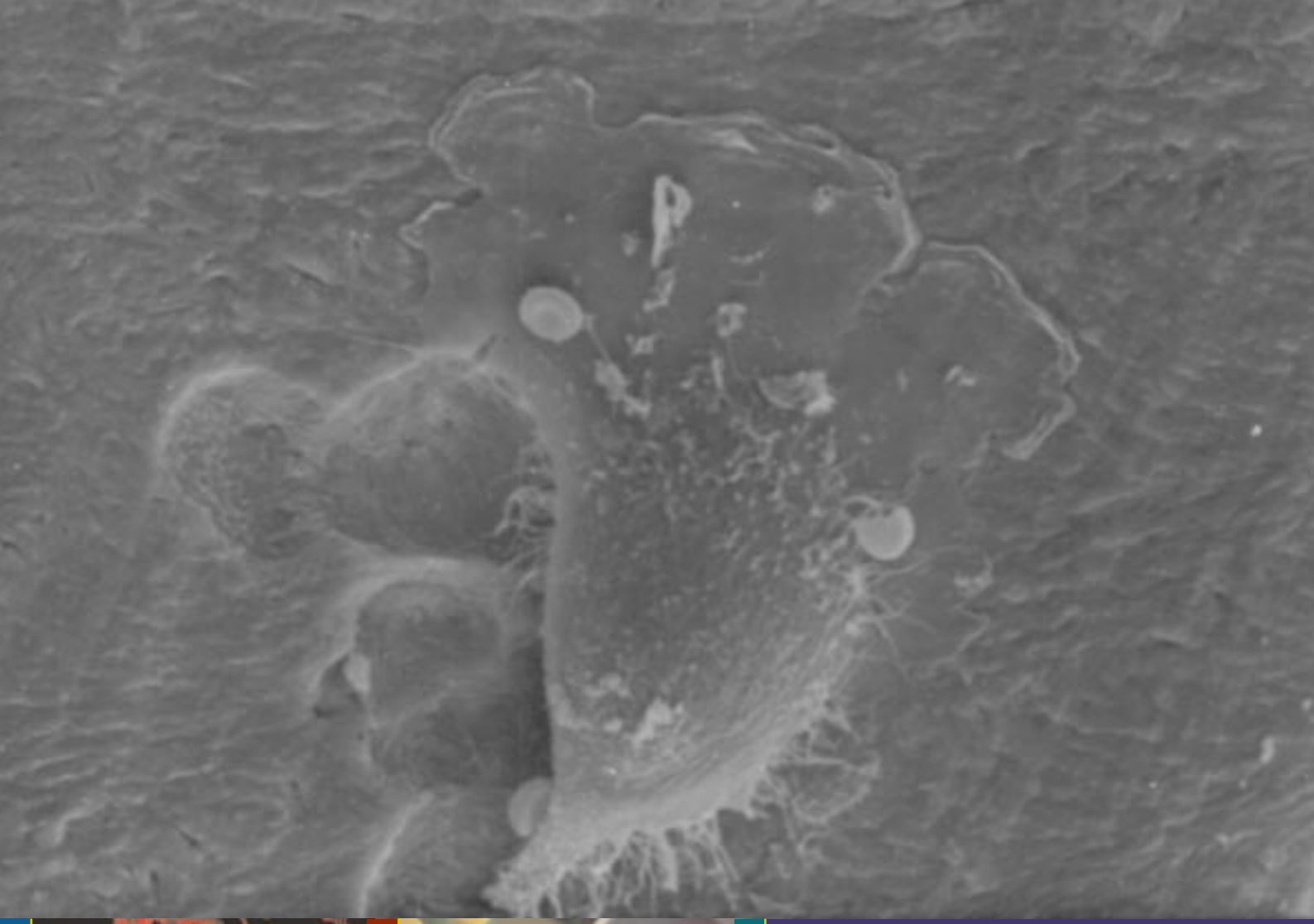


ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH

Annual Report 1999

SVIMR
ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH

Sisters of Charity Health Service

PROTEIN CHEMISTRY

- understanding the three-dimensional shapes of proteins
- regulation of cell function by chemical changes in proteins
- investigating interactions between proteins

CARDIOVASCULAR

- what genes and proteins control the function of blood vessels and heart muscle
- role of peptide hormones in high blood pressure and heart failure, and the effects of drugs on the levels of these hormones

BONE CELL BIOLOGY

- how the cells of bone communicate with each other to develop and maintain a healthy skeleton

BREAST & PROSTATE CANCER

- identification of disordered genes in these cancers
- how do these cancers spread locally in tissues
- how do they grow in distant organs, especially in bone

NATIONAL SEROLOGY REFERENCE LABORATORY

- assuring the quality of Australian laboratory testing for viruses
- viral assay development

CONTENTS

OSTEOCLAST

Scanning electron micrograph of an osteoclast (bone resorbing cell) having moved after excavating a portion of bone.

Left: *Confocal photomicrograph of a mammalian cell over-expressing the phosphatase, TCP45 (green) in the cell nucleus. Actin filaments are stained with folloidin (red) and DNA stained with propidium iodide (blue).*

Right: *Colourful laboratory hardware!*

Back Cover: *Protein crystal of the detoxifying enzyme, glutathione-S-transferase.*

Objectives

St. Vincent's Institute of Medical Research is a centre of excellence in medical research. Its aim is to promote human well-being through prevention and treatment of disease. Its programs of basic and clinical research are applied to the study of certain diseases which are of great cost to the Australian community. These are osteoporosis and other bone diseases, cancers (breast, lung and prostate) which spread to bone, and also heart and blood vessel diseases.

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.

DR HONG ZHOU

"It's exciting to be able to work at the forefront of bone research here at St. Vincent's Institute of Medical Research. It's one of the world's top bone cell biology laboratories.

When I tell my colleagues overseas that I'm working with Professor Martin they say, "Great! Tell us about your research". The international reputation of the Institute has definitely grown in the 12 years that I've been here and its work is well known and very well respected.

The Institute's work has huge implications for future treatments of diseases such as osteoporosis, rheumatoid arthritis and bone cancer."

CHAIRMAN'S REPORT

We can look back upon another bright year in the Institute's history, and one, I am pleased to say, that featured even further Board activity and contributions, building on the efforts of the past few years. The public Forum held again in association with the Annual General Meeting was a notable success, chaired superbly by our Patron, Sir Gustav Nossal.

It attracted a large audience to hear of the social impacts of heart disease from Professor Andrew Tonkin, Director of the National Heart Foundation, the economic impact upon the community from Mr Chris Caton, Chief Economist of Bankers' Trust, and some new research in the Institute from the Deputy Director, Professor Bruce Kemp.

I acknowledge gratefully the service to the Institute over many years of Professor Graeme Ryan, who resigned from the Board this year. Graeme was a great supporter throughout his years as Dean, and continued to be so for some time thereafter.

Throughout the year Board subcommittees were busy. Brenda Shanahan chaired the Development Committee, with the brief to enhance the Institute's community profile and facilitate fundraising and the efforts are already bearing fruit. The Finance Committee chaired by Graham Rogers provided valuable advice and steered the development of a formalised Intellectual Property Policy for the Institute. We see this as essential to achieve our aim of protecting those items of Institute research which might have commercial potential. This work was helped greatly by the efforts of John McDougall, and the full participation of scientists of the Faculty of the Institute was ensured by Michael Parker who was active in convening the Staff Committee.

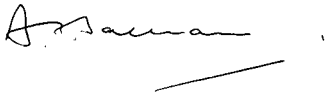
The Director's Research Report informs of details and highlights of research activities, but it is always a pleasure for the Board to note the recognition that its scientists receive in many ways. In 1999 Michael Parker, Head of the Ian Potter Foundation Protein Crystallography Laboratory, received the Gottschalk Medal, the Australian Academy of Science's prestigious award for a young scientist. Nicole Horwood, was awarded a Howard Florey Fellowship to do post-doctoral research at the Kennedy Institute in London. Matthew Gillespie, Head of Molecular Endocrinology, had an extraordinarily busy year as a singularly effective and successful President of the Australian Society of Medical Research. Jamie Rossjohn (Protein Crystallography) was awarded a 4-year RD Wright Fellowship by the NHMRC, and Duncan Campbell, Head of Cardiovascular Research, was appointed Associate Professor in the Department of Medicine by the University of Melbourne. We congratulate each of these individuals as well as the staff at large for their continued high standards of achievement, which reflect so well upon the Institute.

The progressive increase in the Institute's activities and output led the Board in 1999 to decide upon increasing the Executive of the Institute. Accordingly, Michael Parker, Erik Thompson and Matthew Gillespie (pictured) were appointed as Associate Directors to join the Director and Deputy Director in leadership of the Institute. We congratulate them.

As the Institute approaches its half century during the next decade, it has grown in numbers and budget, and needs to grow further. In doing so it works closely with the Hospital as a key research facility of the Sisters of Charity Health Service. What we as a Board believe is that the "common good" of the SCHS and the people it cares for, will be best served if the Institute develops in ways that enhance research elsewhere on the St. Vincent's Hospital campus.

This is my last report as Chairman, and I leave my Board links with the Institute after more than 30 years. It has been gratifying to see it performing to a very high level of science, whether with relatively few staff in the 1960's and 1970's, or with the larger numbers of these latter years. For much of that time I was a member and then Chairman of the Hospital's Advisory Council. I always wanted to ensure that the Institute, although an independent body, would be a powerful contributor to good on this campus. I am glad that I can leave knowing that this is so, but urge that there be no complacency. My colleague throughout those years, Hilton Nicholas, has contributed in the same ways. He too has been on both Boards, was

Chairman of the Institute Board for some years, and shares my great interest in the Institute, and good wishes and exhortations for the future. Sister Paulina Pilkington has been a devoted and loyal supporter of the Institute in her Board activities, and the Institute is very grateful to her, to Hilton Nicholas and to the continuing members of the Board for their great work and support. I am pleased indeed to have been part of the Institute and to have shared the privilege of leadership with such an incomparable leader, our Director, Professor Martin.



Tony Sallmann

MEMBERS OF THE BOARD

Mr Tony Sallmann LVO Chairman
Chairman elect, Parke Rotary (Aust) Ltd.
President International Governing Council, Order of Saint Lazarus. Financial adviser Queens Trust, Member Court of Honour Royal Australasian College of Surgeons, Knight of Malta.

Ms Kerrie Cross BA, BSW, MHA,
Regional Chief Executive Officer, Sisters of Charity Health Service Melbourne Region, member SCHS Melbourne Region Board, member St Vincent's & Mercy Private Hospital Board, Chair of Eastern Palliative Care Committee of Management, member St Vincent's Hospital (Launceston) Ltd Facility Board, member St Vincent's Private Hospital (Melbourne) Ltd Board and member Brotherhood of St Laurence Board.

Mr Charles Griss FCPA, FCA, FAICD,
Director Sisters of Charity Health Service Interim Regional Board, member of Audit & Compliance Committee SCHS, member Conjoint Board Sub-Committee SCHS.

Professor James Best MD, BS, FRACP, FRC Path,
Professor and Head, The University of Melbourne, Department of Medicine, St. Vincent's Hospital, Melbourne.
Co-Head, Department of General Internal Medicine, St. Vincent's Hospital.

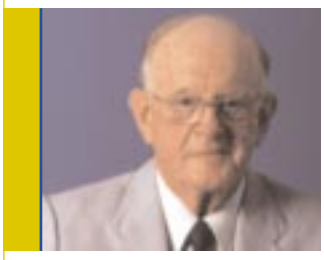
Ms Marcia Griffin BA, DipEd. B. Com,
Board Member PMP Communications Ltd; Tourism Victoria; Queen Victoria Market; Advisory Board Carr Design Group.

Mr John Gurry MBBS, FRCS, FRACS, FACS,
Director of the Vascular Surgery Unit, St. Vincent's Hospital and Senior Associate, The University of Melbourne Department of Surgery. Member, International Society for Cardiovascular Surgery, European Society for Vascular Surgery and International Endovascular Society.

Professor Richard G. Larkins MDBS (Melb), PhD (Lond), FRACP, FRCP,
Dean, Faculty of Medicine, Dentistry and Health Sciences and Head of School of Medicine, University of Melbourne. He is also the Chairman, National Health and Medical Research Council of Australia and Deputy President, Royal Australasian College of Physicians.

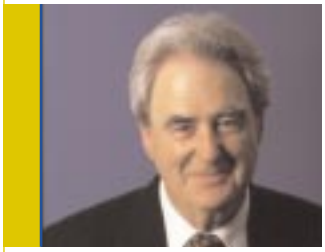
Sr Paulina Pilkington RSC, AM, BA (Hons), PhD,
has a broad background in health policy formation having been a member of the Hospitals and Health Services Commission (Sax Commission), Assistant Director General, Nursing Branch, Australian Department of Health and a World Health Organisation consultant for ten years. Sister was the Director of Mission, Sisters of Charity Health Service, from 1991 to 1997. Sister Paulina is a member of the Boards of The Garvan Institute of Medical Research, Garvan Research Foundation and The Victor Chang Cardiac Research Institute.

Ms Brenda Shanahan
Graduate of Melbourne University in Commerce and Economics, a Fellow of Institute of Directory and Affiliation of Securities Institute. Non executive Director of Australian Wheat Board, V/Line Passenger Corporation and Bankers Trust Funds Management. She had a research background in finance in Australia and overseas economics and sharemarkets. Former member of the Australian Associated Stock Exchange and former Executive Director of stock broking firm, fund management company and actuarial company.



Mr Hilton Nicholas OBE,
has been a member of the Board of St. Vincent's Institute of Medical Research since 1974 and Chairman of that Board from 1988 until 1993.

Mr Graham Rogers FIA, FIAA, ASA,
is an independent director. He is Chairman of SMF Funds Management, a member of the Boards of RACV Financial Services, The Private Health Insurance Administrative Council, the Victorian College of the Arts Foundation, and 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 Matthew Walsh LLM
Barrister and solicitor has been a partner at Mallesons Stephen Jaques since 1970 and was Chairman of the firm from 1988-1990. He is a director of several companies and Past President and an honorary life member of the Law Institute of Victoria and Past Chairman of the Taxation Institute of Australia (Victorian Division).

MEMBERS OF THE INSTITUTE

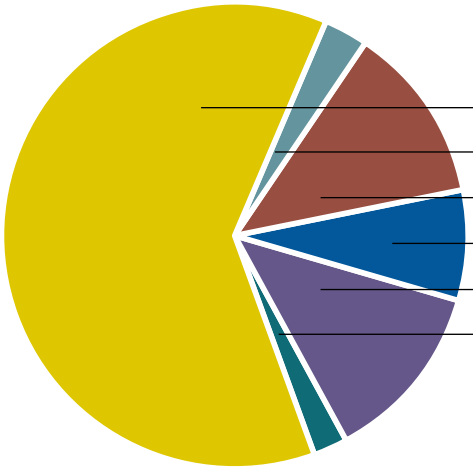
The following is a list of current Members:

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 F P Alford
Professor J D Best
Dr K J Breen
Dr D H Campbell
Mr J C Chappell
Mr W J Clancy
Sr Maryann Confoy
Ms K L Cross
Dr J J Griffin
Ms M Griffin
Mr C A Griss
Mr J F Gurry
Dr D J Hillis
Ms M A Jackson
Professor E D Janus
Professor B E Kemp
Professor R G Larkins
Mr Justice A McDonald
Dr I G McDonald
Professor T J Martin
Mr G C Molyneux
Mr H J Nicholas
Professor D G Penington
Sr P Pilkington
Mr I D Reid
Mr G E N Rogers
Professor G B Ryan
Mr P J Ryan
Mr A F Sallmann
Ms B Shanahan
Mr C Smith
Mr P Spry-Bailey
Mr M J Walsh
Mr D Wright

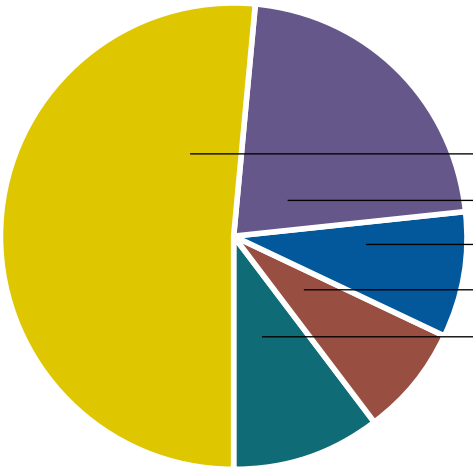
FINANCIAL SNAPSHOT

REVENUE



Competitive Grants - 62%
Commonwealth Government Service Contract - 3%
Industry - 12%
Legacies and Donations - 8%
Victorian Government Infrastructure - 13%
Interest and Dividends - 2%

EXPENDITURE

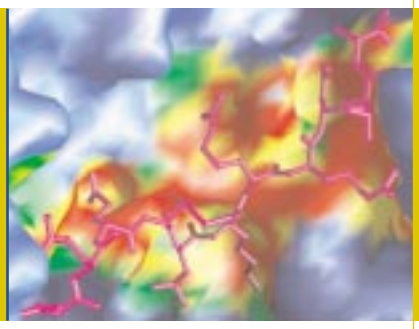


Research Salaries - 51%
Research Consumables - 22%
Depreciation - 9%
Infrastructure General - 8%
Infrastructure Administration & Technical Support Salaries - 10%

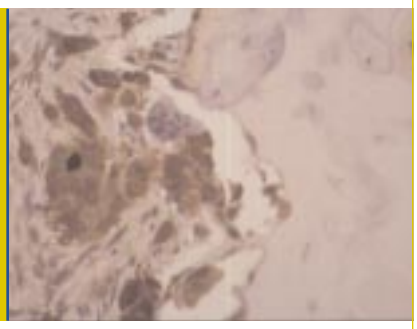
	$'000
Competitive Grants	3,110
Other	1,910
Total Revenue	**5,020**
Research	3,903
Non-research	1,422
Total Expenditure	**5,325**
Net Asset Value	**5,567**

MAJOR ACHIEVEMENTS

- Determination of the structure of human glutathione synthetase. The structure explained how certain mutations in the enzyme lead to a number of genetic diseases.
- Determination of the structure of an antitrypsin polymer. These polymers can cause emphysema and liver disease and the structure provides a molecular understanding of how the polymers form.
- Determination of the structure of the ligand-binding domain of the signalling subunit of the GM-CSF/IL-5 cytokine receptor bound to an antagonist. This receptor is involved in the progression of allergic diseases such as asthma and hence is a prime target for the design of drugs to inhibit its action in such diseases.
- Determination of the structure of the membrane form of the gas gangrene toxin perfringolysin O.



- Discovery that certain pain-producing hormones are produced in excess in the bladder condition of interstitial cystitis, pointing to new approaches to treatment.
- Demonstration that heart bypass pumps increase production of hormones that cause inflammation – a major problem with this procedure.
- AMP-activated protein kinase enhances the use of fatty acids in response to exercise.
- AMP-activated protein kinase activates the nitric oxide synthase in blood vessel linings and relaxes blood vessels.



- Our theory of intrasteric regulation of protein kinases extended to other enzymes and proteins (e.g. phenylalanine hydroxylase and importin α).
- Characterisation of the active site of phenylalanine hydroxylase.
- Solving the structure of the nuclear import receptor, importin α.

- Structural resolution of the membrane fusion activity of the HTLV-1 transmembrane protein.
- Inhibition of experimental breast cancer invasion with inhibitors of matrix metalloproteinase enzymes.
- Identification of genes and proteins contributing to bone metastasis formation in breast cancer.
- T cells can stimulate osteoclast development, a mechanism important in the joint destruction of rheumatoid arthritis.
- Breast cancers metastasize to bone by stimulating bone cells to generate osteoclasts.
- Parathyroid hormone-related protein (PTHrP) enters the cell nucleus by a novel mechanism requiring binding to importin β.
- PTHrP is a substrate for cyclin dependent kinases, whose activity excludes PTHrP from the nucleus.
- Cloning of the gene for Fugu fish PTHrP in collaborative work.

Above left: *3D-structure of importin α showing N-terminal residues bound in the NLS binding site.*

Above right: *Breast cancer stimulates osteoclasts to resorb bone.*

RESEARCH REPORT

With this year as the end of the century, and the Institute having been in operation for almost half of that time it is appropriate to reflect on the Institute's contributions, on the nature of its work, and on the changes that have taken place in its research environment.

An Institute newsletter of April, 1971 described its research as "a steady concentration on the study of the building blocks of the body – molecules. That is why the science is called molecular biology, and it is as different as chalk and cheese from the biology of the past". With good reason, the Institute was celebrating the work of its Director, Pehr Edman, who had recently invented the "sequenator", a machine which used his chemical method to determine the sequence of amino acids (the individual units of structure) in proteins. That heritage has influenced the Institute's path over the years, with its concentration upon the structure and shape of proteins – how normal amounts of proteins of normal amino acid sequence and shape are essential for life, and how the most subtle changes can lead to diseases such as cancer and heart disease.

The philosophy of research in the Institute remains the same – gathering together a group of scientists who are well trained, and have a multitude of ideas to test in their search for new understanding of life processes and of the basis of disease. The tools have changed though. We have to apply the most advanced technology to the tasks in hand. Edman was certainly at the forefront in technology – a great innovator whose work really did provide the basis for modern molecular biology. We keep the Institute abreast of the latest technology in the purification and analysis of proteins and genes, and have often featured this in Research Reports. Much of that has been concerned with the analysis of protein sequence and structure with ever increasing power and sensitivity, and applying this to understanding of protein function. We have also paid special attention to establishing the best ways of studying what is happening inside the cells of the body at a microscopic level – whether this be normal cells, cancer cells or those that are genetically altered. Two great examples of this are laser capture microdissection (LCM) and confocal microscopy. LCM is a new method used by the breast and prostate cancer research groups, in which cancer cells can be selected under a microscope and identified separately from the accompanying non-malignant cells. A laser beam is used to cut around any selected small group of cells, which can be transferred to a test tube for analysis as pure human cancer cells – something that has not previously been possible. Confocal microscopy is a method which allows us to trace how protein molecules move in individual living cells, and to determine how this goes wrong in disease.

All of this is aimed at increasing the likelihood of discovering new facts which will shed light on disease processes. So we still have much in common with the founding Institute scientists. There is one feature of the medical research life which has changed quite a deal in the lifetime of this Institute. Academic institutions are increasingly pressed from all quarters to be entrepreneurial - to commercialise, to seek to direct the results of their research to an economic benefit. To some extent we must now compete in a marketplace which rewards entrepreneurial behaviour. While we accept the challenge, we would always argue strongly that above all we are professionals engaged in the search for new knowledge of the natural biological process, and constantly seek to apply this knowledge to the understanding of diseases. Along the way, we recognise that some of the things we do might be of commercial interest, and be capable of appropriate development. We know that we need to be vigilant in our efforts to recognise these opportunities and do our best to be "entrepreneurial" in exploiting them.

What it amounts to is that we have two major practical end-points. These are the obtaining of knowledge through medical research that improves health and prevents and cures diseases, and also the use of our resources and skills to seek economic benefits through developments in biotechnology and its application to development of new approaches to medicine.

The following account of research in the Institute for 1999 touches on many of the highlights to give a flavour of current work and directions.

OLD & NEW

The original protein sequenator, pictured above left, was developed by Pehr Edman at the Institute during the 1960's and was used to determine the amino acid sequence of proteins. The sequentator is on display in the foyer of the Institute as a reminder of its historical importance.

The control panel of the X-ray generator, pictured above right, is currently used in the 1990's to determine protein structures by X-ray crystallography. First, a crystal of the protein being studied is grown. Then, the crystal is placed in an X-ray beam, causing the X-rays to scatter in a pattern. The pattern can then be used to map the 3-D shape of the protein.

PROFESSOR TJ MARTIN

"My role is to bring together a group of the best possible scientists and to create an atmosphere that helps them to get their work done. They can then work here as a team as well as collaborating with others around the world.

The Institute's work is all about applying basic research to some common diseases. In 1999, there were first class developments in each of our major fields of research, both from the point of view of the science that was done and the achievements of individual people. The achievements of individuals always reflects the contribution of those around them, but there is no doubt that the Institute hit some substantial home runs."

PROTEIN CHEMISTRY AND REGULATION

Bruce Kemp, Head
ZhiPing Chen
Andrew Hammet
James Horne
Frosa Katsis
Belinda Michell
Ken Mitchelhill
Tania Pickersgill
David Stapleton

Each of the cell's proteins has a three-dimensional structure that is required for its function, whether it is a structural protein or an enzyme. Many cellular proteins are modified after they are synthesised to modulate their function. In the case of enzymes this may lead to activation or inhibition or to change their location in the cell. By knowing both their structure and the modifications involved we can understand the dynamics of their function. We are particularly interested in protein kinases that control metabolic stress responses and muscle function. The AMP-activated protein kinase is essential for coordinating the body's metabolism to meet the needs of exercise as well as handling reduced caloric intake.

AMP-activated protein kinase and glucose utilisation

Our aim is to understand the regulation and function of the AMP-activated protein kinase, especially in the important role in protecting the heart and skeletal muscle from metabolic and ischaemic stress.

The AMP-activated protein kinase accelerates glucose uptake as well as burning fat (oxidation of fatty acids) in response to exercise. Its effects on glucose uptake are not dependent on insulin. This has particularly important implications for diabetes, since by understanding how the AMP-activated protein kinase accelerates glucose uptake we may find new ways to help in the control of diabetes. The AMP-activated protein kinase accelerates the oxidation of fatty acids in response to exercise and we have found in collaboration with Glenn McConnel (Monash University) that it does this with volunteers sprint exercising for 30 seconds on bicycles.

AMP-activated protein kinase and blood vessel control

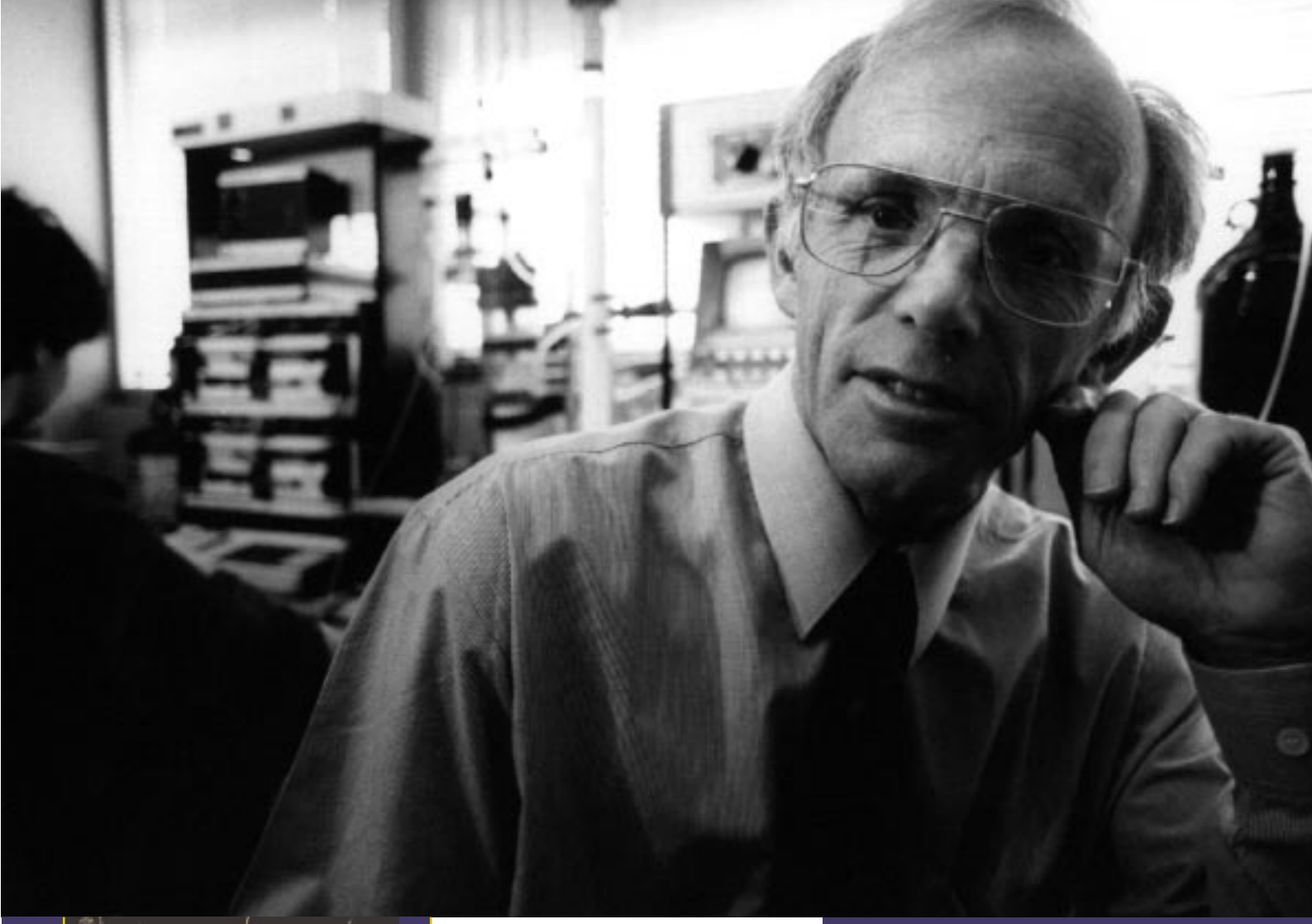
We have found that the AMP-activated protein kinase phosphorylates and regulates endothelial nitric oxide (NO) synthase. This enzyme is responsible for producing NO which in turn causes relaxation of blood vessels and thereby reducing blood pressure. During vigorous exercise NO is produced in the heart to improve the blood flow required to supply nutrients and oxygen as well as suppressing the mechanical activity of the heart to prevent it from exceeding the energy supply. These responses are also important to protect the heart from ischaemia events, from either a mild or major heart attack. Endothelial NO synthase is also phosphorylated by other protein kinases. Protein kinase C phosphorylates and inhibits endothelial NO synthase. This may have important implications for diabetes because high glucose in the blood activates this protein kinase C and inhibition of protein kinase C under these conditions protects against vascular damage. By suppressing the production of NO by endothelial cells and platelets via protein kinase C this may be an important feature in the development of cardiovascular disease that is a serious complication in diabetes.

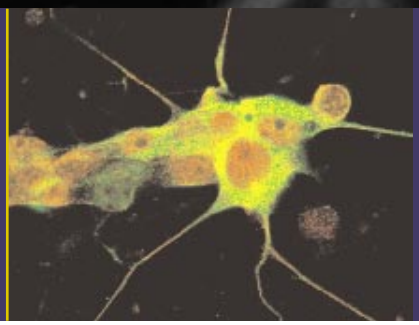
The development of new blood vessels, (a process called angiogenesis) depends on a growth factor, vascular endothelial growth factor (VEGF). We have found that another protein kinase called PKB is responsible for activating endothelial NO synthase in response to VEGF treatment. It turns out that PKB and the AMP-activated protein kinase activate endothelial NO synthase by the same mechanism. Our studies in this area are aimed at understanding in detail the regulatory pathways that control NO production in heart, skeletal muscle and platelets. These are central to understanding why certain risk factors or lifestyles are

associated with disease or good health. This includes, diabetes, obesity, high-cholesterol versus exercise and low body weight.

Metabolic stress and exercise

Another area of emerging importance is the finding that the AMP-activated protein kinase controls which genes are turned on or off in response to metabolic stress. It is known that certain genes involved in the control of fat synthesis are turned on by glucose to allow energy storage in the form of fat. The genes that are turned on by high glucose are turned off by the AMPK that favours the metabolism of fat to provide energy. This will help our understanding of the beneficial effects of exercise that





PROTEINS & LOCALIZATION

Pressure gauges on a modern protein sequenator, pictured above left, ensure reproducible results.

Using a confocal microscope allows the scientist to study a number of different proteins in the same cell at the same time. The photomicrograph is a snapshot of what is happening inside the cell. A confocal photomicrograph of a differentiated PC12 cell stained with antibodies to S100A1 (red) and synapsin (green) is pictured above right. The regions of overlapping expression appear yellow implying possible interactions between these two proteins.

PROFESSOR BRUCE KEMP

"The wonderful thing about research is that you can be continually intoxicated by ideas. Yes, there are many times when research is frustrating and we continually fall short of being able to apply sufficient resources and skills to really nail problems, but overall it's tremendous fun.

One of the Institute's most exciting projects is focused on an enzyme called the AMP-activated protein kinase. It is responsible for co-ordinating energy metabolism with the demands of tissues. It is activated with vigorous exercise and accelerates both glucose and fat metabolism. We call it the "wellness enzyme" because it is activated by exercise and reduced caloric intake, the very things that improve health and well-being."

activates the AMP-activated protein kinase. Moreover, it has been known for many years that calorie restricted diets prolong the lives of animals and delay age onset related diseases.

We are now able to describe the mechanisms underlying the effects of age and disease. Over the next few years we can anticipate a profound increase in knowledge of the determinants of health and disease.

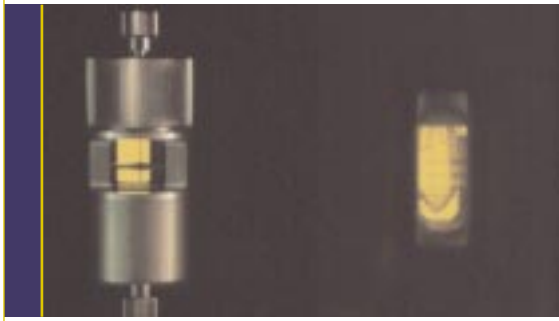
The control of protein function

This year was a landmark in our work on the regulation of protein function, with the publication in Nature of our review on intrasteric regulation. Some thirty-five years ago the French researchers Monod, Wyman and Changeux developed the concept of allosteric control of protein function. They recognised that the catalytic function of enzymes may be affected and controlled by interactions with small molecules not only at the active site but also indirectly at distant secondary sites called allosteric sites. This was to distinguish these activators from the more common activators or inhibitors that act at the catalytic site. The allosteric effectors typically bear no structural resemblance to the enzyme's substrate, however they frequently represent key compounds in important metabolic pathways that bind to the enzyme and modify its activity. Thus for example in synthetic pathways, end products of a series of enzymic reactions may feed back and inhibit an early enzyme step in the pathway. The allosteric regulatory model proved enormously insightful and a large number of enzymes were found to be regulated in this way. Subsequently the three-dimensional structures of many examples proved the allosteric control hypothesis.

Protein kinases are enzymes that put phosphates on proteins to alter their function. Together with phosphatases which remove phosphate from proteins, they are amongst the most important regulatory enzymes in the body, controlling essentially all physiological processes. The human genome is thought to contain approximately 1,500 protein kinases. Given their importance we have been interested in the regulation of protein kinases. Frequently they are present in latent inactive forms and only become active in response to specific signals, involving the binding of small molecules or other regulatory proteins.

For many years it was known that partial proteolysis of protein kinases could often activate them. This implied that they were held in the inactive state by a part of their structure that could be removed by digestion with a protease. In 1986 we identified the sequences responsible for autoinhibition of the myosin light chain kinase (controls blood pressure) and protein kinase C (important in diabetes). We recognized that there were features in these sequences that resembled the local phosphorylation site sequences found in their substrates. This led us to propose that autoinhibition of these protein kinases is due to this part of their structure binding to the active site mimicking the substrate (behaving as a pseudosubstrate). In contrast to allosteric effectors that do not resemble the enzyme's substrates and act at remote sites from the active site, the protein kinase autoregulatory sites were hypothesised to bind directly to the active site. For this reason we termed this form of control intrasteric to emphasise that it was active site-directed protein regulation. We obtained indirect evidence for this mechanism but it was not until we obtained the three dimensional structure of twitchin kinase (a relative of titin kinase present in human muscle) that we obtained unequivocal proof that the enzyme was autoregulated by part of its structure binding to the active site. We call these inhibitory structural elements "intrasteric autoregulatory sequences" or IARS for short.

In the past year we have found that this mechanism of autoregulation is not restricted to protein kinases and protein phosphatases, but extends to proteins with varied functions, including phenylalanine hydroxylase and importin α, a protein



involved in transporting proteins into the nucleus of cells. Significantly activation of autoregulated enzymes frequently requires activators to bind near the autoregulatory sequence, at allosteric sites. Thus classical allosteric control and intrasteric control act in concert to regulate protein functions. We anticipate that over the coming years there will be numerous other examples of intrasteric control found, as was the case for Monod, Wyman and Changeux's allosteric control hypothesis.

SEQUENCING & SIZE

New generation protein sequenators, such as pictured above left, utilise miniaturisation of the Edman "spinning cup" to achieve amino acid sequence from very small quantities of proteins.

The display screen of the Institute's MALDI-TOF mass spectrometer, pictured above right, provides highly precise measurements of the molecular weights of proteins and peptides. Mass spectrometry allows researchers to analyse any changes that may have occurred to proteins or peptides. From there, they can ask the question: what does this change mean?

DR DAVID STAPLETON

"I returned from Toronto to St. Vincent's Institute of Medical Research in July 1999. I spent two years in Canada as the C.J. Martin Fellow. It's a four year training fellowship - two years overseas, then two years in Australia - and is funded by the National Health & Medical Research Council.

In Toronto, I worked in Professor Tony Pawson's lab at Mount Sinai Hospital. He's quite a famous scientist because he was the first person to identify how proteins communicate. My passion lies in this area and it was exciting to work in a lab led by the pioneer.

Now that I'm back in Australia, I'm applying the skills I learnt in Canada to a protein identified here at the Institute - the AMP-activated protein kinase."

PROTEIN CRYSTALLOGRAPHY LABORATORY

Michael Parker, Head
Brett Cromer
Michelle Dunstone
Susanne Feil
William McKinstry
Galina Polekhina
Jamie Rossjohn

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 which control all functions of the body. Essential to understanding the function of proteins, we need to determine their structure. Crystallography offers the means to determine the three-dimensional (3-D) structure of proteins at the atomic level. Knowledge of protein 3-D structure enables the intelligent design of new drugs for the treatment of disease. The major areas of protein crystallography research at the Institute involve proteins involved in mental disease, bacterial toxins that attack cell walls, and proteins that detoxify poisons.

Glutathione synthetase

Glutathione synthetase (GS) catalyses the production of the essential tripeptide, glutathione, from γ-glutamylcysteine and glycine in an ATP-dependent manner. Malfunctioning of the enzyme results in disorders including metabolic acidosis, 5-oxoprolinuria, neurological dysfunction, hemolytic anaemia and in some cases is lethal. We determined the crystal structure of the human enzyme. Mutations that lead to GS deficiency have been mapped onto the structure, providing a molecular basis for understanding their effects. Our studies on glutathione synthetase are performed in collaboration with Professor Philip Board, John Curtin School of Medical Research, Australian National University, Canberra.

Allergic diseases

There are three growth factors or cytokines that are responsible for the production and activation of eosinophils, cells that play a key role in the progression of allergic diseases such as asthma.

These cytokines, GM-CSF, IL-3 and IL-5, are able to signal across cell walls by binding to a cell surface receptor called the GM-CSF/IL-3/IL-5 cytokine receptor. In collaboration with Angel Lopez (Hanson Centre for Cancer Research, Adelaide), we determined the crystal structure of the ligand-binding domain of the GM-CSF/IL-3/IL-5 receptor signaling subunit in complex with an antibody antagonist. The structure suggested how three different cytokines can recognise a single receptor subunit, and analysis of the interface between the antagonist and receptor provides a rational basis for designing single molecule antagonists of all three cytokines, which are directly implicated in allergic inflammation and also myeloid leukemia.

Liver disease

α_1-Antitrypsin deficiency, which can lead to both emphysema and liver disease, is a result of the accumulation of α_1-antitrypsin polymers within the liver cells. A wealth of biochemical and biophysical data suggests that α_1-antitrypsin polymers form via insertion of residues from the reactive center loop of one molecule into the β-sheet of another. However, this long-standing hypothesis had never been confirmed by direct structural evidence. We determined the crystal structure of an α_1-antitrypsin polymer which revealed how the molecules assemble into a polymer.

Membrane proteins

The cells of the body are coated in a lipid membrane that acts as a skin to protect the cell. Some bacteria attack the body by producing toxins that kill cells by punching holes in cell membranes. In order to understand how they do this, we have been determining the 3-D structure of several toxins. We have previously reported the

determination of the 3-D structure of perfringolysin O, which is a member of a large family of similar toxins which are responsible for a variety of diseases including pneumonia and gas gangrene. This year, with our collaboration in the USA and UK, we have determined the structure of the toxin (and its homologue pneumolysin) in various membrane-associated states using a variety of tools including fluorescence spectroscopy and electron microscopy. These exciting discoveries will provide the basis for the design of drugs to prevent the diseases caused by these toxins.

STRUCTURAL BIOLOGY UNIT

Bostjan Kobe, Head
Helen Blanchard
Marcos Fontes
Thomas Gleichmann
James Horne
Ian Jennings
Pierre Scotney
Trazel Teh

The formation of interactions between different macromolecules is a crucial part of essentially every cellular process including signal transduction, apoptosis (cell death), transcription, cell to cell communication and

protein folding. The current knowledge of protein recognition is, however, predominantly qualitative. We aim at a more complete understanding of the mechanisms underlying molecular recognition, through employing X-ray crystallography, computational techniques such as molecular modelling, methods for quantitative evaluation of interactions such as the surface plasmon resonance biosensor, protein chemistry and molecular biology. The increased understanding will simultaneously lead to an improved design of therapeutic agents that modulate cellular processes.

Regulation of phenylalanine hydroxylase

Phenylalanine hydroxylase (PheOH) is the enzyme that converts phenylalanine to tyrosine. It is the rate limiting step in phenylalanine catabolism, protein and neurotransmitter biosynthesis. Phenylalanine is both an essential amino acid and toxic at elevated levels. Consequently, defects in PheOH cause the disease hyperphenylalaninemia and its severe variant, phenylketonuria, which leads to severe mental retardation. For these reasons, phenylalanine hydroxylase is tightly regulated in cells.

Our studies of the structure of PheOH revealed a catalytic domain flexibly linked to a regulatory domain, consisting of an amino-terminal autoregulatory sequence containing the phosphorylatable serine that extends over the active site pocket. Phosphorylation has no major structural effects in the absence of phenylalanine, suggesting phenylalanine binding and phosphorylation act in concert to activate the enzyme through a combination of intrasteric and possibly allosteric mechanisms.

The structure provides the basis for understanding the effects of mutations resulting in phenylketonuria. Our extensive analysis of mutations yielded some simple rules that predict the severity of disease based on the location of the affected residue in the three-dimensional structure.

Regulation of nuclear import

All proteins acting in the nucleus are made in the cytoplasm and need to be imported into the nucleus through the nuclear pore complexes. Such transport is directed by special signals, the most common being the nuclear localization sequences (NLSs).

Importin α is the nuclear import receptor that recognizes these NLSs.

To understand the structural determinants for binding NLSs and the regulation of nuclear import, we have determined the crystal structure of mouse importin α. The structure shows two distinct domains, a large one built from repetitive structural units (the so-called armadillo repeats), and a smaller one bound to the NLS-binding site. This internal binding explains an important regulatory event in the nuclear import process: in the cytoplasm, the receptor gets activated through binding its partner, importin β, which removes the autoinhibitory segment from the NLS-binding site; in the nucleus, on the other hand, importin β dissociates and importin α becomes autoinhibited, so it releases the nuclear proteins.

We determined the crystal structures of complexes of importin α with peptides corresponding to different NLSs. The binding is achieved in a very elegant way, with the armadillo repeats providing a structural framework with a long shallow groove where the peptide can bind, and strategically positioned side chains provide specific pockets for individual NLS side chains.

Substrate specificity of protein kinases

The determination of three-dimensional structures of several protein kinases forms the foundation for understanding the structural basis of the substrate specificity. The three-dimensional structure determines the binding pockets for the amino acids in the vicinity of the phosphorylated residue. We are devising methods to predict the substrate specificities of kinases based on this structural knowledge. We are testing the success of these methods on several protein

kinases with differing degrees of available specificity information.

Leishmania surface proteins
Leishmania parasites cause a variety of human diseases in the tropics, subtropics and the Mediterranean region. Parasite surface proteins are important virulence factors. In collaboration with Dr. Emanuela Handman (Walter and Eliza Hall Institute of Medical Research) we have identified a novel surface protein, proteophosphoglycan (PPG). The amino acid sequence of this protein contains multiple copies of repetitive sequences termed leucine rich repeats. This motif is further shared between several Leishmania surface proteins, and may provide the binding site for a common ligand in the human host. The available three-dimensional structures of leucine-rich repeat proteins allowed us to construct a three-dimensional model of the corresponding region of PPG.

MOLECULAR GENETICS

Jörg Heierhorst, Head
Andrew Hammet
Brietta Pike

We use genetic tools to study the molecular function of proteins involved in the regulation of cell function. A major focus is the identification of physiological functions of the intracellular calcium-binding protein S100A1. A few years ago, we demonstrated that this protein can stimulate the activity of protein kinases by up to 1500-fold when the calcium concentration is raised to levels found in, for example, the heart during normal contraction cycles or stimulated nerve cells. To find out if this mechanism plays an important role in living animals, we have this year generated a mouse strain that lacks the gene for the S100A1 protein, the S100A1-/-, or "knockout" (KO) mouse. Normal mice have a remarkably high concentration of the S100A1 protein in the heart, where it represents approximately 0.2% of the total protein amount, but it is also found at lower levels in other tissues such as the brain. We are currently investigating if the loss of this major heart protein has an impact on organ function. Specifically, we will test if the KO mice develop heart disease as they age, and if not, whether they differ from normal mice in response to chronic treatments that lead to heart failure.

We have begun to develop a new project studying the function of so-called forkhead-associated (FHA) domains in a family of checkpoint protein kinases that make sure that cells respond properly to damage of their genetic material. Mutations in the human FHA-containing kinase Chk2 were recently found to be the cause of a subset of cases of the Li-Fraumeni syndrome, a genetic disorder where patients suffer from multiple independently occurring forms of cancer starting typically at a young age. We found that FHA domains are more than twice as large as expected, and have started to study their function in the regulation of checkpoint kinases.

CELLULAR SIGNALLING

Tony Tiganis, Head
Michelle Fodero
Pei Rong

A cell's ability to respond to its extracellular environment involves a complex and highly organised series of events referred to as cellular signalling. These signalling processes regulate fundamental responses including growth, differentiation, migration, metabolism and survival. Abrogation of these processes can lead to diseased states such as cancer. We focus on a group of enzymes known as protein tyrosine phosphatases (PTPs) which regulate cellular signalling events.

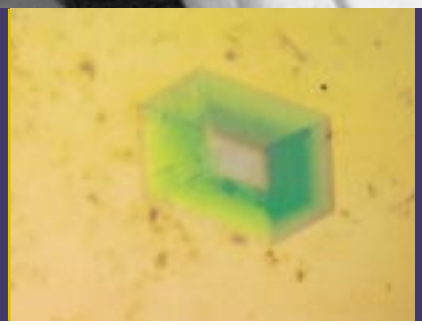
RETROVIROLOGY

Andy Poumbourios, Head
Heidi Drummer
Anne Maerz
Kim Wilson
Kirilee Wilson

Human immunodeficiency virus type 1 (HIV-1) is the retrovirus that causes AIDS. HIV-1 attacks cells of the immune and nervous

systems and infected individuals eventually succumb to opportunistic infections, dementia and cancer. Human T cell leukemia virus (HTLV-1) is a retrovirus that causes adult T cell leukemia and is associated with a neurological disorder called HTLV-1-associated myelopathy. Approximately 10-20 million people are infected with HTLV-1 world-wide.

Retroviruses acquire a lipid bilayer envelope when they bud from infected cells. Before retroviruses can infect new cells, their envelope must first fuse with the target cell membrane. One of our major aims is to better understand the role of the envelope glycoproteins of the retrovirus in the virus-cell membrane fusion process.



COOLING & CRYSTALS

The nozzle of the cryocooler, pictured above left, rapidly chills protein crystals and minimises damage from exposure to X-rays.

A crystal of trans-membrane proteins of the human T cell leukaemia virus is pictured above right. The protein was grown into a crystal as part of the process of mapping the 3 dimensional structure of the protein. Creating a 3-D map is an important part of understanding how parts of a protein work. The structure of this particular protein was published in April 1999.

DR ANDY POUMBOURIOS

"I've been interested in viruses since my under-graduate years. They are fascinating entities, they infect all types of organisms - bacteria, yeast, mammals, fish. They are everywhere!

At the moment, I'm working on two very complex viruses - the Human Immuno-deficiency Virus (HIV) and Hepatitis C. They are both huge global public health issues.

40 million people world-wide currently have HIV and there are 8 million new infections each year. HIV destroys the immune system, so it is generally fatal unless infected people have access to very expensive inhibitors. The second virus, Hepatitis C, infects about 170 million people in the world and about 140,000 Australians."

We have now analysed how the three-dimensional structure of the HTLV-1 transmembrane (TM) protein relates to its membrane fusion activity. We engineered mutations into prominent structural features revealed by the HTLV-1 TM crystal structure and determined the effects of the mutations on the structure and membrane fusion function of the HTLV-1 envelope glycoproteins. This approach allowed us to identify three important regions that cooperate to induce the membrane fusion-active form of HTLV-1 envelope glycoprotein. We will now assess if these regions are appropriate targets for antiviral agents that block HTLV-1 entry into cells.

CARDIOVASCULAR UNIT

Jock Campbell, Head
Todd Briscoe
Ann-Maree Duncan
Athena Kladis
Nora Tenis

The role of peptide hormones in health and disease

Peptide hormones play an important role in the regulation of many different aspects of body function. In addition, these peptide hormones may also contribute to disease if their levels are not properly controlled. Research at the Institute is focused on two peptide hormones, angiotensin and bradykinin, their role in the cause of cardiovascular disease, and in the effects of drugs on the levels of these two hormones.

Angiotensin and bradykinin

Angiotensin plays an important role in the regulation of blood pressure and the salt balance of the body. However, increased levels of angiotensin raise blood pressure by constricting blood vessels and so causing the kidney and adrenal gland to raise the body salt concentration. Angiotensin also acts to stimulate growth of blood vessels and the heart and promotes arrhythmia (electrical disturbance) of the heart. By contrast, bradykinin is a hormone with many actions that are opposite to those of angiotensin. Bradykinin relaxes blood vessels, lowers blood pressure, increases excretion of salt in the urine, and reduces arrhythmia of the heart. However, increased levels of bradykinin can cause inflammation.

Bradykinin peptides in interstitial cystitis

Interstitial cystitis is a distressing inflammation of the bladder causing pain and frequent passing of urine. The cause of interstitial cystitis is not known, and we do not have a specific treatment for this condition. To investigate the role of bradykinin in this condition we measured bradykinin levels in the urine of women with interstitial cystitis. These studies were performed in collaboration with Anne Rosamilia and Judith Clements of Prince Henry's Institute of Medical Research. We found increased levels of bradykinin in the urine of women with interstitial cystitis, suggesting that increased bradykinin formation in the bladder may cause the inflammation and pain in this condition. Moreover, our studies suggest that treatment aimed at blocking the formation of bradykinin or blocking its action may be of benefit in this condition.

Bradykinin peptides during heart bypass operations

Patients having open heart surgery are placed on a heart bypass pump to pump blood around the body during the operation. Sometimes the bypass pump can cause inflammation that, if severe, can retard recovery from the operation. To investigate the role of bradykinin in the inflammation caused by heart bypass, we measured bradykinin levels in the blood of subjects having open heart operations. These studies were performed in collaboration with John Santamaria and Barry Dixon of the Intensive Care Unit, St. Vincent's Hospital.

We found the heart bypass pump causes high levels of bradykinin. The inflammation caused by the increased bradykinin levels caused increased leakage of protein into the urine. We also showed that drugs that block the formation of bradykinin also reduced the inflammation.

These studies will help in the development of heart bypass procedures that cause less inflammation and may therefore result in more rapid recovery from open heart surgery.

BONE CELL BIOLOGY

T J Martin, Head
Matthew Gillespie, Head, Molecular Endocrinology
Kong Wah Ng, Head, Clinical Bone Endocrinology
Jane Moseley, Head, Bone Physiology
Janine Danks, Head, Comparative Endocrinology

Elizabeth Allan
Marian Croft
Hannelore Diefenbach-Jagger
Jan Elliott
Alex Funkat

Vivian Grill
Daphne Hards
Patricia Ho
Zhou Hong
Yun Shan Hu
Nicole Horwood
Gillian Jones
Vicky Kartsogiannis
Leeanne Mead
Peter Niforas
Manabu Nishii
Julian Quinn
Pat Smith
Rachel Thomas (pictured above)
Melanie Trivett
Howard Zeimer

Osteoclasts in health and disease

Bone is a very active organ, constantly being formed by cells known as osteoblasts, and broken down (resorbed) by highly specialised cells known as osteoclasts. We have a major research interest in the control of osteoclast formation. This takes place in bone in a process in which blood cells are induced to differentiate into bone resorbing osteoclasts. This is controlled by a host of locally produced proteins (cytokines) and growth factors, which are produced by cells of the osteoblast lineage and of the immune system (T and B lymphocytes). The whole company of cells comprises bone as an organ, and the dominant feature of its function is a network of intercellular communication by which protein messages pass between the various cells and promote activities which determine how many osteoclasts are formed, and how active they are.

New proteins in osteoclast formation

RANK ligand (RANKL) is a member of the TNF receptor family which is made by osteoblastic stromal cells and acts upon blood cells to promote osteoclast formation. After showing that the production of RANKL is regulated by the hormones and cytokines which stimulate osteoclast formation, we then used in situ hybridization and immunohistology to detect RANKL messenger RNA and protein respectively in bone and other tissues. This showed for the first time that RANKL is produced in many parts of the body other than bone, including particularly skin and brain, where it will be of great interest to determine its role.

Having found RANKL to be produced copiously by activated T lymphocytes, we showed that these cells, when incubated with normal blood cells, are able to promote osteoclast formation. This was a novel finding which led us to investigate RANKL production in the joints of patients with rheumatoid arthritis, finding that it is produced both by the T cells and by the rheumatoid synovial fibroblasts. Its production is likely to be a major contributor to the bone destruction wrought by osteoclasts around rheumatoid joints. This complemented other work during the year, collaboratively with Tatsuo Suda and colleagues (Tokyo), in finding that a new T cell cytokine, interleukin-17 (IL-17), is present in large amounts in rheumatoid synovial fluid.

Osteoclasts and bone metastases

Bone is the commonest site of spread of breast cancer, with 70% of women with secondary spread of the cancer having secondary growths in bone. These cause severe bone pain, easy fracturing, and the complication of a high blood calcium level.

The spread of cancers to distant parts of the body is the major cause of disability and death from the disease. Cancer cells, in order to spread and grow in distant organs, need special properties to suit them to those organs. It has long been recognised that breast cancers are particularly liable to spread to bone.

From our own research and that of others, the single property of breast cancers that contributed most to this was their ability to promote bone resorption. In work published this year we showed that breast cancer cells were able to stimulate osteoclast formation by enhancing the production of RANKL by cells in bone. They did this by producing parathyroid hormone–related protein (PTHrP). This is a property of breast cancer cells we had discovered some years earlier, and this

research supported the theory we proposed at that time, that PTHrP production by breast cancers might contribute to their ability to grow as secondary cancers. When breast cancer cells producing excessive amounts of PTHrP were tested in an in vivo model of bone metastasis – experiments done in collaboration with Theresa Guise (San Antonio, Texas) - they had greatly increased ability to grow in bone as metastases. Such improved understanding of the process of bone metastasis formation provides new targets for drug discovery, and can lead to the design of drugs that specifically target prevention and treatment.

PTHrP: Its many functions extend to the nucleus

When we discovered PTHrP more than 10 years ago, it was as the circulating factor responsible for the high blood calcium in patients with cancer. We soon found that it was produced in many tissues – skin, blood vessels, bone, uterus etc – where it functioned as a local, or "paracrine" factor in normal circumstances, and not reaching the circulation in significant amounts in adults except in those with certain cancers.

What our published work this year has revealed is a completely new area of PTHrP biology. After showing a few years ago that the production of PTHrP by cells in culture was dependent upon the cell cycle – very high production and secretion when the cells are dividing, and very low when they are "resting" – we noted that in the resting cell, PTHrP was located in the nucleus. It then emerged that PTHrP shuttled in and out of the nucleus, that it is an excellent substrate for two of the cyclin – dependent kinases, cdc2 and cdk2, and when they add a phosphate group is added to residue number 85 of the PTHrP protein, the molecule is excluded from the nucleus.

This led us to ask how PTHrP gains entry to the nucleus. We collaborated with David Jans (JCSMR, Canberra) to show that it used an entirely novel mechanism of intranuclear transport, by binding to importin β, which then carries it to the nucleus by an energy – dependent process. The specific mechanisms of transport of PTHrP and its extrusion from the nucleus, make it highly likely that PTHrP is exerting some important functions within the nucleus. One of our aims is to identify those functions.

Comparative endocrinology

Perhaps the pursuit of investigations of physiology in fish and lower vertebrates seem odd in a medical research institute. Since our discovery of PTHrP we have done so however, because PTHrP appeared to have evolved from a primitive gene. We were interested in the possibility that studies of its distribution and function in fish might throw light on its roles in mammals and man.

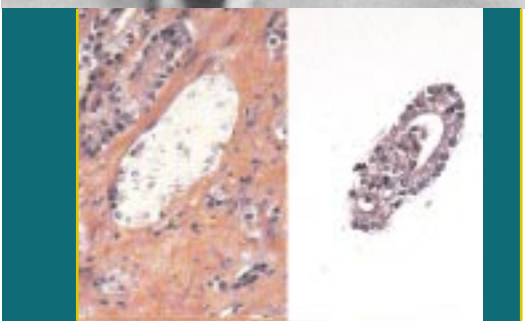
In work this year in collaboration with the Human Genome Mapping Project-Fugu Group (Cambridge, UK), together with Pat Ingleton (Sheffield, UK) and Deborah Power (Faro, Portugal), we have isolated and cloned the gene for Fugu PTHrP. This is the first time PTHrP has been isolated from a lower vertebrate, and this will lead to isolation of the gene from other such species and uncover the evolutionary history of this gene.

VICTORIAN BREAST CANCER CONSORTIUM

Erik Thompson, Head
Margaret Bills
Nicolle Bruengger
Nirada Dhanesuan
Jeannie Javni
John Price
Neeracha Ruangpanit
Julie Sharp
Angus Tester
Mark Waltham
Elizabeth Williams

Primary tumour invasion

The molecular events associated with the initial stages of cancer progression (breast and others) towards local invasion and spread are poorly understood. Using human breast cancer model systems, we have implicated the epithelial to mesenchymal transition (EMT) in this process. This a process well described in embryological development, which results in loss of cell to cell adhesion, increased migration, and increased production of the enzymes capable of degrading the tissue barriers. One of the most reliable indicators that this process has taken place is the switch from expression of keratin to vimentin, which are intermediate filament proteins that make up part of the



LASERS & SECTIONS

Dr Elizabeth Williams uses the laser capture microscope (left) to perform micro-dissection of prostate cancer tissue samples (right).

An extremely thin slice of a frozen tumour sample is put on the glass slide and re-freezes on the slide surface at -20°C, adhering it to the slide. A cap covered with a special polymer is lowered down onto the sample. The laser is fired to cut out the tumour tissue required. When the laser fires it briefly melts the polymer. As the polymer re-sets the cut out section of the frozen tissue slice sticks to the polymer. The cap is then pulled up and the required section of tissue goes up with the cap (middle) and the tissue not required is left behind on the slide (right).

Micro-dissection enables the study of just the targeted tumour tissue type, ensuring that the specific gene and protein information extracted is very specific.

DR ELIZABETH WILLIAMS

"My major projects are at two ends of the prostate cancer spectrum - one aims at cancer prevention and the other aims at reducing the spread of cancer. The first focuses on identifying new molecules that are important in determining whether the cancer will move from the prostate over to the bone - known as metastasizing to bone. If this move happens, the cancer grows and causes complications for the patient. Bone pain is one such complication (because the bone is growing) and it's not easily treatable.

The second project aims to find an agent that will stop prostate cancer developing at all."

cell skeleton. During the year we characterised a breast cancer cell system which shows increased vimentin expression and migration in response to epidermal growth factor (EGF) treatment. This extends our interest in EGF, where we independently characterised the signal transduction pathways which are used by EGF to simulate breast cancer cell migration.

Membrane type matrix metalloproteinases (MT-MMP's)
MT-MMP recruits the abundant enzyme MMP-2 to the cell surface in special structures called invadopodia, which allow the cancer cell to interact with the tissue barriers and cut through them. Because these processes occur on the outside of the cell, they provide a ready target for new drugs which may inhibit this process and offer protection from metastasis. Our initial studies through arrangements with Agouron Pharmaceuticals, USA, have shown profound inhibition of tumour growth in mice with these inhibitors. Notably, our involvement with the company led to the inclusion of St. Vincent's Hospital in a Phase II Clinical Trial against lung cancer.

Identification of bone metastasis genes
We have used gene array analysis on human breast cancer cell clonal variants, which show selective metastasis to bone. Using this system we have identified a number of candidate genes which are being studied. The organ-specific profiles of these cells correlate well with their migration capacities, which relates closely to our cell migration studies mentioned above. Bone sialoprotein (BSP) continues to be implicated further in primary breast and prostate cancer progression, and in collaboration with Michael Henderson (Dept. of Surgery, St. Vincent's Hospital) we reported this year on the localisation of BSP production in breast tumours. Further efforts to investigate the significance of this will make use of a panel of BSP-transfected human breast cancer cell lines.

Prostate-bone metastasis
A number of clonal sublines prostate cancer cells have been generated with a genetic tag. These will enable gene array analysis to identify molecules seen only in those clonal lines which metastasise to bone. In parallel, our collaboration with Tony Costello (Dept. of Urology, Royal Melbourne Hospital) and John Slavin (Dept. of Pathology, St. Vincent's Hospital) provide us with samples of human prostate cancer. We will use laser capture microdissection (LCM) to obtain pure populations of cancer cells with which to confirm the gene array candidates.

Gene array analyses
We have developed the use of MacroArrays, nylon filter based arrays for comparative gene expression. This approach equips us especially to study gene expression in clinical cancers. We are currently using commercial filters from Research Genetics, but availability of quality filters locally within the next year seems highly likely. The use of arrays has become central to many of the continuing projects being undertaken within the Institute.

NATIONAL SEROLOGY REFERENCE LABORATORY

Elizabeth Dax, Director
Thein Thein Aye
Susan Best
Fernando Garcia
Anthony Gust
Elizabeth Johnson (pictured below)
Marina Karakaltsas
Marina Kasatkina
Sally Land
Kate McGavin
Joanne Schlegel
Matt Stephenson

The National Serology Reference Laboratory, Australia (NRL) is responsible for quality assurance of laboratory testing for HIV, HTLV and hepatitis C in blood transfusion and diagnostic laboratories nationally. In addition, the NRL has developed quality assurance for diagnostic programmes for other pathogens, including measles, rubella and *Chlamydia trachomatis*. Our association with the Institute was formed with the aim of developing a mutually beneficial research programme. In March of this year, Dr. Elizabeth Johnson was appointed as Research Co-ordinator to oversee development of the research programme at the NRL.

In addition to quality assurance of serological assays, NRL provides quality assurance for molecular assays (known as NAT) which detect viral nucleic acids. The NAT assay is used to monitor the amount of virus in the blood of persons infected with HIV an important task since the efficacy of anti-HIV treatments varies between individuals. Secondly, because NAT is able to detect the presence of virus in blood earlier than any other available method, it was decided this year that from May 2000, all blood donations will be screened for HIV and hepatitis C by NAT. In research activity related to quality assurance programmes for

NAT, the NRL has developed its own independent confirmatory NAT assay for hepatitis C.

In other diagnostic research, work has advanced on the modification of assays for hepatitis C to accommodate the use of dried blood spot samples which can be obtained from a fingerprick. Such an assay would be useful worldwide to assist accurate epidemiological monitoring of the spread of hepatitis C under circumstances where drawn blood samples may be difficult to obtain.

In September this year, the NRL won a contract with the World Health Organization (WHO) to provide quality assurance for laboratory testing of HIV and hepatitis B and C in the South-East Asian and Western Pacific regions. These links are vital to our research on infectious diseases testing in the developing world and provide us with access to valuable material for research on different strains of viruses which predominate in different regions. In further international research activity, the NRL has joined the International Consortium for Blood Safety (ICBS), an independent organisation established within the last 12 months. The goal of the ICBS is to help prevent the spread of infectious diseases via blood transfusions through improved screening methods, particularly in developing countries.

We have also continued collaborative work with the Macfarlane Burnet Centre for Medical Research, towards the development of an HIV vaccine, with our role being to characterise anti-HIV antibody development upon vaccination. In addition, the NRL has been incorporated into the Australian HIV Vaccine Initiative, the consortium of basic science and clinical research groups behind the development of HIV vaccines in Australia.

CONCLUSION

The Institute scientists have certainly kept up the pace to the end of the century. Really pleasing features are the ways in which fundamental research on proteins and genes contributes to the success of research in cell biology and mechanisms of disease. Increasingly, we see this translate to clinical advances. The challenge is to cultivate to ensure that Institute basic research makes the best possible contribution to health care.

Professor TJ Martin

PROFILE

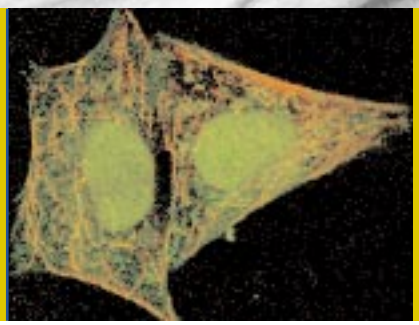
MATTHEW GILLESPIE

Matthew Gillespie is Head of the Molecular Endocrinology Laboratory, and during the year was appointed an Associate Director of the Institute.

After his science degree at Monash University, Matthew's Ph.D. research was in microbiology during which he became thoroughly expert in the new molecular biology. He was introduced to mammalian cells in a post-doctoral immunology year, and joined the bone research group in 1988.

Matthew's laboratory has achieved outstandingly in these last 12 years with his work on the PTHrP gene throughout that time, and for the last several years also on the regulation of osteoclast formation and its significance in cancer and inflammatory bone disease. He has been a great teacher of molecular biology to us all, and to a succession of students and Fellows. He is the first to admit that he himself has been learning all the time about mammalian cells and physiology, coming as he does from such a background in prokaryotic molecular biology – he has done so with remarkable success. He has been sole or joint supervisor of 9 Ph.D. students, many of whom have received major awards or fellowships.

Matthew has been a great collaborator within and outside the Institute, and a wonderful team player in the Institute. His research has been recognised internationally with the International Bone and Calcium Institute Outstanding Investigator Award in 1997. His great leadership, service and application to public affairs in science culminated in his appointment in 1999 as President of the Australian Society for Medical Research, a post he filled with great distinction.



GELS & CELLS

"Running a gel" is a standard laboratory technique often used while researching proteins and genes. The gel pictured above left is of a gene fragment, stained with a DNA binding dye, then viewed under ultra violet light.

A confocal photomicrograph of a bone cell (osteoblast) transfected with PTHrP tagged with green fluorescent protein is pictured above right. Actin filaments in the cell cytoplasm are stained orange, whilst regions of co-localisation of both PTHrP and actin appear yellow. This adds to our understanding of how the PTHrP protein is transported around the cell to carry out its different functions.

DR MATTHEW GILLESPIE

"Some people might find my work in research science frustrating - they'd want to find the cure, find the ultimate answer, close the chapter and move on. They'd want closure.

Scientists find an answer, but we always ask more questions. I think of it as finding new avenues to explore. After all, what are we really contributing to science if we don't pose questions to be answered?

When we noticed joints in patients with rheumatoid arthritis have a major infiltration of T cells we asked: do the T cells produce factors related to the bone destruction around the joint?"

COLLABORATIONS

INTERNATIONAL COLLABORATIONS

Guy M. Benian, Emory University, Atlanta, GA, USA. *Protein kinases.*

Tom Buckley, Department of Biochemistry and Microbiology, University of Victoria, Canada. *Structural studies of aerolysin.*

Gino Cingolani, Scripps Institute, La Jolla, CA, USA. *Structure of PTHrP-importin β.*

Greg Elgar and Melody Clark, Fugu Landmark Mapping Project, UK HGMP Resource Centre, Hinxton, UK. *Isolation of the Fugu parathyroid hormone-related gene.*

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

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

Kevin Foskett, University of Pennsylvania, Philadelphia, PA, USA. *Channel regulation.*

Mathias Gaytel, EMBL, Heidelberg and Max Planck Institute for Molecular Physiology, Dortmund, Germany. *S100A1 in the regulation of titin kinase.*

Paul Greengard and Andrew Czernik, Rockefeller University, NY, USA. *S100A1-synapsin interaction.*

Harold Guenther, University of Bern, Switzerland. *PTHrP regulation of osteoclast formation.*

Theresa Guise, University of Texas, Health and Science Center, San Antonio, TX, USA, *PTHrP in bone metastases.*

Luc Hittinger, INSERM U400, Faculté de Médicine, Creteil, France. *Studies of the effects of ACE inhibition on angiotensin and bradykinin peptides in heart failure.*

Peter Holland, Department of Zoology, University of Reading, UK. *Vertebrate genome evolution.*

Carmine Di Ilio, Dipartimento di Scienze Biomediche, Università 'G. D'Annunzio', Chieti, Italy. *Structural studies of bacterial GSTs.*

Patricia Ingleton, Institute of Cancer Studies, University of Sheffield, UK. *Parathyroid hormones in lower vertebrates.*

Andrey V. Kajava, Center for Molecular Modeling, Division of Computational Bioscience, National Institutes of Health, Bethesda, MD, USA. *Structural features of solenoid proteins.*

Gerard Karsenty, Baylor College of Medicine, Houston, TX, USA. *Genes in skeletal development.*

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

Stefan Mahlmann, Basel Institute for Immunology, Switzerland. *In vivo function of the chk2 kinase in mice.*

George Martin and Volkmor Guenzler, FibroGen, San Francisco, CA, USA. *Collagen inhibitors; effects on breast cancer.*

Mark Matteson, University of Kentucky, Lexington, KY, USA. *Protein kinases.*

Anthony R. Means, Duke University, NC, 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 renal failure.*

Antonio Nanci, McGill University, Montreal, Canada. *Nuclear location of PTHrP.*

Jude Onyia, Lilly Research Laboratories, Indianapolis, IN, USA. *Regulation of osteoprotegerin gene.*

Paul Ortiz de Montellano, University of California San Francisco, CA, USA. *Endothelial nitric oxide synthase.*

Deborah Power and Adelino Canario, Universidade do Algarve, Faro, Portugal. *Parathyroid hormones in lower vertebrates.*

Jeffrey Rubin, National Cancer Institute, Bethesda, MD. USA. *Protein inhibitors of osteoclast development.*

Motoharu Seiki, University of Tokyo and Hiroshi Sato, Kanazawa University, Japan. *MT-MMP and breast and prostate cancer progression.*

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

David Shalinsky, Agouron, San Diego, CA, USA. *Matrix metalloproteinase inhibitors; effects and mechanisms.*

David Stock, Department of Anthropology, Penn State University, Pennsylvania, PA, USA. *Evolution of the vertebrate skeleton.*

James Stull, UT SouthWestern, Dallas, TX, USA. *Nitric oxide synthase.*

Tasuo Suda, Nobuyaki Udagawa and Naoyuki Takahashi, Showa University, Tokyo, Japan. *Development of osteoclasts.*

Tony Treston, Entremed, Bethesda, MD, USA. *New inhibitors of angiogenesis.*

Rod Tweten, Department of Microbiology and Immunology, University of Oklahoma, OK, USA. *Structural studies of pore-forming toxins.*

Lee A. Witters, Dartmouth Medical College, NH, USA. *Protein kinases.*

NATIONAL COLLABORATIONS

Robin Anderson, Peter MacCallum Cancer Institute, Victoria. *Matrix metalloproteinases in a mouse breast cancer model; mechanisms of breast cancer metastasis to bone.*

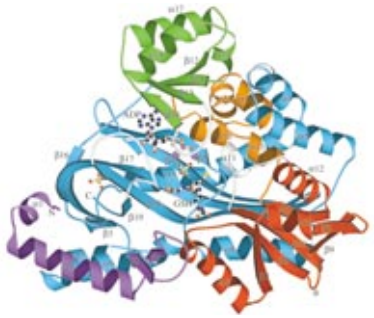
Jane Armes and Ian Campbell, Peter MacCallum Cancer Institute, Victoria. *Genetic analysis of experimental breast cancers.*

Julian A. Barden, Department of Anatomy, The University of Sydney, NSW. *PTHrP structure.*

John Bateman, Royal Children's Hospital, Victoria. *Collagen effects on MMP-2 activation by cancer cells and fibroblasts.*

Philip Board, John Curtin School of Medical Research, ANU, ACT. *Structural studies of glutathione-utilising enzymes.*

Steve Bottomley, Robert Pike and James Whisstock, Department of Biochemistry and Molecular Biology, Monash University, Victoria. *Structural studies of serpins.*



Lynda Campbell, Department of Cytogenetics, St. Vincent's Hospital, Melbourne, Victoria. *Tumour suppressor genes.*

Roberto Cappai and Colin Masters, Department. of Pathology, The University of Melbourne, Victoria. *Structural studies of amyloid precursor protein.*

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

Above left: *Three-dimensional structure of the enzyme glutathione synthetase.*

Above right: *PTHrP localisation in Lamprey spinal column and notochord.*

Tim Cole and Xiaojun Du, Baker Medical Research Institute, Victoria. *Cardiac function of S100A1 knockout mice.*

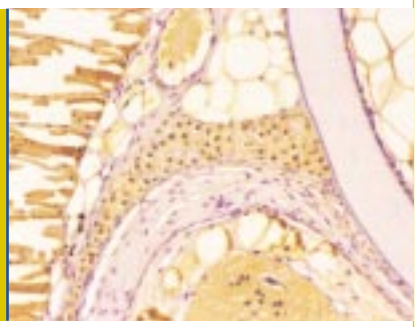
Tony Costello and Helen Crowe, Department of Surgery, Royal Melbourne Hospital, Victoria. *Gene array analysis of selenium chemoprotective mechanism in prostate cancer.*

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

Jeff G. Ellis, CSIRO Plant Industry, Canberra, ACT. *Structure and function of plant disease resistance proteins.*

Peter Gage, John Curtin School of Medical Research, ANU, ACT. *Structural studies of ion channels.*

Murray Esler, Garry Jennings, and Anthony Dart, Baker Medical Research Institute, Victoria. *Studies of kinin peptides in heart failure.*



Thomas P.J. Garrett, Biomolecular Research Institute, Victoria. *Structural features of solenoid proteins.*

Paul Gooley, Department of Biochemistry and Molecular Biology, The University of Melbourne, Victoria. *Structural studies on phenylalanine hydroxylase and FHA domains using NMR spectroscopy.*

Ming Gu, Swinburne University, Victoria. *Two photon confocal analysis of normal and neoplastic tissue.*

Emanuela Handman, The Walter and Eliza Hall Institute of Medical Research, Victoria. *Structure and function of Leishmania surface proteins.*

Michael Henderson, Department of Surgery, The University of Melbourne and St. Vincent's Hospital, Melbourne, Victoria. *Breast tumour biology.*

John Horowitz and Chris Zeitz, Department of Cardiology, Queen Elizabeth II Hospital, Woodville, SA. *Studies of the effects of ACE inhibition on the heart.*

Geoff Howlett, Department of Biochemistry and Molecular Biology, The University of Melbourne, Victoria. *Molecular associations of nuclear transport factors and retroviral envelope proteins.*

Lou Irving, Respiratory Department, Austin and Repatriation Medical Centre, Victoria. *Chromosome 9 in lung cancer.*

David A. Jans and Mark Lam, John Curtin School of Medical Research, ANU, ACT. *Nuclear import mechanisms for PTHrP.*

David A. Jans, John Curtin School of Medical Research, ANU, ACT. *Recognition of nuclear localization sequences by the nuclear import factor importin alpha.*

George Jerums, Austin and Repatriation Medical Centre and The University of Melbourne, Victoria. *AMP kinase in diabetes.*

David Jones, Plant Cell Biology, Research School of Biological Sciences, ANU, ACT. *Structure and function of plant disease resistance proteins.*

Geoff Lindeman and Jane Visvader, The Walter and Eliza Hall Institute of Medical Research, Victoria. *Gene array analysis of developing mammary gland.*

Angel Lopez, Hanson Centre for Cancer Research, SA. *Structural studies of cytokine receptors.*

Bruce Loveland, Austin Research Institute, Victoria. *Structural studies of cell surface receptors.*

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

Glenn McConnel, Department of Physiology, Monash University, Victoria. *Protein kinase and exercise.*

Dale McPhee, MacFarlane Burnet Centre for Medical Research, Fairfield, Victoria. *Role of vif in HIV replication.*

Wayne Morrison and Ken Knight, Bernard O'Brien Institute of Microsurgery, Victoria. *Extracellular matrix in wound healing and angiogenesis.*

Don Newgreen, Murdoch Institute, and Leigh Ackland, Deakin University, Victoria. *Use of PMC42 cells in analysis of epithelial mesenchymal transition.*

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

Gail Risbridger and Ismail Kola, Institute for Reproduction and Development, Monash University, Victoria. *Ets related factors and the TGFβ superfamily in relation to the epithelial mesenchymal transmission.*

Anne Rosamilia and Judith Clements, Prince Henry's Institute of Medical Research, Victoria. *Studies of the role of kinin peptides in interstitial cystitis.*

Sandford Skinner, Department of Physiology, The University of Melbourne. *Studies of the role of angiotensin and bradykinin peptides in diabetic renal disease.*

John Slavin, Department of Pathology, St. Vincent's Hospital, Melbourne, Victoria. *Pathology of breast and prostate cancers and metastases.*

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

Patrick Sexton, Department of Pharmacology, The University of Melbourne, Victoria. *Calcitonin receptors.*

Andrew Stevenson, Dachao Gao and Stephen Wilkins, CSIRO Manufacturing and Technology, Clayton, Victoria. *Phase contrast X-ray radiography in the detection of bone metastatic lesions.*

Roger Truscott, Australian Cataract Research Foundation, University of Wollongong, NSW. *Structural studies of heme enzymes.*

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

Binks W. Wattenberg, Hanson Centre for Cancer Research, SA. *Protein kinase receptors.*

Ray Wood, David Krenus and Bernard Jeffries, X-Ray Technologies, Victoria. *Imaging and high resolution phase contrast X-ray to study bone structure.*

Jeffrey Zajac, Department of Medicine, Royal Melbourne Hospital, Victoria. *Genes for PTHrP in fish.*

WHERE ARE THEY NOW?

Former postgraduate research students and postdoctoral Fellows of the Institute have gone on to work in various parts of the World and we like to keep in touch with them.

The following is an account of the whereabouts and doings of a selection of them.

Larry Suva (Ph.D. 1989). Larry's earlist claim to fame was success in the cloning of PTHrP. After postdoctoral studies with Gideon Rodan at the Merck Osteoporosis and Bone Biology Laboratories in West Point, Philadelphia, Larry moved to Harvard University where he was Assistant Professor of Medicine. Currently, Larry is Associate Director, Bone and Cartilage Biology, Smith Kline Beecham Pharmaceuticals and Adjunct Associate Professor of Medicine, University of Pennsylvania, School of Dental Medicine, USA.

Matthew Wilce (Post-doc, Protein Crystallography Unit 1991-95). Matthew played an important part in his time here with Michael Parker in helping to re-establish the protein crystallography laboratory, and elucidating the structure of a number of glutathione-S-transferases. After working with Dr. Mitchell Guss at the University of Sydney, Matthew now heads his own laboratory as Senior Research Fellow and Group Leader, Crystallography Centre, Department of Pharmacology, University of Western Australia, where his interests are in structural studies of ATPases and mechanosensitive ion channels.

Wally Ahmar (Ph.D. 1996). Wally's medical research training at SVIMR fostered his career in clinical medicine. He went on to pursue a medical degree at the University of Queensland, and is now a resident medical officer at the Mater Hospital in Brisbane.

Julie Blasioli (Ph.D. 1996). Following her Ph.D, Julie undertook postdoctoral studies with the late Matthew Thomas at Howard Hughes Medical Institute, Washington University School of Medicine, St. Louis, researching tyrosine phosphatases. Julie has recently returned to a postdoctoral position with Professor Chris Goodnow at the John Curtin School of Medical Research, working on B-cell signalling. Julie has been funded by the Human Frontiers Program Science Organization since 1996.

Aaron Oakley (Ph.D. 1997). After completing his Ph.D on the structure of Pi class glutathione-S-transferases, Aaron left to pursue post-doctoral research within Matthew Wilce's laboratory in Western Australia.

Wayne Rankin (Ph.D. 1998). Wayne joined the laboratory of Theresa Guise and Greg Mundy at the University of Texas at San Antonio to work on mechanisms of breast cancer metastases to bone. He has recently arrived back in Australia to work at the Hanson Centre in Adelaide with Tom Gonda on leukemia.

Justine Southby (Ph.D. 1996). Justine holds a Wellcome Fellowship in the Department of Biochemistry, University of Cambridge, UK. Where she is studying the mechanisms by which genes are spliced.

NEAR & FAR

Rick Pearson (Ph.D. 1993). Rick, pictured above left, is now a Senior Scientist at the Trescowthick Laboratories, Peter MacCallum Cancer Institute working on the protein kinase, Akt. Previous to this, Rick was a post-doctoral fellow in the laboratory of George Thomas at the Basel Institute of Immunology, Switzerland.

Maree Faux (Ph.D. 1996). After completing her Ph.D with Bruce Kemp, Maree, pictured above, worked with John Scott at the Vollum Institute, Portland, Oregon, on signal transduction and anchoring proteins. Maree has recently returned to Melbourne to work as Senior Scientist within Tony Burgess's group at the Ludwig Institute for Cancer Research.

JUSTINE SOUTHBY

"My time at the Institute was an exciting one, with the discovery that PTHrP was so important in the spread of breast cancers to bone. At that time I was also able to study the PTHrP gene in detail and I was fascinated by the "splicing" patterns that the gene showed. That led me to my wonderful few years in Cambridge, where I now work on how genes are spliced to produce different proteins. It's emerging as a very important biological process and our laboratory in the Biochemistry Department at Cambridge is a world leader."

AWARDS, FELLOWSHIPS & GRADUATIONS

MAJOR AWARDS

Michael Parker. 1999 Gottschalk Medal of the Australian Academy of Science.

Right: *1999 Gottschalk Medal of the Australian Academy of Science*

MAJOR FELLOWSHIPS

Nicole Horwood

Howard Florey Fellowship, awarded by the Royal Society and administered by the Association of Commonwealth Universities, to an outstanding young Australian biomedical scientist. Nikki will work for 3 years at the Kennedy Institute of Rheumatology, London, in the Cytokine and Immunology Department with Professors Marc Feldmann and Ravinda Maini.

Jamie Rossjohn

R.D. Wright Fellowship, awarded by NHMRC, 2000-2003 for research in protein structure using X-ray crystallography.

Mark Lam

Australian Post Doctoral Fellowship (NHMRC), 2000-2002, to work at John Curtin School of Medical Research on nuclear targetting of proteins.

John Price

Fellowship from Association for International Cancer Research (headquarters in UK), 1999-2002 for studies on gene array analysis of breast cancer metastases in bone.

Michelle Dunstone

Dora Lush Postgraduate Research Scholarship and 2000 International Centre for Diffraction Data Crystallography Scholarship Award.

Elizabeth Williams

Travel Fellowship from the International Union against Cancer, for training in gene array analysis and its application to understanding of the mechanism of selenium prevention in prostate cancer.

GRADUATIONS

The following graduated Doctor of Philosphy:

Nicole J. Horwood – "Identification and characterisation of bone–specific manuscripts"

Vicky Kartsogiannis – "Parathyroid hormone–related protein and bone formation in vivo".

Melanie Trivett – "Parathyroid hormone–related protein in lower vertebrates"

Kirilee Wilson – "The molecular basis of HIV envelope protein assembly and function"

Yun Shen Hu – "The cloning of homeobox gene rHOX, its tissue distribution and regulation of gene expression"

Evange Romas – "The role of interleukin 11 and gp130 mediated signals in osteoclast differentiation"

The following graduated Master of Science:

Leeanne Mead – "Localisation of chromosome 9p deletions and search for tumour suppressor genes in lung cancer"

INVITED LECTURES

INVITED INTERNATIONAL LECTURES BY INSTITUTE SCIENTISTS

Professor T.J. Martin

- Keystone Conference on Bone Cell and Molecular Biology, Lake Tahoe, CA, USA.
- Human Genome Mapping Project Resource Centre, Wellcome Genome Campus, Hinxton, UK.
- International Workshop on Osteobiology, Gallipoli, Italy.
- 6th International Conference on Alternative Actions of PTH, Valetta, Malta.
- Molecular Endocrinology 1999, Institute of Endocrinology, Sheffield, UK.
- International Symposium on Postmenopausal Health, Satellite of 9th International Menopause Conference, Kyoto, Japan.

Professor B. Kemp

- Division of Molecular Biology and Cancer, Samuel Lunenfeld Research Institute, Mt.Sinai Hospital, Toronto, Canada.
- Sanders-Brown Research Center on Aging and Department of Anatomy and Neurobiology, University of Kentucky, Lexington, KY, USA.
- Department of Chemistry and Biochemistry Cellular and Molecular Medicine, School of Medicine, University of California at San Diego, La Jolla, CA, USA.
- Aurora Biosciences Corporation San Diego, CA, USA.
- Second Messengers and Protein Phosphorylation Gordon Conference, Kimball Union Academy, Meriden, NH, USA.
- Department of Molecular Biology, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA.
- New England Biolabs Inc. Beverly, MA, USA.
- Department of Pharmacology and Cancer Biology, Duke University Medical Centre, Durham, NC, USA.
- FASEB Summer Conference Protein Kinases, Snowmass, Colorado, USA.
- ICOS Corporation Bothel, WA, USA.
- Department of Medicine and Wisconsin Regional Primate Research Center, University of Wisconsin, Madison, WI, USA.
- Department of Physiology, University of Texas Southwestern Medical Center, Dallas, TX, USA.
- Hoechst Marion Roussel Protein Kinase Meeting, Westin La Paloma, Canyon II Tucson, AZ, USA.

Associate Professor Michael Parker

- Symposium on Biocrystallography for Medicine and Biotechnology, Rome, Italy.
- Department of Biology, University of Rome "Tor Vergata", Rome, Italy.
- Molecular models for prediction of metabolism and toxicology, British Toxicology Society, Keele, UK.

Associate Professor Rik Thompson

- National Institute of Dental Research, National Institutes of Health, Bethesda, MD, USA
- Entremed, Inc., Rockville, MD, USA.
- Molecular Urology and Therapeutics Program, Department of Urology, University of Virginia Health Sciences Center, Charlottesville, VA, USA.
- Women's Health Seminar Series. The Ohio State University Medical Center, Ohio, USA.
- Agouron Pharmaceuticals, Inc. San Diego, CA, USA.
- Ligand Pharmaceuticals, San Diego, CA, USA.
- 4th Pan Pacific Connective Tissue Societies Symposium, Queenstown, NZ.

Dr. Matthew Gillespie

- Endocrine Society, San Diego, CA, USA.

Professor Peter Choong

- 2nd Military Hospital, Xian, China.
- University Hospital, Beijing, China.
- National University Hospital, Singapore
- University Hospital, Kuala Lumpur, Malaysia.
- Western Pacific Orthoapedic Association, Penang, Malaysia.

Professor Robin Marks

- UCSF Cancer Center, San Francisco, USA.
- International Meeting of the International League of Dermatological Societies, Florence, Italy.
- Skin Cancer & Precursor Lesions Meeting, Lisbon, Portugal.
- 8th European Academy of Dermatology & Venereology Meeting, Amsterdam, Netherlands.
- World Congress of Dermatology Site Meeting, Paris, France.
- Joint Japanese Dermatology Association & Australiasian College of Dermatology, Kyoto, Japan.

Dr. Bostjan Kobe

- International Union of Crystallography, XVIII Congress and General Assembly, Glasgow, Scotland, UK.

Dr. Duncan Campbell

- Third Vasoactive Peptides International Symposium, Belo Horizonte, Minas Gerais, Brazil.

Dr. Jorg Heierhorst

- EMBL, Heidelberg, Germany.
- University of Hamburg, Hamburg, Germany.
- Max Planck Institute for Molecular Physiology, Dortmund, Germany.
- Basel Institute for Immunology, Basel, Switzerland.
- Laboratory of Molecular & Cellular Neuroscience, The Rockefeller University, NY, USA.
- Department of Pathology, Emory University, Atlanta, GA, USA.

Dr. Andy Poumbourios

- 11th International Congress of Virology, Sydney, NSW, Australia.
- National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA.

Dr. Jamie Rossjohn

- International Union of Crystallography, XVIII Congress and General Assembly, Glasgow, Scotland, UK.

Dr. Elizabeth Williams

- Chemoprevention Workshop, NCI, NIH, Baltimore, MD, USA.

Dr. Jane Fisher

- The British Society for Matrix Biology with the Bone and Tooth Society, Aberdeen, Scotland, UK.

Dr. Kirilee Wilson

- 11th International Congress of Virology, Sydney, NSW, Australia.

Dr. Hong Zhou

- 2nd International Osteoporosis Workshop, Xian, China.

Dr. Galina Polekhina

- National Light Source Laboratory, Campinas. Sao Paulo. Brazil.

Dr. Elizabeth Dax

- IX Congress of the International Society of Hematology, Bangkok, Thailand.
- Workshop on Transfusion Transmitted HIV. Workshop conducted jointly by Dr. Dax and Dr. Gordon Whyte, Bangkok, Thailand.

Dr. Susan Best

- 2nd International Conference on AIDS India 2000, Chennai, India.

MEMBERS OF STAFF

PATRON

Gustav J.V. Nossal
AC Kt CBE MBBS BSc(Med) Syd PhD Melb HonMD Mainz HonMD Ncl HonMD Leeds HonMD UWA HonDSc Syd HonDSc Qld HonDSc ANU HonDSc UNSW HonDSc La Trobe HonDSc MacMaster HonLLD Melb HonLLD Mon FRCP FRACP FRCPA FRACOG Hon FRCPath FRSE FTSE FAA FRS

RESEARCH

Director of Institute and Professor, Department of Medicine, The University of Melbourne
T. John Martin, AO FAA MD DSc Melb Hon *MD Sheffield* FRACP FRCPA

Deputy Director and NHMRC Senior Principal Research Fellow, Professor, Department of Medicine, The University of Melbourne
Bruce E. Kemp, BAgSci Hons Adel PhD Flinders

Associate Director and NHMRC Senior Research Fellow
Matthew T. Gillespie, BSc Hons PhD Monash

Associate Director, Australian Research Council Senior Research Fellow, Associate Professor and Principal Fellow, Department of Biochemistry and Molecular Biology, The University of Melbourne
Michael W. Parker, BSc Hons ANU DPhil Oxon

Associate Director, Head of VBCRC Invasion and Metastasis Unit, Associate Professor, Department of Surgery, The University of Melbourne
Erik W. Thompson, BSc Hons PhD Griffith

Professor (Dermatology)
Robin Marks, MBBS MPH Monash FRACP FACD

Professor (Orthopaedics)
Peter Choong, MBBS MD Melb FRACS FAORTHA

Associate Professor (Clinical)
Kong Wah Ng, MBBS Hons Monash MD Melb FRACP

NHMRC Principal Research Fellow, Associate Professor, Department of Medicine, The University of Melbourne
Jane M. Moseley, BSc PhD Lond

NHMRC Senior Research Fellow and Associate Professor, Department of Medicine, The University of Melbourne
Duncan J. Campbell, BMedSci MBBS PhD Melb FRACP Grad Dip Epid Biostat

Wellcome Senior Research Fellow in Medical Science in Australia
Bostjan Kobe, MSc University of Ljubljana, PhD UT South Western

NHMRC Research Fellow, Fellow, Department of Zoology, The University of Melbourne
Janine Danks, BSc LaTrobe MSc Melb PhD Monash

Senior Lecturer/Research Fellow
Vivian Grill, MBBS Syd FRACP

CARG Senior Research Officer
Pantelis Poumbourios, BSc Hons PhD Melb

NHMRC RD Wright Fellow
Jörg Heierhorst, MD University of Hamburg

CJ Martin Fellows
David Stapleton, BSc Hons La Trobe PhD Melb
Robert Center, BSc Hons La Trobe PhD Melb

ARC Postdoctoral Fellow
Jamie Rossjohn, BSc Hons PhD Bath University

CR Roper Fellows
Julian Quinn, BSc Hons MSc DPhil Oxon
Mark Waltham, BSc Hons PhD Qld

Thomaïy Research Fellow
Julie Sharp, BAppSc RMIT PhD Melb

Association of International Cancer Research Fellow
John Price, BSc Hons PhD Aberdeen

Visiting Research Fellows
Toshi Kunisada, MD Nagasaki PhD Okalama
Manabu Nishii, BSc PhD Kitasato University
Marcos Roberto de Mattos Fontes, MSc PhD Universidade de São Paulo

Senior Research Officers
Helen Blanchard, BSc Hons PhD London
Heidi Drummer, BSc Hons PhD Melb
Ian Jennings, BSc Melb
Kenneth I. Mitchelhill, BAppSc RMIT
William J. McKinstry, BSc Hons Tas PhD Melb
Tony Tiganis, BSc Hons PhD Melb
Hong Zhou, MBBS Ningxia PhD Melb

Research Officers
Elizabeth H. Allan, BSc Otago, PhD Melb
Zhiping Chen, BSc Shanghai PhD ULP France
Brett Cromer, BSc Hons PhD ANU
Jane Fisher, BSc Hons PhD Monash
Thomas Gleichmann, BSc PhD University Karlsruhe
James Horne, BSc Hons Tas PhD Melb
Nicole J. Horwood, BSc MSc (prelim.) PhD Melb
Yun Shan Hu, MBBS Shanghai PhD Melb
Vicky Kartsogiannis, BSc Hons Melb
Frosa Katsis, BAppSc IIC PIT
Peter Niforas, BSc Hons Monash, PhD Monash
Galina Polekhina, MSc Hons Moscow State PhD Aarhus
Pei Rong, BSc Hons PhD Melb
Pierre D. Scotney, BSc Hons Liverpool PhD Bristol
Angus Tester, BSc Hons PhD Monash
Melanie Trivett, BSc Hons PhD Melb
Elizabeth Williams, BSc Hons PhD Melb
Kirilee A. Wilson, BSc Hons PhD Melb

Research Assistants
Margaret Bills, BSc Macquarie
Todd Briscoe, BSc Hons Griffith MSc La Trobe
Nirada Dhanesuan, DDS Chulalongkorn
Michelle A. Dunstone, BSc Hons Monash
Cathy Field, BSc Hons Melb
Susanne C. Feil, BSc MSc Stockholm
Andrew Hammet, BSc Hons Melb
Monique Howard, BSc Hons La Trobe
Jeannie Javni, BSc Hons Melb
Athena Kladis, BSc Melb
Anne Maerz, BAppSc RMIT
Leeanne J. Mead, BSc MSc Melb
Belinda J. Michell, BSc Hons MBA Monash
Tania Pickersgill, BSc Deakin BSc Hons Melb
Brietta Pike, BSc Hons Melb
Neeracha Ruangpanit, DDS Hons Chulalongkorn
Trazel Teh, BSc Hons Monash
Nora Tenis, BSc Monash, Grad Dip Med Lab Sc Uni of SA
Rachel J. Thomas, BSc Hons Melb
Kim M. Wilson, BAppSc QIT

Radiographers
Gillian A. Jones, Dip Radiography Edinburgh
Colleen E. Fietz, Assoc Dip Radiography Adel

Research Nurses
Marian Croft, Gen Nursing SVH Midwifery RMH

Chief Technical Officers
Hannelore Diefenbach-Jagger, Chem TechCert Augsburg
Virginia A. Leopold, BSc Hons La Trobe

Senior Technical Officers
Daphne K. Hards, BAppSc RMIT
Patricia Wai Ming Ho, BSc Monash
Patricia M. Smith, Dip Med Lab Tech RMIT

Technical Officers
Nicolle Bruengger, Assoc Dip Animal Tech Box Hill
Jan Elliott

Junior Technical Assistants
Ingrid Kriechbaum, Dip Health (Med Lab) RMIT

Laboratory Assistant
Sally Emini

Postgraduate Scholars
Doctor of Philosophy
Lindus Conlan, BSc Hons Melb
'Transcriptional properties of PTHrP'

Michelle Dunstone, BSc Hons Monash
'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'

Michelle Fodero, BSc Hons Melb
'Identification of endothelial protein tyrosine phosphatases'

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

Karl Hausler, BAppSc Phillip MAppSc RMIT
'Osteoblastic and lymphocytic factors in osteoclastogenesis'

Nicole J. Horwood, BSc MSc (prelim.) Melb
'Identification and characterization of novel osteoclastogenic factors'

Vicky Kartsogiannis, BSc Hons Melb
'Temporal and spartial localization of parathyroid hormone–related protein (PTHrP) in bone and other tissues in vivo'

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

Ken Mitchelhill, BAppSc RMIT
'Structure and function studies of the AMP-activated protein kinase and related kinases'

Tania Pickersgill, BSc Deakin BSc Hons Melb
'Phosphorylation and regulation of GAPDH by AMP – activated protein kinase'

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

Rachel Thomas, BSc Hons Melb
'The involvement of PTHrP in the metastasis of breast cancer to bone'

Melanie Trivett, BSc Hons Melb
'Parathyroid hormone-related protein in lower vertebrates'

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

Kirilee Wilson, BSc Hons Melb
'HIV envelope proteins: structure and function'

Sing Yiah Wong, BS BA (Oklahoma City)
'Mechanisms of post-transcriptional action of retinoic acid in osteoblasts'

Degree of 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'

Howard Zeimer, MBBS FRACP Monash
'Role of PTHrP in sarcoidosis and multiple myeloma'

Master of Science
Leeanne Mead, BSc Melb
'Localisation of chromosome 9p deletions and search for tumour suppressor genes in lung cancer'

Undergraduate Scholar
Bachelor of Science (Hons)
Alex Funkat, BA Melb
'Parathyroid hormone-related protein in sharks'

ADMINISTRATION

Senior Associate
John McDougall, BSc Hons PhD Melb MBA Deakin

Laboratory Manager
David Murfitt, HNC AppBiol Cambridge CAT

Business Manager
David Rees, Bach Bus, CPA

Administrative Officer
Gayle M. McMurray

Administrative Secretaries
Wendy Banks
Marisa P. Bertocchi
Dimitra Samaras

NATIONAL SEROLOGY REFERENCE LABORATORY

RESEARCH

Director and Associate Professor
Elizabeth Dax, MBBS MD Melb PhD Monash

Senior Scientist
Susan Best, Dip Med Tech MAppSc RMIT

Research Co-ordinator
Elizabeth Johnson, BSc Hons PhD Melb

Scientists
Thein Thein Aye, MBBS Burma PhD Japan
Anthony Gust, BSc Hons Grad Dip Stats Monash
Marina Karakaltsas, BSc La Trobe
Marina Kasatkina, BSc Bio PhD Kiev
Sally Land, BSc Hons Melb
Kate McGavin, BSc AmusA Melb
Joanne Schlegel, BAppSc RMIT
Matt Stephenson, BSc La Trobe
Sandy Walker, BSc Hons La Trobe

Data Technician - Advanced
Rosanna Fahmy

Laboratory Assistant
Frank Torzillo
Fernando Garcia

ADMINISTRATION

Executive Assistant
Nikki Busch

Informatics Officer
Kara Tuck, BA Hons Canada

Computer Systems Manager
John Tomasov, BSc Hons PhD La Trobe Grad Dip Comp Sci Monash

Office Manager
Noel Shugg, BA Dip Account CPA RMIT

Data Management Officer
Penelope Webster, BA Maine, USA

Quality Manager
Anna Karopoulos, BSc Monash
Roderick Chappel, BAgrSc PhD Melb MASM

PUBLICATIONS

Allocati, N., Casalone, E., Masulli, M., Ceccarelli, I., Carletti, E., Parker, M.W. & Di Ilio, C. Functional analysis of the evolutionarily conserved proline 53 residue in Proteus mirabilis glutathione transferase B1-1. FEBS Letters, 26:445:347-50, 1999.

Bedi, H., Kaufman, D., Choong, P.F.M. & Slavin, J. Osteosarcoma of the scapula arising in osteogenesis imperfecta. Pathology 31:52-54, 1999.

Blomme, E.A.G., Zhou, H., Kartsogiannis, V., Capen, C.C. & Rosol, T.J. Spatial and temporal expression of parathyroid hormone-related protein during wound healing. Journal of Investigative Dermatology, 112:788-795, 1999.

Caccuri, A.M., Antonini, G., Board, P.G., Parker, M.W., Nicotra, M., Lo Bello, M., Federici, G. & Ricci, G. Proton release upon binding of glutathione to alpha, mu and delta class glutathione transferases. Biochemistry Journal, 344:419-425, 1999.

Campbell, D.J., Kladis, A., Briscoe, T.A. & Zhuo, J. Type 2 bradykinin receptor antagonism does not modify kinin or angiotensin peptide levels. Hypertension, 33:1233-1236, 1999.

Campbell, D.J., Kelly, D.J., Wilkinson-Berka, J.L., Cooper, M.E. & Skinner S.L. Increased bradykinin and 'normal' angiotensin peptide levels in streptozotocin-diabetic Sprague Dawley and TGR(mRen-2)27 rats. Kidney International, 56:211-221, 1999.

Campbell, D.J., Duncan, A.M. & Kladis, A. Angiotensin converting enzyme inhibition modifies angiotensin, but not kinin peptide levels in human atrial tissue. Hypertension, 34:171-175, 1999.

Chappel, R.J. & Dax, E.M. Blood screening – the next generation in testing. Australian and New Zealand Journal of Medicine, 29:763-764, 1999.

Carter, R., Marks, R. & Hill, D. Could a national skin cancer primary prevention campaign in Australia be worthwhile? An economic evaluation. Health Promotion International, 14:73-82, 1999.

Chen, Z.-P., Heierhorst, J., Mann, R.J., Mitchelhill, K.I., Michell, B.J., Witters, L.A., Lynch, G.S., Kemp, B.E. & Stapleton, D. Expression of the AMP-activated protein kinase β1 and β2-subunits in skeletal muscle. FEBS Letters, 460:343-348, 1999.

Chen, Z-P., Mitchelhill, K.I., Michell, B.J., Stapleton, D., Rodriguez-Crespo, I., Witters, L.A., Power, D.A., Ortiz de Montellano, P.R. & Kemp, B.E. AMP-activated protein kinase phosphorylation of endothelial NO synthase. FEBS Letters, 443:285-289, 1999.

Choong, P.F.M., Qureshi, A.A., Sim, F.H. & Unni, K.K. Osteosarcoma of the foot. Acta Ortopedics Scandinavica, 70:361-364, 1999.

Cornish, J., Callon, K., Lin, C., Xiao, C., Moseley, J.M. & Reid, I.R. Stimulation of osteoclast proliferation by C-terminal fragments of parathyroid hormone-related protein. Journal of Bone & Mineral Research, 14:915-922, 1999.

Crute, B.E., Seefeld, K., Gamble, J., Kemp, B.E. & Witters, L.A. AMP-activated protein kinase α1 subunit functional domains. Journal of Biological Chemistry, 273:85347-85354, 1999.

Cuthbertson, R.M., Kemp, B.E. & Barden, J.A. Structure study of osteostatin PTHrP[Thr107](107-139). Biochimica Biophysica Acta, 1432:64-72, 1999.

Daci, E., Udagawa, N., Martin, T.J., Bouillon, R. & Carmeliet, G. The role of the plasminogen system in bone resorption in vitro. Journal of Bone & Mineral Research, 14:946-952, 1999.

Dax, E.M. Serological testing algorithms for the diagnosis of HIV infection. AIDS, 13:133-134, 1999.

Dax, E.M. & O'Connell, R. Standardisation of subjectively scored HIV immunoassays: developing a quality assurance program to assist in reproducible interpretation of results using an anti-HIV particle agglutination assay as a model. Journal of Virology Methods, 82:113-118, 1999.

Di Nicolantonio, R., Williams, E.D. & Wlodek, M.E. Milk factors and the development of hypertension. In: Development of the hypertensive phenotype: basic and clinical studies. Editors: McCarty, R., Blizard, D.A. & Chevelier, R.L. Series Title: The Handbook of Hypertension. Series Editors: Birkenhager, W.H. & Reid, J.L. Elsevier, Amsterdam, 1999.

Dowsey, M., Kilgour, M., Santamaria, N. & Choong, P.F.M. Clinical pathways in hip and knee joint arthroplasy: a prospective randomised controlled study. Medical Journal of Australia, 170:59-62, 1999.

Drummer, H.E., Studdert, M.J. and Crabb, B.S. Equine herpesvirus 4 (EHV4) gG is secreted as a disulfide linked homodimer and is present in multiple homodimeric forms in the virion. Journal of General Virology, 79:1205-1213, 1999.

Duncan, A-M., James, G.M., Anastasopoulos, F., Kladis. A., Briscoe. T.A. & Campbell, D.J. Interaction between neutral endopeptidase and angiotensin converting enzyme inhibition in rats with myocardial infarction: effects on cardiac hypertrophy, and angiotensin and bradykinin peptides. Journal of Pharmacology & Experimental Therapeutics, 289:295-303, 1999.

Dyall-Smith, D. & Marks, R. Dermatology at the Millennium: The Proceedings of the 19th World Congress of Dermatology. London: The Parthenon Publishing Co., 1999.

Flanagan, J.U., Rossjohn, J., Parker, M.W., Board, P.G. & Chelvanayagam, G. Mutagenic analysis of conserved arginine residues in the novel sulfate binding pocket of the human theta class glutathione transferase T2-2. Protein Science, 8:2205-2212, 1999.

Gilbert, R.J.C., Heenan, R.K., Timmins, P.A., Rossjohn, J., Parker, M.W., Andrew, P.W. & Byron O. Biophysical studies of the structure and mechanism of a bacterial protein toxin. Journal of Molecular Biology, 293:1145-1160, 1999.

Gilbert, R.J., Jimenez, J.L., Chen, S.,. Tickle, I.J., Rossjohn, J., Parker, M., Andrew, P.W. & Saibil, H.R. Two structural transitions in membrane pore formation by pneumolysin, the pore-forming toxin of Streptococcus pneumoniae. Cell 97:647-655, 1999.

Gill, D. & Marks, R. A review of the epidemiology of tinea unguium in the community. Australasian Journal of Dermatology, 40:6-13, 1999.

Grugg, G., Hoctor, V., Venter, D. & Choong, P. Inversion (6) (p23q15) as the sole anomaly in a low-grade intraosseous osteosarcoma. Cancer Genetics and Cytogenetics, 109:70-1, 1999.

Hall, A.P. & Marks, R. Common red scaly rashes: Traps for the unwary. Part 1. Australian Family Physician, 28:911-914, 1999.

Hall, A.P. & Marks, R. Common red scaly rashes: Traps for the unwary. Part 2. Australian Family Physician, 28:1021-1024, 1999.

Hausler, K.D., Rich, P.A., Smith, P.C. & Barry, E.B. Relationships between static histomorphometry and ultrasound in the human calcaneus. Calcified Tissue International, 64:477-480, 1999.

Heierhorst, J., Mitchelhill, K.I., Mann, R.J., Tiganis, T., Czernik, A.J., Greengard. P. & Kemp, B.E. Synapsins as major neuronal Ca2+/S100A1 interacting proteins. Biochemical Journal, 344:577-583, 1999.

Holloway, S. A., Lindquester, G. J., Studdert, M. J. & Drummer, H. E. Identification, sequence analysis and characterisation of equine herpesvirus 5 glycoprotein B. Archives of. Virology, 144:287-307, 1999.

Hook, S.S., Kemp, B.E. & Means, A.R. Peptide specificity determinants at P-7 and P-6 enhance the catalytic efficiency of Ca2+/calmodulin-dependent protein kinase I in the absence of activation loop phosphorylation. Journal of Biological Chemistry, 274:20215-20222, 1999.

Horwood, N.J., Kartsogiannis, V., Quinn, J.M.W., Romas, E., Martin, T.J. & Gillespie, M.T. Activated T lymphocytes support osteoclast formation in vitro. Biochemical and Biophysical Research Communications, 265:144-150, 1999.

Ingleton, P.M., Hubbard, P.A., Danks, J.A. & Balment R.J. An immunohistochemical study of the calcium-sensing receptor in flounder tissues. Calcium Metabolism: Comparative Endocrinology, eds Danks, J.A., Dacke, C., Flik, G. & Gay, C. pp45-48, Dacke, C., Flik, G. & Gay, C. Bioscientifica, Bristol, UK, 45-48, 1999.

Kartsogiannis, V., Zhou, H., Horwood, N.J., Niforas, P., Ng, K.W., Martin, T.J. & Gillespie, M.T. Localization of RANKL (receptor activator of NFkB ligand) mRNA and protein in skeletal and extraskeletal tissues. Bone, 25:525-534, 1999.

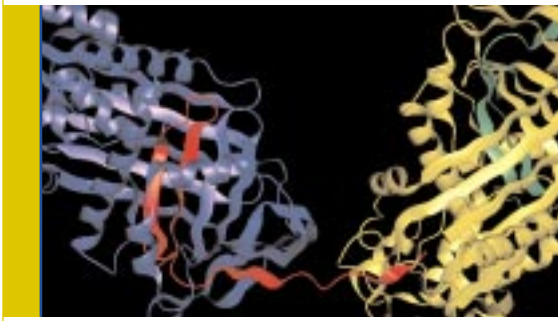
Kemp, B.E., Mitchelhill, K.I., Stapleton, D., Michell, B.J., Chen, Z.-P. & Witters, L.A. Dealing with energy demand: the AMP-activated protein kinase. Trends in Biochemical Science, 24:22-25, 1999.

Kobe, B. Autoinhibition by an internal nuclear localization signal revealed by the crystal structure of mammalian importin α. Nature Structural Biology, 6:388-397, 1999.

Kobe, B., Center, R. J., Kemp, B.E. & Poumbourios, P. Crystal structure of human T cell leukemia virus type 1 gp21 ectodomain crystallized as a maltose-binding protein chimera reveals structural evolution of retroviral transmembrane proteins. Proceedings of the National Academy of Sciences USA, 96:4319-4324, 1999.

Kobe, B., Gleichmann, T., Horne, J., Jennings, I.G., Scotney, P.D. & Teh, T. Turn up the HEAT. Structure, 7:R91-R97, 1999.

Kobe, B., Gleichmann, T., Teh, T., Heierhorst, J. & Kemp, B.E. in: Protein Phosphorylation: A Practical Approach, 2nd Ed., pp. 387-421 (Hardie, D.G., Ed.) Oxford University Press, Oxford. "Crystallization of protein kinases and phosphatases" pp 387-421, 1999.



Kobe, B., Jennings, I.G., House, C.M., Michell, B.J., Goodwill, K.E., Santarsiero, B.D., Stevens, R.C., Cotton, R.G.H. & Kemp, B.E. Structural basis of autoregulation of phenylalanine hydroxylase. Nature Structural Biology, 6:442-448, 1999.

Kobe, B. & Kemp, B.E. Active-site directed protein regulation. Nature, 402:373-376, 1999.

Kotake, S., Udagawa, N., Takahashi, N., Matsuzaki, K., Itoh, K., Ishiyama, S., Saito, S., Inoue, K., Kamatani, N., Yasuda, H., Higashio, K., Gillespie, M.T., Martin, T.J. & Suda, T. IL-17 is a potent stimulator of osteoclast differentiation via osteoclast differentiation factor (ODF) synthesis, and is detected in synovial fluids from rheumatoid arthritis patients. Journal of Clinical Investigations, 103:1345-1352, 1999.

Lam, M., Briggs, L.J., Hu, W., Martin, T.J., Gillespie, M.T. & Jans, D.A. Importin β recognizes parathyroid hormone-related protein (PTHrP) with high affinity and mediates its nuclear import in the absence of importin α. Journal of Biological Chemistry, 274:7391-7398, 1999.

Above: *Three-dimensional structure of the anti-trypsin polymer.*

Lam, M.H.C., House, C.M., Tiganis, T., Mitchelhill, K.I., Sarcevic, B., Cures, A., Ramsay, R., Kemp, B.E., Martin, T.J. & Gillespie, M.T. Phosphorylation at the cyclin dependent kinases p34cdc2 and p33cdk2 site (Thr85) of parathyroid hormone-related protein negatively regulates its nuclear localization. Journal of Biological Chemistry, 274:18559-18566, 1999.

Lelekakis, M., Moseley, J.M., Martin, T.J., Hards, D.K., Williams, E., Ho, P., Lowen, D., Javni, J., Miller, F.R., Slavin, J. & Anderson, R.L. A novel orthotopic model of breast cancer metastasis to bone. Clinical & Experimental Metastasis, 17:163-170, 1999.

Manji, S.S., Pearson, R.B., Pardee, M., Paspaliaris, V., d'Apice, A., Martin, T.J. & Ng, K.W. Dual post-transcriptional targets of retinoic acid-induced gene expression. Journal of Cellular Biochemistry, 72:411-422, 1999.

Mar, A. & Marks, R. The descriptive epidemiology of atopic dermatitis in the community. Australasian Journal of Dermatology, 40:73-78, 1999.

Mar, A., Tam M., Jolley D. & Marks R. The cumulative incidence of atopic dermatitis in the first 12 months amongst Chinese, Vietnamese and Caucasian infants born in Melbourne, Australia. Journal of the American Academy of Dermatology, 40:597-602, 1999.

Marks, R., Kilkenny, M., Plunkett, A. & Merlin, K. The prevalence of common skin conditions in Australian school children: 2. Atopic Dermatitis. British Journal of Dermatology, 140:468-473, 1999.

Marks, R. Photoprotection and prevention of melanoma. European Journal of Dermatology, 9:406-412, 1999.

Marks, R. Two decades of the public health approach to skin cancer control in Australia: Why, how and where are we now. Australasian Journal of Dermatology, 40:1-5, 1999.

Marks, R. Solarium use: Why pay money for something when we already receive more than we need, for nothing? Medical Journal of Australia, 171:456-457, 1999.

Marks, R. Solar damage, moles, solar keratoses and skin cancer. In: Mashford L., Ed. Therapeutic Guidelines: Dermatology. Version 1, Melbourne: Therapeutic Guidelines. pp 225-235, 1999.

Merlin K., Kilkenny M., Plunkett A. & Marks R. The prevalence of common skin conditions in Australian school students: 4. Tinea Pedis. British Journal of Dermatology, 140:897-901, 1999.

Michell, B.J., Griffiths, J.E., Mitchelhill, K.I., Rodriguez-Crespo, I., Tiganis, T., Bozinovski, S., Kemp, B.E. & Pearson, R.B. Akt/PKB phosphorylates and activates endothelial nitric oxide synthase. Current Biology, 9:845-848, 1999.

Mitchelhill, K.I. & Kemp, B.E. in: Protein Phosphorylation: A Practical Approach, 2nd Ed., pp. 127-151 (Hardie, D.G., Ed.) Oxford University Press, Oxford. "Phosphorylation site analysis by mass spectrometry", 1999.

Mori, K., Imamaki, A., Nagata, K., Yonetomi, Y., Kiyokage-Yoshimoto, R., Martin, T.J., Gillespie, M.T., Nagahama, M., Tsuji, A. & Matsuda, Y. Subtilisin-like proprotein convertases, PACE4 and PC8, as well as furin, are endogenous proalbumin convertases in HepG2 cells. Journal of Biochemistry, 125:627-633, 1999.

Nordengrahn, A., Merza, M., Svedlund, G., Roneus, M., Berndtsson, T. L., Lindolm, A., Drummer, H. E., Studdert, M. J., Abusugra, I., Gunnarsson, E. & Klingeborn, B.A. Field study of the application of a type-specific test distinguishing antibodies to equine herpesvirus-4 and –1. Equine Infectious diseases Diseases VIII pp125-128, 1999.

Oakley, A.J., Lo Bello, M., Nuccetelli, M., Mazzetti, A.P. & Parker, M.W. The ligand in (Non-substrate) binding site of human Pi class glutathione transferase is located in the electrophile binding site (H-site). Journal of Molecular Biology, 291:913-926, 1999.

Oldfield, B.J., Allen, A.M., Hards, D.K., McKinley, M.J., Schlawe, I. & Mendelsohm, F.A.O. Distribution of angiotensin II receptor binding in the spinal cord of sheep. Brain Research, 650:40-48, 1999.

Oldfield, B.J., Badoer, E., Hards, D.K., & McKinley, M.J. Fos production in retrogradely-labelled neurons of the lamina terminalis following intravenous infusion of either hypertonic saline or angiotensin II. Neuroscience, 60:255-262, 1999.

Parker, M.W., Oakley, A.J. & Lo Bello, M. (1999) Three-dimensional structures of glutathione transferases and their interactions with drugs. Human Experimental Toxicology, 18:500, 1999.

Plunkett, A., Merlin, K., Gill D., Zuo, Y., Jolley, D. & Marks, R. The frequency of common non-malignant skin conditions in adults in central Victoria, Australia. International Journal of Dermatology, 38:901-908, 1999.

Polekhina, G., Board, P.G., Gali, R.G., Rossjohn, J. & Parker, M.W. Molecular basis of glutathione synthetase deficiency and a rare gene permutation event. EMBO Journal, 18:3204-3213, 1999.

Poumbourios, P., Center, R.J., Wilson, K.A., Kemp, B.E. & Kobe, B. Evolutionary conservation of the membrane fusion machine. Life, 48:151-156, 1999.

Price, J.T. & Thompson, E.W. Models for studying cellular invasion of basement membranes in Integrin protocols: Methods in Molecular Biology, Ed A.R. Howlett, Humana Press, New Jersey, pp 231-249, 1999.

Price, J.T., Tiganis, T., Agarwal, A., Djakiew, D. & Thompson E.W. EGF promotes MDA-MB-231 breast cancer cell migration through a MAP kinase-independent mechanism. Cancer Research, 59:5475-5478, 1999.

Quinn, J.M.W., Morfis, M., Lam, M.H.C., Elliott, J., Kartsogiannis, V., Williams, E.D., Gillespie, M.T., Martin, T.J. and Sexton, P.M. Osteoclast identification by antibodies specific for the rat and mouse calcitonin receptors. Bone, 25:1-8, 1999.

Rosamilia, A., Clements, J.A., Dwyer, P.L., Kende M. & Campbell, D.J. Activation of the kallikrein kinin system in interstitial cystitis. Journal of Urology, 162:129-134, 1999.

Rossjohn, J., Cappai, R., Feil, S.C., Henry, A., McKinstry, W.J., Galatis, D., Hesse, L., Multhaup, G., Beyreuther, K., Masters, C.L. & Parker, M.W. Crystal structure of the N-terminal, growth factor-like domain of Alzheimer amyloid precursor protein. Nature Structural Biology, 6:327-331, 1999.

Rossjohn, J., Tweten, R.K., Rood, J.I. & Parker, M.W. Perfringolysin O. In: "The Comprehensive Sourcebook of Bacterial Protein Toxins", (Alouf, J.E. & Freer, J.H., eds), Academic Press, London, 406-420, 1999.

Sharp, J.A., Sung, V., Slavin, J., Thompson, E.W. & Henderson, M.A. Tumour cells are the source of osteopontin and bone sialoprotein expression in human breast cancer. Laboratory Investigations, 79:869-877, 1999.

Shatursky, O., Heuck, A.P., Shepard, L.A., Rossjohn, J., Parker, M.W., Johnson, A. E. & Tweten. R. K. The mechanism of membrane insertion for a thiol-activated cytolysin: A new paradigm for pore-forming toxins. Cell, 99:293-299, 1999.

Stapleton, D., Balan, I., Pawson, T. & Sicheri, F. The crystal structure of an Eph receptor SAM domain reveals a mechanism for modular dimerization. Nature Structural Biology, 6:44-49, 1999.

Stura, E.A. & Gleichmann, T. Soaking techniques. In "Crystallization of nucleic acids and proteins: A practical approach. Second Edition, Eds, A. Ducruix & R. Geige. Oxford University Press, Oxford, UK, pp 365-390, 1999.

Su, J.B., Barbe, F., Crozatier, B., Campbell, D.J. & Hittinger, L. Increased bradykinin levels accompany the hemodynamic response to acute inhibition of angiotensin converting enzyme in dogs with pacing-induced heart failure. Journal of Cardiovascular Pharmacology, 34:700-710, 1999.

Suda, T., Takahashi, N., Udagawa, N., Jimi, E., Gillespie, M.J. & Martin, T.J. Modulation of osteoclast differentation and function by the new members of the TNF receptor and ligand families. Endocrine Reviews, 20:345-357, 1999.

Teh, T., Tiganis, T., and Kobe, B. Crystallization of importin α the nuclear import receptor. Acta Crystallographica, D55:561-563, 1999.

Thomas, R.J., Guise, T.A., Yin, J.J., Elliott, J., Horwood, N.J., Martin, T.J. & Gillespie, M.T. Breast cancer cells interact with osteoblasts to support osteoclast formation. Endocrinology, 140:4451-4458, 1999.

Thompson, E.W., Sung, V., Lavigne, M., Baumann, K., Aaron, A.D., Azumi, N.,& Clarke, R. LCC15-MB: A human breast cancer cell line from a femoral bone metastasis. Clinical and Experimental Metastasis. 17:193-204, 1999.

Thompson, E.W. & Sledge, G.W., Jnr. Towards the therapeutic targeting of matrix metalloproteinases in breast cancer. In Breast Cancer: Molecular Genetics, Pathogenesis, and Therapeutics. A. M. Bowcock, Ed. Humanna Press, Inc, Totowa, N.J, pp. 437-452, 1999.

Tiganis, T., Kemp, B.E. & Tonks, N.K. The protein tyrosine phosphatase TCPTP regulates epidermal growth factor receptor mediated and phosphatidylinositol 3-kinase dependent signalling. Journal of Biological Chemistry, 274:27768-27775, 1999.

Trivett, M.K., Officer, R.A, Clement, J.G., Walker, T.I., Joss, J.M., Ingleton, P.M., Martin, T.J. & Danks, J.A. Parathyroid hormone-related protein (PTHrP): Localization in cartilaginous fish tissues. Calcium Metabolism: Comparative Endocrinology, eds Danks, J.A., Dacke, C., Flik, G. & Gay, C. Bioscientifica, Bristol, UK, pp 49-58, 1999.

Trivett, M.K., Officer, R.A, Clement, J.G., Walker, T.I., Joss, J.M., Ingleton, P.M., Martin, T.J. & Danks, J.A. Parathyroid hormone-related protein (PTHrP) in cartilaginous and bony fish tissues. Journal of Experimental Zoology, 284:541-548, 1999.

Turnley, A.M., Stapleton, D., Mann, R.J., Witters, L.A., Kemp, B.E. & Bartlett, P.F. Cellular distribution and developmental expression of AMP-activated protein kinase isoforms in mouse central nervous system. Journal of Neurochemistry, 72:1707-1716, 1999.

Udagawa, N., Takahashi, N., Jimi, E., Matsuzaki, K., Tsurukai, T., Itoh, K., Gillespie, M.T., Martin, T.J. & Suda, T. Osteoblasts/stromal cells stimulate osteoclast function through the expression of RANK ligand but not macrophage colony-stimulating factor. Bone 25:517-523, 1999.

Wang, F., Nohara, K., Olivera, A., Thompson, E.W. & Spiegel, S. Sphingosine-1-phosphate-inhibited motility of human breast cancer cells: Involvement of focal adhesion kinase. Experimental Cell Research, 247:17-28, 1999.

VISITING SCIENTISTS

Dr. Helen Blanchard obtained her Ph.D at the University of London, UK in the field of small molecule crystallography. She subsequently moved to protein crystallography, undertaking postdoctoral studies in highly regarded research laboratories in Canada, USA and Switzerland. Helen recently arrived at the Institute to pursue protein structural studies in collaboration with Dr. Bostjan Kobe. Her studies are aimed at characterising molecular recognition processes in proteins that have important physiological roles in signal transduction and apoptotic pathways.

Dr. Marcos Fontes, an Assistant Professor within the Physics Department, Universidade Estadual Paulista (UNESP), Sao Paulo, Brazil, received a Visiting Scientist's Fellowship from the Fundacao de Amparo a Pesquisa do Estado de Sao Paulo, Brazil, to work with Dr. Bostjan Kobe. Whilst at the Institute, Dr. Fontes investigated structural aspects of proteins involved in nuclear transport and cell signalling pathways by X-ray crystallography.

Professor Gary Johnson and his wife Nancy, from the National Jewish Medical Center in Denver, Colorado spent a two month summer sabbatical in our Protein Chemistry laboratory. They came to do protein chemistry studies on the protein kinase MEKK2, important in signal transduction events. Gary is an international expert in hormone regulation and we benefited from his wise council and great contributions to our lab meetings. Whilst at the Institute, Gary and Nancy successfully purified recombinant MEKK2 and identified a number of phosphorylation sites using mass spectrometry.

Dr. Manabu Nishii obtained his Ph.D in comparative endocrinology, studying the evolution of growth factors in fish. He joined us in 1996 and quickly learned the skills of molecular biology. Manabu has worked in collaboration with Dr. Jeffrey Zajac (Department of Medicine, Royal Melbourne Hospital) and Drs Elgar and Clark (UK-HGMP, Hinxton, UK) to isolate and clone the gene for PTHrP in fish. In addition, Manabu has contributed largely towards the cloning of the RANK gene.

Penny Blackwell is a Ph.D. student from the University of Nottingham, UK, supervised by Dr. David Hosking. With their interest in plasma PTHrP levels in pregnant and lactating women, Penny visited on two occasions, working with Pat Ho on the assay for PTHrP.

DIRECTORS' REPORT

TO THE MEMBERS OF THE ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

Your Directors submit the Financial Accounts of the Institute and report as follows on the results of the Institute for the year ended 31 December 1999 and on the state of the Institute's affairs as at that date.

1. BOARD OF MANAGEMENT

The members of the Board of Management in office at the date of this report are: James Donovan Best, Kerrie Lynette Cross, Marcia Griffin, Charles Anthony Griss, John Francis Gurry, Richard Graeme Larkins, Hilton John Nicholas, Paulina Pilkington, Graham Eric Norman Rogers, Graeme Bruce Ryan, Anthony Frederick Sallmann, Brenda Mary Shanahan, Matthew John Walsh. Details of Board Members' experience, qualifications and organisations in which each of the Board Members has declared an interest are provided on pages 3 and 4 of the Annual Report.

2. BOARD MEETINGS

The number of Board Meetings and number of meetings attended by each of the Board Members of the Institute during the year ended 31 December 1999 were:

Board Member	Board Meetings	
	No of Meetings held	No of Meetings attended
JD Best	6	3
KL Cross	6	5
M Griffin	6	4
CA Griss	6	6
JF Gurry	6	5
RG Larkins	6	3
HJ Nicholas	4	4
P Pilkington	6	6
GEN Rogers	6	6
GB Ryan	3	0
AF Sallmann	6	4
BM Shanahan	6	5
MJ Walsh	6	2

3. PRINCIPAL ACTIVITIES

The principal activity of the Institute during the financial year was medical research. No significant change in the nature of this activity occurred during the year.

4. OPERATING RESULTS

The Institute is a non-profit organisation; therefore it does not earn profits nor incur losses in the sense in which a commercial enterprise may do so. However, the operating result for the year for the General Fund was a deficit of $304,858 compared to a surplus of $540,687 for the previous year. No income tax is applicable for the Institute, in accordance with its area of operation.

5. DIVIDENDS

In accordance with the Institute's Memorandum and Articles of Association no funds are distributed either to members of the Board or members of the Institute.

6.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;

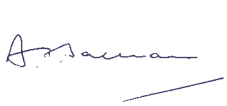
with the exception of the following matters.

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: James Donovan Best, Kerrie Lynette Cross, Marcia Griffin, Charles Anthony Griss, John Francis Gurry, Richard Graeme Larkins, Hilton John Nicholas, Paulina Pilkington, Graham Eric Norman Rogers, Graeme Bruce Ryan, Anthony Frederick Sallmann, Brenda Mary Shanahan and Matthew John Walsh.

7. BENEFITS TO MEMBERS OF THE BOARD OF MANAGEMENT

Since the end of the previous financial year, no member of the Board of the Institute has received or become entitled to receive a benefit (other than a benefit of a kind referred to in Note 19 or a benefit included in the aggregate amount of emoluments shown in the Accounts), by reason of a contract made by the Institute or a Related Corporation with the Board member or with a firm of which he is a member or with a Company in which he has a substantial financial interest.

Signed this 17th day of April 2000 in accordance with a resolution of the Board of Management.



A.F. Sallmann
Member of Board

G.E.N. Rogers
Member of Board

REVENUE & EXPENDITURE STATEMENT

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 1999

1998 $		Note	$	1999 $
	GENERAL FUND			
	Revenue			
	Grants:			
1,333,454	National Health & Medical Research Council	Note 4	1,396,848	
212,643	Therapeutic Goods Administration		154,109	
307,453	Other Commonwealth Government	Note 5	353,420	
568,234	Victorian Government Infrastructure		630,874	
2,372,689	Other	Note 6	1,837,106	4,372,357
132,372	Interest – Debentures & Deposits		116,918	
2,485	Dividends from Investments		2,781	119,699
371,954	Legacies & Bequests			377,595
40,175	Donations			56,907
37,954	Other Income			93,660
5,379,413				5,020,218
	Expenditure			
3,007,095	Salaries & Wages			3,305,762
84,935	Consultants			50,598
57,762	Equipment under $2,000			63,050
705,984	Laboratory Supplies			801,212
124,558	Travelling & Seminar Expenses			154,500
93,872	Maintenance & Repairs			34,847
3,692	Minor works			44,705
29,873	Computing Costs			27,412
14,206	Library Supplies			13,959
15,578	Legal, Patent & License Fees			29,797
10,770	Insurance			10,985
41,766	Public Relations			25,583
16,475	Advertising			2,394
9,416	Conference promotions			1,000
53,627	Printing & Stationery			62,164
38,774	Postage & Freight			40,256
11,481	Telephone & Facsimile			6,548
51,928	Contract Services			46,529
2,524	Cleaning			5,373
15,067	Catering			13,005
4,200	Audit Fees			4,750
99,554	Miscellaneous			66,172
4,493,137				4,810,601
886,276	SURPLUS BEFORE PROVISIONS AND ABNORMAL ITEMS			209,617

The accompanying notes form part of these accounts

REVENUE & EXPENDITURE STATEMENT

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 1999

1998 $		Note	$	1999 $
	Provisions			
477,724	Depreciation Expense			464,427
6,145	Employee Entitlements	Note 1		50,048
402,407	OPERATING SURPLUS/(DEFICIT) BEFORE ABNORMAL AND EXTRAORDINARY ITEMS			(304,858)
	Abnormal items			
	Add			
138,280	Funds provided for NSRL Leave Provisions as at 6 July 1997		–	–
540,687	OPERATING SURPLUS /(DEFICIT) AFTER ABNORMAL AND BEFORE EXTRAORDINARY ITEMS			(304,858)
	Extraordinary items			
	Add			
–	Reallocation of 1998 surplus	Note 2		8,859
540,687	OPERATING SURPLUS /(DEFICIT) AFTER ABNORMAL AND EXTRAORDINARY ITEMS			(295,999)
	Accumulated Funds			
540,687	Operating surplus/(deficit) after abnormal and extraordinary items			(295,999)
1,478,632	Accumulated funds at the beginning of the financial year			2,019,319
2,019,319	Accumulated funds at the end of the financial year			1,723,320
	BUILDING FUND			
	Revenue			
–	Grants			–
–	Interest			–
–	Operating surplus for year			–
	Accumulated Funds			
–	Operating surplus			–
2,778,262	Accumulated funds at the beginning of the financial year			2,778,262
2,778,262	Accumulated funds at the end of the financial year			2,778,262

The accompanying notes form part of these accounts

BALANCE SHEET

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640
FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 1999

1998 $		Note	$	1999 $
	Current Assets			
516,243	Cash at Bank and on hand		678,384	
250,000	Imprest Advance – St. Vincent's Hospital		250,000	
603,627	Receivables	Note 7	528,255	
1,725,392	Investments	Note 8	1,771,689	
3,095,262	**Total Current Assets**			**3,228,328**
	Non-Current Assets			
43,431	Investments	Note 9	46,431	
2,542,226	Property, Plant & Equipment	Note 10	2,292,376	
2,585,657	**Total Non-Current Assets**			**2,338,807**
5,680,919	**Total Assets**			**5,567,135**
	Current Liabilities			
68,588	Accounts Payable		22,202	
138,280	Funds held in Trust for NSRL accrued leave		138,280	
400,111	Provisions – Employee Entitlements	Note 1	415,248	
159,303	Other – Grants in Advance	Note 11	337,857	
766,282	**Total Current Liabilities**			**913,587**
	Non-Current Liabilities			
117,055	Provisions – Employee Entitlements	Note 1	151,966	
117,055	**Total Non-Current Liabilities**			**151,966**
883,337	**Total Liabilities**			**1,065,553**
4,797,582	**NET ASSETS**			**4,501,582**
	Accumulated Funds	Note 12		
2,019,320	General Fund			1,723,320
2,778,262	Building Fund			2,778,262
4,797,582	**TOTAL FUNDS**			**4,501,582**

The accompanying notes form part of these accounts.

STATEMENT OF CASH FLOWS

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640
FINANCIAL STATEMENTS FOR THE YEAR ENDED 31 DECEMBER 1999

	Note	1999 $ Inflows (Outflows)	1998 $ Inflows (Outflows)
CASH FLOWS FROM OPERATING ACTIVITIES			
Grants received		4,626,128	4,432,960
Donations received		56,907	40,175
Interest received		118,373	126,707
Dividends received		2,781	2,485
Other Revenue		469,955	517,188
		5,274,144	5,119,515
Payments to Suppliers and Employees		(4,856,987)	(4,986,923)
Net Cash Generated From Operating Activities	Note 15	**417,157**	**132,592**
CASH FLOWS FROM INVESTING ACTIVITIES			
Payment for purchase of plant and equipment		(214,578)	(483,984)
Payment for investments		(43,223)	(39,152)
Cash reallocation of 1998 surplus		8,859	-
Net Cash Flows Used In Investing Activities		**248,942**	**(523,136)**
Net Increase/(Decrease) In Cash Held		168,215	(390,544)
CASH AT 1 JANUARY 1999		1,734,772	2,125,316
CASH AT 31 DECEMBER 1999	Note 16	1,902,987	1,734,772

The accompanying notes form part of these accounts.

NOTES

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

NOTES TO AND FORMING PART OF THE ACCOUNTS FOR THE YEAR ENDED 31 DECEMBER 1999

NOTE 1: STATEMENT OF ACCOUNTING POLICIES

The financial statements are a general purpose financial report that have been prepared in accordance with applicable Accounting Standards and other mandatory professional reporting requirements (Urgent Issues Group Consensus Views) and the Corporations Law. The financial statements have also been prepared on the basis of historical costs and do 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 accounting policies have been consistently applied, unless otherwise stated.

The following is a summary of the significant accounting policies adopted by the Institute in preparation of the accounts.

Income Tax

The Institute is granted exemption for income tax under section 23(j) (iii) of the Income Tax Assessment Act because of the areas within which it operates.

Fixed Assets

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.

Property, plant and equipment are brought to account at cost or directors' valuation, less, where applicable, any accumulated depreciation. The carrying amount of depreciable assets is reviewed annually to ensure it is not in excess of the recoverable amount from these assets. The recoverable amount may be 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.

Employee Entitlements

Based on pay rates current at balance date. On-costs such as Work Cover, superannuation and annual leave loading are included in the calculation of leave provisions.

Long Service Leave

The provision for long service leave is determined in accordance with Accounting Standard AASB 1028. Generally, the entitlement under the awards becomes payable upon completion of ten years' service. The proportion of long service leave estimated to be payable within the next financial year is a current liability. The balance of the provisions are classified as a non-current liability measured at the present value of the estimated future cash outflow arising from employees' services to date.

The St. Vincent's Institute long service leave liability of $160,301 represents a gross liability of $345,195 offset by net present value contractual obligations of $184,893 from National Health and Medical Research Council (NHMRC). This payment will be receivable upon payment of long service leave by the Institute on behalf of eligible employees. NHMRC reimburse long service leave payments on a pro-rata basis for the period of their grant support.

Annual Leave

Liabilities for annual leave are recognised and are measured as the amount unpaid at the reporting date in respect of employees' services up to that date. The employee entitlements provision of $406,913 includes untaken leave and leave loading.

NOTE 2: EXTRAORDINARY ITEM

The National Serology Reference Laboratory (NSRL) previously formed part of the SVIMR consolidated accounts for 1997 and 1998. A recent review of the operating and organisation structure of the two organisations, particularly the application of Accounting Standard AASB 1024 in terms of the business operations, has resulted in a change to the financial reporting. The NSRL is now excluded from SVIMR's financial reports and this has been backdated to 1998 for prior year comparative purposes. In separating the 1998 accounts, an adjustment of $8,858.54 has been made at the 1 January 1999, representing the misallocation of items between the NSRL and SVIMR in the consolidated accounts system prior to 1st January 1999.

NOTES

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

NOTES TO AND FORMING PART OF THE ACCOUNTS FOR THE YEAR ENDED 31 DECEMBER 1999

	1999 $	1998 $
NOTE 3: OPERATING SURPLUS (DEFICIT)		
Operating surplus/(deficit)	**(304,858)**	**540,687**
Operating deficit for the year has been determined after		
(a) Charging as Expense:		
Depreciation	464,427	477,724
Employee Entitlements	50,048	6,145
Auditors Remuneration		
– Audit	4,750	4,200
The auditors received no other benefits		
(b) Crediting as Income		
Dividends received or receivable from		
– Other corporations	2,781	2,485
Interest received or receivable from		
– Other corporations	116,918	132,372
NOTE 4: GRANTS – NATIONAL HEALTH & MEDICAL RESEARCH COUNCIL		
Project Grants	1,256,316	1,083,581
Scholarships/Fellowships	140,532	249,873
	1,396,848	**1,333,454**
NOTE 5: GRANTS – OTHER COMMONWEALTH GOVERNMENT		
Australian Research Council	353,420	307,453
	353,420	**307,453**
NOTE 6: GRANTS – OTHER		
Agouron Pharmaceuticals Inc	23,078	–
AMRAD	–	27,500
Anti-Cancer Council of Victoria	56,000	61,237
Asahi Chemical Industry Co	–	23,000
Assoc International Cancer Research	40,005	–
Australian Centre for Clinical Neuropharmacology	–	23,910
Australian Kidney Foundation	–	19,500
AZA Research	50,000	106,827
Bayer Inc	–	14,500
Chugai Pharmaceutical Co	227,929	233,519
Eli Lilly Aust	92,196	143,178
Gastroenterological Society of Australia	24,997	12,315
International Bone & Calcium Institute	–	29,261
Kathleen Cunningham Foundation	–	40,000
Merke Sharp & Dohme	–	40,000
National Heart Foundation of Australia	46,800	45,400

	1999 $	1998 $
NOTE 6: GRANTS – OTHER (Continued)		
National Institutes of Health	108,548	183,887
Perpetual Trustees Aust Ltd	15,000	–
Sanofi Winthrop	–	30,114
Servier Laboratories	123,850	165,928
Sisters of Charity Health Service	41,666	–
St. Vincent's Hospital, Melbourne	–	107,369
US Army Medical Research Command	255,503	52,433
Victorian Breast Cancer Research Consortium	529,545	537,261
Wellcome Trust	156,079	437,554
William Buckland Foundation	20,000	25,000
Other (under $10,000)	25,910	12,996
	1,837,106	**2,372,689**
NOTE 7: RECEIVABLES		
ANZ Banking Group Ltd	4,210	5,665
Australian Centre for Clinical Neuropharmacology	–	23,910
AXA Australia	14,250	–
Eli Lilly Australia Pty Ltd	16,318	23,065
Francis Finlay Foundation	23,000	–
K & A Bongiorno Medical Research Endowment Fund	9,300	14,000
M J Polinelli Estate	–	17,000
National Health & Medical Research Council	65,104	53,112
National Mutual Trustees Ltd	–	12,003
National Serology Reference Laboratory	11,624	28,507
Perpetual Trustees Australia	15,000	–
Sisters of Charity Health Service	–	8,334
Skin & Cancer Foundation	56,674	36,206
St. Vincent's Hospital	131,459	171,237
US Army Medical Research Command	52,500	–
University of Melbourne	50,860	135,883
Wellcome Trust	77,956	74,705
	528,255	**603,627**
NOTE 8: INVESTMENTS (CURRENT)		
Debentures – At cost	–	–
ANZ Bank Term Deposit	797,086	756,864
Unsecured Deposits at call		
– National Mutual Trustees	835,476	835,476
– Macquarie Treasury Fund	139,127	133,052
	1,771,689	**1,725,392**

NOTES

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

NOTES TO AND FORMING PART OF THE ACCOUNTS FOR THE YEAR ENDED 31 DECEMBER 1999

	1999 $	1998 $
NOTE 9: INVESTMENTS (NON-CURRENT)		
Shares in listed Corporations – at cost:	46,431	43,431
Market value of listed Corporations	**61,273**	**57,407**
NOTE 10: PROPERTY, PLANT & EQUIPMENT		
At Directors valuation 1/1/90	841,359	841,359
Less accumulated depreciation	616,530	588,031
Written down value	**224,829**	**253,328**
At cost	5,066,959	4,852,381
Less accumulated depreciation	2,999,412	2,563,483
Written down value	**2,067,547**	**2,288,898**
Total written down value	**2,292,376**	**2,542,226**
NOTE 11: GRANTS IN ADVANCE		
Agouron Pharmaceuticals Inc	23,153	–
Australian Research Council	27,319	26,598
Chugai Pharmaceutical Co	150,000	–
AXA Australia	50,000	–
National Health & Medical Research Council	87,385	107,705
Servier Laboratories	–	25,000
	337,857	**159,303**

NOTE 12: CONTINGENT LIABILITIES

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

NOTE 13: MEMBERS' GUARANTEE

The Institute is a company incorporated in Victoria and limited by guarantee. Every member of the Institute undertakes to contribute to the assets of the Institute 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 Institute 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 1999 is 34 (1998; 41).

NOTE 14: FUNDS HELD IN PERPETUITY

The accumulated funds at the end of the financial year for the General Fund of $1,723,320 include funds held in perpetuity of $400,418. The income from these funds is directed to the Institute's medical research program.

	1999 $	1998 $
NOTE 15: RECONCILIATION OF NET CASH USED IN OPERATING ACTIVITIES TO OPERATING RESULT		
Operating Result – General Fund	(304,858)	540,687
Depreciation – Plant and Equipment	464,428	477,724
Profit on Sale of Assets	-	-
(Increase)/Decrease in Debtors & Accrued Revenue – Other Debtors	75,373	(316,367)
Increase/(Decrease) in Creditors	(46,386)	(493,685)
Increase/(Decrease) in Accrued Expenses – Other Accrued Expenses	178,552	(81,912)
Increase in provision for employee entitlements	50,048	6,145
Net Cash From Operating Activities	**417,157**	**132,592**

NOTE 16: RECONCILIATION OF CASH

For the purpose of the statement of cash flows, the Institute considers cash to include cash on hand and in banks and investments in money market investments and short term (up to 30 days) bank bills. Cash at the end of the reporting period as shown in the statement of cash flows is reconciled as follows:

Cash on hand and cash advances	974,603	968,528
Advance amount – St. Vincent's Hospital	250,000	250,000
Unsecured Deposits (at call)	678,384	516,244
	1,902,987	**1,734,772**

NOTE 17: FINANCIAL INSTRUMENTS

(a) Interest Rate Risk

The Institute'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 on classes of financial assets and financial liabilities, is as follows:

	Weighted Average Effective Interest Rate	1999 $
Cash on Hand	0.00	100
Cash at Bank	3.45	678,284
Imprest Advance	0.00	250,000
Receivables	0.00	528,255
Investments	4.20	1,771,689
Total Financial Assets		**3,228,328**
Accounts Payable	0.00	160,482
Income in Advance	0.00	337,857
Total Financial Liabilities		**498,339**

NOTE 17: FINANCIAL INSTRUMENTS (Continued)

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 balance sheet 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 debtors are determined by discounting the cash flows, at the market interest rates of similar securities, to their present values.

The net fair values of other loans and amounts due are determined by discounting the cash flows, at market interest rates of similar borrowings, to their present values. No financial assets are readily traded on organised markets in standardised form. Aggregate net fair values and carrying amounts of financial assets and financial liabilities at balance date:

	Carrying Amount	Net Fair Value
Financial Assets	**$**	**$**
Cash on Hand	100	100
Cash at Bank	678,284	678,284
Imprest Advance	250,000	250,000
Receivables	528,255	528,255
Investments	1,771,689	1,771,689
	3,228,328	**3,228,328**
Financial Liabilities		
Accounts Payable	160,482	160,482
Income in Advance	337,857	337,857
	498,339	**498,339**

NOTE 18: SUPERANNUATION COMMITMENTS

The Institute contributes to three employee superannuation funds managed by external fund managers, of which two are accumulation/defined contribution funds with National Mutual Life Association of Australasia Ltd. and Tertiary Education Superannuation Scheme and the other is a defined benefit fund with Superannuation Scheme for Australian Universities. 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 Institute contributes 14% of employees' gross salaries for the members of National Mutual Life Association of Australasia Ltd. and Superannuation Scheme for Australian Universities Funds.

Contributions to Tertiary Education Superannuation Scheme are to meet the Institute's Superannuation Guarantee and Award obligations to all its employees and currently amount to 7% of employees' gross salaries for employees who are not members of the National Mutual Life Association of Australasia Ltd and Superannuation Scheme for Australian Universities funds and 3% for employees who are members of these funds.

The Institute is under no legal obligation to make up any shortfall in the fund's assets of the Superannuation Scheme for Australian Universities to meet payments due to employees.

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 21 October 1997. The Superannuation Scheme for Australian Universities has been able to provide audited figures for 1999, shown below.

As at 31 December 1999 (being the last reporting date of the fund)

	1999
	$
Fund assets at net market value	1,647,628
Accrued benefits	1,407,041
Excess of fund assets over accrued benefits	**240,587**
Vested benefits	1,407,041

Year ended 31 December 1999	
Employer contributions to the fund by the Institute	195,018.24

The accrued benefits for each member of the Defined Benefit Plan 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 inflation 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 19: RELATED PARTY INFORMATION

Mr. Matthew J. Walsh, a Director of St. Vincent's Institute of Medical Research, is a Director of National Mutual Trustees Limited with which the Institute has funds invested.

STATEMENT BY DIRECTORS

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

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

The directors of the company declare that:

1. The financial statements and notes, as set out on pages 38 to 48:
   (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 1999 and performance for the year ended on that date of the company and economic entity;
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.

Member of Board
A.F. Sallmann

Member of Board
G.E.N. Rogers

Dated this 17th day of April 2000

INDEPENDENT AUDIT REPORT

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

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

Scope

We have audited the financial report of St. Vincent's Institute of Medical Research, comprising the Directors Declaration, Income and Expenditure Statement, Balance Sheet, Statement of Cash Flows and notes to and forming part of the accounts for the year ended 31 December 1999. The company's directors are responsible for the preparation and presentation of 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 as to 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 as to 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 their operations and 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 Law, including:
   (i) giving a true and fair view of the company's financial position as at 31 December 1999, and of their 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

Lindsay K. Holloway –
Partner

Dated 17 April 2000

DONATIONS

DONATIONS

The fields 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.

Enquiries will be welcomed by Professor T.J. Martin, the Director of the Institute on (03) 9288 2480.

Contributions are used directly on 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 ..... bequeath unto St. Vincent's Institute of Medical Research, 9 Princes Street, Fitzroy, 3065 in the State of Victoria for its general purposes (indicate 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."

PLEASE INDICATE YOUR CONTRIBUTION

☐ My **cheque** is enclosed (cheque payable to St. Vincent's Institute of Medical Research)

or

☐ **Please debit my credit card**

☐ American Express ☐ Visa ☐ Mastercard

☐ Bankcard

For the amount of $ _____

Credit Card details

☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Expiry date of card ☐☐/☐☐

Name on card _____

Signature _____

Date _____

Donor's name _____

Address _____

_____

State _____

Postcode _____

Please detach and forward to:
St. Vincent's Institute of Medical Research,
9 Princes Street,
Fitzroy Victoria 3065

DONATION FORM

DONATIONS

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH ACN 004 705 640

We are grateful to the following donors who during the year ended 31 December 1999 made valuable contributions directed to research activities.

Bequests and Donations from Estates and Charitable Trusts	
	$
John Holt Medical Research Endowment Fund	144,600
BHP Community Trust	50,000
Francis Finlay Foundation	46,638
K & A Bongiorno Medical Research Endowment Fund	29,800
MJ Polinelli Estate	28,250
Anonymous	25,000
J & R McGauran Trust	23,000
Bankers Trust Charities Aid Foundation	15,307
Estate of Teressa M. Wardell	14,000
William Angliss (Victoria) Charitable Fund Foundation	1,000
	377,595
Donations - General	
Ms BM Shanahan	15,000
Prof J Best	10,000
Carr Design Group Pty Ltd	7,500
Trust Company of Australia Ltd	7,500
Mr M O'Shannassy	5,000
Mr G Garson	2,500
Mr P Spry-Bailey	2,000
Mayo Consulting Ltd	1,600
Warburg Dillon Read Australia	1,500
Mr JC & Mrs JM Chappell	1,000
Mr S & Mrs R Smith	1,000
Prof TJ Martin	550
Fantech Pty Ltd	350
Mr B & Mrs V Paton	200
AXA Aust staff	170
Mr M Naphtali & family	100
Mr WJ Clancy	100
Ms R Oxer	100
Eaton Pty Ltd	50
Scotch College students	41
Mr HJ Horne	36
	56,297
In Memoriam Donations	
In memory of the late Mr Armando Salvatori	610
Permanent Invested Funds	
The following permanent funds are included in the Institute's pool of invested funds with income being directed to the Institute's Medical Research Program.	
The Mary Porter Research Grant	90,797
Diane B Jones Endowment	970
Lorna M Miller Endowment	208,651
Albert H Maggs Endowment	100,000
	400,418

Graphic Design Celsius Graphic Design **Photography** David Paul

St. Vincent's Institute
of Medical Research
ACN 004 705 640
9 Princes Street
Fitzroy Victoria 3065

Postal Address:
41 Victoria Parade
Fitzroy Victoria 3065

Telephone: 03 9288 2480
Facsimile: 03 9416 2676

SVIMR

ST. VINCENT'S INSTITUTE OF MEDICAL RESEARCH

CARITAS CHRISTI URGET NOS