, and that this explains the metabolic changes seen in patients taking the drug. We have verified this important observation. The results of the major clinical trial under the Diabetes Prevention Program, USA, involving 3,234 people with obesity and impaired glucose tolerance showed that 29% of the untreated subjects developed diabetes within 3 years compared to 22% of subjects receiving metformin treatment and only 14% of subjects prescribed diet and increased exercise. These results have aroused intense interest in the development of other drugs that activate AMPK and may be useful for the treatment of diabetes and obesity, in addition to reducing cholesterol and triglyceride levels and improving health.

Another major milestone this year was the "Second-Messengers and Phosphoproteins, 11th International Meeting" held in April at the Melbourne Convention Centre, for which SVIMR was the host. The Minister for State and Regional Development Mr. John Brumby MHA opened the meeting. This conference provided extensive international recognition for the Institute because it was linked to the annual Gordon Research Conference on Second-Messengers and Phosphoproteins. Furthermore, the prestigious scientific journal Science and the on line Science's Signal Transduction Knowledge Environment (STKE at http://www.stke.org/) joined forces with the Institute to make the conference a major international event. There were 750 delegates

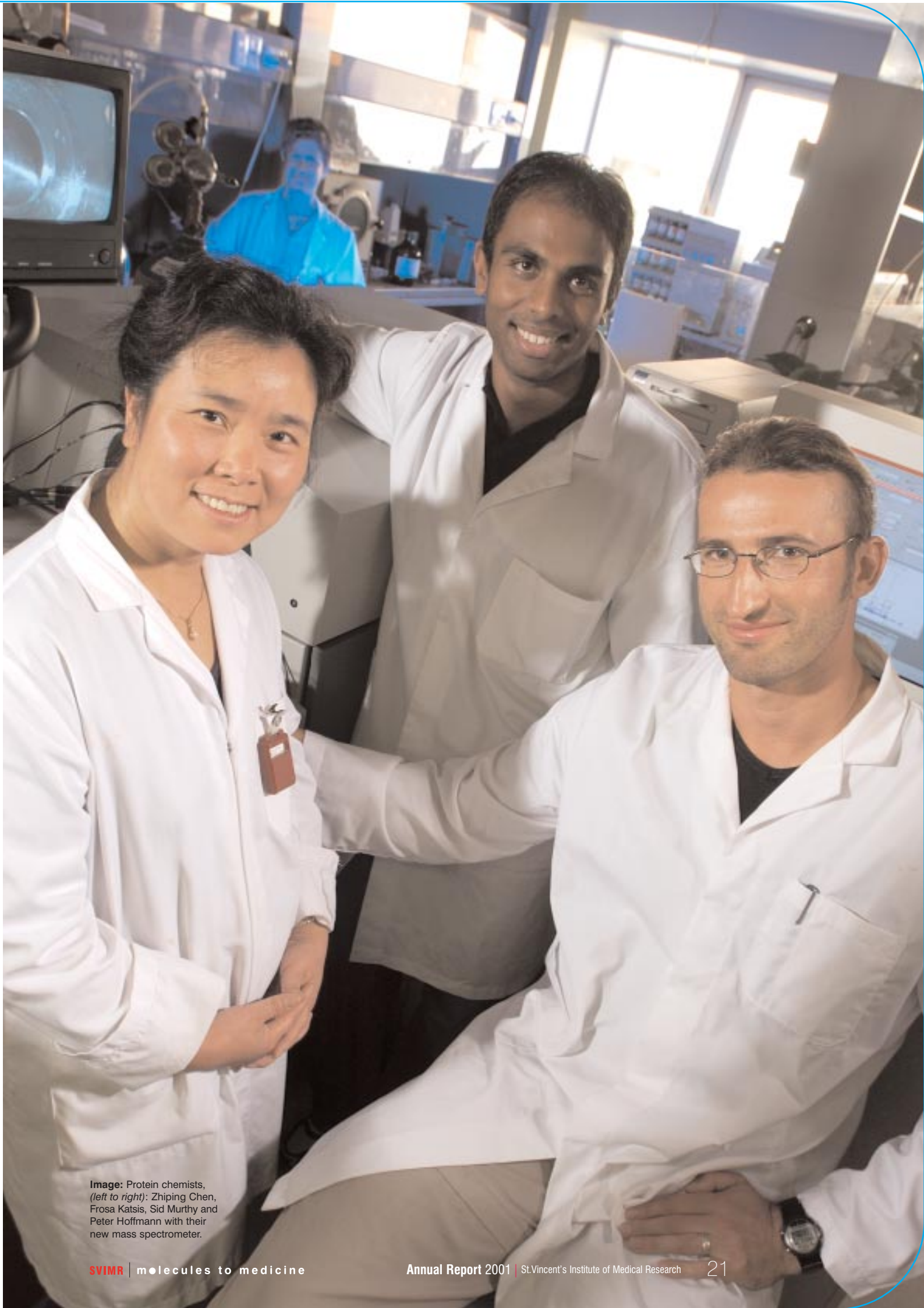


Image: Protein chemists, *(left to right)*: Zhiping Chen, Frosa Katsis, Sid Murthy and Peter Hoffmann with their new mass spectrometer.

The combination of the genome project, the rapid acceleration of protein research, and powerful computers, provides a tremendous opportunity to advance understanding of the molecular basis of disease.

Functional Protemics

David Stapleton, Head
Abhilasha Gupta
Tristan Iseli
Matthew Bird
John Huynh

including 500 from overseas. This Conference is the leading international gathering for Signal Transduction Research that is concerned with how proteins are regulated in cells. The conference has a rich history beginning with the inaugural meeting in Milan, Italy in 1971 and this was the first time it was held in the Southern Hemisphere.

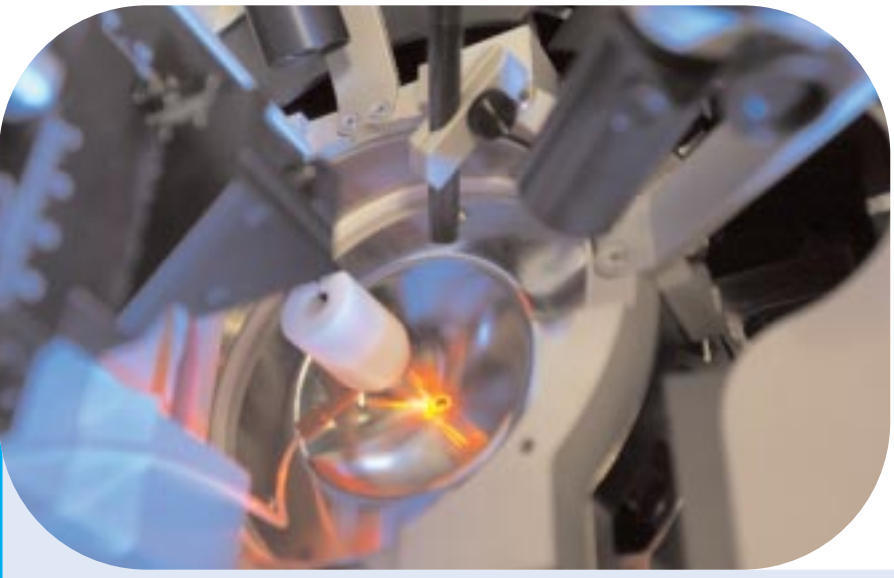


Image: Close-up of our new quadripole time-of-flight mass spectrometer.

FUNCTIONAL PROTEOMICS

The combination of the genome project, the rapid acceleration of protein research, and powerful computers, provides a tremendous opportunity to advance understanding of the molecular basis of disease. Our research focuses on the function of individual domains within proteins that are implicated in medically important diseases. Protein domains are individual compact units within a protein that vary in size from 40 - 700 amino acids. While some proteins consist of a single domain others consist of a few or many domains. We are using several freely available internet-based programs to identify potential domains within proteins. We express these candidate domains in bacteria and study their properties using the Institute's mass spectrometry and protein sequencing facilities. The domain is then re-made with this new information and used in biochemical, structural and cell biology studies to elucidate its role within the protein and its wider role in biology. We are applying this approach to further our understanding of AMPK, in particular the domains of the different subunits of this complex enzyme.

MOLECULAR CARDIOLOGY

New strategies for the prevention and treatment of heart failure

Heart failure affects 3% – 5% of people in Western societies aged over 65 years and 10% of those over 75, and is the leading cause of hospital admission and readmission in the over 65 year age group. Although cardiovascular research has reduced deaths due to coronary artery disease and stroke, the increased survival of people with coronary artery disease, coupled with the aging of society, has been accompanied by an increase in the number of people with heart failure. It is estimated that heart failure affects at least 300,000 Australians, with 30,000 new cases diagnosed each year, and results in an average mortality of 50% after 5 years. Heart failure hospitalisation costs exceed those for myocardial infarction and cancer combined. Improving the diagnosis and care of patients with heart failure is therefore likely to have a major impact on morbidity, mortality, and health care costs.

A major focus of research by the Molecular Cardiology Laboratory is the role of hormones in cardiovascular disease. Heart failure increases the levels of several hormones. The kidneys release increased amounts of renin, an enzyme that, together with angiotensin converting enzyme (ACE) produces the hormone angiotensin. Angiotensin makes the heart muscle cells grow bigger. The sympathetic nerves release increased amounts of noradrenaline that stimulate the heart to pump faster. Although increased amounts of angiotensin and noradrenaline may initially improve heart function, prolonged elevation of the levels of these hormones causes deterioration in heart function. Heart failure is associated with a tendency for the kidneys to reduce the excretion of salt and water in the urine. One of the body's mechanisms to counteract this reduced excretion of salt and water is the production of natriuretic hormones by the heart. These natriuretic hormones cause the kidney to increase excretion of salt and water.

We developed a test that measures the blood level of a natriuretic hormone called NT-proBNP. With our colleagues at St. Vincent's Hospital we showed that blood NT-proBNP levels are markedly increased in heart failure and can assist in the

These findings are important because they provide an explanation for the benefits produced by the combination of ACE inhibitor and ß-blocker therapy.

diagnosis of this condition. We also showed that the blood NT-proBNP level is a sensitive test for early heart failure. Therefore, measurement of NT-proBNP levels in older members of the general community may enable the detection of undiagnosed heart failure, and the prescription of treatment to prevent further deterioration in heart function. In collaboration with our cardiology colleagues at St. Vincent's Hospital we are investigating the value of the NT-proBNP blood test for screening for early heart failure in the general community.

We are also investigating ways to improve treatment of heart failure. The main treatments for heart failure are diuretic drugs, ACE inhibitors, and ß-blocker drugs. Diuretics increase excretion of salt and water in the urine. ACE inhibitors block the formation of angiotensin and ß-blocker drugs block the effects of noradrenaline. For many patients with heart failure, angiotensin levels remain elevated despite ACE inhibitor therapy. In collaboration with cardiologists at the Alfred Hospital Heart Centre, we recently showed that ß-blockers reduce angiotensin levels in heart failure patients taking ACE inhibitor therapy. These findings are important because they provide an explanation for the benefits produced by the combination of ACE inhibitor and ß-blocker therapy. Moreover, our findings serve to encourage doctors to use this combination of therapies when treating patients with heart failure.

Molecular Cardiology

DJ Campbell, Head
Barry Dixon
Athena Kladis

Image: DJ (Jock) Campbell surrounded by scientific chaos.

DNA damage can cause cancer, and cells have sophisticated mechanisms to repair DNA damage to prevent cancer.

Molecular Genetics

Jörg Heierhorst, Head
Lindus Conlan
Andrew Hammet
Carolyn McNees
Brietta Pike
Nora Tenis

Virology

Andy Poumbourios, Head
Heidi Drummer
Chan-Sien Lay
Anne Maerz
Trazel Teh
Kirilee Wilson

MOLECULAR GENETICS

The Molecular Genetics Group has two main areas of research interest: heart function and cancer.

Our study of the heart focuses on the regulation of the efficiency of the heart as a pump. We have been interested in a protein in heart cells called S100A1. To identify the function of this protein we generated mice that do not have this protein, known as S100A1 gene knockout mice. These mice have normal heart function when resting but their hearts have less than normal increase in contraction when stimulated. The hearts of S100A1 gene knockout mice also deteriorate when they have to pump against an increased pressure. These studies demonstrate that the S100A1 protein is essential for the normal cardiac response to increased stress. Our S100A1 gene knockout mice will be very valuable for investigation of how the S100A1 protein affects heart function.

Image: Protein blot analysis of S100A1.

Our study of cancer is focussed on the way cells protect themselves from damage to their DNA. DNA damage can cause cancer, and cells have sophisticated mechanisms to repair DNA damage to prevent cancer. These DNA repair mechanisms are very similar in yeast and animal cells, but yeast are much easier to study. We are studying two yeast proteins, Dun1 and Rad53, as experimental models for a condition of hereditary cancer that occurs in some families called the Li-Fraumeni multi-cancer syndrome, in which a protein called Chk2 is abnormal. One central question concerns the function of the so-called FHA domain in these proteins. We found that the Rad53 FHA1 domain can stop the growth of yeast cells by preventing them from duplicating their genome as a prerequisite for cell division. We also showed that changes in the Rad53 FHA1 domain can make yeast cells more susceptible to DNA damage. These studies demonstrate that the FHA1 domain contributes to the DNA damage response function of Rad53, and we are currently identifying other proteins that protect cells from DNA damage.

VIROLOGY

The human immunodeficiency virus (HIV), human T cell leukemia virus (HTLV), and hepatitis C virus (HCV) have each had a devastating impact on the human population, infecting approximately 250 million individuals. HIV-1 and HTLV-1 are human retroviruses that predominantly infect T cells. T cells play an essential role in protecting us from infection. HIV-1 infected individuals eventually succumb to opportunistic infections, dementia and cancer, whereas HTLV-1 causes adult T cell leukaemia and is associated with a neurological disorder called tropical spastic paraparesis. HCV is a member of the Flaviviridae family of viruses and is therefore more closely related to Dengue and Yellow Fever viruses than to the retroviruses HIV and HTLV. HCV infects approximately 180 million humans world-wide with almost 200,000 infections in Australia alone. Because approximately one fifth of chronic HCV carriers develop liver cirrhosis and 1-5% develop liver cancer, HCV is now the leading single indicator for liver transplantation in developed countries.

A major aim of the Virology Unit is to better understand how viruses produce infection so that we can develop treatments to prevent it. Critical elements in this infection process are the proteins on the surface of the virus. These proteins dock with proteins on the cell surface, like a key in a lock, allowing the virus to enter the cell it infects. The proteins on the surface of retroviruses comprise 2 subunits: the surface glycoprotein mediates viral attachment to proteins on the cell surface and the transmembrane (TM) glycoprotein causes the virus envelope and cell membrane to fuse. We used the technique of protein crystallography to show that retroviral TM proteins are trimeric rod-like molecules termed "helical hairpins". Knowing the shape of this protein provides new understanding of how it causes infection by the virus. Importantly, this protein structure helps us understand how many other viruses infect cells.

HCV produces liver damage by at least two mechanisms. In addition to infecting liver cells, HCV makes T cells more aggressive. T cells are part of the normal defence against infection by viruses.

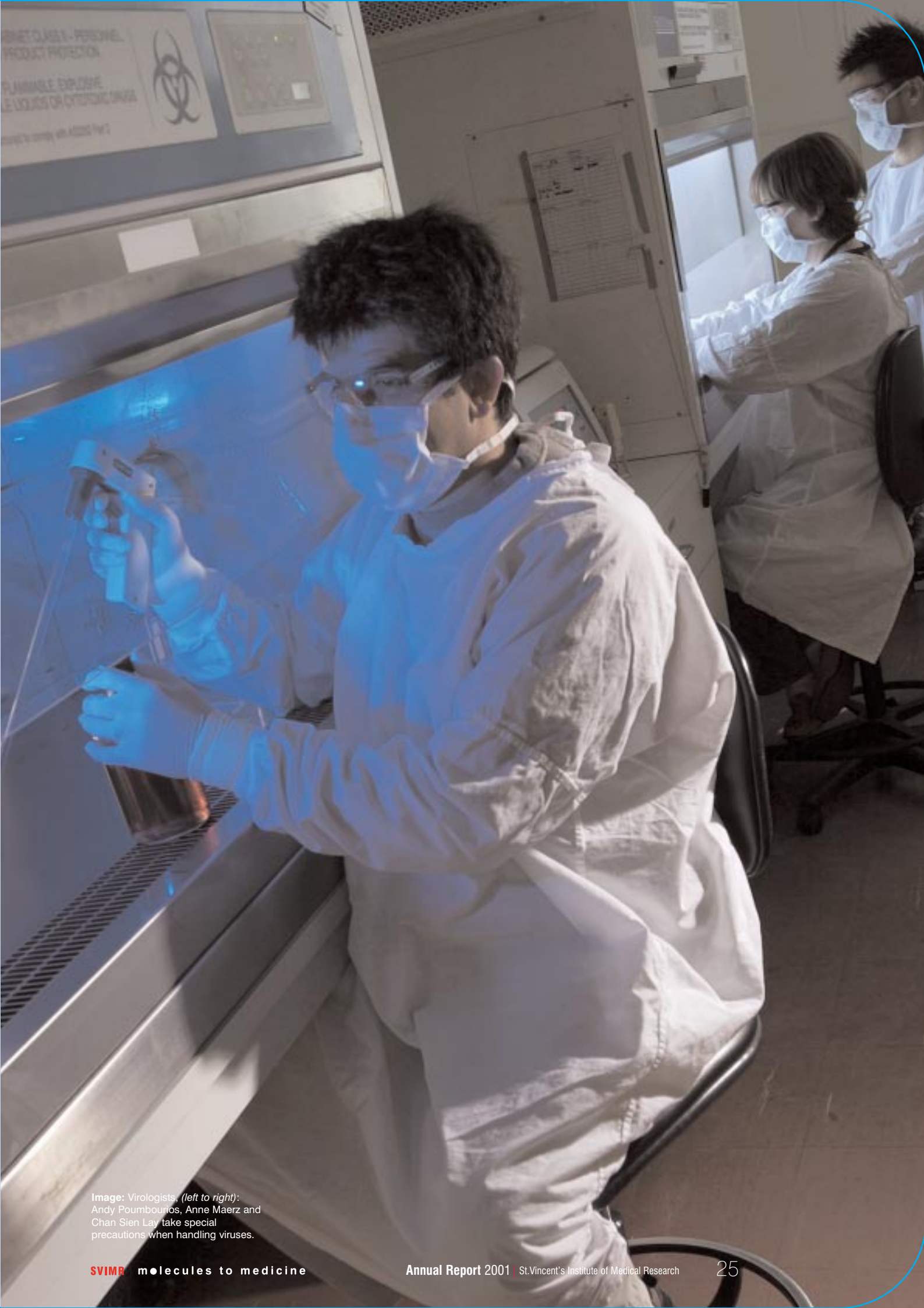


Image: Virologists, *(left to right)*: Andy Poumbourios, Anne Maerz and Chan Sien Lay take special precautions when handling viruses.

Protein crystallography offers the means to determine the three-dimensional (3-D) structure of proteins at the atomic level.

Biota Structural Biology Laboratory

Michael Parker, Head
Brett Cromer
Michelle Dunstone
Susanne Feil
Geoffrey Kong
William McKinstry
Craig Morton
Joanne Parsons
Galina Polekhina
Belinda Rizzo

BIOTA STRUCTURAL BIOLOGY LABORATORY

KNOWLEDGE OF PROTEIN 3-D STRUCTURE ENABLES THE INTELLIGENT DESIGN OF NEW DRUGS

Proteins are one of the body's most 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 that control all functions of the body. Essential to understanding the function of proteins, we need to determine their structure: their shape and size. Protein 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. Our protein crystallography research covers three broad areas: proteins involved in neurological disease, bacterial toxins that attack cell walls, and proteins that detoxify poisons.

Images: Photomicrographs of protein crystals.

However, when HCV infects liver cells, the increased aggression of T cells amplifies liver damage. One way in which the HCV virus may make T cells more aggressive is by the viral E2 glycoprotein attaching to the CD81 protein on the surface of the T cell. Our discovery how the viral E2 glycoprotein attaches to the CD81 protein provides new approaches to the development of drugs that block this process.

PROTEIN DEGRADATION AND DISEASE

Proteins are being continually built and broken down. The breakdown of proteins is important for the removal of damaged proteins. Malfunction of the mechanism of protein breakdown causes diseases such as muscle wasting (often seen in cancer, AIDS and untreated diabetes), Parkinson's, Huntington's, and Alzheimer's disease. Drugs that prevent protein breakdown may be helpful in the treatment of conditions such as cancer, stroke, heart attack, and various neurological diseases.

We determined the 3-D structure of a protein called Siah. This protein participates in protein breakdown and the 3-D shape of this protein provides many clues as to how it does this. These studies provide the foundation for the design of drugs to prevent the protein breakdown that occurs in some illnesses. Our work on Siah is a collaboration with Associate Professor David Bowtell and Colin House of the Peter MacCallum Cancer Institute, Melbourne.

BACTERIAL TOXINS

Some bacteria kill cells by producing toxins that punch holes in the cell membrane. To understand how these toxins punch holes in cell membranes we determined the 3-D structure of several toxins. We previously reported the 3-D structure of perfringolysin O (PFO). This toxin is a member of a large family of similar toxins that are responsible for a variety of diseases including pneumonia and gas gangrene. This year we determined new structures of PFO that reveal the molecular details of how the toxin changes its shape to produce the hole in the cell membrane. This exciting discovery allows us to design drugs to prevent the diseases caused by these toxins. Our work on protein toxins is performed in collaboration with Professor Rod Tweten, Department of Microbiology and Immunology, University of Oklahoma, USA.

Image: Crystallographers, from *(front to back)*: Michael Parker, Michelle Dunstone and Craig Morton analysing protein structures using powerful computers.

The ultimate aim of this work is to devise a novel assay to distinguish between recent (incident) and established HIV infection.

Protein Crystallography

Jamie Rossjohn, Head
Craig Clements
Brendon Classon
Joseph Pereira

National Serology Reference Laboratory

Elizabeth Dax, Director
Thein Thein Aye
Susan Best
Rod Chappel
Wayne Dimech
Sara Egan
Fernando Garcia
Anthony Gust
Callum Haig
Chris Hamilton
Darren Jardine
Elizabeth Johnson
Marina Karakaltsas
Sally Land
Adrian McCall
Kate McGavin
Anita Sands
Joanne Schlegel
Kathy Smeh
Matt Stephenson
Sandy Walker
Kim Wilson

PROTEIN CRYSTALLOGRAPHY

We are using protein crystallography to study proteins on the surface of cells that control cell behaviour. Recent studies have focussed on a protein on the surface of T cells called the T cell receptor. T cells are an essential part of the normal defence mechanism against infection by viruses and the recognition of foreign cells. The T cell uses the T cell receptor to recognise foreign cells or cells infected by virus.

To understand how the T cell receptor operates we used protein crystallography to determine the structure of the T cell receptor that recognises the Ebstein Bar virus. This virus causes glandular fever and, in some patients, can cause cancer. Knowing the detailed structure of this T cell receptor provides valuable information how this receptor identifies foreign cells and cells infected by viruses. This information will help us prevent rejection of organ transplants and also to treat virus infections more effectively.

NATIONAL SEROLOGY REFERENCE LABORATORY

The National Serology Reference Laboratory (NRL) works to ensure the highest possible quality of testing for infection by the HIV and hepatitis viruses by clinical laboratories. In addition, the NRL has an active research program. In collaboration with Professor Bruce Kemp's laboratory at SVIMR and the Centre for Immunology at St. Vincent's Hospital, Sydney, we are investigating new methods to diagnose HIV infection at its earliest stages. The ultimate aim of this work is to devise a novel assay to distinguish between recent (incident) and established HIV infection.

The NRL also continues to participate in the Australian collaborative initiative to develop an HIV vaccine. Our role is to characterise the antibody response to vaccines and we participated in the first Australian clinical trial of an HIV vaccine sponsored by the Melbourne-based biotechnology company Virax.

The NRL's work in developing new approaches to assure the quality and accuracy of diagnostic testing for infectious diseases, both here in Australia and in our neighbouring countries in South-east Asia and the Western Pacific, is continuing. It received a significant boost in 2001 with the development of our Pathology Quality Project, funded by the Diagnostic Technologies Branch of the Federal Department of Health and Ageing. The aim of this project is to improve the quality of all diagnostic pathology in Australia. The first stage of this project was to establish an internet-based program that allows diagnostic laboratories to enter quality control results into a database and to view results generated by different laboratories. This will act as an early-warning system to laboratories so that poor performance of tests due to problems with instrument, operator, or reagent can be readily identified.

Images: *(right)*: Fluorescently labelled cells. *(below)*: Laboratory specimens for analysis and photomicrograph of HIV infected cells.

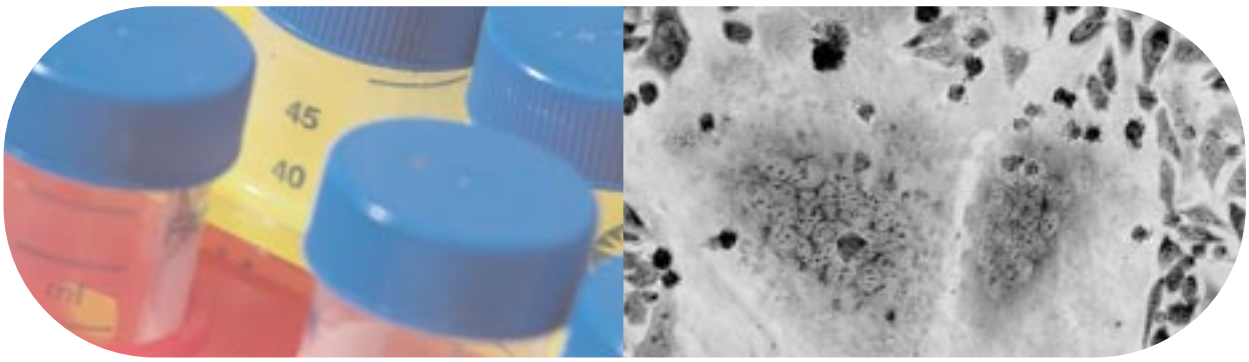


Image: Scientists at work in the NRL, *(left to right)*: Thein Thein Aye, Frank Torzilla, Anita Sands, Sandy Walker and Kathy Smeh.

INTERNATIONAL COLLABORATIONS

Collaborators

INTERNATIONAL COLLABORATIONS

Antonio Aceto and Carmine Di Ilio, Institute of Biomedical Science, Università "G D'Annunzio", Chieti, Italy. Structural studies of glutathione transferases.

Blood Safety Unit, WHO, Geneva, Switzerland. Inter-regional laboratory quality assurance scheme.

Tom Buckley, Department of Biochemistry and Microbiology, University of Victoria, British Columbia, Canada. Structural studies of the bacterial toxin, aerolysin.

Oscar Carretero and Jia Long Zhuo, Division of Hypertension and Vascular Research, Henry Ford Hospital, Detroit, MI, USA. Study of angiotensin and bradykinin peptides levels ingenetic models of cardiovascular disease.

Stephen Elledge, Baylor College of Medicine, Houston, Texas, USA. Checkpoint kinases.

Larry Fisher, NIDCR, NIH, Bethesda, MD, USA. BSP and breast cancer progression.

Ingrid Fleming, Klinikum der JWG-Universitat, Frankfurt, Germany. Endothelial NOS.

Jonathon Green, Novartis, Basel, Switzerland. Bisphosphonate analysis of prostate bone metastasis.

Volkmar Guenzler and George Martin, FibroGen, California, USA. Collagen and cancer inhibitors.

Theresa Guise, University of Texas Health Science Center at San Antonio, Texas, USA. Parathyroid Hormone-related Protein in breast cancer.

Rudy Hartskeerl, Royal Tropical Institute, Amsterdam, The Netherlands, and Martin Palmer, Public Health Laboratory Service, Hereford, UK. Leptospirosis proficiency testing programme.

Ken Holmbeck and Henning Birkedal-Hansen, NIDCR, NIH, Bethesda, MD, USA. Collagen regulation of MMP-2-activation in cells lacking MT1-MMP.

Christopher Kovacs, University of Nova Scotia, Canada. Role of PTHrP in the placenta.

Venkatesh Krishnan, Jude Onyia, Linda Ma and Kannan Thirunavukkarasu, Gene Regulation, Bone and Inflammation, Lilly Research Laboratories, Eli Lilly Co., Indianapolis, IN, USA. PTHrP in bone formation.

Jeremy Lakey, Department of Biochemistry and Genetics, The University of Newcastle-upon-Tyne, Newcastle, UK. Structural studies of colicins.

Mario Lo Bello and Giorgio Ricci, Department of Biology, University of Rome "Tor Vergata", Rome, Italy. Structural studies of glutathione transferases.

Anthony Magliocco, University of Calgary, Calgary, Canada. Role of HSP90 in breast-bone metastasis.

Bengt Mannervik, Department of Biochemistry, Uppsala University, Sweden. Structural studies of glutathione transferases.

John Marshall, ICRF Laboratories, St Thomas Hospital, London, UK. Role of the $\alpha v\beta 3$ integrin in cancer progression.

Mark Mattson, Laboratory of Neurosciences, National Institute of Ageing, Baltimore, MD, USA. Neuronal survival.

Anthony R. Means, Duke University, North Carolina, USA. Protein kinases.

Tim Meyer and Fiona Mackie, Stanford University Medical Center, CA, USA. Studies of the role of angiotensin and bradykinin in the development of the remnant kidney model of renal failure in the rat.

Paul Oritz de Montellano, University of California, San Fransciso, California, USA. Endothelial nitric oxide synthase.

Chris Overall, Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, Canada. Mechanism of MMP-2-activation by MT1-MMP.

Bharat Parekh, Centers for Disease Control and Prevention, Atlanta, GA, USA. Laboratory markers of recent HIV infections.

Neal Rosen, Memorial Sloan-Kettering Cancer Centre, New York, NY. USA. Role of HSP90 in breast-bone metastasis.

Ryuichi Sakai, National Cancer Center Research Institute, Tokyo, Japan. Identification of new domains in p130 (cas).

Hiroshi Sato, Kanazawa Medical School, Kanazawa, and Motoharu Seiki, University of Tokyo, Tokyo, Japan. MT-MMP regulation by collagen.

William Sessa, Yale School of Medicine, New Haven, Connecticut, USA. Endothelial NOS.

David Shalinsky, Agouron / Pfizer, San Diego, California, USA. MMP inhibitors.

Bill Stetler-Stevenson, NCI, NIH, Bethesda, MD, USA. Role of TIMP-2 in MMP-2-activation.

David Stock, Department of Zoology, University of Colorado, Denver, Colarado, USA. Evolution of the vertebrate skeleton.

James Stull, UT South Western Dallas, Texas, USA. Nitric oxide synthase.

Tatsuo Suda, Naoyuki Takahashi and Nobuyaki Udagawa, Showa University, Tokyo, Japan, and Jeffrey Rubin, NIH, Maryland, USA. Osteoclast formation and activation.

Rupert Timpl, Max Planck Institute, Martinsreid, Germany. SPARC / osteonectin / BM40 effects on MMP-2-activation in breast cancer cells.

Ming-Daw Tsai, Ohio State University, Columbus, OH, USA. Structural and genetic analyses of FHA domain functions.

Rod Tweten, Department of Microbiology and Immunology, University of Oklahoma, Alabama, Oklahoma, USA. Pore-forming toxins and receptors.

Gisou van der Goot, Department of Biochemistry, University of Geneva, Geneva, Switzerland. Structural studies of aerolysin.

Richard Venema, Medical College of Georgia, Atlanta, Georgia, USA. Nitric oxide synthase.

Stéphane Vuilleumier, Institute for Microbiology, ETH, Zurich, Switzerland. Glutathione transferases.

John Weinstein, Laboratory of Molecular Pharmacology, Division of Basic Research, National Cancer Institute, NIH, Bethesda, Maryland, USA. Bioinformatics and cancer molecular pharmacology.

Lee A Witters, Dartmouth Medical College, New Hampshire, USA. Regulation of the AMP kinase.

NATIONAL COLLABORATIONS

Robin Anderson, Peter MacCallum Cancer Institute, East Melbourne, Victoria. MMP-inhibition in mouse mammary metastasis model, and the role of PTHrP and novel genes in breast cancer and bone metastasis.

John Bateman, Royal Children's Hospital, Flemington, Victoria. Collagen effects on cell surface activation of MMP-2.

Philip Board, John Curtin School of Medical Research, Australian National University, Canberra, ACT. Glutathione transferases.

Steve Bottomley, Robert Pike and James Whisstock, Department of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria. Serpins.

David Bowtell and Colin House, Peter MacCallum Cancer Institute, East Melbourne, Victoria. Proteins involved in ubiquitination.

Roberto Cappai, Kevin Barnham, and Colin Masters, Department of Pathology, The University of Melbourne, Parkville, Victoria. Proteins implicated in Alzheimer's disease.

Bruno Catimel, Ludwig Institute for Cancer Research, Parkville, Victoria, and Philip Cunningham, Garvan Institute, Darlinghurst, NSW. Laboratory markers of recent HIV infection.

Michael Clark, Department of Biochemistry, The University of Tasmania, Hobart, Tasmania. Protein kinases in ischaemic muscle.

Christine Clarke, Westmead Institute for Cancer Research, Sydney, NSW. Progesterone receptor effects on cell migration.

John Clement, Department of Dental Science, The University of Melbourne, Parkville, Victoria. Comparative physiology of calcium regulating hormones.

Tony Costello and Helen Crowe, The University of Melbourne and Department of Surgery, Urology Division, Royal Melbourne Hospital, Parkville, Victoria. Prostate cancer invasion and metastasis and gene array analysis of selenium chemoprotective mechanism.

Richard GH Cotton, Mutation Research Centre, St. Vincent's Hospital, Fitzroy, Victoria. Structure/function studies of phenylalanine hydroxylase and the structural basis of phenylketonuria.

Lea Delbridge and Stephen Harrap, Department of Physiology, The University of Melbourne, Parkville,

NATIONAL COLLABORATIONS

Victoria. Study of the renin angiotensin and kallikrein-kinin systems in a genetic model of cardiac hypertrophy in the rat.

Barry Dixon and John Santamaria, Intensive Care Unit, St. Vincent's Hospital, Fitzroy, Victoria. Studies of the activation of the kallikrein-kinin system during cardiopulmonary bypass.

Xiaojun Du and Tim Cole, Baker Medical Research Institute, Prahran, Victoria. Characterisation of the cardiac function of S100A1 knockout mice.

Murray Esler, Baker Medical Research Institute, Prahran, Victoria. Studies of the relationship between the renin angiotensin system and sympathetic nervous system activity in hypertensive subjects.

Murray Esler and Henry Krum, Baker Medical Research Institute and Alfred Hospital, Prahran, Victoria. Studies of the effects of AT1 receptor antagonists on blood levels of angiotensin and kinin peptides in hypertensive subjects.

Rosemary French, Department of Paediatrics, Sydney Children's Hospital, NSW, Huon O'Sullivan, Department of Obstetrics and Gynaecology, Royal Women's Hospital, Carlton, Victoria, and Katrina Watson, Department of Gastroenterology, St. Vincent's Hospital, Fitzroy, Victoria. Hepatitis C in pregnancy.

Albert Frauman, Department of Medicine, The University of Melbourne, and Austin & Repatriation Medical Centre, Heidelberg, Victoria. KAI-1 in prostate cancer metastasis.

Peter Gage, John Curtin School of Medical Research, Australian National University, Canberra, ACT. Neurobiology.

James Goding, Department of Pathology and Immunology, Monash University, Victoria. Structural studies on cell surface receptors.

Greg Goodall, Hanson Centre for Cancer Research, Adelaide, South Australia. Crystallographic studies of Poly-A binding protein.

Ming Gu and Xiaosong Gan, Centre for Microphotonics, Swinburne University of Technology, Hawthorn, Victoria. 2 photon confocal analysis of normal and neoplastic tissues.

Susan Hahnemann and Roger Peverill, Departments of Emergency Medicine and Cardiology, Monash Medical Centre. Evaluation of the use of plasma NT-proBNP level for the diagnosis of patients presenting to the Emergency Department with acute dyspnoea.

John Horowitz and Chris Zeitz, Department of Cardiology, Queen Elizabeth Hospital, Woodville, South Australia. Studies of the effects of ACE inhibition on the human heart.

David Horsfall, Flinders Cancer Centre, Bedford Park, South Australia. Proteoglycan analys is of experimental breast and prostate cancers.

David A Jans and Mark Lam, John Curtin School of Medical Research, Australian National University, Canberra, ACT. Parathyroid hormone-related protein location.

George Jerums, Austin and Repatriation Medical Centre and The University of Melbourne, Heidelberg, Victoria. Protein kinases and diabetes.

David Kaye, Heart Centre, Alfred Hospital, Prahran, Victoria. Studies of the renin-angiotensin and kallikrein-kinin system in heart failure.

Stephen Kent, Department of Microbiology, The University of Melbourne, Parkville, Victoria. Development of HIV vaccines.

Bostjan Kobe, Institute of Molecular Sciences, University of Queensland, St. Lucia, Queensland. X-ray crystallographic analysis of FHA domains. Structure and function of HTLV-1 transmembrane protein.

Peter Leedman, Western Australian Institute for Medical Research, Perth, Western Australia. Transcriptional regulation of osteonectin.

Trevor Lithgow and Paul Gooley, Department of Biochemistry and Molecular Biology, The University of Melbourne, Parkville, Victoria. Structural studies of receptors.

Angel Lopez, Hanson Centre for Cancer Research, Adelaide, South Australia. Structural studies of cytokine receptors.

Bruce Loveland and Mauro Sandrin, Austin Research Institute, Heidelberg, Victoria. Structural studies of cell surface receptors.

Gordon Lynch, Department of Physiology, The University of Melbourne, Parkville, Victoria. Protein kinases and skeletal muscle.

James McCluskey and Anthony Purcell, Department of Microbiology and Immunology, The University of Melbourne, Parkville, Victoria. Allo-recognition at a structural level.

Glenn McConell, Department of Physiology, Monash University, Clayton, Victoria. Protein kinase and exercise.

Michael McKinley, Howard Florey Institute of Experimental Physiology and Medicine, Parkville, Victoria. Study of the renin angiotensin and kallikrein-kinin systems in mouse models of ACE and angiotensinogen gene knockout

Dale McPhee and Alison Greenway, MacFarlane Burnett Centre for Medical Research, Fairfield, Victoria. Role of vif in HIV replication.

Johnson Mak, MacFarlane Burnett Centre for Medical Research, Fairfield, Victoria, Structural evolution of HIV-1 envelope glycoproteins.

Christine Mitchell and James Whisstock, Department of Biochemistry, Monash University, Clayton, Victoria. Structural studies of signalling enzymes.

Wayne Morrison, Bernard O'Brien Institute of Microsurgery and The University of Melbourne Department of Surgery, St. Vincent's Hospital, Fitzroy, Victoria. Use of antibrotic agents against experimental tendon adhesions.

Wayne Morrison and Ken Knight, Bernard O'Brien Institute of Microsurgery, St. Vincent's Hospital, Fitzroy, Victoria. Generation of vascularised bioengineered soft tissue.

Brendan Murphy, Department of Nephrology, St. Vincent's Hospital, Fitzroy, Victoria. Complement proteins.

Don Newgreen, Murdoch Institute, Flemington, Victoria, and Leigh Ackland, Deakin University, Geelong, Victoria. PMC42 cell analysis of the EMT in breast cancer.

Geoff Nicholson, The University of Melbourne Department of Medicine and Geelong Hospital, Geelong, Victoria. Osteoclast biology.

Ron Pace, Department of Chemistry, Australian National University, Canberra, ACT. Membrane proteins.

Richard Pearson, Peter MacCallum Cancer Institute, East Melbourne, Victoria. Growth factor dependent protein kinases.

David Power, Austin and Repatriation Medical Centre, Heidelberg, Victoria. Regulation of AMP Kinase.

David Prior and Andrew MacIsaac, Department of Cardiology, St. Vincent's Hospital, Fitzroy, Victoria. Evaluation of the use of plasma NT-proBNP level to screen for cardiac dysfunction in the general community.

Anne Rosamilia, Prince Henry's Institute of Medical Research, Clayton, Victoria, and Judith Clements, Queensland University of Technology, Brisbane, Queensland. Studies of the role of kinin peptides and substance P in interstitial cystitis.

David Sayer, Department of Clinical Immunology, Royal Perth Hospital, Perth, WA. Quality assurance of HIV genotypic testing.

Hans Schneider, Department of Pathology, Alfred Hospital, Prahran, Victoria. Multiple myeloma effects on bone.

Andrew Stevenson and Stephen Wilkins, CSIRO, Manufacturing & Technology, Clayton, Victoria. Phase-Contrast X-Ray Radiography in Biomedical Research.

Sepehr Tabrizi, Department of Molecular Microbiology, Women's and Children's Health Network, Carlton, Victoria. Chlamydia trachomatis diagnostic testing.

Cheryl Taylor and Rob Fairclough, Victoria University of Technology, Victoria. Gene Expression Profiling of Xenoestrogen Action on Breast Cancer Cell Lines.

Wayne Tilley, Flinders University Cancer Centre, Bedford Park, South Australia. Androgen receptor analysis in new prostrate cancer cell lines.

Roger Truscott, Department of Chemistry, University of Wollongong, Wollongong, NSW. Metalloenzymes.

Virax Immunotherapeutics P/L, Kew, Victoria. Phase 1/11a safety and biological activity of an HIV vaccine.

Terry Walker, Marine and Freshwater Research Institute, Queenscliff, Victoria. Comparative physiology of calcium regulating hormones.

Binks Wattenberg, Hanson Centre for Cancer Research, Adelaide, South Australia. Protein kinase receptors.

Marelyn Wintour, Howard Florey Institute of Experimental Physiology and Medicine, Parkville, Victoria. Changes in renin angiotensin system in hypertensive sheep, and the effects of Ang-(1-7) in foetal sheep.

Jeffrey Zajac, Department of Medicine, Austin & Repatriation Medical Centre, Heidelberg, Victoria. Genes for PTHrP in fish.

It is the enthusiastic contribution of every member that helps the Institute live up to the vision of our original benefactor.

Staff Members

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NATIONAL SEROLOGY REFERENCE LABORATORY

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Wayne Dimech, *BAppSc RMIT FAIMS GdipMgt.*
Fernando Garcia, *BAppSc RMIT.*
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Penelope Webster, *BA Maine USA.*

Image: Administrative Staff of the Institute, *(back)*: David Murfitt; *(middle row, left to right)*: Diane Losa, Gayle McMurray, David Rees; *(front row, left to right)*: Dimi Samaras and Sally Emini.

"SVIMR offered a wide variety of projects, great facilities, a close interaction with the hospital and opportunities to attend conferences, retreats and network with other researchers."

Natasha Ilievska, PhD Student.

Students & Seminars

SCHOLARS

DOCTOR OF PHILOSOPHY:

Angela Arvanitis, *BSc Hons Melb*
'Gene expression profiling in breast cancer cells'

Lindus Conlan, *BSc Hons Melb*
'Transcriptional properties of PTHrP'

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

Michelle Dunstone, *BSc Hons Mon*
'Structural studies of human complement pathway proteins'

Nirada Dhanesuan, *DDS Chulalongkorn*
'SPARC/Osteonectin regulation of MMP-2 activation at the cell surface'

Susanne Feil, *MSc Stockholm*
'Structural studies of medically important proteins'

Andrew Hammet, *BSc Hons Melb*
'Regulation of DNA damage repair mechanisms by protein phosphorylation'

Karl Häusler, *BAppSc Phillip MAppSc RMIT*
'Osteoblastic and lymphocytic factors affecting osteoclastogenesis'

Natasha Ilievska, *BSc Hons VUT*
'Role of PTHrP in DNA repair'

GRADUATIONS

THE FOLLOWING GRADUATED DOCTOR OF PHILOSOPHY:

Ian Jennings *'Structure-function studies of phenylalanine hydroxylase'*

Belinda Michell *'Regulation of endothelial nitric oxide synthasse by multiple signalling pathways'*

Neeracha Ruangpanit *'Collagen regulation of cell surface activation of MMP-2'*

Kim Wilson *'Autologous red cell agglutination assay'*

THE FOLLOWING GRADUATED DOCTOR OF MEDICINE:

Esther Yenson Chu *'Regulatory role of interleukin 17 in cytokine production by human synovial fibroblasts'*

THE FOLLOWING GRADUATED BACHELOR OF SCIENCE HONOURS:

Geoffrey Kong *'Structural studies of human Pi glutathione transferase using X-ray crystallography'*

Tristan Iseli *'Affinity purification of AMP-activated protein kinase interactive proteins'*

Ian Jennings, *BSc Melb*
'Structure-function studies of phenylalanine hydroxylase'

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

Belinda Michell, *BSc Hons Mon*
'Regulation of endothelial nitric oxide synthase by multiple signalling pathways'

Danijela Mirosavljevic, *BSc Hons LaTrobe* *'Lymphocyte-derived factors affecting osteoclastogenesis'*

Neeracha Ruangpanit, *DDS Hons Chulalongkorn* *'Collagen regulation of cell surface activation of MMP-2'*

Joseph Pereira, *BSc Hons LaTrobe*
'An investigation into the role of the integrin $\alpha v\beta 3$ and the matrix-metallo-proteinase-2 in cancer'

Brietta Pike, *BSc Hons Melb*
'FHA domains in the regulation of cell cycle check point protein kinases'

Kim Wilson, *BAppSc QIT*
'Autologous red cell agglutination assay'

DOCTOR OF MEDICINE

Esther Yenson Chu, *MBBS London UK*
'Regulatory role of interleukin 17 in cytokine production by human synovial fibroblasts'

P Scott Mackie, *MBBS Melb*
'The role of bisphosphonates as an adjunct treatment for osteosarcoma'

BACHELOR OF SCIENCE (HONOURS)

Tristan Iseli, *BSc Melb*
'Affinity purification of AMP activated protein kinase interactive proteins'

Geoffrey Kong, *BSc Melb*
'Structural studies of human Pi glutathione transferase using X-ray crystallography'

SEMINAR PROGRAM

Professor Lung T. Yam
Department of Medicine, V.A. Medical Centre, Louisville, Kentucky, USA. "Tartrate-resistant acid phosphatase as a cell marker"

Dr. Hong Zhou
Department of Medicine/St. Vincent's Institute of Medical Research. "A novel osteoblast-derived C-type lectin that inhibits osteoclast formation"

Dr. Craig Morton
Biota Structural Laboratory, St. Vincent's Institute of Medical Research. "Adventures in biophysics:- SH3-ligand interactions"

Dr. David Thomas
Department of Medicine/St. Vincent's Institute of Medical Research. "A role for the retinoblastoma protein in osteogenic differentiation"

Professor James Goding
Department of Pathology and Immunology, Monash Medical School, Alfred Hospital. "Ecto-nucleotide pyrophosphatase/ phosphodiesterase: What does it do?"

Dr. James Whisstock
Department of Biochemistry & Molecular Biology, Monash University. "Blasting the sequence databases"

Dr. David Stapleton
St. Vincent's Institute of Medical Research. "Celera: is it worth it?"

Dr. Damien Myers
The University of Melbourne Department of Biomedical Sciences, Barwon Health, Geelong Hospital. "Cell biology and cytokine control of bone turnover"

Dr. Andrew Hill
Department of Pharmacology, The University of Melbourne. "The molecular analysis of prion strains and species barriers"

Ms. Belinda Michell
St. Vincent's Institute of Medical Research. "Regulation of endothelial NOS by protein phosphorylation"

Associate Professor Paul Simmons
Peter MacCallum Cancer Institute. "Stem cells in adult mammalian tissues: identification and developmental plasticity"

Associate Professor Piroska Rakoczy
Molecular Ophthalmology, Lions Eye Institute of Western Australia. "Gene therapy as a research and therapeutic tool"

Professor Jeffrey Zajac
Department of Medicine, Austin & Repatriation Medical Centre. "Design and construction of animal models of type 2 diabetes"

Dr. Natalie Sims
Department of Medicine/St. Vincent's Institute of Medical Research. "DofosB: an AP-1 family regulator of bone formation"

Dr. Mike Ryan
Department of Biochemistry, LaTrobe University. "The general import pore complex for the translocation of protein into mitochondria"

Dr. Don Newgreen
Embryology Laboratory, The Murdoch Children's Research Institute. "Epithelial-mesenchymal transitions in development and cancer: a double edged sword"

Dr. Marc LaFleur
St. Vincent's Institute of Medical Research. "The involvement of matrix metalloproteinases in angiogenesis"

Dr. Robert Kapsa
Muscular Dystrophy Research Unit, Melbourne Neuromuscular Research Institute, St. Vincent's Hospital. "Genetic correction of stem cells in the mdx mouse: Towards an autologous cell replacement strategy for Duchenne muscular dystrophy"

Ms. Lindus Conlan
St. Vincent's Institute of Medical Research. "Identification of protein interactors with Parathyroid Hormone related Protein (PTHrP)"

Professor Clyde Denis
Department of Biochemistry & Molecular Biology, Program in Genetics, University of New Hampshire, USA. "The CCR-4NOT proteins play multiple roles in mRNA synthesis and degradation"

Dr. Tony Hughes
Department of Pharmacology, The University of Melbourne. "Molecular design of growth factor mimetics"

Dr. Trevor Lithgow
Department of Biochemistry, The University of Melbourne. "Importing proteins into mitochondria: structure and function of the receptors that do the job"

Dr. Masha Fridman
St. Vincent's Institute of Medical Research. "Conformational isomers of H-Ras/GTP with distinct binding properties"

Dr. Manuel Baca
The Walter and Eliza Hall Institute of Medical Research. "How do SOCS proteins suppress cytokine signalling?"

Professor Ian Young
John Curtin School of Medical Research, Australian National University. "Molecular regulation of eosinophilia: structural biology of the β common receptor"

Dr. Robyn Anderson
Peter MacCallum Cancer Institute. "Regulation of apoptosis by heat shock proteins"

Dr. Mike Lawrence
CSIRO Health Sciences & Nutrition, Parkville. "Membrane fusion mechanisms in paramyxoviruses - a structural perspective"

Professor Tony d'Apice
Immunology Research Centre, St. Vincent's Hospital, Melbourne. "Xenotransplantation"

Dr. Evange Romas
Departments of Medicine and Rheumatology, St. Vincent's Hospital, Melbourne. "Involvement of RANK Ligand (RANKL) in skeletal complications of rheumatoid arthritis"

Dr. Stephen Nutt
Division of Immunology, The Walter and Eliza Hall Institute of Medical Research. "The role of Pax5 in B-lineage commitment"

Dr. Joe Trapani
Peter MacCallum Cancer Institute. "Cytotoxic T cells kill virus infected cells and perform immune surveillance against lymphoma"

Dr. Ryuichi Sakai
National Cancer Center Research Institute, Tokyo, Japan. "Functional analysis of docking proteins, Cas and Shc families: Involvement in cancer proliferation and metastasis"

Mr. Tristan Iseli
St. Vincent's Institute of Medical Research. "Functional analysis of AMP-activated protein kinase: protein-protein interactions of the beta-1 subunit""

Mr. Geoffrey Kwai-Wai Kong
St. Vincent's Institute of Medical Research. "GST's - Doing a good service to protein science"

Dr. Phil Darcy
Peter MacCallum Cancer Institute. "Immunotheraphy of cancer using genetically engineered T cells"

Professor John Clement
School of Dental Science, The University of Melbourne. "Proof of Identity: a common problem for the forensic investigator"

Professor David Fairlie
Centre for Drug Design & Development, Institute of Molecular Bioscience, University of Queensland. "Bioactive small molecules that structurally mimic protein surfaces"

Professor Jack Martin
Director, St. Vincent's Institute of Medical Research. "Bench to bedside and back again - PTHrP and the skeletal complications of cancer"

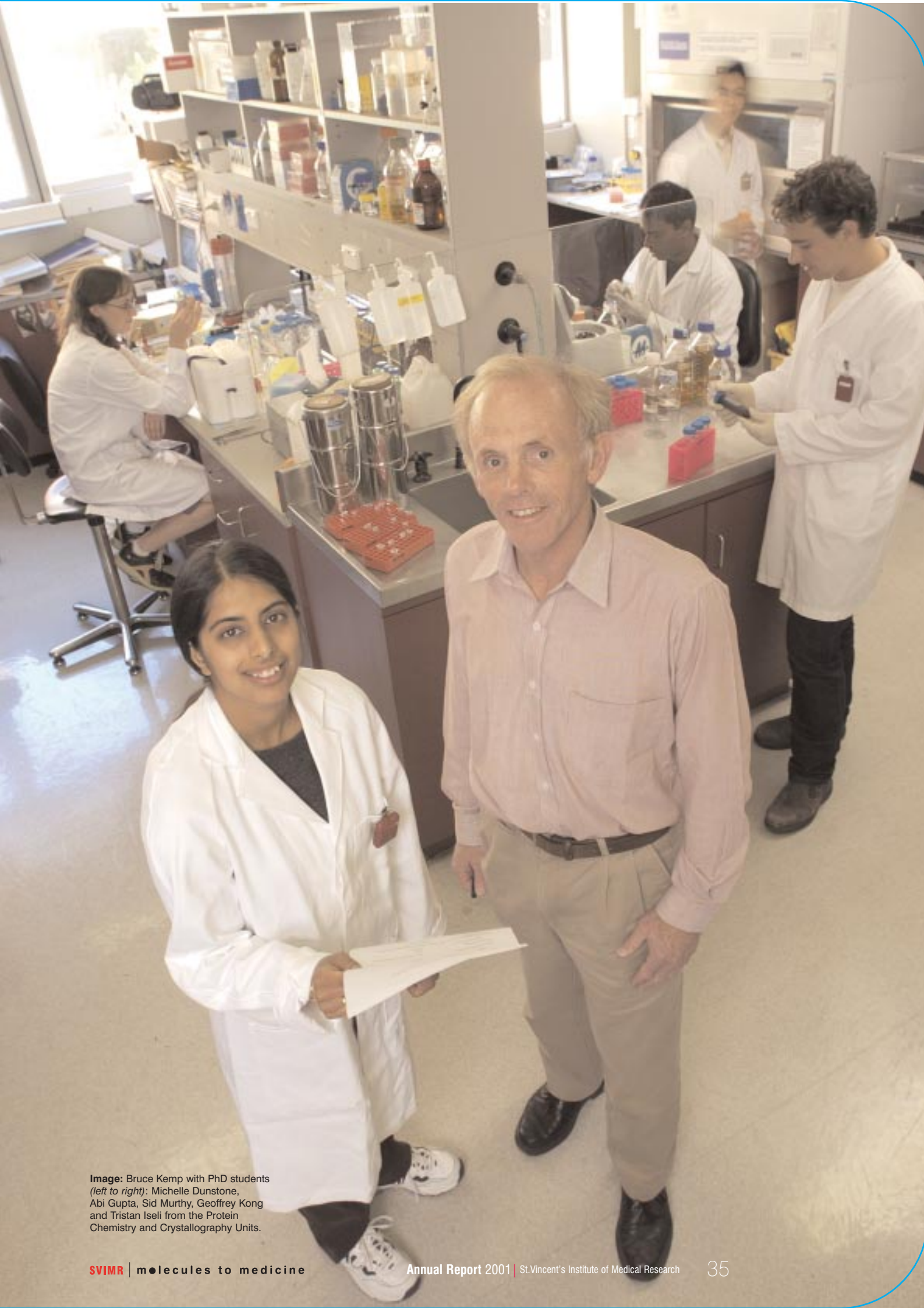

Image: Bruce Kemp with PhD students *(left to right)*: Michelle Dunstone, Abi Gupta, Sid Murthy, Geoffrey Kong and Tristan Iseli from the Protein Chemistry and Crystallography Units.

EDUCATING TOMORROW'S SCIENTISTS

Through the Virtual Laboratory we hope to stimulate students' interest in science and encourage continued science education beyond secondary school.

St. Vincent's Institute of Medical Research is about to embark on a "world first" - with the incorporation of a "Virtual Laboratory" into the current Unit 3 and 4 Biology curriculum. "The Virtual Laboratory" was the concept of Dr David Stapleton and Dr Jane Fisher, scientists at SVIMR, and was recommended for funding by the Department of Education, Employment and Training's (DEET) Science Partnership Initiative to the tune of $25,000. DEET has developed the Science Partnership Projects to support science education in government primary and secondary schools. Kew, Lilydale and Box Hill High Schools and Norwood and Maroondah Secondary Colleges will participate in the development of the program, together with Ann Osman, Eastern Metropolitan Regional Project Officer for Science, and Pam Smith, Science Network and Professional Development Leader for Secondary Schools in the Eastern Metropolitan Region.

Virtual Lab

The aim of "The Virtual Laboratory" project is to develop a multimedia program that will enhance the quality of the current Unit 3 and 4 Biology curriculum for both students and teachers. The program will initially focus on two areas of the curriculum that have been identified as topics that are difficult for students to interpret and currently have limited resources, namely, immunology and gene technology and its applications. Each unit will consist of three modules: the virtual laboratory experiments, background theory and an interactive project.

The program will open with an interactive view of a real life laboratory at St. Vincent's Institute of Medical Research. This will enable users to pan around 180∞, select items in the laboratory to access explanations of what the items are called, how they work and their use.

The first module will consist of video footage of case studies in the Virtual Laboratory experiments, being performed at St. Vincent's Institute of Medical Research. A soundtrack of scientists discussing their work will provide an explanation of the procedures and enable students to follow entire experiments both visually and audibly. In this manner the Virtual Laboratory will be able to deliver real life situations that occur in a modern research facility, a service that is unavailable through the normal school system. The Virtual Laboratory module will be accessible using either the internet or CD-ROM.

The second module will consist of computer animations detailing the processes of interest. Students will be asked multi-choice questions throughout the program to assess their understanding and must be able to demonstrate an acceptable level of understanding before proceeding to the next step. Feedback loops will allow participants to return to subjects that they have difficulty with or to the Virtual Laboratory, at any stage of the program. This module will include various levels of complexity, through which the student can traverse, depending on their ability and the level of interest. Multi-levels will also allow for professional development for Biology teachers.

The third module will be an Interactive Laboratory module that the teachers can use in their student assessments. This module will be flexible to allow the teachers to design the direction of individual experiments as required. The experiences and knowledge gained in the previous two modules will allow the students to take part in an assessment program.

Through the Virtual Laboratory we hope to stimulate students' interest in science and encourage continued science education beyond secondary school.

Image: Jane Fisher and David Stapleton demonstrating the "Virtual Laboratory" to school students Fançoise and Duncan Campbell.

Publications

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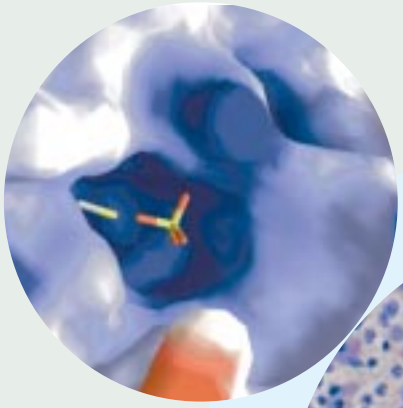

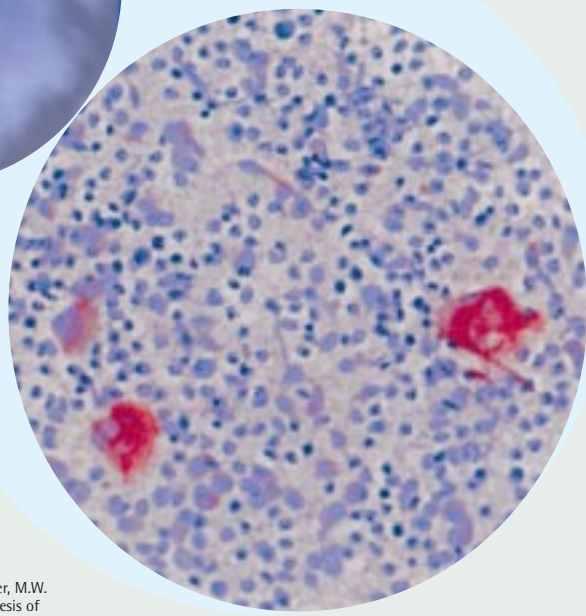

Images: *(Above left)* Active site of the enzyme GST zeta. *(Above right)* Osteoclasts (pink) in bone marrow.

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Image: Belinda Rizzo examines transformed bacterial colonies.

DIRECTORS' REPORT

Your Directors present their report on the company for the financial year ended 31 December 2001.

1. Board of management

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

Mr James D Best
Ms Marcia Griffin
Sr Kathleen Higgs
Mr Terrence R Power
Mr Ian D Reid
Mr Douglas A Wright
Mr Laurie Clemens (from 28 May 2001)
Mr John F Gurry (retired 28 May 2001)
Ms Kerrie L Cross
Mr Charles A Griss
Ms Brenda M Shanahan
Mr Richard G Larkins
Mr Graham EN Rogers

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 amounted to $775,650.

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

During the financial year the company's revenue increased by 38% ($2.1 mil) on last year. The major reasons for this are the continued growth in research activities and the raising of $720,000 for the purchase of a mass spectrometer. The higher than normal operating surplus of $775,650 reflects the capitalisation of the equipment purchase. The company, in terms of operating research activities, shows a more balanced picture with revenue and expenses being more closely aligned.

6. Significant changes in state of affairs

There have been no significant changes in the state of affairs of the company during the financial year.

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 directors continue to support future growth in the company's research activities. An expansion of the existing research facilities is planned to commence in 2002.

9. Environmental issues

The directors are not aware of any significant breaches of environmental regulation during the financial year.

DIRECTORS' REPORT

10. Meetings of directors

During the financial year, 12 meetings of directors (including committees) were held. Attendees were:

	Directors Meeting		Committee Meetings Finance Committee	
	Number eligible to attend	Number Attended	Number eligible to attend	Number Attended
JD Best	6	6	-	-
L Clemens	2	1	-	-
KL Cross	6	5	-	-
M Griffin	6	4	-	-
CA Griss	6	6	6	5
JF Gurry	3	3	-	-
Sr K Higgs	6	1	-	-
RG Larkins	6	4	-	-
TR Power	6	4	-	-
ID Reid	6	6	6	6
GEN Rogers	6	5	6	6
BM Shanahan	6	5	6	3
DA Wright	4	4	-	-

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: JD Best, L Clemens, KL Cross, M Griffin, CA Griss, JF Gurry, Sr K Higgs, RG Larkins, TR Power, ID Reid, GEN Rogers, 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
ID Reid

Director
GEN Rogers

Dated this 8th day of April 2002, Melbourne, Australia

STATEMENT OF FINANCIAL PERFORMANCE FOR THE YEAR ENDED 31 DECEMBER 2001

	Note	2001 ($)	2000 ($)
Revenues from ordinary activities	2	7,553,662	5,447,270
Consumables used	3	(1,313,329)	(998,609)
Employee benefits expense		(4,310,726)	(3,338,802)
Depreciation and amortisation expenses		(484,003)	(442,982)
Other expenses from ordinary activities	3	(669,954)	(1,234,607)
Net surplus from ordinary activities	14	775,650	(567,730)
Total changes in equity		**775,650**	**(567,730)**

The accompanying notes form part of these financial statements.

STATEMENT OF FINANCIAL POSITION FOR THE YEAR ENDED 31 DECEMBER 2001

	Note	2001 ($)	2000 ($)
CURRENT ASSETS			
Cash assets	8	2,845,601	3,100,697
Receivables	7	617,355	446,490
TOTAL CURRENT ASSETS		3,462,956	3,547,187
NON-CURRENT ASSETS			
Receivables	7	250,000	-
Other financial assets	9	67,588	46,431
Property, plant & equipment	10	2,646,763	2,015,774
TOTAL NON-CURRENT ASSETS		2,964,351	2,062,205
TOTAL ASSETS		6,427,307	5,609,392
CURRENT LIABILITIES			
Payables	11	167,099	110,225
Funds held in trust for NSRL accrued leave		138,280	138,280
Provisions	12	729,381	468,834
Other – grants in advance	13	597,982	774,870
TOTAL CURRENT LIABILITIES		1,632,742	1,492,209
NON-CURRENT LIABILITIES			
Provisions	12	85,063	183,331
TOTAL NON-CURRENT LIABILITIES		85,063	183,331
TOTAL LIABILITIES		1,717,805	1,675,540
NET ASSETS		**4,709,502**	**3,933,852**
EQUITY			
Retained surplus	14	4,709,502	3,933,852
TOTAL EQUITY	16	**4,709,502**	**3,933,852**

The accompanying notes form part of these financial statements.

STATEMENT OF CASH FLOWS FOR THE YEAR ENDED 31 DECEMBER 2001

	Note	2001 ($) Inflows (Outflows)	2000 ($) Inflows (Outflows)
CASH FLOW FROM OPERATING ACTIVITIES			
Grants received		6,167,430	5,377,949
Payments to suppliers and employees		(6,315,880)	(4,950,690)
Donations, Legacies and Bequests		611,377	61,103
Other revenue		245,853	359,346
Interest received		169,632	162,683
Dividends		2,641	4,966
Net cash used in operating activities	20	**881,053**	**1,015,357**
CASH FLOW FROM INVESTING ACTIVITIES			
Purchase of plant and equipment		(1,114,992)	(166,381)
Payments for investments		(21,157)	(45,833)
Cash transfer (reclassification of investments as cash)		842,920	(448,353)
Net cash (used in) investing activities		**(293,229)**	**(660,567)**
Net Increase/(decrease) in cash held		587,824	354,790
Cash at the beginning of the year		2,257,777	1,902,987
Cash at the end of the year	20	2,845,601	2,257,777

The accompanying notes form part of these financial statements.

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2001

Note 1: Statement of Significant Accounting Policies

The financial report is a general purpose financial report that has been prepared in accordance with Accounting Standards, Urgent Issues Group Consensus Views, other authoritative pronouncements of the Australian Accounting Board and the Corporations Act 2001. The financial report covers St Vincent's Institute of Medical Research, a company limited by guarantee, incorporated and domiciled in Australia. The financial report has been prepared on an accrual basis and is based on historical costs and does not take into account changing money values or, except where stated, current valuations of non-current assets. Cost is based on the fair values of the consideration given in exchange for assets.

The following is a summary of the material accounting policies adopted by the company in the preparation of the financial report. The accounting policies have been consistently applied, unless otherwise stated.

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2001

(a) Income Tax
The company is granted exemption from income tax under Subdivision 50-B of the Income Tax Assessment Act 1997 because of the charitable nature of the business within which it operates.

(b) Property, Plant and Equipment
Plant and equipment are carried at cost or at Independent or directors' valuation, less, where applicable, any accumulated depreciation or amortisation. The company does not own property. The carrying amount of plant and equipment is reviewed annually by directors to ensure it is not in excess of the recoverable amount from these assets. The recoverable amount is assessed on the basis of the expected net cash flows which will be received from the assets' employment and subsequent disposal. The expected net cash flows have not been discounted to their present values in determining recoverable amounts.

(c) Depreciation
Depreciable assets with a cost in excess of $2,000 are capitalised and depreciation has been provided over their estimated useful lives using the diminishing value method for pre 1 January 1998 and straight line method for assets purchased after this date. The depreciation rate used for Plant and Equipment is from 10% to 33%.

(d) Foreign Currency Transactions and Balances
Foreign currency transactions during the year are converted to Australian currency at the rates of exchange applicable at the dates of the transactions. Amounts receivable and payable in foreign currencies at balance date are converted at the rates of exchange ruling at that date. The gains and losses from conversion of short-term assets and liabilities, whether realised or unrealised, are included in operating surplus from ordinary activities.

(e) Employee Entitlements
Provision is made for the company's liability for employee entitlements arising from services rendered by employees to balance date. Employee entitlements expected to be settled within one year together with entitlements arising from wages and salaries and annual leave, which will be settled after one year, have been measured at their nominal amount. Other employee entitlements payable later than one year have been measured at the present value of the estimated future cash outflows to be made for those entitlements.
Contributions are made by the company to employee superannuation funds and are charged as expenses when incurred.
The company's long service leave liability of $295,488 represents a gross liability of $463,472 offset by net present value contractual obligations of $167,984 from National Health and Medical Research Council (NHMRC). This payment will be receivable upon payment of long service leave by the company on behalf of eligible employees. NHMRC reimburse long service leave payments on a pro-rata basis for the period of their grant support.

(f) Cash
For the purpose of the statement of cash flows, cash includes cash on hand and at call deposits with banks or financial institutions, investments in money market instruments maturing within less than two months and net of bank overdrafts.

(g) Revenue
Grant income is recognised upon performing the research associated to the specific grant. Donation income is recognised upon receipt or when spent, if funds were received for a specific purpose. Interest income is recognised as it accrues.
All revenue is stated net of the amount of goods and services tax (GST).

(h) Change in Accounting Policy
The company changed it's accounting policy in the financial year ending 31 December 2001 by consolidating the General Fund and the Building Fund in the financial statements. The financial effect of this change in accounting policy has been to combine the accumulated funds into a single figure.

(i) Equipment Purchases
The company's revenue generated from ordinary activities includes funds raised for the purchase of assets. In the financial year ending 31 December 2001, revenue raised for asset purchases was $1,114,992.

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2001

Note 2: Revenue

	Note	2001 ($)	2000 ($)
Operating activities			
- grants	4-6	5,625,382	3,927,413
- infrastructure support (Victorian State Government)		716,677	680,238
- contract services		242,642	229,111
- legacies and bequests		415,440	197,662
- donations		195,937	61,103
- dividends	2 (a)	2,641	4,966
- interest	2 (b)	169,632	167,451
- royalty		82,794	9,025
- conference		43,660	69,904
- other		58,857	100,397
Total revenue	2 (c)	**7,553,662**	**5,447,270**
(a) Dividends from:			
- other corporations		2,641	4,966
		2,641	4,966
(b) Interest from:			
- other corporations		169,632	167,451
		169,632	167,451
(c) Significant Revenues			
The following significant revenue item is relevant in explaining the financial performance:			
- revenue raised for asset purchases		1,114,992	166,380
		1,114,992	166,380

Note 3: Surplus from Ordinary Activities

	2001 ($)	2000 ($)
Surplus from research activity has been determined after:		
(a) Direct cost of research activities:		
Direct research expenses		
- consumables	1,035,524	905,888
- salaries and on costs	3,368,816	2,613,945
- other	450,132	338,855
Transfer of funds to external joint collaborations	87,059	216,749
Abnormal item - funds transfer	-	448,353
(b) Infrastructure cost of research activities:		
- administration	366,361	279,381
- salaries and on costs (includes laboratory technical support)	919,070	677,390
- other	67,047	91,458
Depreciation of non-current assets	484,003	442,982
	6,778,012	**6,015,001**

Note 4: Grants – National Health and Medical Research Council

	2001 ($)	2000 ($)
Project Grants	1,672,839	1,338,178
Scholarships/Fellowships	477,703	186,475
Program Grant (via University Melbourne)	465,286	180,000
	2,615,828	**1,704,653**

Note 5: Grants – Other Commonwealth Government

	2001 ($)	2000 ($)
Australian Research Council	**184,445**	**252,030**

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2001

Note 6: Grants Other

	2001 ($)	2000 ($)
Agouron Pharmaceuticals Inc	83,467	47,932
Anti-Cancer Council of Victoria	173,050	104,900
Arthritis Foundation	-	9,000
Assoc International Cancer Research	86,418	115,819
AXA Asia Pacific Holdings Ltd	150,000	-
AZA Research Pty Ltd	-	20,000
Biota Holdings Limited	103,830	-
Centers for Disease Control and Prevention – USA	-	132,698
Chugai Pharmaceutical Co	225,000	190,528
Diabetes Australia Research Trust	-	33,520
Eli Lilly Aust Pty Ltd	-	11,240
Gastroenterological Society of Australia	27,234	-
International Centre for Deffraction Data	-	3,409
Juvenile Diabetes Foundation Australia	-	94,969
Max Planck Research Award	10,444	-
Mercury Therapeutics Inc	51,231	-
National Heart Foundation of Australia	82,780	45,900
Novartis Pharma AG	69,994	-
Pfizer Pty Ltd	326,832	163,416
Servier Laboratories (Aust) Pty Ltd	25,000	46,397
Solvay Pharmaceuticals Co	47,557	-
St Vincent's Hospital, Melbourne	21,379	31,000
Thomai Breast Cancer Research Fund	48,000	-
University of Melbourne	131,789	88,231
US Army Medical Research Command	127,433	182,303
Victorian Breast Cancer Research Consortium	503,877	540,864
Wellcome Trust	529,794	98,004
William Buckland Foundation	-	10,600
	2,825,109	**1,970,730**

Note 7: Receivables

	2001 ($)	2000 ($)
CURRENT		
Grants and reimbursements	617,355	446,490
NON-CURRENT		
St Vincent's Hospital – Imprest Advance	250,000	-
	867,355	**446,490**

Note 8: Cash Assets

	2001 ($)	2000 ($)
Cash at bank and on hand	918,106	1,025,195
Debentures – At cost		
- ANZ Bank Term Deposit	888,601	842,920
Deposits at call		
- Perpetual Trustees	885,206	835,476
- Macquarie Treasury Fund	153,688	147,106
St Vincent's Hospital – Imprest Advance	-	250,000
	2,845,601	**3,100,697**

Note 9: Other Financial Assets

	2001 ($)	2000 ($)
Shares in listed Corporations – At cost:	67,588	46,431
Market value of listed Corporations	62,687	56,841

Note 10: Property, Plant & Equipment

	2001 ($)	2000 ($)
Plant and equipment at:		
- Directors valuation 1/1/90	841,359	841,359
Less accumulated depreciation	678,795	641,823
Written down value	162,564	199,536
- Post 1/1/90 assets at cost	6,348,332	5,233,340
Less accumulated depreciation	3,864,133	3,417,102
Written down value	2,484,199	1,816,238
Total plant and equipment	**2,646,763**	**2,015,774**

Movements in Carrying Amounts

Movement in the carrying amounts for each class of property plant and equipment between the beginning and end of the current financial year.

Balance at the beginning of the year	2,015,774	2,292,376
Additions	1,114,992	166,380
Disposals	-	-
Depreciation expense	(484,003)	(442,982)
Carrying amount at the year end	**2,646,763**	**2,015,774**

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2001

Note 11: Payables

	2001 ($)	2000 ($)
CURRENT		
Trade creditors	165,823	68,930
Sundry creditors	1,276	41,295
	167,099	**110,225**

Note 12: Provisions

	2001 ($)	2000 ($)
CURRENT		
Employee entitlements	729,381	468,834
	729,381	**468,834**
NON-CURRENT		
Employee entitlements	85,063	183,331
	85,063	**183,331**
(a) Aggregate employee entitlement liability	814,444	652,165
(b) Number of employees at year end	88	74

Note 13: Grants in Advance

	2001 ($)	2000 ($)
Agouron Pharmaceuticals Inc	-	54,881
Australian Research Council	-	26,432
AXA Australia	-	100,000
Mr G Carson	25,000	50,000
Chugai Pharmaceutical Co	95,000	320,000
John Holt Estate	87,000	70,000
Max Planck Award	44,721	-
National Health & Medical Research Council	64,485	-
Ms B Shanahan	45,000	50,000
Pfizer Pty Ltd	163,416	-
Solvay Pharmaceuticals Co	-	47,557
US Army Medical Research Command	-	56,000
Victorian Dept of Human Services	56,860	-
Victorian Dept of Education, Training & Development	16,500	-
	597,982	**774,870**

Note 14: Retained Surplus

	2001 ($)	2000 ($)
Retained surplus at the beginning of the financial year	3,933,852	4,501,582
Net surplus/(deficit) attributed to the company	775,650	(567,730)
Retained surplus at the end of the financial year	**4,709,502**	**3,933,852**

Note 15: Contingent Liabilities

No contingent liabilities or commitments for capital expenditure are known to exist at the date of this report.

Note 16: Members' Guarantee Funds

The company is incorporated in Victoria and limited by guarantee. Every member of the company undertakes to contribute to the assets of the company in the event of its being wound up while it or he/she is a member or within one year afterwards for payment of the debts and liabilities of the company contracted before the time at which he/she ceases to be a member and the costs, charges and expenses of winding up and for an adjustment of the rights of contributories among themselves such amount as may be required not exceeding twenty dollars. The number of members at 31 December 2001 is 38 (2000; 37).

Note 17: Segment Reporting

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

Note 18: Related Party Transactions

Ms B Shanahan, a Director, is a Director of a company which provided investment advice during the year under normal commercial terms and conditions.

Note 19: Funds Held In Perpetuity

The accumulated funds at the end of the financial year of $4,709,502 include funds held in perpetuity of $400,418. The income from these funds is directed to the company's medical research program.

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2001

Note 20: Cash Flow Information

	2001 ($)	2000 ($)
(a) Reconciliation of Cash:		
Cash on hand and cash advances	918,106	982,582
Unsecured Deposits (at call)	1,927,495	1,025,195
Advance – St Vincent's Hospital	-	250,000
	2,845,601	**2,257,777**
(b) Reconciliation of cash flow from operations with surplus from ordinary activities:		
Surplus from ordinary activities	775,650	(119,377)
Non-cash flows in surplus from ordinary activities		
Depreciation – Plant and Equipment	484,003	442,982
Changes in assets and liabilities:		
(Increase)/Decrease in Debtors & Accrued Revenue	(170,865)	81,764
(Increase)/Decrease in Non-current Receivable	(250,000)	-
Increase/(Decrease) in Creditors	56,874	88,024
Increase/(Decrease) in Grants and Donations in Advance	(176,888)	437,013
Increase in Provision for Employee Entitlements	162,279	84,951
Cash flows from operations	**881,053**	**1,015,357**

Note 21: Auditor's Remuneration

	2001 ($)	2000 ($)
Remuneration of the auditor of the company for:		
- audit or review	7,750	7,650
- other services	-	-
	7,750	**7,650**

Note 22: Remuneration and Retirement Benefits

	2001 ($)	2000 ($)
(a) Directors' Remuneration		
Income paid or payable to all the directors of the company, directly or indirectly, by the company or any related party.	-	-
(b) Retirement and Superannuation Payments		
Amounts of a prescribed benefit given during year by the parent entity or a related party to a director or prescribed superannuation fund in connection with the retirement from a prescribed office.	-	-

The names of the company's directors, who held office during the financial year are:

ID Reid	L Clemens (from 28 May 2001)
JD Best	Sr K Higgs
KL Cross	RD Larkins
CA Griss	GE Rogers
T Power	JF Gurry (to 28 May 2001)
BM Shanahan	DA Wright
M Griffin	

Note 23: Financial Instruments

(a) Interest Rate Risk

The company's exposure to interest rate risk, which is the risk that a financial instrument's value will fluctuate as a result of changes in market interest rates and the effective weighted average interest rates those financial assets and financial liabilities, is as follows:

	Weighted Average Effective Interest Rate %	2001($)
Financial Assets		
Cash at bank and on hand	2.5	918,106
Deposits at call	5.4	1,038,894
Debentures	5.1	888,601
Total Financial Assets		**2,845,601**
Financial Liabilities		
Funds held in trust		138,280
Total Financial Liabilities		**138,280**

(b) Credit Risk

The maximum exposure to credit risk, excluding the value of any collateral or other security, at balance date to recognised financial assets is the carrying amount, net of any provisions for doubtful debts, as disclosed in the statement of financial position and notes to the financial statements.

The company does not have any material credit risk exposure to any single debtor or group of debtors under financial instruments entered into by the company.

(c) Net Fair Values

The net fair values of assets and liabilities approximates their carrying value.

No financial assets are readily traded on organised markets in standardised form other than listed investments.

The aggregate net fair values and carrying amounts of financial assets and liabilities are disclosed in the statement of financial position and in the notes to the financial statements.

NOTES TO THE FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 2001

Note 24: Superannuation Commitments

The company contributes to employee superannuation funds managed by external fund managers. Members of the funds are entitled to benefits on retirement, disability or death. Employees contribute to the funds at 7% of their gross salaries and the company contributes 14% of employees' gross salaries. Contributions to the Tertiary Education Superannuation Scheme (TESS) are to meet the company's Superannuation Guarantee and Award obligations to all its employees and currently amount to 8% of employees' gross salaries for employees who are not members of the employee contribution schemes and 3% for employees who are members of the employee contribution schemes.

The company is under no legal obligation to make up any shortfall in the fund's assets of the superannuation schemes to meet payments due to employees. 93% of the company's superannuation contributions are made to Unisuper Ltd, which managers the Superannuation Scheme for Australian Universities and TESS. The last actuarial assessment of the Superannuation Scheme for Australian Universities defined benefits superannuation fund was completed by Mr. Grant Harslett FIA, FIAA of Towers Perrin on 18 May 2000. The Superannuation Scheme for Australian Universities has been able to provide an interim, unaudited estimate for June 2001, also shown below.

As at 30 June 2001 (being the latest available information):

	2001 ($)
Fund assets at net market value	1,762,137
Accrued benefits	1,596,859
Excess of fund assets over accrued benefits	165,278
Vested benefits	1,596,859
Employer contributions to the various funds by the company for the 12 month period ending 31 December 2001	389,476

The accrued benefits for each member of the Superannuation Scheme for Australian Universities (SSAU) have been calculated as the greater of:

(a) the present value of future payments of benefits to the member which arise from membership of SSAU up to the reporting date, determined using the actuary's current expectations of earnings on SSAU's assets, future inflations and salary levels and other relevant assumptions, and

(b) the vested benefits.

Vested benefits are benefits which are not conditional upon the continued membership of the fund or any factor, other than resignation from the fund.

Note 25: Company Details

The registered office of the company is:
St. Vincent's Institute of Medical Research
9 Princes Street
Fitzroy, Vic 3065

DIRECTORS' DECLARATION

The directors of the company declare that:
1. The financial statements and notes, as set out on pages 45 to 54 are in accordance with the Corporations Act 2001:
a) comply with Accounting Standards and the Corporations Law: and
b) give a true and fair view of the financial position as at 31 December 2001 and performance for the year ended on that date of the company:
2. In the directors' opinion there are reasonable grounds to believe that the company will be able to pay its debts as and when they become due and payable.
This declaration is made in accordance with a resolution of the Board of Directors.

Director
ID Reid

Director
GEN Rogers

Dated this 8th day of April 2002, Melbourne, Australia

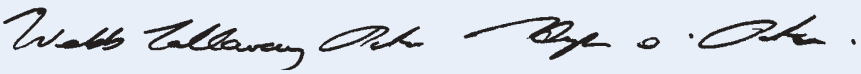
INDEPENDENT AUDIT REPORT TO THE MEMBERS OF ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH

Scope

We have audited the financial report of St. Vincent's Institute of Medical Research for the year ended 31 December 2001, comprising the Statement of Financial Performance, Statement of Financial Position, Statement of Cash Flows, Notes to the Financial Statements and Directors Declaration. The company's directors are responsible for the financial report. We have conducted an independent audit of this financial report in order to express an opinion on it to the members of the company.
Our audit has been conducted in accordance with Australian Auditing Standards to provide reasonable assurance whether the financial report is free of material misstatement. Our procedures included examination, on a test basis, of evidence supporting the amounts and other disclosures in the financial report, and the evaluation of accounting policies and significant accounting estimates. These procedures have been undertaken to form an opinion whether, in all material respects, the financial report is presented fairly in accordance with Accounting Standards and other mandatory professional reporting requirements and statutory requirements so as to present a view which is consistent with our understanding of the company's financial position and performance as represented by the results of its operations and its cash flows.
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 is in accordance with:
a) the Corporations Act 2001:
   i) giving a true and fair view of the company's financial position as at 31 December 2001, and of its performance for the year ended on that date, and
   ii) complying with Accounting Standards and the Corporations Regulations; and
b) other mandatory professional reporting requirements.



WEBB CALLAWAY PATON
Chartered Accountants

HD PATON

Dated this 8th day of April 2002, Melbourne, Australia

DONATIONS

Bequests and Donations from Estates and Charitable Trusts

Anon	70,800
The Jack Brockhoff Foundation	50,000
Estate of Lorna Josephine Paterson	19,427
Francis Findlay Foundation	29,985
George Castan Family Foundation	15,000
Helen Macpherson Smith Trust	25,000
John Holt Medical Research Endowment Fund	103,626
K & A Bongiorno Medical Research Endowment Fund	36,041
M J Polinelli Foundation	26,061
Perpetual Trustees (Clive and Vera Ramaciotti Foundations)	30,000
Trust Co of Aust Ltd (Estate of Late William George Maxwell)	7,500
William Angliss (Victoria) Charitable Fund Foundation	2,000
	415,440

LIST OF DONORS

$50,000 plus

Carson, Mr G

Shanahan, Ms B

$40,001 – $50,000

Shanahan, Ms B (specific purpose donation, c/fwd to 2002)

$30,001 – $40,000

Anonymous

$20,001 – $30,000

Carson Mr G (specific purpose donation, c/fwd to 2002)

$10,001 – $20,000

Australian Racing Hall of Fame Inc

$5001 – $10,000

Anonymous

UBS Warberg Australia staff

$1,000 – $5,000

Anon

Bankers Trust Funds Management

Barker, R

Dax, Dr E

Mayo Pty Ltd

Myer, S

Nicoll, G

O'Shannassy, M

Reid, I

Smith, JFM

Smith, S & R

Spry-Bailey, P

UBS Warburg

Wantirna Hill Club Patrons

Under $1,000

Anon	Fahey, Dr K
Attard, C	Fantech Pty Ltd
Bailey, W	Flack, Dr J
Ball, I	Hogg, TF
Bank of Melbourne	Jeffries, B
Birrell, N	Liow, K
Brydon, DJ	Masel, L
Butt, GP	May, K
Carson, I	Ng, KH
Cator, H	Rees R & T
Clancy, WJ	Richardson, G
Coles Myer Ltd	Ryan, A
Cowen, A	Schneider M
Dolkas, C	Stanley, T & J
Eaton Pty Ltd	Wirawan Liauw L

In Memoriam Donations

In memory of the late P Hassell

195,937

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 program.

The Mary Potter Research Grant	90,797
Diane B Jones Endowment	970
Lorna M Miller Endowment	208,651
Albert H Maggs Endowment	100,000
	400,418

Acknowledgements

We are also grateful for the generous support provided by:

Bank of Melbourne

Crown Limited

Origin Design

Staging Connections

St Vincent's Hospital Foundation Victoria

Sisters of Charity Health Service

Your donation will accelerate the pace of our discovery of new treatments for illnesses.

DONATIONS AND BEQUESTS

DONATIONS

The field of research in which the Institute is engaged touch the lives of many Australians. The scientific research of the Institute aimed at the treatment and cure of illness has depended heavily on the support of the community. Your financial support will have a direct effect on the Institute's research.

There are many ways in which you can help. These include making annual or more frequent gifts, making bequests via a Will or making a donation in memory of a loved one or esteemed person. Donations to St. Vincent's Institute of Medical Research are tax deductible. In claiming a tax deduction you may be required to quote the Institute's ABN 52 004 705 640.

Enquiries will be welcomed by the Director of the Institute on (03) 9288 2480.

Contributions are used directly in research, not on administrative costs.

BEQUESTS

The Institute will be pleased to accept the directions of the donor and use capital and income arising from a bequest according to the donor's wishes. However, it is not necessary to specify a particular purpose as all available Institute funds are used solely for medical research. It is advisable that legal assistance be obtained in making such a provision.

Suggested wording for bequests:

"I ....., bequest unto St. Vincent's Institute of Medical Research, 9 Princes Street, Fitzroy, 3065 in the State of Victoria for its 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."

DONATION FORM

Please detach form below and forward to
St. Vincent's Institute of Medical Research
41 Victoria Parade Fitzroy Vic 3065
Phone: 03 9288 2480 Fax: 03 9416 2676

My contribution to the Appeal for Life fund

Name: _____

Address: _____

_____

Suburb: _____ Post Code: _____

Phone: _____ Fax: _____

I wish to donate the amount of: $ _____

I wish to pay by:

Single payment ☐ Annual payment ☐ Other

My payment is by: ☐ Cheque or money order is enclosed
(made payable to St.Vincent's Institute of Medical Research)

☐ Credit Card ☐ Amex ☐ Visa

☐ Bankcard ☐ Mastercard ☐ Diners

_____ _____ _____ _____

Expiry Date: ___ / ___ Signature: _____

Please do not send any further promotional material

Thank you for your support

SVIMR Australian Business Number: 52 004 705 640
All amounts of $2.00 and over are fully tax deductible.

Appeal for Life Gift

SVIMR is seeking financial support from the community to build on our achievements by expanding our research program. Your donation will accelerate the pace of our discovery of new treatments for illnesses that many of us and members of our families may suffer.

For further information about the Institute and our Appeal for Life connect to our website or contact us on (03) 9288 2480 during business hours.

www.svimr@unimelb.edu.au

St. Vincent's Institute of Medical Research
41 Victoria Parade Fitzroy Vic 3065
Phone: 03 9288 2480 Fax: 03 9416 2676
Email: svimr@medstv.unimelb.edu.au

Appeal for Life | St.Vincent's Institute of Medical Research

SVIMR
MOLECULES TO MEDICINE

St. Vincent's Institute
of Medical Research
ACN 004 705 640

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Fitzroy Victoria 3065

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