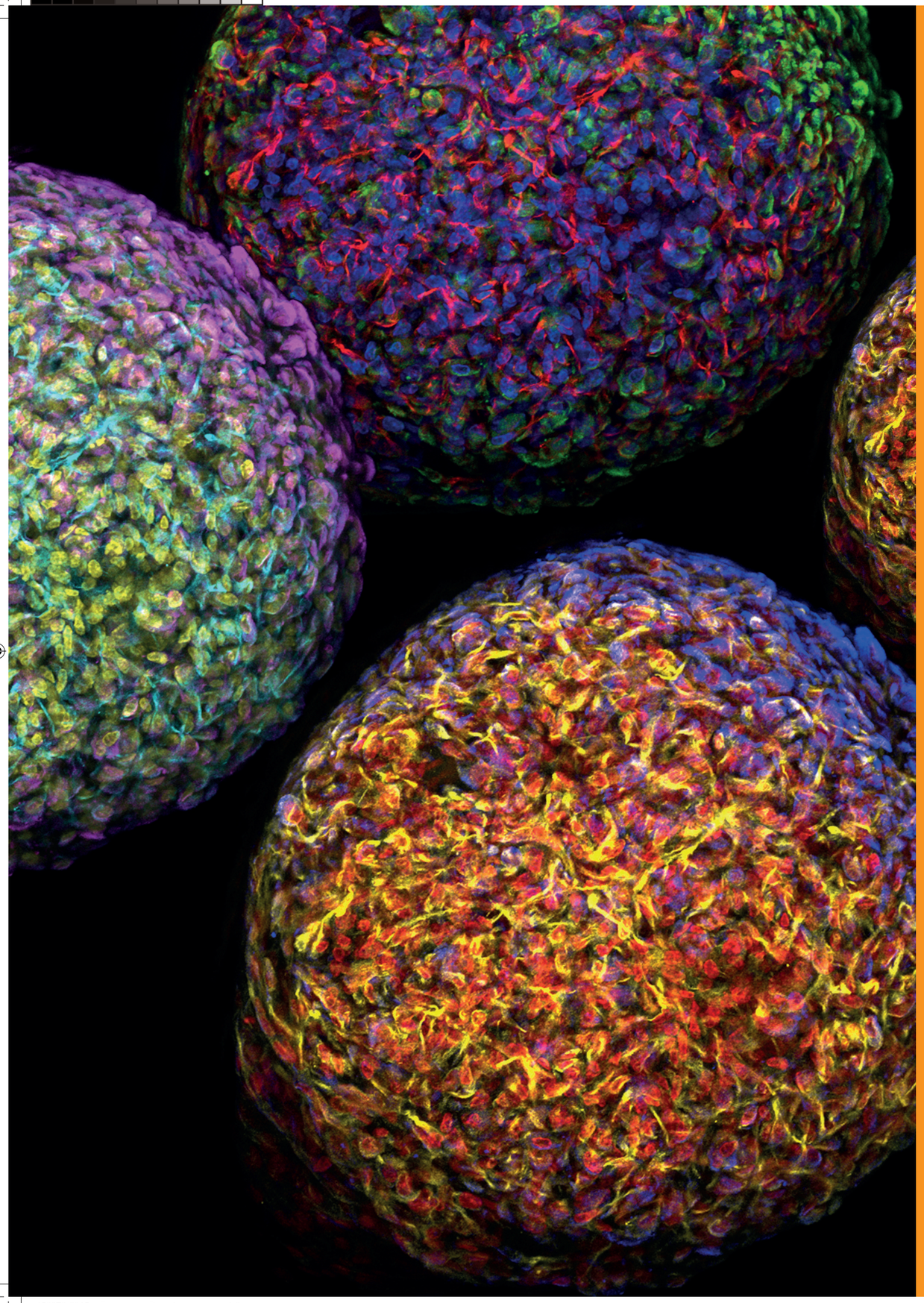


Walter and Eliza Hall Institute of Medical Research

ANNUAL REPORT 2015

100 YEARS 1915-2015

FIAT LUX

Walter+Eliza Hall
Institute of Medical Research

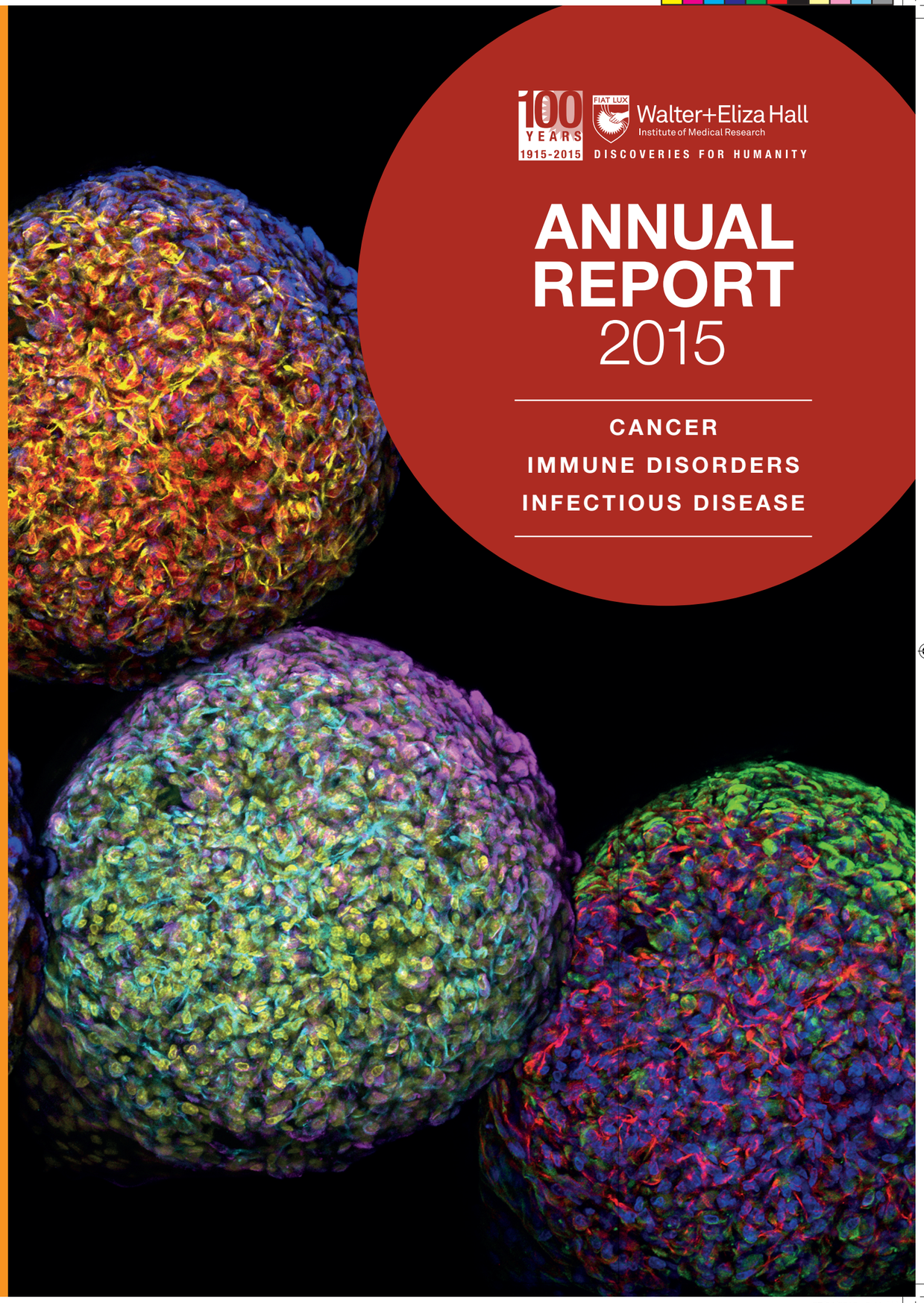
DISCOVERIES FOR HUMANITY

ANNUAL REPORT 2015

CANCER

IMMUNE DISORDERS

INFECTIOUS DISEASE



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We acknowledge the traditional owners and custodians of the land on which our campuses are located, the Wurundjeri people of the Kulin nation, and pay our respects to their elders past and present.

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Produced by the Walter and Eliza Hall Institute's Communications and Marketing department

Cover image
Art of Science Director's Choice Award 2015

Pop Planet
by Ms Clare Weeden, Postgraduate Student
ACRF Stem Cells and Cancer division

In Pop Planet we see a series of fluorescent planets suspended in space. The spheres start out as a single lung stem cell that multiples. By identifying and culturing lung stem cells, we can develop a broader understanding of how the lung functions, to see what goes awry in diseases such as lung cancer.

EXTENDED ANNUAL REPORT

An extended version of the Walter and Eliza Hall Institute 2015 Annual Report is online at www.wehi.edu.au/annualreport-2015 and contains the full annual report as well as the following:

DOING GREAT SCIENCE

Scientific staff list

Attendance at major meetings

Full publications list

EXCEPTIONAL PEOPLE

List of PhD, MRes and Honours projects in progress

List of vacation scholars, UROP students and visiting research trainees

List of presentations that were given as part of our Wednesday Seminar program and Postgraduate Lecture Series

SECURING SUPPORT

WEHI.TV celebrates 150 years of modern genetics

A SUSTAINABLE ORGANISATION

Full financial statements

Membership lists of institute and board committees

Professional services staff list

OUR MISSION

Mastery of disease through discovery

OUR VISION

To be an innovative medical research institute that enriches society through discovery and education and improves health outcomes through translation

OUR VALUES

- **Pursuit of excellence**
- **Integrity and mutual respect**
- **Collaboration and teamwork**
- **Creativity**
- **Accountability**
- **Contribution to society**

INSTITUTE AT A GLANCE

1000
staff and students

40+
diseases impacted by institute research

86
publications with impact factor >10

410
publications

100
national and international trials based on institute discoveries

PRESIDENT'S REPORT

During the past year we have celebrated the centenary of our institute, the oldest in Australia. Many special events took place during the year both at the institute and at other venues. These provided us with the opportunity to thank all those stakeholders who have supported our scientists and have therefore helped them build the institute's outstanding reputation.

A highlight of the year was the ongoing Centenary Campaign, which is achieving its two key objectives of raising greater awareness of our activities and achievements, and developing further funding from philanthropists. Our donors were incredibly generous, contributing substantially more funds than previous years. It is also encouraging that we have already secured 12 centenary pledges underwriting support for emerging scientists, including commitments from board members Mrs Jane Hemstritch, Mr Malcolm Broomhead, The University of Melbourne (Professor James McCluskey) and Ormond College (co-funding the Thwaites Gutch Fellowship) (Associate Professor Rufus Black).

The ongoing support is vital for our researchers because uncertainty continues regarding government funding at both a federal and state level. The passing of legislation for the Medical Research Future Fund was a real positive, but it is not yet clear exactly what its more specific impact will be. In the meantime, NHMRC grants and Victorian Government indirect cost funding amounts are being spread even more thinly.

"FORTUNATELY, AS A RESULT OF A CENTURY OF STRONG PHILANTHROPIC SUPPORT, THE INSTITUTE IS IN A SOUND FINANCIAL POSITION"

Fortunately, as a result of a century of strong philanthropic support, the institute is in a sound financial position and can weather these storms better than most. However, we are increasingly emphasising the need for translational research and drug development. These investments can have a substantial commercial payoff to complement our outstanding record of basic research. We also continue to seek efficiencies in all that we do.

Our centenary year was our first full financial year with a 31 December year end, following the transitional six month financial period in 2014. Whilst this makes comparisons of operating performance over the past two reporting periods a little challenging, the institute's underlying financial performance has been consistent and in line with the board's expectations. The institute's net surplus for 2015 of $1.25 million has been adversely impacted by the recent share market decline. However, the investment portfolio remains sound and provides an essential source of revenue to fund our scientific and support activities.

Finally, I wish to thank all board members for their contributions and support throughout the year. We are fortunate to have such a dedicated and diverse group who, like me, are inspired by our scientists, and the professional services teams, and the work they do. The board was stable over the past year and only one person left, Professor Stephen Smith from The University of Melbourne, who returned to the UK. We thank him for his valuable contribution.

Mr Christopher Thomas
President
Walter and Eliza Hall Institute

DIRECTOR'S REPORT

The past year has been memorable at the institute. Not only did we reflect on the successes of our first 100 years of discoveries for humanity, but we also saw the strength of our community's support for our mission.

Sincere thanks to all our supporters who joined with us in celebrating our centenary. It was wonderful to reconnect with the many people and organisations who support us. In particular, I would like to recognise the generosity and foresight of our founding centenary donors, as well as everyone who contributed to the Metcalf Scholarship Fund. You have ensured that our brightest young researchers have every opportunity to fulfill their potential.

The institute is also a beneficiary of the support of the broader Australian community, through federal government funding. 2015 was a landmark year for the Australian medical research sector, with the establishment of the Medical Research Future Fund.

The year at the institute was also notable for many exciting research discoveries. These ranged from intricate molecular studies and revelations about the complex processes that allow our bodies to function, through to field work, clinical studies and clinical trials that have ensured our research reaches people who are affected by disease.

"IF ONE MESSAGE CAME FROM OUR RESEARCHERS AND OUR SUPPORTERS IN 2015, IT WAS THAT THERE IS GREAT OPTIMISM AND HOPE FOR ALL THAT THE INSTITUTE CAN ACHIEVE IN ITS SECOND CENTURY"

This year has seen advances in our understanding of how malaria persists in populations, the development of potential new treatments for cancers, and new insights into immune disorders, including immunodeficiencies, allergies and coeliac disease.

Our research efforts constantly evolve with global scientific advances, and the institute must also ensure it maintains the personnel, facilities and ethos that facilitate outstanding research. Our *Strategic Plan 2015-2020* focused on these areas, providing a road map towards our best possible research achievements.

Collaboration and teamwork, a long-term strength of the institute, has also been important in 2015. During this year we strengthened our position as the research partner in the Victorian Comprehensive Cancer Centre, a consortium that is improving the lives of people with cancer.

If one message came from our researchers and our supporters in 2015 it was that there is great optimism and hope for all that the institute can achieve in its second century. I look forward to sharing this journey with you.

Professor Douglas Hilton
Director
Walter and Eliza Hall Institute

Board president Mr Christopher Thomas (left) and institute director Professor Douglas Hilton

HEALTH IMPACTS

The institute is committed to making fundamental scientific discoveries that can be translated to better treatments, bringing real benefits to the community on a global scale. Clinical trials based on discoveries made at the institute include trials of vaccines for coeliac disease, diabetes and malaria; and trials of a new class of anti-cancer drugs, called BH3-mimetics, for treating people with leukaemia and other cancers.

- **Cancer**
  - Bowel cancer
  - Brain cancer
  - Breast cancer
  - Leukaemia
  - Lung cancer
  - Lymphoma
  - Melanoma
  - Myeloma
  - Myeloproliferative disease
  - Ovarian cancer
  - Pancreatic cancer
  - Prostate cancer
  - Stomach cancer
- **Immune disorders**
  - Allergy
  - Asthma
  - Coeliac disease
  - Inflammatory bowel disease
  - Lupus
  - Multiple sclerosis
  - Psoriasis
  - Rheumatic fever and rheumatic heart disease
  - Rheumatoid arthritis
  - Sepsis
  - Type 1 and type 2 diabetes
- **Infectious disease**
  - Filariasis
  - Hepatitis B
  - HIV
  - Leishmania
  - Malaria
  - Scabies
  - Toxoplasmosis
  - Tuberculosis

ABOUT THE INSTITUTE

The Walter and Eliza Hall Institute is Australia's oldest medical research institute. It was founded in 1915 with financial support from a trust established by Eliza Hall, following the death of her husband Walter. The vision was for an institute that 'will be the birthplace of discoveries rendering signal service to mankind in the prevention and removal of disease and the mitigation of suffering'.

Throughout the institute's history its researchers have focused on understanding the fundamental principles of medical biology and using this knowledge to mitigate disease.

Our current researchers and students continue to work on solving basic science questions through curiosity-driven research. We are committed to innovative science that expands and improves our understanding of basic human biology and the disruptions to systems that cause disease. Our scientists also undertake blue-sky research that creates and explores new areas of biology.

Three nationally and globally significant areas of health have been long-term, central interests of our research:

- cancer – understanding the basic processes that are disrupted to generate cancer cells and how these can be targeted to treat disease;
- immunology – discovering how the body fights infection, and how errors in the immune system lead to disease; and
- infectious diseases – today with a focus on globally significant pathogens, especially malaria and chronic infections.

We take a multidisciplinary approach to addressing major research questions, integrating expertise in bioinformatics, clinical translation, genomics, medicinal chemistry, personalised medicine, proteomics, structural biology and systems biology.

The institute offers postgraduate training as the Department of Medical Biology of The University of Melbourne, and is affiliated with The University of Melbourne and The Royal Melbourne Hospital.

DOING GREAT SCIENCE

Our success rests on our capacity to advance scientific knowledge and health outcomes through basic research and translation.

Our strategy builds on our existing strengths and emerging opportunities.

CANCER AND HAEMATOLOGY

The Cancer and Haematology division is working to understand the production and function of the billions of blood cells used each day to fight infections and repair tissues, and how they are regulated at the molecular level.

Our aim is to understand how this process is disrupted in disease in order to develop new therapies for immune disorders, inflammatory diseases, blood clotting disorders and cancers.

Understanding blood cell production

All the different blood cell types, including red blood cells, platelets and immune cells are produced by specialised stem cells in the bone marrow.

Dr Stanley Lee and colleagues showed that a protein complex, called PRC2, involved in regulating gene expression is essential for maintaining blood stem cell numbers and is required for the formation of immune cells.

Alterations in PRC2 have been linked to cancer development, and the team's findings may inform new cancer treatment strategies that target PRC2.

Finding the key to Down syndrome

Down syndrome is an intellectual disability caused by having an extra copy of chromosome 21. The syndrome is associated with a predisposition to certain types of leukaemia.

Dr Ashley Ng and colleagues are investigating which genes on chromosome 21 contribute to leukaemia in people with Down syndrome.

They discovered that having an extra copy of the *Erg* gene triggers changes in blood cells that can drive leukaemia development.

Investigating childhood leukaemia

Acute lymphoblastic leukaemia is the most common type of childhood cancer. It is caused by overproduction of immature white blood cells.

Acute lymphoblastic leukaemia (ALL) cells grow uncontrollably because they have gained 'self-renewal' capacity: the ability to propagate themselves indefinitely.

Dr Ben Shields and colleagues discovered that a protein called Hhex is a critical factor that allows T-cell ALL cells to self-renew. The finding will help in developing new treatments for leukaemia.

Health impact

Cancers: leukaemia, lymphoma, myeloma, myeloproliferative diseases

Immune disorders: asthma, Crohn's disease, rheumatoid arthritis

Other areas: blood-clotting diseases, heart disease and stroke, personalised medicine

Division heads

Professor Warren Alexander

Professor Nick Nicola

Laboratory heads

Dr Jeff Babon

Dr Stefan Glaser

Professor David Huang

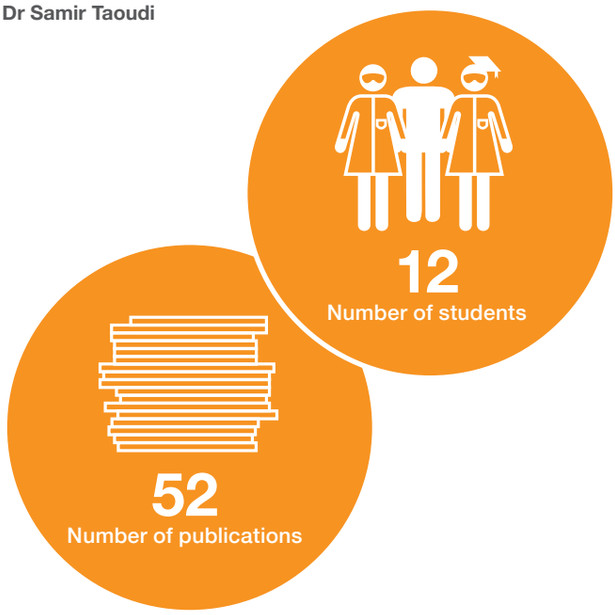
Dr Emma Josefsson

Dr Ian Majewski

Dr Matthew McCormack

Professor Andrew Roberts

Dr Samir Taoudi



Cell death discovery brings hope for new leukaemia treatment

Three decades of research at the institute into the control of cell death have underpinned a potential new anti-cancer treatment that is in clinical trials.

Dr Mary Ann Anderson, a PhD student in the Cancer and Haematology division and a clinical haematologist at The Royal Melbourne Hospital, is part of the team investigating venetoclax, an agent that inhibits the cell survival protein BCL-2.

"THE WALTER AND ELIZA HALL INSTITUTE CAN BE VERY PROUD OF ITS ROLE IN BRINGING VENETOCLAX TO THE CLINIC"

High levels of BCL-2 are found in many cancer cells, and protect the cells from dying in response to conventional anti-cancer treatments. Phase 1 and 2 clinical trials of venetoclax conducted at centres including The Royal Melbourne Hospital and the Peter MacCallum Cancer Centre have shown it to be an effective treatment for many people with advanced forms of chronic lymphocytic leukaemia (CLL) after conventional treatment options have been exhausted.

Venetoclax was discovered by AbbVie scientists as part of a joint research collaboration that involved Walter and Eliza Hall Institute scientists, and was co-developed for clinical use by AbbVie and Genentech.

Dr Anderson's PhD studies have focused on understanding which people with CLL will respond best to venetoclax. "Our goal is to define 'biomarkers', or special pathology tests, that can be used to identify those people with CLL who stand to benefit most from venetoclax," she said.

One focus of Dr Anderson's studies has been on CLL that lacks a protein called p53. "Loss of p53 is associated with more aggressive disease and a poor response to standard therapy," she said. "Promisingly we found that venetoclax is still effective for people with this high-risk form of CLL for whom conventional therapies are often indadequate".

"The Walter and Eliza Hall Institute can be very proud of its role in bringing venetoclax to the clinic," Dr Anderson said.

Collaborating divisions:

Cancer and Haematology, Molecular Genetics of Cancer, ACRF Chemical Biology

Collaborating organisations:

AbbVie, Genentech (a member of the Roche Group), The Royal Melbourne Hospital, Peter MacCallum Cancer Centre, Dana-Farber Cancer Institute (US), Swedish Medical Center, Seattle (US), Washington University, St. Louis (US), University of Arizona (US), Memorial Sloan Kettering Cancer Center (US), Weill Cornell Medical College (US), University of California, San Diego (US), and University of Texas M.D. Anderson Cancer Center (US)

Funding partners:

Australian National Health and Medical Research Council, the Leukemia & Lymphoma Society (US), the Webster Bequest, Cancer Council Victoria, the Australian Cancer Research Foundation, the Victorian Cancer Agency, the Victorian Government Operational Infrastructure Support Program

More information:

Roberts AW *et al*. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *New England Journal of Medicine* 2016 Jan 28;374(4):311-22

PhD student Dr Mary Ann Anderson is a clinician scientist focusing on new treatments for leukaemia and lymphoma.

Her research has investigated potential anti-cancer agents that target the proteins that keep cancer cells alive.

New approach to childhood leukaemia gains momentum

Outcomes for children with leukaemia have improved greatly in the past two decades but some children still have poor outcomes. Dr Ian Majewski and colleagues are searching for novel genetic changes in childhood leukaemia in the hope of improving treatment for these children.

A five-year Centenary Fellowship from The Alfred Felton Bequest proved vital in getting the project up and running in 2015.

> "WE CAN SEE GREAT POTENTIAL FOR IMPROVING THE OUTCOMES FOR CHILDREN WITH LEUKAEMIA"

Dr Majewski is collaborating with Dr Paul Ekert and Dr Alicia Oshlack from the Murdoch Childrens Research Institute to investigate fusion genes – hybrid genes that form after chromosomes break and join together in the wrong way. Fusion genes hijack the systems that control cell growth, and drive leukaemia development.

The researchers are exploiting advances in DNA sequencing technology to look at previously undiscovered fusion genes in samples taken from children with leukaemia.

"We're trying to determine why these children have developed the disease, and how best to guide their treatment," Dr Majewski said.

"It's about building evidence to improve the design of clinical trials and to foster the development of new, more personalised therapies."

Dr Majewski said The Alfred Felton Bequest Centenary Fellowship had been a fantastic show of support and an important foundation for gaining further funding. "It's helped us build a strong team and provide the first proof of principle results," he said.

The team, which includes postdoctoral researcher Dr Christopher Flensburg and Murdoch Childrens Research Institute bioinformatician Dr Nadia Davidson, is excited about the work to date.

"We can see great potential for improving the outcomes for children with leukaemia," Dr Majewski said. "We believe this system will have broad utility, and we'd like to see the work expand to other paediatric cancers and to adult cancers."

The chairman of The Alfred Felton Bequest, Sir Andrew Grimwade, said that, in its philanthropic grants, the bequest was proud of its long tradition of encouraging innovative and cutting-edge projects, especially those benefiting women and children. "The bequest's grant to the Walter and Eliza Hall Institute, and its support for Dr Ian Majewski, continue this tradition through novel genetic medical research to benefit the young," he said.

Acute lymphoblastic leukaemia (ALL) is the most common type of childhood cancer. Dr Ben Shields (left) and Dr Matthew McCormack (right) are investigating how gene changes cause ALL, with a goal of developing new treatments.

ACRF STEM CELLS AND CANCER

The ACRF Stem Cells and Cancer division is focused on breast, ovarian and lung cancers. Our goal is to understand normal organ development and perturbations that give rise to cancer in order to discover new therapies.

Unlocking breast cancer secrets

Researchers discovered the protein MCL-1 is critical for keeping milk-producing cells alive and sustaining milk production in the breast.

Dr Nai Yang Fu, Professor Geoff Lindeman and Professor Jane Visvader found that breast stem cells and luminal progenitor cells both required MCL-1 for their survival. Both cell types have been implicated in some breast cancers, suggesting MCL-1 may be an important target for breast cancer drugs. The research also identified the growth factor EGF was a key inducer of MCL-1 during lactation. Determining whether this mechanism also operates in breast cancer could reveal new ways of targeting the disease.

Gift of hope for rare cancers

People with rare cancers are more likely to die from their disease than people with more common cancers, and rare cancers cause one in three cancer-related deaths in Australia. Cancer researcher and clinician Associate Professor Clare Scott is working with bioinformatics researcher Associate Professor Tony Papenfuss to develop new strategies to select the best treatments for people diagnosed with rare cancers

The institute's rare cancer research effort has been boosted by a $3 million gift from the Stafford Fox Medical Research Foundation, which will fund the Stafford Fox Centenary Fellowship in rare cancer biology and genomics, and the Stafford Fox Centenary Fellow in bioinformatics.

Clifford Prize for cancer research

For almost two decades, Professor Jane Visvader and Professor Geoff Lindeman have investigated how normal breast tissue develops, to help understand how normal processes go awry during breast cancer development. Their team was the first to identify and isolate breast stem cells. Subsequent research implicated these stem cells as the potential cell of origin for breast cancer, and helped explain why female hormones are linked to increased breast cancer risk.

In recognition of these contributions, Professor Visvader was a joint recipient of the Centre for Cancer Biology's 2015 Clifford Prize, with Professor Inder Verma of the Salk Institute (US).

Health impact

Cancers: breast cancer, lung cancer, ovarian cancer

Other areas: chronic lung disease, personalised medicine

Division heads

Professor Geoff Lindeman

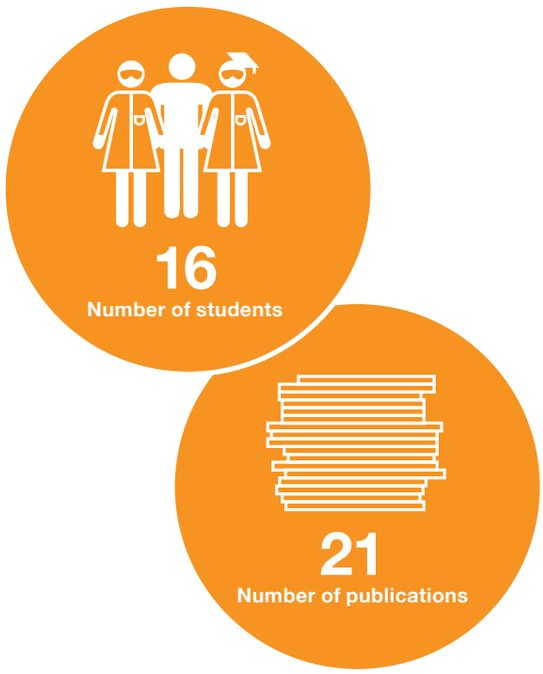
Professor Jane Visvader

Laboratory heads

Dr Marie-Liesse Asselin-Labat

Associate Professor Clare Scott

Dr Kate Sutherland



One in eight Australian women will be diagnosed with breast cancer by the age of 85.

Dr Ewa Michalak was awarded a National Breast Cancer Foundation career development fellowship which is enabling her to progress her research into understanding how normal and cancerous cells develop in the breast.

New insights into lung development and chronic lung diseases

Premature babies often suffer from significant and lifelong respiratory problems due to their underdeveloped lungs at birth.

Treatments based on a better understanding of the way that lungs develop are urgently needed.

Dr Marie-Liesse Asselin-Labat is investigating how lungs develop to better understand chronic lung disease in premature babies – and adults – as well as how lung cancer develops.

"STUDYING HOW EZH2 AND IGF1 CONTROL LUNG DEVELOPMENT WILL HELP US UNDERSTAND WHAT GOES WRONG IN LUNG DISEASE AND ULTIMATELY ENABLE US TO DEVELOP BETTER TREATMENTS"

Lung development is a complex process resulting in the formation of a highly branched network of airways that allow gas exchange. Many different cell types work together to enable normal lung function.

Dr Asselin-Labat and her team are investigating the molecules that control lung development, which could lead to better treatments for respiratory problems.

They found that a protein called EZH2 is essential for healthy lung formation.

"Without EZH2, lungs fail to form their normal branching pattern and display altered development of multiple different cell types, preventing the lungs from functioning," Dr Asselin-Labat said.

EZH2 is an 'epigenetic factor' that plays a role in silencing other genes.

The team showed that EZH2 regulates lung development in part through controlling production of the hormone IGF1 which stimulates growth.

"We discovered that EZH2 acts as a sensor for lung development, detecting when there is too much or too little IGF1 and readjusting the balance to produce a healthy lung," Dr Asselin-Labat said.

Without EZH2, too much IGF1 is produced, disrupting the development of mature lung cells. As a result, the lungs cannot function properly, leading to fatal respiratory disease.

"Studying how EZH2 and IGF1 control lung development will help us understand what goes wrong in lung disease and ultimately enable us to develop better treatments," Dr Asselin-Labat said.

Collaborating divisions:

ACRF Stem Cells and Cancer, Bioinformatics, Molecular Medicine

Collaborating organisations:

Monash University, The University of Melbourne

Funding partners:

Australian Research Council, Australian National Health and Medical Research Council, Strathmore Community College, Victorian Government Operational Infrastructure Support Program

More information:

Galvis LA *et al.* Repression of Igf1 expression by Ezh2 prevents basal cell differentiation in the developing lung. *Development*. 2015 Apr 15; 142(8):1458-69

Going pink for breast cancer research

When three members of the Rotary Club of Point Gellibrand survived breast cancer, the club decided to throw its support behind breast cancer research. The Rotary club's director of fundraising, Mrs Faye Lanyon, wanted to create an annual fundraising event, and so the Pink Breakfast was born.

"WITH SEVERAL MEMBERS WHO HAVE SURVIVED BREAST CANCER, WE HAVE A VERY PERSONAL INTEREST IN HELPING TO FURTHER RESEARCH INTO THIS INSIDIOUS DISEASE"

Since 2011 the Rotary Club of Point Gellibrand has raised more than $35,000 through its Pink Breakfast fundraiser in support of breast cancer research at the Walter and Eliza Hall Institute.

With these funds, the institute's breast cancer team has been able to purchase vital equipment for the laboratory including a microscope camera, a centrifuge and two machines for genetic analyses. This equipment enables our researchers to develop a better understanding of how breast cancer arises.

Rotary Club of Point Gellibrand past president Mr Ron Coleman said the club's members were acutely aware of the impact breast cancer has on the broader community. "With several members who have survived breast cancer, we have a very personal interest in helping to further research into this insidious disease," he said.

Professor Geoff Lindeman, joint head of the institute's breast cancer research program, said the team's relationship with Rotarians was very important.

"Community support from organisations such as the Rotary Club of Point Gellibrand is vital for our research aimed at finding better treatments for breast cancer patients," he said.

Over the past five years, the Rotary Club of Point Gellibrand has raised more than $35,000 through its annual Pink Breakfast fundraiser. This money has enabled the purchase of research equipment used by breast cancer researchers at the institute.
Photo credit: Mr Ross Magor

MOLECULAR GENETICS OF CANCER

The Molecular Genetics of Cancer division is investigating how our cells normally die and how defects in this process cause disease, particularly cancer. Better understanding of the processes of cell death will help us to develop improved treatments for both cancers and immune disorders.

Visionary cancer research funded

Professor Andreas Strasser and Dr Marco Herold, with Professor Jane Visvader and Professor Geoff Lindeman from the ACRF Stem Cells and Cancer division, received a $1 million Cancer Council Victoria Metcalf Venture Grant to discover the processes that drive tumour development to help identify potential new anti-cancer targets.

The grant will enable the researchers to use CRISPR/Cas9 gene modification technology to search for novel tumour suppressor genes and pathways that are critical for cancer development in blood and breast cancers. As well as revealing new molecular targets for treating cancer, this information will have potential future applications for matching patients with the best treatment for their particular cancer type.

Novel cancer drug target

Targeting a cell 'survival' protein could help treat some lymphomas, including those cancers with genetic defects that make them resistant to many existing therapies.

Dr Stephanie Grabow, Dr Alex Delbridge, Dr Liz Valente, Professor Andreas Strasser and colleagues found that removing the pro-survival protein MCL-1 killed lymphoma-initiating cells and thereby prevented the development of this type of blood cell cancer.

This discovery, and the previous finding by Dr Gemma Kelly, other members of the Strasser laboratory and Dr Stefan Glaser that MCL-1 is essential for the sustained expansion of several other types of lymphoma and leukaemia, has led to a fruitful collaboration with the French pharmaceutical company Servier. The collaboration is investigating how well a MCL-1-specific inhibitor kills various types of cancer cells. A major goal is to identify which cancers would be the best candidates for treatment in potential clinical trials of the inhibitor.

Inflammatory link discovered

Dr Philippe Bouillet, Dr Derek Lacey and colleagues discovered a potential link between excess production of inflammatory proteins that cause rheumatoid arthritis and the development of heart valve disease.

People with rheumatoid arthritis have too much of the protein TNF in their joints and in their blood. The team identified a previously unknown way that the body destabilises molecules during the process of TNF production to stop too much of the protein being made. The research could lead to improved treatments for rheumatoid arthritis and heart valve disease by developing agents that stop TNF production.

Health impact

Cancers: gastric cancers, leukaemia, lymphoma, myeloma, myeloproliferative disorders, stomach cancer

Immune disorders: lupus, rheumatoid arthritis, type 1 diabetes

Other areas: personalised medicine

Division heads

Professor Jerry Adams

Professor Andreas Strasser

Laboratory heads

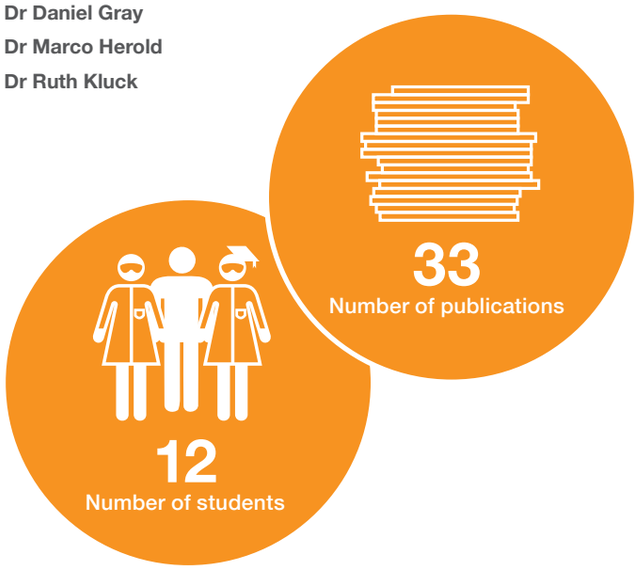
Dr Philippe Bouillet

Professor Suzanne Cory
(honorary distinguished research fellow)

Dr Daniel Gray

Dr Marco Herold

Dr Ruth Kluck



New gene technology boosts cancer fight

CRISPR/Cas9 is an exciting new gene editing technology being adapted to accelerate institute discoveries that could be translated to better diagnostics and treatments.

Walter and Eliza Hall Institute researchers showed for the first time that CRISPR could be used in cancer therapy. The institute has one of the most advanced CRISPR laboratories in Australia.

Dr Brandon Aubrey, Dr Gemma Kelly and Dr Marco Herold from the Molecular Genetics of Cancer division have adapted CRISPR to target and kill human lymphoma cells with incredible accuracy.

"WORLDWIDE, THERE IS INCREASING EXCITEMENT ABOUT - AND INVESTMENT IN - USING CRISPR TECHNOLOGY FOR TREATING PATIENTS"

PhD student Dr Aubrey, who is also a clinical haematologist at The Royal Melbourne Hospital, said the team used CRISPR to delete the *MCL-1* gene, which is essential for the survival and growth of blood cancer cells. "Using preclinical models, we were able to kill human Burkitt lymphoma cells by deleting the gene *MCL-1*.

"The CRISPR system is a powerful tool as it can either target a gene to introduce mutations that make it non-functional, or introduce changes that make mutated genes function normally again," Dr Aubrey said.

Dr Herold said CRISPR offered many advantages over existing gene editing tools. "CRISPR is fast, easy and efficient, delivering the best results for genome editing," he said. "In addition to its potential for disease treatment, we are using CRISPR to identify novel cancer-causing mutations, which will help us to identify how cancer development is initiated or accelerated.

"Worldwide, there is increasing excitement about - and investment in - using CRISPR technology for treating patients," Dr Herold said.

Collaborating divisions:

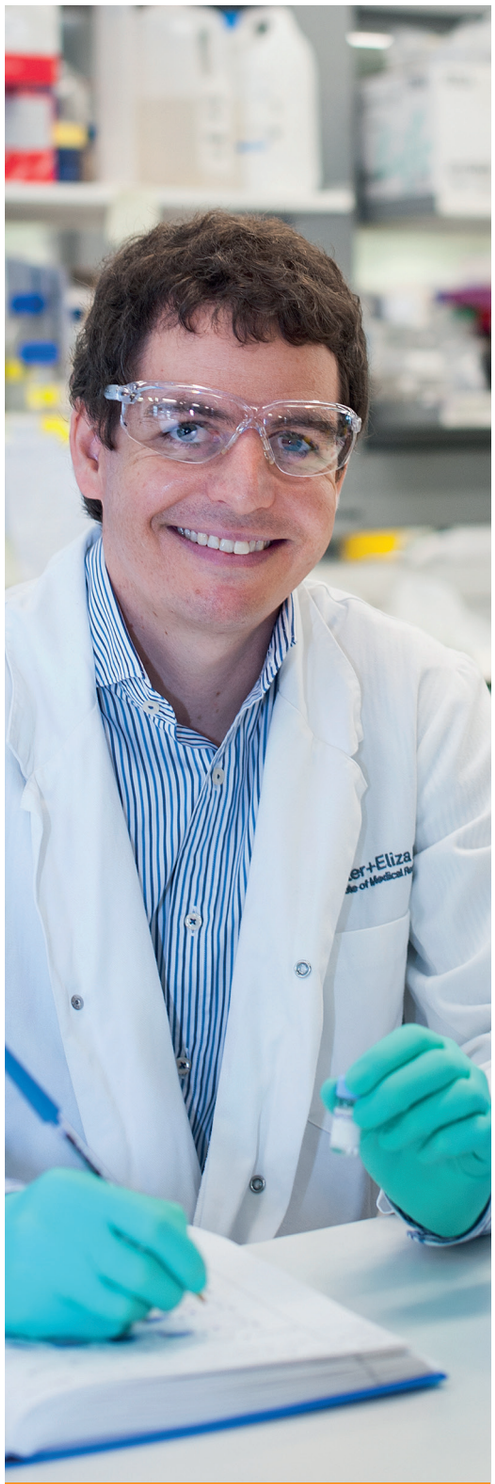
Molecular Genetics of Cancer, Systems Biology and Personalised Medicine

Funding partners:

Cancer Council Victoria, Australian National Health and Medical Research Council, Leukaemia Foundation of Australia, Kay Kendall Leukemia Fund, the Victorian Government Operational Infrastructure Support Program

More information:

Aubrey BJ *et al.* An inducible lentiviral guide RNA platform enables the identification of tumoressential genes and tumor-promoting mutations *in vivo*. *Cell Reports*. 2015 Mar 3;10(8):1422-32



CRISPR is a powerful new technology being used at the institute to specifically modify genes within living cells.

PhD student Dr Brandon Aubrey, who is also a clinical haematologist at The Royal Melbourne Hospital, has used CRISPR technology to show human lymphoma cells can be killed by deleting the gene *MCL-1*.

Supporting innovative cancer research

As a senior business leader with extensive experience in industrial and mining companies, Mr Malcolm Broomhead appreciates the importance of applying innovative technologies to advance knowledge.

He was therefore excited when he heard of Dr Marco Herold's research using Australian-first genome-engineering technology to investigate cancer. Mr Broomhead decided to support Dr Herold with a five-year Centenary Fellowship, enabling him to investigate new treatments of lymphoma and leukaemia.

"CRISPR/CAS9 HAS REVOLUTIONISED HOW WE GENERATE LABORATORY MODELS OF DISEASES FOR RESEARCH"

The technology, called CRISPR/Cas9 genome editing, makes it possible to modify or delete specific genes of mammalian cells in a fraction of the time previously required.

Dr Herold, who heads the Melbourne Advanced Genome Editing Centre (MAGEC) at the institute, is an Australian leader in the use of CRISPR/Cas9 technology and is using it to find better ways of treating lymphoma and leukaemia.

Leukaemia and lymphoma are aggressive diseases that can develop quickly and often have a poor prognosis. Existing treatments have serious side effects and often fail to control the disease. New treatments are urgently required.

"CRISPR/Cas9 has revolutionised how we generate laboratory models of diseases for research," Dr Herold said. "We can now generate highly sophisticated laboratory models of lymphoma and leukaemia that are allowing us to precisely pinpoint why lymphoma and leukaemia frequently relapse, and identify new drugs to treat people with established lymphoma and leukaemia."

Mr Broomhead said he was proud to support such innovative research. "Dr Herold is an Australian leader in gene editing and is tackling an important problem for people with cancer. I am pleased to be able to commit to long-term support for this outstanding research."

Dr Marco Herold (left), pictured with masters student Mr Bruce Yang (right), has received a five-year Centenary Fellowship that is supporting his investigations of new treatments for lymphoma and leukaemia.

ACRF CHEMICAL BIOLOGY

The ACRF Chemical Biology division investigates key biological processes and pathways critical in disease development to discover potential drug targets important for human disease. Our researchers use chemical, biochemical, structural and biological approaches to establish how dysregulation of critical cell signalling pathways contributes to disease, and apply this to guide novel therapeutic development.

Targeting inflammatory disease

Dr Isabelle Lucet and Associate Professor Guillaume Lessene are leading a collaboration with institute colleagues to discover small molecules that could block necroptosis, an inflammatory cell death pathway. Necroptosis has been linked with inflammatory diseases such as rheumatoid arthritis, Crohn's disease and psoriasis.

The team tested a range of small molecules and identified one that inhibited the protein MLKL by 'jamming the switch' that makes it active. The team has embarked on a collaborative project with the biotech company Catalyst Therapeutics to develop a potent new drug based on the small molecule identified in the study.

Award for blood researcher

Professor Benjamin Kile was awarded the 2015 Merck Millipore Research Medal by the Australian Society for Biochemistry and Molecular Biology for his discoveries shedding new light on blood cell formation and function.

Professor Kile's discoveries include pinpointing the mechanism responsible for the survival of blood platelets, a finding that informed the development of a new class of cancer drugs called the BH3 mimetics. He also found that a gene linked to cancer was critical for blood stem cell function, and identified how dying cells are silenced by the body to avoid unnecessary immune responses.

Developing a cure for HIV

In recent times, treatments have been developed that can allow people with HIV to live longer, healthier lives. However, the ability to continue treating people with HIV for their lifetime has a high economic cost, even in well-resourced countries. There remains the need for a curative treatment for HIV.

An NHMRC Development Grant is enabling a collaboration between Dr Brad Sleebs and researchers at the Doherty Institute and The University of Melbourne. The multidisciplinary team is working to identify new compounds that have the potential to be developed as drugs that may cure HIV.

Health impact

Cancers: blood cancer, breast cancer, myeloproliferative disease, stomach cancer

Immune disorders: Crohn's disease, inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatic fever and heart disease

Infectious disease: HIV, malaria, toxoplasmosis, vaccines

Other areas: heart disease and stroke, neurodegenerative disease, personalised medicine, thalassemia

Division heads

Professor Benjamin Kile

Associate Professor Guillaume Lessene

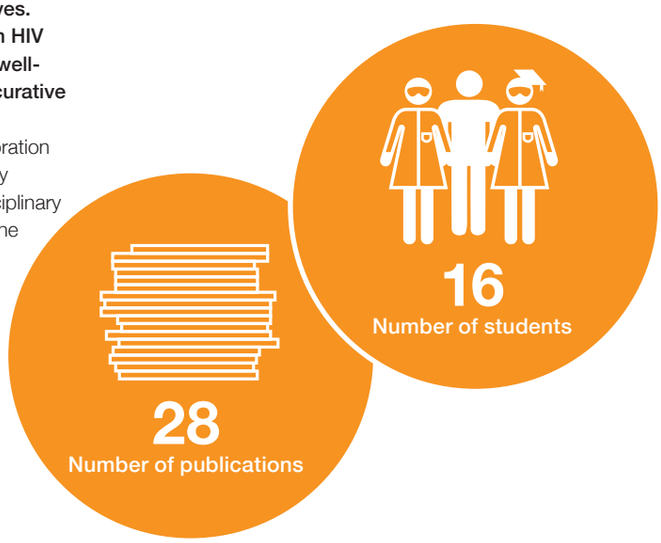
Laboratory heads

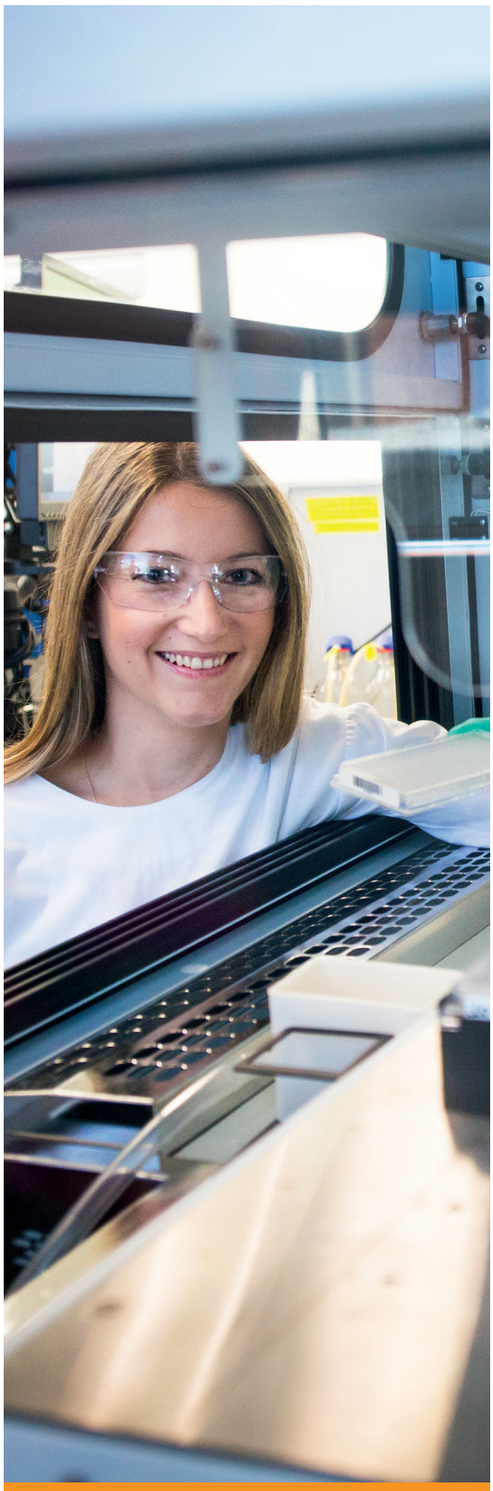
Dr Chris Burns

Dr Ethan Goddard-Borger

Dr Isabelle Lucet

Professor Keith Watson (honorary)





The intricate interactions between proteins are key to almost every event in biology, and are targeted by many medications.

Dr Marija Dramicanin is studying the complexes formed between proteins, and developing better ways to detect changes in these complexes that are brought about by drug-like compounds.

New molecule could halt MS progression

Multiple sclerosis (MS) is an inflammatory disease that damages the central nervous system including the brain, spinal cord and optic nerves. There is no cure and there is a desperate need for new and better treatments.

Institute scientists working to understand the signals that trigger inflammation have discovered how to control the body's over-active immune response to disease and halt inflammation. This finding has shown promise in preventing the progression of MS.

"THESE RESULTS ARE EXTREMELY IMPORTANT, AS THERE ARE CURRENTLY NO GOOD PREVENTIVE TREATMENTS FOR MS"

Dr Ueli Nachbur, Associate Professor Guillaume Lessene, Professor John Silke, Professor Andrew Lew and colleagues developed a small drug-like molecule called WEHI-345 that binds to and inhibits a key immune signalling protein called RIPK2 – preventing the release of inflammatory signalling molecules called cytokines.

Professor Lew said the team examined WEHI-345's potential in experimental models of MS. "We treated preclinical models with WEHI-345 after symptoms of MS first appeared, and found it could prevent further progression of the disease in 50 per cent of cases," he said. "These results are extremely important, as there are currently no good preventive treatments for MS."

Associate Professor Lessene, who developed the molecule with colleagues in the institute's ACRF Chemical Biology division, said WEHI-345 had great potential as an anti-inflammatory agent. "This molecule will be a great starting point for a drug-discovery program that may one day lead to new treatments for MS," Associate Professor Lessene said.

With the help of WEHI-345, scientists have a tool to investigate the signalling pathway that produces inflammatory cytokines in order to develop a better, stronger inhibitor of RIPK2 for treating inflammatory disease.

Collaborating divisions:

ACRF Chemical Biology, Cancer and Haematology, Cell Signalling and Cell Death, Immunology, Inflammation, Systems Biology and Personalised Medicine

Collaborating organisations:

The University of Melbourne, University of Copenhagen, Ludwig Cancer Research, University of Oxford, Cancer Therapeutics CRC, St Vincent's Institute of Medical Research, The Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, Bio21 Molecular Science and Biotechnology Institute

Funding partners:

Australian National Health and Medical Research Council, Swiss National Science Foundation, Australian Research Council, the Victorian Government Operational Infrastructure Support Program

More information:

Nachbur U *et al*. RIPK2 inhibitor delays NOD signalling events yet prevents inflammatory cytokine production *Nature Communications*. 2015 6:6442

Potential new approaches to therapy for motor neurone disease

Motor neurone disease (MND) is an incurable disease that causes progressive disability due to nerve degeneration and muscle weakness. People with MND lose the use of their limbs and ability to speak, swallow and breathe. The average life expectancy for people diagnosed with MND is two-and-a-half years.

A research grant from the Motor Neurone Research Institute of Australia (MNDRIA) is enabling Associate Professor Guillaume Lessene, Professor Benjamin Kile and Professor David Huang to investigate new ways to halt the progression of MND.

Associate Professor Lessene said MND was associated with apoptosis, a specialised form of cell death leading to the death of nerve cells. "This contributes to the progressive disability seen in MND," he said

The team is using its expertise in targeting the apoptosis machinery to develop new treatments that have the potential to prevent neuronal apoptosis in MND.

Professor Kile said the institute's researchers had made great advances in understanding how apoptosis worked. "This has allowed us to develop the first pharmacological inhibitors that block apoptosis," he said. "We now hope to develop these inhibitors into new drugs that might slow or even stop the progression of MND."

Ms Janet Nash, Executive Director of Research at MNDRIA, welcomed Associate Professor Lessene and colleagues as new recipients of MNDRIA funding in 2016.

> "WE NOW HOPE TO DEVELOP THESE INHIBITORS INTO NEW DRUGS THAT MIGHT SLOW OR EVEN STOP THE PROGRESSION OF MOTOR NEURONE DISEASE"

"The MNDRIA Research Committee awards grants only to the best research that has the greatest chance of realising the vision of a world without MND," she said. "Associate Professor Lessene and the team join the race to find a way to stop this disease which kills two people in Australia each day."

Every cell in our body is covered with complex sugar molecules called glycans. Dr Ethan Goddard-Borger is investigating the role of glycans in diseases as diverse as malaria, fungal infections, cancer and arthritis.

MOLECULAR MEDICINE

Researchers in the Molecular Medicine division are investigating how biological systems function and are controlled in normal and disease states. With programs focused on blood cell production and function, epigenetics and cancer, our goal is to pinpoint molecular targets for disease diagnosis and treatment.

New therapies for muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is a progressive wasting disease that affects the face, arms and shoulders. No treatments are currently available.

Dr Marnie Blewitt and colleagues are investigating the gene *Smchd1*, which plays a role in switching other genes off. In FSHD, genetic changes in *SMCHD1* prevent it from working properly, contributing to disease.

By understanding the function of *Smchd1*, the team hopes in the long-term to develop drugs that help people with FSHD.

Understanding platelet production

Platelets are tiny blood cells essential for clotting. Learning how platelets are produced is key to understanding diseases where too many or too few platelets are made.

Dr Samir Taoudi and colleagues are comparing the genes that control platelet development before birth versus in the adult.

The team discovered prenatal platelet-forming cells do not require the *Mpl* gene, which is an essential regulator of platelet development in the adult. This indicates there are different processes contributing to prenatal and adult platelet development.

A fine-grained look at biology

Cell populations, tissues and organisms have traditionally been studied in bulk, masking processes that occur in individual cells.

Research in the Molecular Medicine division has used recent technological developments that are spearheading an appreciation of biology at the single cell level. Single cell RNA sequencing provides insight into which genes are switched on within an individual cell. A genetic technique called 'cellular barcoding' traces behaviour of single cells within a population.

These techniques, along with novel computational tools, are unmasking cell types that are hidden in conventional analyses of cells at the population level.

Health impact

Cancers: blood cancer, leukaemia

Immune disorders: allergy, asthma, multiple sclerosis, rheumatoid arthritis

Other areas: developmental biology, epigenetics, muscular dystrophy, personalised medicine, regenerative medicine

Division head

Professor Doug Hilton

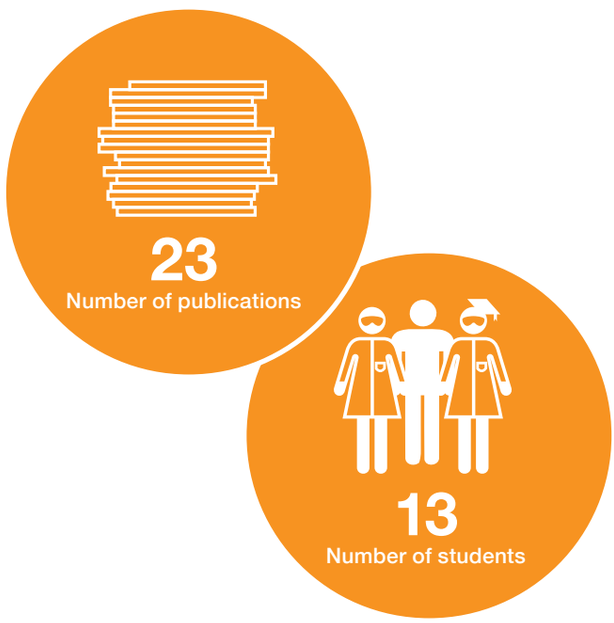
Laboratory heads

Dr Marnie Blewitt

Dr Shalin Naik

Dr Matthew Ritchie

Dr Samir Taoudi



Boosting stem cells could help treat blood disorders

Blood stem cells are responsible for the production of all types of blood cells in the human body, developing into either white blood cells, which are essential for immunity, red blood cells that transport oxygen or platelets for clotting.

Walter and Eliza Hall Institute scientists have discovered a way of improving the function of these vital cells, with possibilities for new therapeutic treatments that could help people with blood diseases and patients undergoing bone marrow transplantation or chemotherapy.

Dr Marnie Blewitt, Dr Sarah Kinkel and colleagues found that depleting a protein called Jarid2, using a technique called short hairpin technology, boosted the repopulation of blood stem cells.

"THIS COULD BE PROGRESSED TO ENHANCE STEM CELL FUNCTION IN A MULTITUDE OF DIFFERENT MEDICAL ARENAS"

The *Jarid2* gene encodes the genetic instructions for a protein that is an accessory to a complex of proteins called PRC2, which are important to every cell. Targeting the whole protein complex therapeutically would be damaging, but manipulating Jarid2 has a more muted, specific effect, Dr Blewitt said.

"Based on the human studies in this research, we hope this could be progressed to find molecules that target JARID2, which could enhance stem cell function in a multitude of different medical arenas," Dr Blewitt said.

The findings may lead to treatments for people whose stem cell function is affected by blood diseases, such as aplastic anaemia, and could make chemotherapy more tolerable, she said.

"Often chemotherapeutic drugs hit these stem cells so that's why you tend to get a severely depleted blood cell count, which often means you can't have the appropriate dose of chemotherapy you need," Dr Blewitt said.

The scientists hope the study will lead to a way of growing large vats of blood stem cells, which are rare. "The blood stem cell field is still in its infancy in being able to grow these cells well," she said.

Collaborating divisions:

Molecular Medicine, Cancer and Haematology

Collaborating organisations:

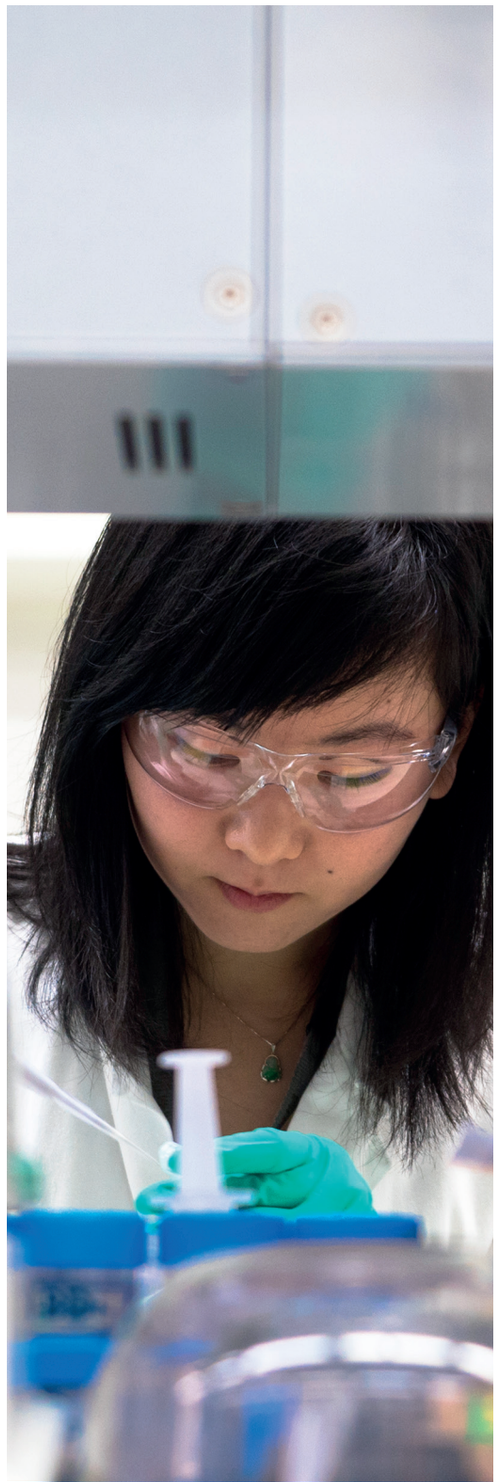
Murdoch Childrens Research Institute, Lund University (Sweden), Peter MacCallum Cancer Centre

Funding partners:

Australian National Health and Medical Research Council, the Dyson Bequest, the DHB Foundation, the Victorian Government Operational Infrastructure Support Program

More information:

Kinkel SA *et al.* Jarid2 regulates hematopoietic stem cell function by acting with polycomb repressive complex 2. *Blood*. 2015 Mar 19; 125(12): 1890–1900



PhD student Dr Kelan Chen, working with Dr James Murphy and Dr Marnie Blewitt, has made a critical discovery about a gene involved in muscular dystrophy. It is hoped this could lead to future therapies for this currently untreatable disease.

Equipment grant transforms our view of biology

Revolutionary technology will enable institute scientists to dissect the differences between individual cells in a tissue or tumour.

The research will underpin the development of new treatments for cancer, immune disorders and infectious disease.

The Harold and Cora Brennen Benevolent Trust, as managed by Equity Trustees, has provided funding for a machine that can affordably measure patterns of gene expression in thousands of cells per day.

The machine, called a 'DROP-Seq', will be located in the Molecular Medicine division and made available to support research across the institute.

Dr Shalin Naik, one of the researchers benefiting from the equipment funding, said it would transform how scientists look at biology.

"Traditionally, researchers have been restricted to studying biological systems by looking at aggregated samples of cells," he said.

"This approach tells us nothing about variability between individual cells – just as you might fail to distinguish the features of any individual person when looking at a photo of a large crowd."

Dr Naik said the DROP-Seq would provide insight into how variation between cells influences their behaviour, both during normal development and in the context of disease.

"IMPLEMENTATION OF THIS TECHNOLOGY WILL BE A MAJOR BOOST TO SINGLE CELL GENOMICS RESEARCH IN AUSTRALIA"

"For example, investigating variation within the immune system could help us understand why some people respond better to immunotherapy."

The technology will be adopted by at least 20 research groups at the institute, as well as by collaborators across the country.

Division head and institute director Professor Doug Hilton said he was delighted the Harold and Cora Brennen Benevolent Trust had supported the purchase of the DROP-Seq.

"Implementation of this technology will be a major boost to single cell genomics research in Australia," he said.

Dr Shalin Naik's research focuses on how immune cells are formed from blood stem cells. New technologies are enabling Dr Naik to look beyond populations of cells to single cells, revealing previously unrecognised diversity.

STRUCTURAL BIOLOGY

The Structural Biology division is interested in discovering new medicines through studies of the three-dimensional structure of large biological molecules that are either targets for drugs or potential therapeutic agents in their own right.

Cell death trigger pinpointed

Institute researchers are closing in on the molecular detail of how the cell death machinery is switched on. Structural biology research has provided new views of how the protein Bax interacts with so-called 'BH3-only proteins', the critical event that triggers apoptotic cell death.

BH3-only proteins bind to Bax, triggering cell death, in cells that have been exposed to stresses such as DNA damage or exposure to chemotherapeutic drugs. An understanding of the atomic detail of this process could lead to new classes of drugs that either prevent unwanted cell death – with potential applications in conditions such as neurodegeneration – or promote cell death in cancer cells.

Grant delivers new equipment

Measuring how tightly two molecules interact – such as a drug binding to its target protein – is a key step in the design cycle of prospective drugs and can be key to producing a medication that will have minimal side effects.

A grant from the Harry Secomb Foundation has allowed the institute to purchase a Microscale Thermophoresis instrument, which measures the strength of such molecular interactions. This instrument is a valuable new resource for 15 research teams investigating cancer.

Top academy medal

Dr Peter Czabotar was awarded the Australian Academy of Science's 2015 Gottschalk Medal for his research to understand the proteins involved in cell life and death. The medal recognises outstanding research in the medical sciences by young and mid-career scientists.

Dr Czabotar's research focuses on elucidating the three-dimensional shapes and structures of key cell death proteins. This research is helping to improve knowledge of the key structural and molecular changes that control cell death, and is guiding the development of new drugs that can prevent or promote cell death, with applications for many different conditions including cancer and neurodegeneration.

Health impact

Cancers: bowel cancer, brain cancer, leukaemia, lymphoma, myeloma, myeloproliferative disorders

Immune disorders: type 1 diabetes, type 2 diabetes

Infectious disease: malaria

Other areas: heart disease and stroke, neurodegenerative disease

Division head

Professor Peter Colman

Laboratory heads

Dr Jeff Babon
Professor Tony Burgess
Dr Matthew Call
Dr Melissa Call
Dr Peter Czabotar
Dr Jacqui Gulbis
Associate Professor Mike Lawrence
Dr Colin Ward (associate research fellow)

Cells are surrounded by a membrane that restricts the movement of many molecules into or out of the cell.

Dr Jacqui Gulbis studies the three-dimensional structure of proteins that span this membrane, transporting molecules that are important for cellular functions.

Shining a light on the 'black box' of cell receptors

Receptors are proteins found on cell surfaces or membranes that receive chemical signals from outside and transmit them into the cell, which then responds to the information. But a key part of this important process – how information is physically passed across the barrier of the cell membrane – has been a mystery.

Institute researchers, led by Dr Melissa Call and Dr Matthew Call, have been investigating the parts of receptors that span that barrier for clues to how they work. They liken this area to being the 'gearbox' of receptor machinery.

"There's this black box that we think is one of the most important parts of how receptors work but it is incredibly difficult to look at," Dr Matthew Call said.

"THIS WILL HELP US SOLVE SOME REALLY IMPORTANT PROBLEMS IN RECEPTOR BIOLOGY."

The scientists had two problems to overcome. The membrane is very oily so they had to develop methods to isolate the areas of the receptor in question and keep them in a stable environment while they studied the function of these areas.

"The other problem was that the receptor pieces are embedded in a two-dimensional environment on the cell surface. Most of our techniques rely on high-quality three-dimensional protein crystals to be formed," Dr Melissa Call said.

To negotiate this challenge, the researchers made use of a technique that 'stacked' two-dimensional protein-containing membranes into three-dimensional structures to allow them to be crystallised and then, using the Australian Synchrotron, shot the crystals with X-rays, creating 3-D images. Determining the shapes of molecules allows researchers to see how they interact with other molecules – like parts of a machine. The institute scientists published two papers last year showing for the first time that the technique, called lipidic cubic phase technology, could be used to study certain classes of receptors.

"Five years ago we would have believed this wasn't possible – like everyone else," Dr Matthew Call said.

The researchers are looking forward to the insights the technique will yield.

"By zooming in on these images and looking at how the parts of the machine interact we can understand how mutations in these regions might be associated with diseases and look at strategies to alter them using drugs," Dr Matthew Call said.

"Treatments could regulate such functions as insulin production, blood cell development and immune activation," he said.

"This will help us solve some really important problems in receptor biology."

Collaborating organisations:

University of Kansas (US), CSIRO, RMIT University

Funding partners:

Australian National Health and Medical Research Council, Australian Research Council, veski, Human Frontier Science Program (US), the Victorian Government Operational Infrastructure Support Program

More information:

Trenker R *et al.* Crystal Structure of the Glycophorin A Transmembrane Dimer in Lipidic Cubic Phase. *Journal of the American Chemical Society*. 2015 Dec 23; 137 (50): 15676-9

Knoblich K *et al.* Transmembrane Complexes of DAP12 Crystallized in Lipid Membranes Provide Insights into Control of Oligomerization in Immunoreceptor Assembly. *Cell Reports*. 2015 May 26;11(8):1184-92

Research takes a fresh look at bowel cancer

Bowel cancer is the second most common cancer in Australia. More than 80 per cent of cases of bowel cancer are associated with a mutation in a gene called *APC*.

Precancerous cells carrying this mutation can persist as polyps in the bowel, sometimes for years until other cancerous mutations occur and an invasive tumour develops. Building on previous findings in his laboratory, Professor Tony Burgess is leading research designed to kill these precancerous cells in the bowel.

> "WE COULDN'T MOVE THIS PROJECT FORWARD WITHOUT THIS EQUIPMENT"

The laboratory research, carried out with Associate Professor Gregor Brown from The Alfred and Epworth Hospitals, is studying the effects of a two-drug combination on bowel polyps and adenoma (benign tumour). Not all people with these polyps and adenoma respond to the same drugs so the team is testing several drug combinations to determine the most appropriate form of treatment. If effective this new approach could significantly reduce the incidence of bowel cancer arising from precancerous polyps.

The lab's work received a huge boost last year with the introduction of imaging equipment funded by The Angior Family Foundation. The equipment – a specialised camera and lenses – is attached to a microscope to capture the effects of the anti-cancer drugs on both precancerous and cancerous bowel cells growing in the laboratory.

"The Angior Foundation's generosity enabled us to purchase the equipment at the appropriate time for our project," Professor Burgess said. "It is allowing us to measure the effects of more drug combinations on many more cancer samples," he said.

Post-doctoral biomedical engineer and cancer researcher Dr Chin Wee Tan said scanning the three-dimensional images of the cells once took more than an hour but could now be done in five minutes, with more informative measurements, better image quality and resolution. "We couldn't move this project forward without this equipment," Dr Tan said.

Scans using the equipment are now run daily, greatly accelerating the research program.

The equipment has proved so successful in measuring bowel cancer cells that the team will use the same approach on other tumours such as pancreatic cancer.

The Burgess lab is already sharing the equipment, and the new techniques developed with it, with colleagues at other institutions in Melbourne and Adelaide.

Bowel cancers are often preceded by precancerous polyps that can persist for years in the bowel. New imaging equipment is accelerating the research by Professor Tony Burgess (left) and Dr Chin Wee Tan (right) into how precancerous cells in polyps could be killed to prevent bowel cancer.

BIOINFORMATICS

The Bioinformatics division collaborates with institute and external researchers in designing, conducting and analysing genomic and molecular sequence studies to understand biology and disease. The division also conducts research to improve existing methods and develop novel methods for analysing data.

Removing unwanted variation

Technologies that reveal the secrets of DNA and the genome are vital for medical research, however much of the data from these technologies – including microarray, mass spectrometry or DNA sequencing – contains variations that occur due to time, space, equipment, operators, reagents, sample source and quality and environmental conditions.

Professor Terry Speed and colleagues have developed an approach to removing unwanted variation in such data that will greatly streamline the information gained from these studies.

Archaeology of immunity

MHC class I genes contribute to the development of long-lasting immunity. These genes have evolved over time in all species of jawed vertebrates, which include humans, chickens and fish.

Associate Professor Tony Papenfuss and colleagues developed a new strategy to study the evolution of MHC class I genes in selected species of jawed vertebrates. Remarkably, they found dozens of previously undiscovered genes in several species. Most notable was a new family of MHC class I genes found in marsupials and monotremes, but missing from other mammals including humans. The role of these genes is now being investigated.

Revealing gene regulation

Chip-seq is a powerful sequencing technology that can identify sites across a whole genome used by different molecules, and in different ways, to switch genes on or off. It can be used to explore transcription factors, epigenetic factors and other regulatory elements that modulate gene expression.

Professor Gordon Smyth and PhD student Mr Aaron Lun developed algorithms and software for exploring how these regulatory elements change during normal development, and in diseased cells. These tools are critical for our research teams to discover potential new targets for treating cancers, immune disorders and infectious diseases.

Health impact

Cancers: bowel cancer, breast cancer, leukaemia, lymphoma, lung cancer, myeloma, ovarian cancer, rare cancers, stomach cancer

Immune disorders: acute rheumatic fever, lupus, multiple sclerosis, rheumatoid arthritis, thyroid orbitopathy, transplantation, type 1 diabetes

Infectious disease: malaria, scabies, tuberculosis, toxoplasmosis

Other areas: congenital disease, Down syndrome, heart disease and stroke, neurodegenerative disease, personalised medicine

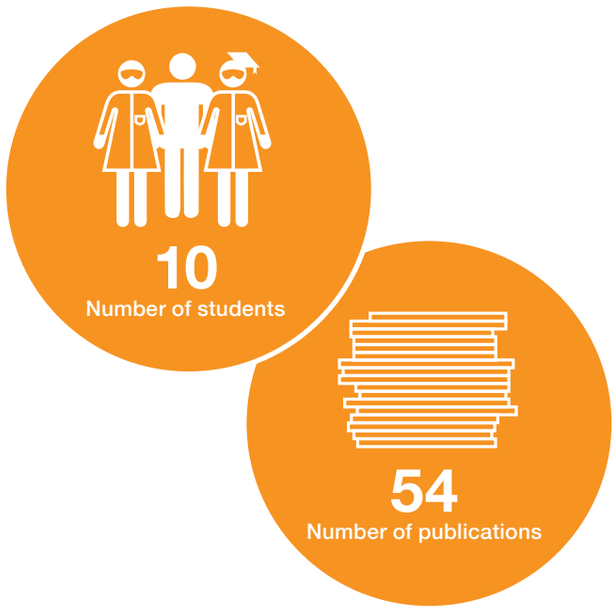
Division head

Professor Gordon Smyth

Laboratory heads

Associate Professor Tony Papenfuss

Professor Terry Speed



Antibody-forming immune cells come in a variety of 'flavours'

Plasma cells are specialised immune cells that produce large amounts of antibody, which is vital for lifelong immunity to infection.

By using bioinformatics techniques to tackle an immunology research question, our researchers have gained new insights into how plasma cells are formed, and revealed a previously unrecognised diversity in these antibody-forming cells.

Dr Wei Shi, Professor Lynn Corcoran, Professor Stephen Nutt and colleagues used complex biological and computational techniques to map the 'transcriptome' of plasma cells, indicating which genes were switched on and functioning in the cells.

"THIS GIVES US A HOST OF NEW GENES TO LOOK AT IN SEARCH OF POTENTIAL THERAPEUTIC TARGETS FOR IMMUNE DISORDERS AND MYELOMA"

The gene signature revealed that there was a stark transcriptional divide between plasma cells and B cells, Dr Shi said. "We used the bioinformatics pipeline we developed to identify 301 signature genes that define antibody-secreting cells. We also discovered that, despite this common gene signature, different plasma cells also have unique patterns mapped in their transcriptome," he said. "These help tell the story of how each plasma cell was activated, where it lives in the body and potentially what infection it fights."

Professor Corcoran said the research had provided new clues to how defective plasma cells could cause disease.

"We were surprised to find a number of genes were active that hadn't previously been identified as important in immune cells," she said. "This gives us a host of new genes to look at in search of potential therapeutic targets for diseases driven by defective plasma cells, including immune disorders such as lupus, and myeloma, a cancer of plasma cells."

Dr Shi said the investigations were the most comprehensive analysis to date of how plasma cells form. "It's a great example of how new insights into biological processes can come from collaborations between 'dry lab' scientists – computational biologists – and the more traditional 'wet lab' scientists – in this case, immunologists."

Collaborating divisions:

Bioinformatics, Molecular Immunology, Immunology

Collaborating organisations:

The University of Melbourne

Funding partners:

Multiple Myeloma Research Foundation, the Australian Research Council, the Australian National Health and Medical Research Council, the Victorian Government Operational Infrastructure Support Scheme

More information:

Shi W *et al*. Transcriptional profiling of mouse B cell terminal differentiation defines a signature for antibody-secreting plasma cells. *Nature Immunology*. 2015 Jun;16(6):663-73

Bioinformatics approaches to analysing biological data are providing previously unachievable insights into important research questions.

A research fellowship from CSL Ltd is supporting Dr Wei Shi's development of advanced computational tools that are enabling the analysis of complex biological data. Based in the Bioinformatics division, Dr Shi's research focuses on immunology and cancer.

Medical research fellowships commemorate a 100-year partnership

For the past 100 years, the institute has enjoyed a successful partnership with the Australian biotechnology company CSL Limited.

Collaborations between CSL and the institute have underpinned many healthcare advances, including Australia's first commercially available snakebite anti-venom (in 1930) and anti-inflammatory agents now in clinical trials.

In recognition of this longstanding relationship, and to commemorate the centenaries of both CSL and the institute, CSL is supporting two research fellowships at the institute. One fellowship is in the area of bioinformatics and one is in the field of immunology.

"ANALYSIS ENABLED BY BIOINFORMATICS HAS LED TO ADVANCES IN GENETICS, DRUG DISCOVERY AND OTHER AREAS OF MEDICAL RESEARCH"

The recipient of the bioinformatics fellowship is Dr Wei Shi, who develops advanced computational tools for biological investigations.

Dr Shi has devised analysis methods for data obtained by a genomic technology called next generation sequencing (NGS).

"NGS technology has transformed medical research, however it is a huge challenge to process the massive volumes of data it generates," he said.

"My team has developed highly efficient and accurate algorithms to deal with this data. Our methods are now being used by researchers worldwide."

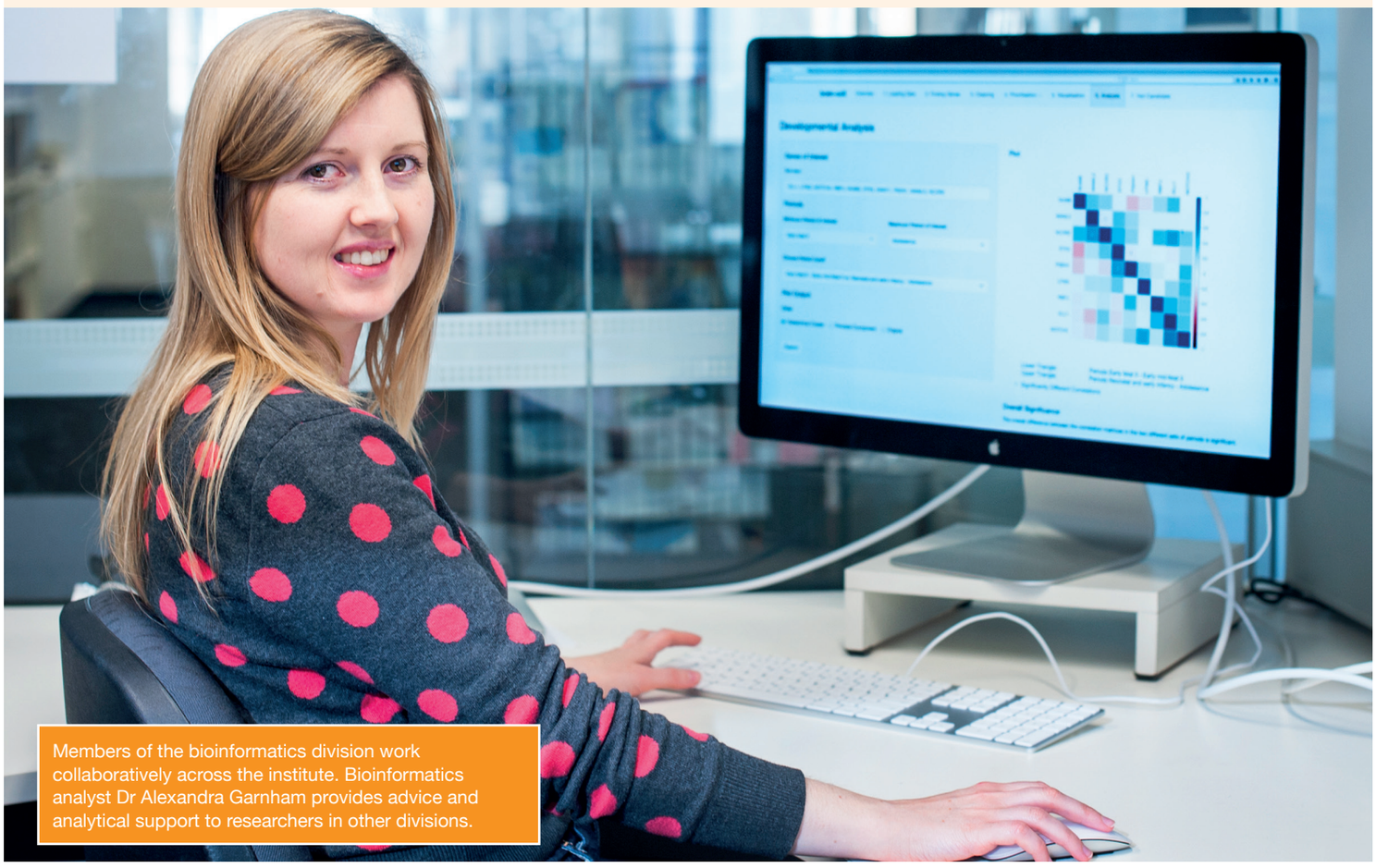
Division head Professor Gordon Smyth said the fellowship would strengthen and expand the institute's bioinformatics capability, which is essential for doing cutting-edge science.

"Analysis enabled by bioinformatics has led to advances in genetics, drug discovery and other areas of medical research," he said.

"It is vital that we continue investing in bioinformatics to keep up with growing demand from scientists in many fields."

Dr Andrew Nash, CSL Senior Vice President of Research, said the fellowship would consolidate the existing bioinformatics collaboration.

"CSL is pleased to formally acknowledge the centenary celebrations of two great organisations. For CSL, research and development is our past and our future. We are committed to fostering research excellence in Australia and supporting our best and brightest minds. We value our long-standing partnership with the institute and look forward to continuing to help address the world's unmet medical needs together".



Members of the bioinformatics division work collaboratively across the institute. Bioinformatics analyst Dr Alexandra Garnham provides advice and analytical support to researchers in other divisions.

INFECTION AND IMMUNITY

Malaria, tuberculosis and HIV are three of the major global infectious diseases causing significant death and disease, particularly in resource-poor countries. The Infection and Immunity division aims to understand how infectious agents cause human disease and use this knowledge to develop new treatments.

'Hijacking' parasite

Dr Chris Tonkin, Dr Justin Boddey and colleagues discovered how a common parasite called *Toxoplasma* hijacks host cells to enable its own growth and survival, hibernating for decades by creating its own food reserve.

Some of these proteins may even change the host's behaviour or personality, potentially explaining a fascinating association between *Toxoplasma* infection and psychiatric diseases including schizophrenia and bipolar disorder.

The findings could lead to a vaccine to protect pregnant women from *Toxoplasma* infection, which carries a serious risk of miscarriage or birth defects, as well as drugs to clear chronic infections in people with compromised immune systems, such as cancer patients.

New map of key malaria protein

The *Plasmodium vivax* parasite is the predominant cause of malaria in countries outside Africa, and is the biggest cause of relapsing malaria infections that complicate malaria elimination efforts.

Dr Wai-Hong Tham, Dr Jakub Gruszczyk and colleagues have created the first atomic-resolution structure of the protein PvRBP that is used by *P. vivax* parasites to infect human red blood cells. The research could allow scientists to generate new tools that block *P. vivax* infection, and could potentially lead to a vaccine preventing this form of malaria.

Awards for hepatitis B research

Professor Marc Pellegrini, Dr Greg Ebert and colleagues identified a potential cure for hepatitis B virus (HBV), with a promising new drug, birinapant, proving 100 per cent successful in eliminating HBV in preclinical models. US biotech company TetraLogic Pharmaceuticals hopes to begin clinical trials of birinapant for treating hepatitis B in Asia in 2016.

The team received the 2015 Australian Museum Eureka Prize in Infectious Disease for the research, and Dr Ebert was awarded the Centenary Institute's Lawrence Creative Prize 2015. The team is now looking at whether birinapant could be used to treat other chronic infections.

Health impact

Immune disorders: sepsis

Infectious disease: chronic infections, hepatitis B, HIV, malaria, toxoplasmosis, tuberculosis, vaccines

Division heads

Professor Alan Cowman

Professor Marc Pellegrini

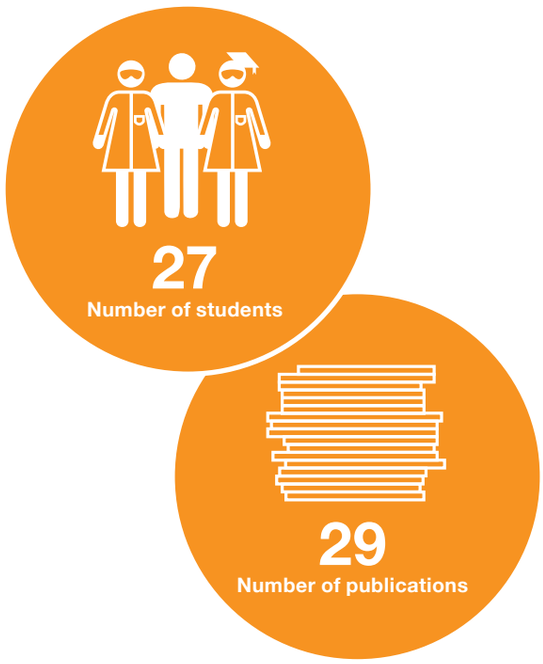
Laboratory heads

Dr Justin Boddey

Dr Diana Hansen

Dr Chris Tonkin

Dr Wai-Hong Tham



Our immune system protects us against infections, usually providing immunity that prevents repeated infections with the same microbe.

Dr Diana Hansen's research has revealed that inflammation caused by malaria dampens the immune system's ability to develop protective immunity to this parasitic disease.

'Self-sabotage' prevents immune protection against malaria

For many infections, lifelong immunity can be developed after a single exposure. This is not the case for malaria: people may require up to 20 years to build up protective immunity to the causative *Plasmodium* parasite. During this time, people exposed to malaria are susceptible to repeated infections, becoming sick many times as well as spreading the disease.

A research team led by Dr Diana Hansen, Dr Axel Kallies and Dr Victoria Ryg-Cornejo has answered the longstanding question of why the immune system fails to develop immunity during malaria infection.

The researchers discovered that the same inflammatory molecules that drive the immune response in clinical and severe malaria also prevent the body from developing protective antibodies against the parasite.

"THIS RESEARCH OPENS THE DOOR TO NEW THERAPEUTIC APPROACHES TO ACCELERATE DEVELOPMENT OF PROTECTIVE IMMUNITY TO MALARIA AND IMPROVE EFFICACY OF MALARIA VACCINES"

Dr Hansen said inflammation was a double-edged sword in malaria. "The strong inflammatory reaction that accompanies and in fact drives severe clinical malaria is also responsible for silencing the key immune cells needed for long-term protection against the parasite," she said.

The discovery opens up the possibility of improving new or existing malaria vaccines by boosting key immune cells needed for long-lasting immunity. This could even include vaccines that have previously been ineffective in clinical trials.

"This research opens the door to new therapeutic approaches to accelerate development of protective immunity to malaria and improve efficacy of malaria vaccines," Dr Hansen said.

"Until now, malaria vaccines have had disappointing results. We can now see a way of improving these responses, by tailoring or augmenting the vaccine to boost development of helper T cells that will enable the body to make protective antibodies that target the malaria parasites."

Collaborating divisions:

Infection and Immunity, Molecular Immunology

Collaborating organisations:

Monash University

Funding partners:

National Health and Medical Research Council, the Australian Research Council, the Sylvia and Charles Viertel Charitable Foundation, the Victorian Government Operational Infrastructure Support Program

More information:

Ryg-Cornejo V *et al*. Severe Malaria Infections Impair Germinal Center Responses by Inhibiting T Follicular Helper Cell Differentiation. *Cell Reports*. 2016 Jan 5;14(1):68-81

Grant aids development of new antimalarial drugs

Walter and Eliza Hall scientists are working to improve treatments for malaria, a disease that kills more than 400,000 people each year, predominantly children under the age of five.

Current antimalarial drugs are becoming less effective as the parasite develops resistance to the drugs, making the search for new drug targets critical.

> "TARGETING PLASMEPSIN V WOULD EFFECTIVELY KILL THE TWO SPECIES OF MALARIA THAT CAUSE SIGNIFICANT DEATH AND DISEASE"

A team led by Dr Justin Boddey, Dr Brad Sleebs and Professor Alan Cowman recently made a breakthrough in the search for new antimalarials, developing a compound that kills the malaria parasite.

This compound targets a critical malaria protein called plasmepsin V, which controls the export of proteins from the malaria parasite into infected red blood cells.

Plasmepsin V is an attractive drug target for malaria treatment as it is expressed at all stages of the malaria lifecycle and is essential for parasite survival.

"Targeting plasmepsin V would effectively kill the two species of malaria that cause significant death and disease," Professor Cowman said.

The biggest challenge is developing a drug that can cross the barriers that protect the malaria parasite inside its host cell.

The team is now collaborating with the pharmaceutical company Merck & Co., Inc., Kenilworth, New Jersey, US, to identify drugs that can penetrate these barriers and act in the same way to treat people with malaria.

The Wellcome Trust has granted this team a Pathfinder Award to develop a new therapeutic for treating malaria.

"The Pathfinder Award enables us to work together with Merck to identify drugs that can access the parasite hidden deep inside the red blood cell," Professor Cowman said. "This collaboration could lead to an entirely new class of drugs to treat malaria."

The rapid spread of drug resistance presents a challenge for global malaria control and elimination efforts. Dr Justin Boddey (left), Dr Brad Sleebs (right) and Professor Alan Cowman have developed a new drug-like compound that inhibits plasmepsin V, a protein that is essential for the survival of the malaria parasite. A Wellcome Trust Pathfinder Award is now enabling the team to translate this research into potential new antimalarial drugs.

IMMUNOLOGY

The Immunology division asks how the many different types of immune response are regulated. Our aim is to improve vaccine performance and treatment of autoimmune and immunodeficient conditions, including type 1 diabetes and coeliac disease.

New genetic culprit in immunodeficiency

Common variable immune deficiency (CVID) is one of the most common forms of primary (inherited) immunodeficiency. People with CVID usually require life-long therapy to supplement their immune system.

Dr Vanessa Bryant and Dr Charlotte Slade, with Professor Jo Douglass, head of immunology and allergy at The Royal Melbourne Hospital, have contributed to an international collaboration investigating the genetic causes of CVID. The team has identified that some people with CVID carry genetic defects that alter the NF-kappaB signalling pathway in cells. It is hoped that identifying disease-causing genetic changes in CVID will lead to more rapid and accurate diagnosis of this condition, as well as guiding personalised therapies in the future.

Catching diabetes-causing cells

A $60,000 Diabetes Australia Research Program grant will support Dr Charis Teh to determine whether rogue immune cells that attack the pancreas, causing type 1 diabetes, can be foiled.

Dr Teh hopes to pinpoint which genes control the immune attack by using CRISPR/Cas9 technology to put individual 'suspect' genes out of action. This will reveal which genes can speed up or slow down the process of diabetes formation. In the long term, it is hoped this research will give clues to new treatment strategies that could prevent the immune attack that is at the root of diabetes.

Switch for long-term immunity

Antibody-producing plasma cells are produced when our immune system is exposed to pathogens such as viruses or bacteria. The antibodies they secrete are crucial for long-term immunity.

Dr Kim Good-Jacobson, Professor David Tarlinton and colleagues discovered that a protein called Myb was essential for antibody-producing plasma cells to migrate into bone marrow, preserving them for many years or even decades. Without Myb, plasma cells remained in the blood stream and perished after a few days.

The research offers hope that understanding how to activate Myb production in plasma cells may be the key to encouraging the immune system to develop long-term immunity for infections such as malaria.

Health impact

Cancers: leukaemia, lymphoma, myeloma

Immune disorders: allergy, coeliac disease, lupus, primary immune deficiencies, type 1 diabetes

Infectious disease: influenza, vaccines

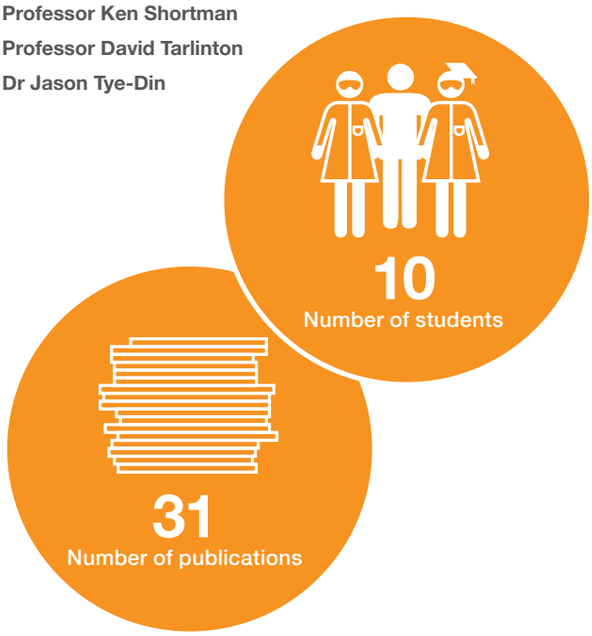
Other areas: personalised medicine, transplantation

Division head

Professor Phil Hodgkin

Laboratory heads

Dr Bob Anderson (honorary)
Dr Daniel Gray
Dr Joanna Groom
Dr Edwin Hawkins
Professor Andrew Lew
Emeritus Professor Jacques Miller
Dr Shalin Naik
Professor Ken Shortman
Professor David Tarlinton
Dr Jason Tye-Din



Multi-talented molecule controls blood production

A typical adult makes billions of white blood cells each day, which are essential for our immune response to infection and cancer, blood clotting and other important functions.

Researchers from the Immunology division have discovered the essential role of a well-known enzyme in white blood cell production. The multi-talented molecule uses a previously unknown mechanism to ensure the daily mass production of white blood cells.

"NO MATTER HOW URGENT OR CRITICAL THE NEED FOR BLOOD CELL PRODUCTION, EVEN AFTER SUBSTANTIAL BLOOD LOSS OR INFECTION, WITHOUT DROSHA NEW WHITE BLOOD CELLS WILL NOT BE MADE"

Dr Tim Johanson, Professor Andrew Lew and colleagues discovered the enzyme – Drosha – blocks signals that normally inhibit stem cells from making new blood cells, effectively restarting the blood cell 'assembly line'.

Drosha bypasses the signals that halt the stem cell 'factory' from manufacturing new blood cells, Professor Lew said. "This is the first time we have seen the enzyme play this type of role in the cell; as a master controller of blood cell production," he said.

Dr Johanson said the surprising discovery was that – without Drosha – no amount of coercion could convince the body to make more blood cells.

"No matter how urgent or critical the need for blood cell production, even after substantial blood loss or infection, without Drosha new white blood cells will not be made," Dr Johanson said.

The team made the discovery while studying dendritic cells – the immune 'sentinel' cells in the body. However the effects of losing Drosha were clear many generations back, in the grandparents and great-grandparents of dendritic cells.

"The findings may even help explain how blood stem cells are able to retain their ability to self-renew," Dr Johanson said. "It will be important to further study this mechanism, which we may in the future be able to use to mimic useful stem cell properties in other cells."

Collaborating organisations:

St Vincent's Institute of Medical Research

Funding partners:

Australian National Health and Medical Research Council, Diabetes Australia Research Trust, JDRF, the Victorian Government Operational Infrastructure Support Program

More information:

Johanson TM, *et al*. Drosha controls dendritic cell development by cleaving messenger RNAs encoding inhibitors of myelopoiesis. *Nature Immunology*. 2015 Nov;16(11):1134-41

Professor Andrew Lew leads a research team investigating how to alter immune responses to improve health.

Immune sentinels called dendritic cells are a particular focus of the team's research, which aims to improve the success of vaccination, transplantation and the treatment of autoimmune diseases.

A shared journey to understanding immunodeficiencies

With support from the community, our researchers are uncovering the causes of primary immunodeficiencies, conditions in which the immune system fails to protect the body from infections.

Our supporter Mr Nick Tesch knows too well the impact of primary immunodeficiency. Both he and his nephew Brodie have the condition, which leaves them vulnerable to infections with common bacteria and viruses.

> "NICK'S CHARITY PROVIDED THE SEED FUNDING THAT ALLOWED OUR TEAM TO GENERATE PILOT RESULTS WHICH MADE US MORE COMPETITIVE FOR OTHER GRANTS"

They need lifelong replacement antibody therapy to supplement their weakened immune systems, and are at risk of serious complications including autoimmune disease and cancer.

Primary immunodeficiency usually runs in families, and although Mr Tesch knows the genetic mutation responsible for his family's disease, for most patients the underlying genetic cause is unknown.

To help others find this critical information, which can help with diagnosis and may lead to better treatments, Mr Tesch established the Bloody Long Way Charity.

The charity was inspired by research performed by Dr Vanessa Bryant and Dr Charlotte Slade, in collaboration with The Royal Melbourne Hospital, into the genetic causes of primary immunodeficiency.

Dr Bryant said the team sequences the genomes of people with primary immunodeficiency, and their families, to identify the gene changes that are associated with disease. "We hope this will lead to genetic-based diagnoses of immunodeficiency that will guide personalised targeted therapies in the future," she said.

Dr Bryant said that funding from Bloody Long Way was critical for launching her team's research.

"Nick's charity provided the seed funding that allowed our team to generate pilot results which made us more competitive for other grants," she said.

"This has enabled us to build a research program with great potential to improve the management and treatment of immune disorders."

Funding from the Bloody Long Way Charity, established by Mr Nick Tesch (second from left), has supported immunodeficiency research conducted by Dr Charlotte Slade (left), Dr Vanessa Bryant (centre), Professor Phil Hodgkin (centre right) and Professor Jo Douglass (right).

CELL SIGNALLING AND CELL DEATH

The Cell Signalling and Cell Death division investigates the molecular mechanisms by which cells kill themselves, and the control processes that switch cell death on and off.

Many diseases are characterised by too much or too little cell death, and understanding how this process occurs will help us develop new treatments for cancers and immune disorders.

Research impact recognised

Professor John Silke and his colleagues were awarded the 2015 Thomson Reuters Citation Award in Molecular Biology and Genetics. The award recognised that the research papers they published in the past seven years were the most frequently cited of any Australian researchers in molecular biology and genetics.

The team's publications had contributed to an understanding of the process of cell death, and their research has linked defects in the molecules that control cell death to diseases including cancer and inflammatory conditions.

Flicking cell death switch

Necroptosis is a vital cell death pathway that can lead to immune disorders such as Crohn's disease and psoriasis when it is inappropriately activated.

Institute researchers investigated how the critical protein MLKL changes shape to trigger necroptosis. They discovered a part of the protein becomes 'unlatched' when activated, similar to flicking a switch, allowing it to trigger cell death.

MLKL is an appealing target because blocking the protein is very specific, reducing the chance of unwanted side-effects. Understanding how MLKL is activated has led to a collaboration to identify inhibitors that could be used to treat disease.

New international cell death dialogue

Cell death is an important process contributing to many diseases, and our researchers collaborate with many colleagues around the world. This has enabled numerous research advances that have the potential for global health impacts.

In 2015 the institute hosted the inaugural Japan Australia Meeting on Cell Death. More than 150 delegates from both countries were able to learn from and engage with researchers at the forefront of the cell death research field. The meeting will be a biennial event, with the next one hosted in Japan, strengthening ties between the two nations' researchers.

Health impact

Cancers: bowel cancer, breast cancer, lung cancer, leukaemia, lymphoma, myeloproliferative disorders, stomach cancer

Immune disorders: inflammatory bowel disease, multiple sclerosis, psoriasis, rheumatoid arthritis

Division heads

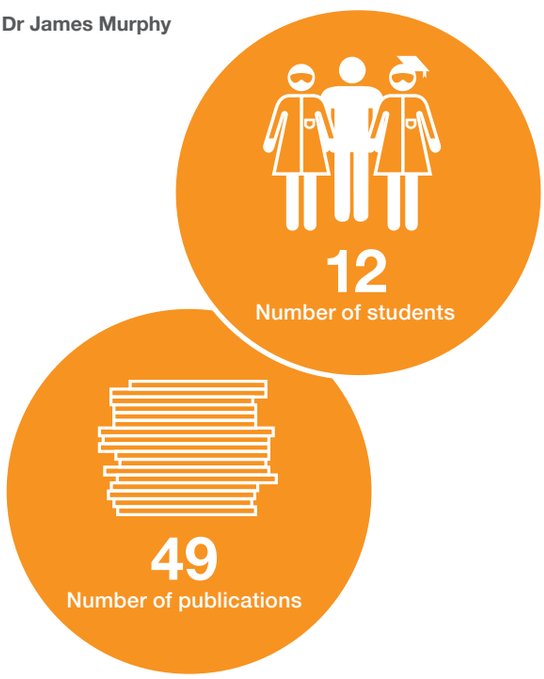
Professor David Vaux

Professor John Silke

Laboratory heads

Dr Grant Dewson

Dr James Murphy



Inflammatory diseases such as psoriasis and inflammatory bowel disease may be the result of abnormal activation of cell death processes.

Dr James Rickard is investigating the link between inflammation and cell death in these diseases.

Visualising cancer protein aids search for new drugs

Characterising the three-dimensional structure of a protein can help researchers understand how the protein functions and guide the development of drugs to block protein activity.

Dr James Murphy and Dr Isabelle Lucet, in collaboration with Dr Peter Mace from the University of Otago, New Zealand, have created the first three-dimensional image of a key protein known to be involved in the development of cancer.

The protein, called TRIB1, plays a vital role in controlling how and when other proteins are degraded.

"WE CAN NOW SEE HOW TRIB1 IS ABLE TO TRIGGER PROTEIN DESTRUCTION, WHICH WILL PROVIDE CRITICAL CLUES FOR DEVELOPING DRUGS THAT TARGET TRIB1 TO TREAT CANCERS"

Dr Murphy said the amount of protein in a cell depended on the balance between production and degradation. "Defects in protein degradation disrupt this balance and can lead to diseases such as cancer," he said.

Excess TRIB1 has been implicated in the development of acute myeloid leukaemia (AML), the deadliest blood cancer in Australia.

"Some people with AML have too much TRIB1, which destroys the proteins that normally prevent cancer," Dr Murphy said.

Using the Australian Synchrotron, Dr Murphy and his team obtained detailed three-dimensional images of TRIB1. The images showed how TRIB1 acted as a scaffold to bring many proteins together, forming a large complex that caused specific proteins to be degraded.

The structure allowed the team to explain a longstanding mystery about the protein.

"TRIB1 is an unusual type of protein called a pseudokinase – a protein class once thought to be an evolutionary dead end. We now know that pseudokinases play vital roles in cells, and visualising TRIB1 finally allowed us to explain why TRIB1 is important," Dr Murphy said.

"We can now see how TRIB1 is able to trigger protein destruction, which will provide critical clues for developing drugs that target TRIB1 to treat cancers."

Collaborating divisions:

Cell Signalling and Cell Death, ACRF Chemical Biology

Collaborating organisations:

University of Otago (NZ), Australian Synchrotron

Funding partners:

Health Research Council of New Zealand, the New Zealand Government, the Australian Cancer Research Foundation, the Australian National Health and Medical Research Council, the Victorian Government Operational Infrastructure Support Program

More information:

Murphy JM *et al.* Molecular Mechanism of CCAAT-Enhancer Binding Protein Recruitment by the TRIB1 Pseudokinase. *Structure*. 2015 Nov 3;23(11):2111-21

Supporting psoriasis research

Psoriasis is a long-term inflammatory skin condition characterised by red scaly patches, itchiness and flaking.

As well as being an annoying and visible condition, psoriasis is associated with an increased risk of serious conditions including cardiovascular disease, inflammatory bowel disease, depression and arthritis.

"INVESTIGATING HOW CELL DEATH PATHWAYS CONTRIBUTE TO PSORIASIS MAY LEAD TO NEW OPPORTUNITIES FOR TREATMENTS"

Funding from the Thomas William Francis & Violet Coles Trust, specifically for skin research, is enabling a collaboration between Professor George Varigos, head of dermatology at The Royal Melbourne Hospital, Dr James Rickard and Professor John Silke to investigate whether cell death pathways contribute to the development of psoriasis. It is hoped that this will indicate new approaches to treating the condition at an early stage.

Dr Rickard said abnormal activation of cell death pathways may contribute to disease in some patients with inflammatory skin conditions such as psoriasis.

"Cell death pathways are normally activated to remove cells that are infected, cancerous or simply unnecessary to the body. The cells can be instructed to die in numerous ways, including via the processes of apoptosis and necroptosis. Both of these have been implicated in the development of immune disorders."

The team recently made a surprising finding about the role of cell death pathways in a model of psoriasis, discovering that increased apoptosis was the main culprit in causing the inflammatory skin lesions.

"This was quite unexpected, because apoptosis is not normally associated with inflammation," Dr Rickard said.

Professor Varigos hopes that understanding how the early stage of psoriasis develops in the skin will lead to better treatments for the condition.

"Psoriasis affects the whole person on a daily basis," he said. "Most new treatments target late stages of the condition, have significant side effects and usually lose their effectiveness over time. Investigating how cell death pathways contribute to psoriasis may lead to new opportunities for treatments."

Donations from the Thomas William Francis & Violet Coles Trust are supporting the research of Professor George Varigos (right), who is collaborating with Professor John Silke (left) and colleagues including Ms Holly Anderton (centre).

INFLAMMATION

The Inflammation division seeks to understand the complex series of biological and molecular mechanisms that regulate inflammation. Our aim is to improve the diagnosis, treatment and prevention of human inflammatory diseases such as rheumatoid arthritis, lupus, sepsis and rheumatic fever.

Discovering drivers of inflammation

Changes to our DNA can cause immune disorders by activating – or inactivating – genes that drive unwanted inflammatory responses, causing immune cells to inappropriately attack our own tissues.

Dr Man Lyang Kim, Dr Seth Masters and colleagues identified the cellular pathway by which mutations in the gene *Wdr1* trigger inflammation. Loss of *Wdr1* causes the build-up of a critical cell structural protein called actin, which is inappropriately recognised by the immune sensor protein Pyrin, triggering inflammation. This discovery has implications for diagnosing and treating chronic inflammatory diseases and infections that alter actin dynamics.

Biomarkers for acute rheumatic fever and rheumatic heart disease

Rheumatic heart disease is a serious heart condition that results from complications of acute rheumatic fever (ARF), a disease that can follow bacterial infection. Rheumatic fever and heart disease are highly prevalent in Australia's Aboriginal and Torres Strait Islander community, and a significant cause of early death.

Dr Willy-John Martin and Professor Ian Wicks are working to improve the diagnosis and treatment of ARF, and hopefully avoid long-term cardiac complications. They have identified novel biomarkers and an existing drug that modulates the immune system, which may hold potential for diagnosing and treating ARF.

Unravelling the causes of inflammation

The cell signalling molecule interleukin-1β (IL-1β) has a central role in promoting the inflammation that underlies conditions such as rheumatoid arthritis. There are several molecular pathways identified as producers of IL-1β, each of which may contribute to inflammation.

Dr Kate Lawlor, Dr James Vince and colleagues have revealed a previously unrecognised way that a protein called RIPK3 contributes to IL-1β production. RIPK3 had been thought to contribute to inflammation through its role in a form of cell death caused necroptosis. The team's discovery that RIPK3 could drive IL-1β production without necroptosis may influence the design of new classes of anti-inflammatory drugs.

Health impact

Cancers: bowel cancer, breast cancer, melanoma, myeloproliferative disorders, pancreatic cancer, stomach cancer

Immune disorders: inflammatory bowel disease, lupus, psoriasis, rheumatic fever and heart disease, rheumatoid arthritis, sepsis

Infectious disease: chronic infections, influenza, vaccines

Division head

Professor Ian Wicks

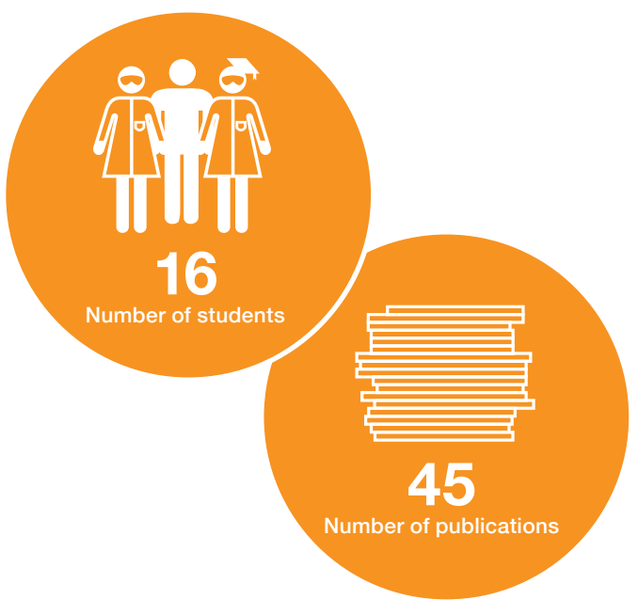
Laboratory heads

Dr Seth Masters

Dr Sandra Nicholson

Dr James Vince

Dr Tracy Putoczki



Protein discovery targets obesity epidemic

Obesity is a global health threat, leading to health issues such as heart disease and type 2 diabetes. More than 850,000 Australians have type 2 diabetes, a chronic, potentially life-threatening disease.

Dr Seth Masters is working to understand the immune mechanisms that the body uses to prevent obesity, insulin resistance and the development of type 2 diabetes.

"THIS DISCOVERY COULD BE EXTREMELY USEFUL FOR DEVELOPING NEW WAYS OF TREATING OBESITY AND TYPE 2 DIABETES"

A study led by Dr Masters, in collaboration with colleagues at the Baker IDI Heart and Diabetes Institute, has identified an internal 'sensor' that could play a major role in the fight against obesity and other metabolic diseases including diabetes.

The study found that a protein called NLRP1 is activated when increased food intake triggers the cell to become 'unstable'. When activated, NLRP1 instructs cells to use up their energy or fat stores to prevent the accumulation of excess fat.

Dr Masters said NLRP1 was activated if it detected that the body's energy intake was too high.

"We showed that without NLRP1, fat stores continue to build up, especially with a high-energy diet, leading to obesity," he said.

The team showed for the first time that NLRP1 controls an important lipid-regulating hormone called interleukin-18 (IL-18), explaining how it acts to reduce obesity.

"Our long-term goal would be to develop a small molecule that activates the pathway to produce IL-18. In people who are obese, this would help the body to switch on this system and burn existing fat stores," Dr Masters said.

Collaborating divisions:

Inflammation, ACRF Chemical Biology, Cancer and Haematology, Molecular Immunology, Population Health and Immunity, Systems Biology and Personalised Medicine

Collaborating organisations:

Baker IDI Heart and Diabetes Institute, The University of Melbourne, Garvan Institute, Tel Aviv University (Israel), Boston Children's Hospital (US)

Funding partners:

Australian National Health and Medical Research Council, veski, Diabetes Australia Research Trust, the Victorian Government Operational Infrastructure Support Scheme

More information:

Murphy AJ *et al*. IL-18 Production from the NLRP1 Inflammasome Prevents Obesity and Metabolic Syndrome. *Cell Metabolism*. 2016 Jan 12; 23(1):155-64

Inflammation protects our body against infection, but can also drive diseases including rheumatoid arthritis, Crohn's disease and type 2 diabetes.

Dr Seth Masters' research is revealing the molecules that drive inflammation. This is explaining how inflammatory diseases develop, and potentially identifying new approaches to treating these conditions.

Improving treatments for pancreatic cancer

A generous gift by institute board member Mrs Jane Hemstritch, who lost her husband Philip to pancreatic cancer six years ago, has led to the establishment of the Philip Hemstritch Pancreatic Cancer Research Program.

Pancreatic cancer is one of the most devastating of all cancers, according to institute scientist Dr Tracy Putoczki, because by the time this silent disease is identified it is very advanced.

"Most of the treatments that are available to patients after diagnosis are palliative," Dr Putoczki said.

"TRAGEDY OFTEN GALVANISES CHANGE"

The Philip Hemstritch Pancreatic Cancer Research Program, led by Dr Putoczki and Associate Professor Peter Gibbs, will focus on identifying new drugs – and combinations of drugs – to treat the disease as well as investigating new strategies to overcome resistance to current therapies.

"Our focus is on looking at new combinations of therapies for use in pancreatic cancer, which is a complex disease and even more difficult to understand because not a lot of research is conducted in Victoria," Dr Putoczki said.

The Philip Hemstritch Pancreatic Cancer Research Program will add much needed additional funding to research that has already produced promising discoveries.

Dr Putoczki said her research had identified a molecule that helps pancreatic cell growth and also causes cancer cells to become resistant to current chemotherapies.

"With these additional funds, we will be able to investigate how other molecules like this work and determine whether inhibiting them could also make pancreatic tumour cells responsive to chemotherapy," she said.

Institute director Professor Doug Hilton said more options and better treatments for patients with pancreatic cancer were urgently needed. "Tragedy often galvanises change and, in this case, a shared sense of loss led to conversations and then commitments that resulted in an expanded research program at the institute," he said. "Just like our many donors, our researchers are motivated to make a difference."

Associate Professor Gibbs said the team would also look to develop simple and cost effective biomarker assays. These would allow early warning of disease, targeted follow-up and appropriate treatment of patients.

"Ultimately, these biomarkers could be routinely used as part of standard blood testing performed by cancer specialists to improve treatment selection and outcomes," Associate Professor Gibbs said.

Inflammation is a two-edged sword in health: beneficial inflammatory responses protect against infection, but damaging inflammation underlies many conditions. Dr Sandra Nicholson's research is pinpointing how the body initiates and maintains inflammation.

MOLECULAR IMMUNOLOGY

The Molecular Immunology division aims to understand the immune system and how it functions to protect us from pathogens, such as bacteria and viruses, while at the same time ignoring the harmless or beneficial microbes in our environment. By understanding the normal immune response, we aim to pinpoint the events that go awry in diseases such as lymphoma, autoimmunity or chronic infections.

Building collaborations on innate lymphocytes

Innate lymphocytes are a recently identified component of the immune system that respond spontaneously to pathogen encounter via direct recognition or activation by inflammatory molecules. These cells are emerging as critical for the prevention of many diseases, including gastrointestinal infections, asthma and type 2 diabetes.

The first Australian Innate Lymphocyte Symposium was convened at the institute in 2015. Organised by Dr Nicholas Huntington and Professor Gabrielle Belz, the meeting brought together more than 90 Australian and international researchers with the aim to promote collaboration in this new research field.

Myeloma research supported

Multiple myeloma is an incurable cancer of a type of immune cell called a plasma cell. Clinical haematologist Dr Pasquale Fedele has received a PhD scholarship from the Leukaemia Foundation of Australia to support his investigations into the genetic network underpinning multiple myeloma.

Dr Fedele's research extends the research discoveries of his supervisor Professor Stephen Nutt, into the genetic control of plasma cell development. Dr Fedele is investigating how two genes called *Ikaros* and *Aiolos* control normal plasma cells, and how the therapeutic degradation of these factors may lead to myeloma cell death. This research will contribute to a better understanding of how myeloma can be treated with existing therapies and potentially identify novel treatment targets.

Unleashing immune attack on melanoma

Melanoma is the most serious form of skin cancer and accounts for 10 per cent of cancers diagnosed in Australia. Funding from the Harry J. Lloyd Charitable Trust is enabling Dr Nicholas Huntington to develop new treatments for this disease.

Dr Huntington has studied the immune system's natural killer (NK) cells for more than a decade, identifying how they develop and function. NK cells have an immune 'surveillance' role, detecting and eliminating abnormal cells from the body. The grant is supporting Dr Huntington's investigations into how to enhance NK cell attacks on melanoma cells.

Health impact

Cancers: leukaemia, lymphoma, melanoma, myeloma

Immune disorders: allergy, asthma, inflammatory bowel disease, lupus, multiple sclerosis, type 2 diabetes

Infectious disease: chronic infections, influenza, listeria, vaccines

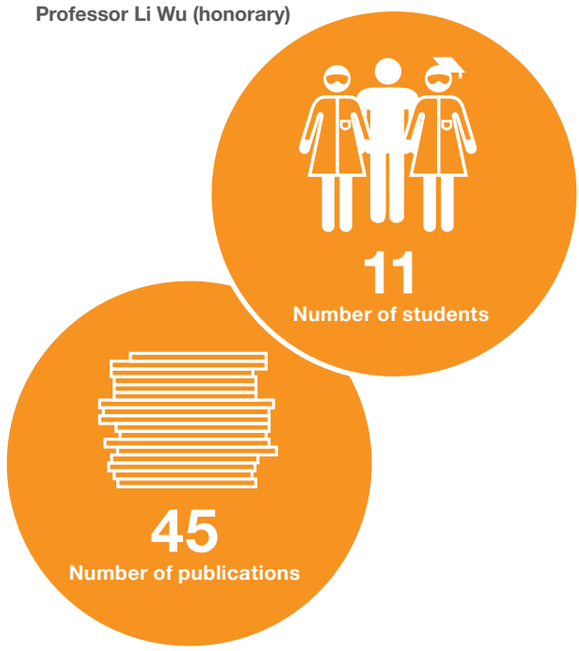
Other: epigenetics

Division head

Professor Stephen Nutt

Laboratory heads

Dr Rhys Allan
Professor Gabrielle Belz
Professor Lynn Corcoran
Dr Joanna Groom
Dr Nicholas Huntington
Dr Axel Kallies
Professor Li Wu (honorary)



Inflammation in the fat tissue of obese people is thought to contribute to the development of type 2 diabetes.

Dr Ajithkumar Vasanthakumar has discovered how immune cells control inflammation in fat tissue. This could lead to future treatments that prevent the development of type 2 diabetes in obese people.

Healthy fat tissue could be key to reversing type 2 diabetes

Obesity is an important contributor to type 2 diabetes, a condition in which cells fail to respond appropriately to insulin, a hormone that normally triggers glucose uptake.

Long-term, low-level inflammation in the fat tissue of obese people is thought to contribute to the insulin resistance that causes type 2 diabetes.

Dr Ajith Vasanthakumar, Dr Axel Kallies and colleagues from the RIKEN Institute, Japan, discovered that specialised immune cells, called regulatory T cells (Tregs), played a key role in controlling inflammation in fat tissue and maintaining insulin sensitivity.

"TREATMENTS THAT MIMIC IL-33 COULD HAVE THE POTENTIAL TO REDUCE OBESITY-RELATED INFLAMMATION AND TYPE 2 DIABETES"

Fat tissue has its own unique type of Tregs, which disappear from fat tissue during development of obesity, Dr Vasanthakumar said. "Without Tregs, the number of inflammation-causing cells increases, which eventually leads to insulin resistance and high blood glucose levels, a classic hallmark of type 2 diabetes," he said.

The research team discovered a key hormone called interleukin-33 (IL-33) was able to selectively boost Treg populations in fat tissue, effectively halting the development of type 2 diabetes, or even reversing the disease in preclinical models.

"Treatments that mimic IL-33 could have the potential to reduce obesity-related inflammation and type 2 diabetes," Dr Vasanthakumar said.

Dr Kallies said the research underscored the importance of 'healthy' fat tissue in preventing disease. "We can no longer think of fat tissue simply as energy storage," Dr Kallies said. "Fat tissue is increasingly being recognised as a crucial organ that releases hormones and regulates development. Keeping our fat tissue healthy is important for our general wellbeing, and our research highlights the important role it plays in preventing disease."

Collaborating divisions:

Molecular Immunology, Bioinformatics, Inflammation, Population Health and Immunity

Collaborating organisations:

RIKEN Center for Integrative Medical Sciences (Japan), Japan Science and Technology Agency, Yokohama City University (Japan), The University of Tokyo (Japan), National Research Institute for Child Health and Development (Japan), National Institutes of Health (US), Keio University School of Medicine (Japan)

Funding partners:

National Health and Medical Research Council, the Australian Research Council, the Sylvia and Charles Viertel Foundation, the Victorian Government Operational Infrastructure Support Scheme

More information:

Vasanthakumar, A *et al*. The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue–resident regulatory T cells. *Nature Immunology*. 2015 Mar;16(3):276-85

Powering T cells for their fight against cancer

Cytotoxic T cells are an important part of the immune system's defense against viruses and tumors. When cytotoxic T cells recognise infected or cancerous cells, they unleash a payload that destroys the cells, preventing the spread of the cancer or infection.

Cancer cells have evolved strategies to escape this immune protection. Working with Dr Axel Kallies, Dr Kevin Man has investigated molecules on the surface of cancer cells, called 'inhibitory receptors', that switch off cytotoxic T cell function, protecting the cancer from immune attack. Blocking these inhibitory receptors is currently one of the most successful approaches in cancer immunotherapy. However, it is still not completely understood how these receptors work and how we can further improve cancer treatment.

A Cancer Council Victoria postdoctoral fellowship allowed Dr Man to capitalise on the experience he had gained during his PhD studies with Dr Kallies.

Dr Man said the one-year fellowship had allowed him to extend his PhD research that investigated immune cell metabolism. "During my PhD I was able to unravel some of the complex metabolic changes that occur when cytotoxic T cells are activated," he said. "The funding for an additional year of research provided me with time to apply this research to the important question of how tumour cells evade the immune system through their interactions with cytotoxic T cells.

"We showed that inhibitory receptors on cancer cells switch cytotoxic T cells into a less active metabolic state. This provides clues to how anti-cancer therapies could awaken cytotoxic T cells to fight cancers," he said.

"THIS PROVIDES CLUES TO HOW ANTI-CANCER THERAPIES COULD AWAKEN CYTOTOXIC T CELLS TO FIGHT CANCERS"

Mr Todd Harper, CEO of Cancer Council Victoria, said harnessing the immune system to fight cancer was an exciting new avenue that was starting to show promise in clinical trials. "We are delighted that a Cancer Council Victoria postdoctoral fellowship has enabled Dr Man to address the important question of how cancer cells evade immune defences," he said.

Dr Man said the Cancer Council Victoria postdoctoral fellowship provided valuable assistance for him to transition towards becoming an independent researcher. "The fellowship provides support to young Victorian researchers at a particularly productive point of their career, allowing them to remain at the forefront of cancer research," he said.

Professor Lynn Corcoran and Dr James Murphy have collaborated with the Menzies Institute of Medical Research at the University of Tasmania, as part of the effort to save Tasmanian devils from a deadly cancer. Professor Corcoran is pictured here releasing a vaccinated Tasmanian devil into the wild.

SYSTEMS BIOLOGY AND PERSONALISED MEDICINE

The Systems Biology and Personalised Medicine division uses high-throughput technologies to understand global changes in biological systems, and to inform therapeutic decisions. The technologies – including genomics, transcriptomics, proteomics, chemical and genetic screens – are improving our understanding of cancers, immune disorders and infectious diseases.

Improving bowel cancer treatment

Recent advances in bowel cancer research have increased the number of treatment strategies available for this disease. For many people with bowel cancer, an effective treatment is only identified after they have failed to respond to one or more other treatments.

Dr Jeanne Tie and Associate Professor Peter Gibbs have used changes in the level of tumour DNA in bowel cancer patients' blood to identify early responses to treatment, well before changes could be detected with currently used imaging tests. This discovery may accelerate decisions about whether people with bowel cancer are responding to a treatment, enabling those who are not responding to switch to a potentially better treatment for their disease far sooner than is currently feasible.

New equipment boosts MS research

Flow cytometry is a powerful technique that allows researchers to separate individual cells within a sample. The institute's flow cytometry facility, headed by Mr Simon Monard, is part of the Systems Biology and Personalised Medicine division.

In recognition of the institute's centenary, the Walter and Eliza Hall Trust provided funds for the purchase of a flow cytometry instrument that is aiding the institute's research into multiple sclerosis (MS), a debilitating, chronic neurological condition. Dr Simon Willis is using the new instrument to purify specific types of immune cells from the blood of people with MS, as part of his research into the causes of this condition. Dr Willis is the recipient of the Walter and Eliza Hall Trust Centenary Fellowship which will support his research work into MS over the next four years.

Uncovering the causes of chemoresistance

A gift from the Janko-Inge Foundation is allowing division scientists to understand why some people with cancer do not respond to their treatment. The donation has enabled a study by Professor Liam O'Connor that is using gene editing technology to understand the genetic changes that occur in cancer cells when they become resistant to chemotherapy.

The outcomes of this research have the potential to shift cancer treatment from a 'one size fits all' approach to a new personalised strategy where gene sequencing data is used to determine the most effective treatment for an individual with cancer.

Health impact

Cancers: bowel cancer, leukaemia, lymphoma, melanoma, stomach cancer

Immune disorders: rheumatoid arthritis, rheumatic fever and rheumatic heart disease

Infectious disease: malaria, vaccines

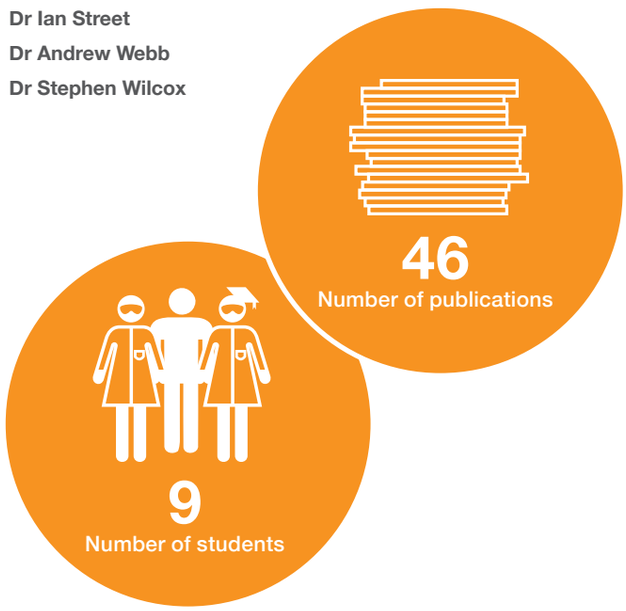
Other areas: antivenoms, congenital disease, personalised medicine

Division head

Professor Liam O'Connor

Laboratory heads

Associate Professor Peter Gibbs
Associate Professor Oliver Sieber
Mr Simon Monard
Dr Kelly Rogers
Dr Hélène Jousset Sabroux
Dr Ian Street
Dr Andrew Webb
Dr Stephen Wilcox



A step closer to personalised bowel cancer treatment

Bowel cancer affects one in 12 Australians in their lifetime and is Australia's second biggest cancer killer. Walter and Eliza Hall Institute researchers have discovered that a mutated gene commonly found in bowel cancer patients could potentially be used to predict whether a patient will relapse and his or her overall chance of survival, enabling more tailored treatment.

In 80 to 90 per cent of bowel cancer cases patients have mutations in a gene, called *APC*, that normally suppresses tumours. Associate Professor Oliver Sieber led a large, long-term study of patients in Victoria, South Australia and New South Wales that specifically investigated the mutated gene's prognostic value.

"THE HOPE IS WE COULD MAKE A MORE PERSONALISED DELIVERY OF TREATMENT"

All 746 patients had already had surgery for their primary cancer and received standard chemotherapy treatment according to the stage of their disease. Researchers found that in patients in whom the primary tumour had been located in the proximal bowel (on the right-hand side) the absence of *APC* mutations indicated a higher risk of the tumour recurring and higher risk of mortality.

"The study showed for the first time that *APC* mutation status has prognostic value and has the potential to become a prognostic marker in patients who present with cancer in the proximal bowel," Associate Professor Sieber said. "It also points to a different molecular type of tumour in the proximal colon which is not initiated by *APC* mutation," he said.

The study's findings could be used in conjunction with clinical information to develop what is called a cancer "nomogram" – a predictive algorithm for risk of relapse and survival.

"Currently in clinical practice you would take into account the pathology of the tumour, how large it is, how far it has spread and the age and gender of the patient, which would all allow the clinician to determine whether to recommend chemotherapy or which type of chemotherapy regimen to advise," Associate Professor Sieber said.

"The hope is that if we had molecular information it could be used together with the patient's clinical data to make the estimation of the risks more precise and allow more personalised delivery of treatment," he said.

Collaborating divisions:

Systems Biology and Personalised Medicine, Structural Biology

Collaborating organisations:

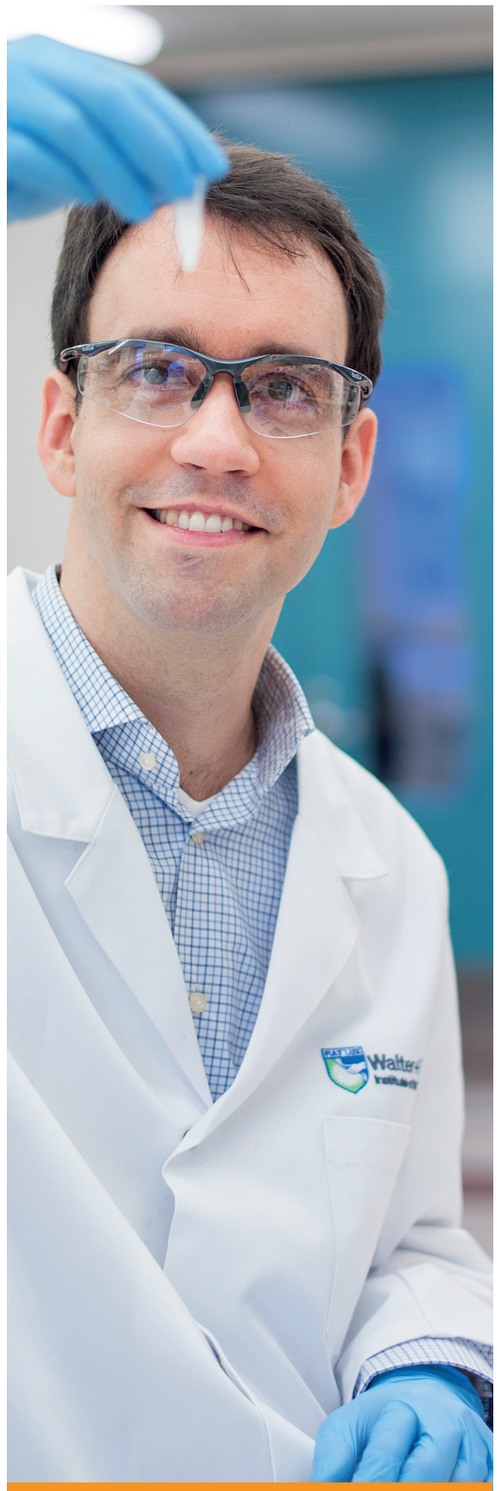
St Vincent's Hospital Sydney, The Royal Melbourne Hospital, Western Hospital, J. Craig Venter Institute (US), Royal Adelaide Hospital

Funding partners:

Cancer Council Victoria, Cancer Australia, Ludwig Cancer Research, Australian National Health and Medical Research Council, the Victorian Government Operational Infrastructure Support Program

More information:

Jorissen RN *et al*. Wild-type APC predicts poor prognosis in microsatellite-stable proximal colon cancer. *British Journal of Cancer*. 2015 September 15; 113 13(6):979-88



More than 14,000 Australians are diagnosed with bowel cancer each year, many with cancers at later, difficult to treat stages.

Associate Professor Oliver Sieber uses genomics to understand how genetic changes contribute to bowel cancer development and response to treatment.

Improving cancer treatments through genomics

Genomics research is enabling rapid advances in the detection and treatment of cancer, revealing gene changes that are hallmarks of particular types of cancer, or that contribute to how cancer cells respond to treatment.

Many of the institute's cancer research teams rely on the ability to rapidly sequence the thousands of genes within tumour samples from individual patients. This has enabled institute researchers to develop new approaches to diagnosing cancer samples based on their genetic sequence, as well as identifying which treatments will be most effective for individual cancer patients.

"GENOMICS IS A RAPIDLY ADVANCING FIELD, AND IT IS IMPORTANT FOR OUR RESEARCHERS TO HAVE ACCESS TO THE MOST ACCURATE AND EFFICIENT SEQUENCING METHODOLOGIES"

A Perpetual Impact Philanthropy Partnership Grant has provided an important boost to the institute's cancer research capacity, by enabling the purchase of new gene sequencing technology.

Professor Liam O'Connor, who leads a cancer genomics research team at the institute, said the new equipment was a significant upgrade to the institute's gene sequencing capabilities.

"Genomics is a rapidly advancing field, and it is important for our researchers to have access to the most accurate and efficient sequencing methodologies," he said. "The new equipment provided by Perpetual's Impact Philanthropy program is helping our researchers to home in on the genetic changes that are at the root of how cancer cells respond to treatment."

Ms Caitriona Fay, National Manager Philanthropy and Non Profit Services at Perpetual Limited, said cancer was one of the most significant health challenges facing Australia. "New approaches to diagnosis and treatment are urgently needed," she said. "We are delighted that Perpetual clients are helping to keep Australian scientists at the forefront of the international cancer research effort through the provision of an Impact Philanthropy Partnership Grant."

Dr Hélène Jousset Sabroux leads the institute's screening laboratory, which tests and evaluates small molecules to develop potential new medications.

DEVELOPMENT AND CANCER

Researchers from the Development and Cancer division investigate mechanisms regulating cell growth and differentiation in normal embryonic development and in cancer. The molecular mechanisms underlying the rapid, but regulated, growth of cells during embryonic development are frequently deregulated in cancer.

Embryo blueprint revealed

Researchers identified two key proteins that act as genetic 'architects', creating the blueprint needed by embryos during the earliest stages of their development.

Dr Bilal Sheikh, Associate Professor Tim Thomas, Associate Professor Anne Voss and colleagues discovered that the proteins MOZ and BMI1 played opposing roles in giving developing embryos the set of instructions needed to ensure that body segments including the spine, nerves and blood vessels developed correctly and in the right place.

Substances or environmental challenges that impact MOZ or BMI1 expression severely affect the developing embryo's 'instructions', and cause developmental defects.

Barrier to cancer

The cells of the intestinal lining provide a selective barrier between the external environment and internal tissues, allowing entry of water and nutrients while excluding microbes, toxins and dietary allergens. Impairment of this barrier can promote hypersensitivity to foods, inflammatory bowel disease and colitis-associated cancer.

Dr Ben Williams, Associate Professor Joan Heath and colleagues discovered that the intestinal cell surface protein and bowel cancer marker glycoprotein A33 (GPA33) contributes to the integrity of the intestinal barrier. In the absence of this molecule exposure to carcinogens and inflammatory stimuli greatly increases the incidence of bowel tumours. Models with defects in GPA33 could be useful for testing potential drugs for treating inflammatory bowel disease and bowel cancer.

Research excellence awarded

At the 2015 National Health and Medical Research Council (NHMRC) Research Excellence Awards, division head Associate Professor Anne Voss received the Elizabeth Blackburn Fellowship Award for Biomedical Science. The award recognises the highest ranked female applicant in the NHMRC's annual Research Fellowship scheme.

Associate Professor Voss has made significant contributions to the understanding of embryonic development, laying the foundations for the discovery of the genetic causes of human intellectual disability syndromes, as well as explaining the contribution of certain molecular pathways to cancer formation.

Health impact

Cancers: bowel cancer, gastric cancers, lung cancer, leukaemia, lymphoma, stomach cancer

Immune disorders: inflammatory bowel disease

Other areas: congenital diseases, epigenetics, regenerative medicine, vascular diseases

Division head

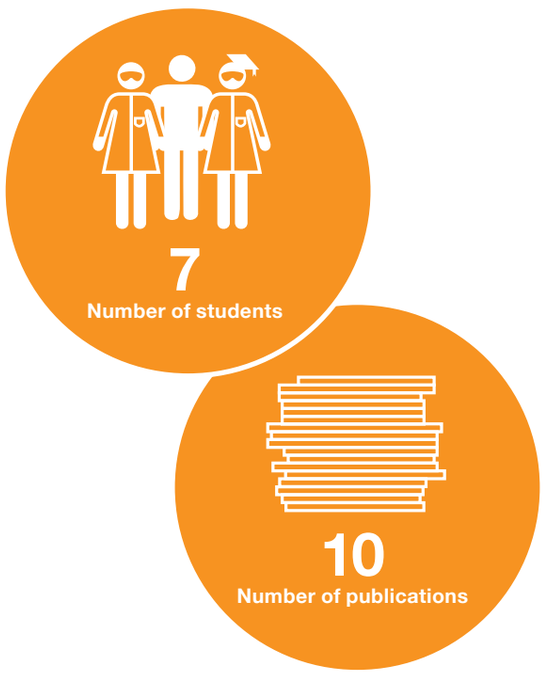
Associate Professor Anne Voss

Laboratory heads

Dr Leigh Coultas

Associate Professor Joan Heath

Associate Professor Tim Thomas



Many of the dynamic molecular processes occuring during embryonic development are dysregulated in cancer. Associate Professor Joan Heath's research group is identifying genes that drive the growth of tissues during development, and investigating whether these genes are commandeered by cancer cells.

Protein removal slows blood cancer growth

The protein MOZ (monocytic leukemia zinc finger protein) is critical for controlling blood cell production, regulating the haematopoietic stem cells from which the different types of blood cells arise. MOZ was originally identified some 20 years ago as a driver in a particularly aggressive blood cancer called acute myeloid leukaemia.

Walter and Eliza Hall Institute researchers decided to investigate the effect of MOZ on cancer growth more broadly and, after a lengthy series of experiments, arrived at some startling conclusions.

Associate Professor Tim Thomas, Associate Professor Anne Voss, Dr Bilal Sheikh and colleagues discovered in preclinical models that removing one copy of the *MOZ* gene – halving MOZ protein production in blood cells – could significantly delay and impair lymphoma development.

Associate Professor Thomas said the team knew MOZ was an important protein, regulating the fundamental processes of proliferation and differentiation in the haematopoietic system. "We wanted to see what effect MOZ itself had on the progression of cancer," he said.

"HALVING THE AMOUNT OF MOZ DRAMATICALLY RETARDED THE CANCER GROWTH"

"Halving the amount of MOZ present in the cancer cell dramatically retarded the development of cancer growth and, in some instances, the cancer did not develop at all," Associate Professor Thomas said.

The results showed that suppressing the action of MOZ slowed blood cell replication and reduced the chance of these cells picking up the extra mutation that would make them cancerous.

Associate Professor Voss said the study was the first to find that by altering the gene dose of *MOZ* you could slow cancer development.

The discovery, published in the journal *Blood*, opens the possibility of therapeutic intervention to prevent the development of blood cancers such as lymphoma and leukaemia.

Associate Professor Thomas said one of the problems with leukaemia was that chemotherapy did not necessarily eliminate every cancer cell, so patients could relapse after the cells proliferated again.

"We're hopeful that if we're able to inhibit the action of MOZ we might delay that process of deregulated proliferation, maybe indefinitely," he said.

Walter and Eliza Hall Institute scientists are now working with the Cancer Therapeutics Cooperative Research Centre (CTx) to produce a compound inhibiting MOZ, which could potentially become a novel class of anti-cancer drug.

Collaborating divisions:

Development and Cancer, Bioinformatics, Cancer and Haematology, Molecular Genetics of Cancer, Molecular Immunology

Collaborating organisations:

Cancer Therapeutics Cooperative Research Centre

Funding partners:

Australian National Health and Medical Research Council, Lady Tata Research Award, Cancer Council Victoria, Leukemia and Lymphoma Society (US), Australian Cancer Research Foundation, the Australian Research Council, the Victorian Government Operational Infrastructure Support Program

More information:

Sheikh BN *et al*. MOZ regulates B-cell progenitors and, consequently, Moz haploinsufficiency dramatically retards MYC-induced lymphoma development. *Blood*. 2015 March 19;125(12):1910-1921

Blocking tumour blood supply key to improved treatments

Just like healthy cells in our body, cancer cells need a blood supply to survive and grow.

A better understanding of how blood vessels grow could lead to improved treatments that attack the blood vessels supplying tumours.

The L.E.W. Carty Charitable Fund has funded a five-year Centenary Fellowship to support Dr Leigh Coultas in his quest to investigate how new blood vessels form, a process called angiogenesis.

"IT IS IMPORTANT TO BE ABLE TO GIVE BRIGHT YOUNG SCIENTISTS A DEGREE OF SECURITY IN THE EARLY STAGES OF THEIR CAREER SO THAT THEY CAN FOCUS ON BEING INNOVATIVE AND MAKE MAJOR DISCOVERIES"

Dr Coultas said angiogenesis usually occurred before birth, and was uncommon in adult tissues. "Tumours have the ability to re-activate angiogenesis, thus allowing the formation of new blood vessels that feed the tumour and enable it to grow," he said.

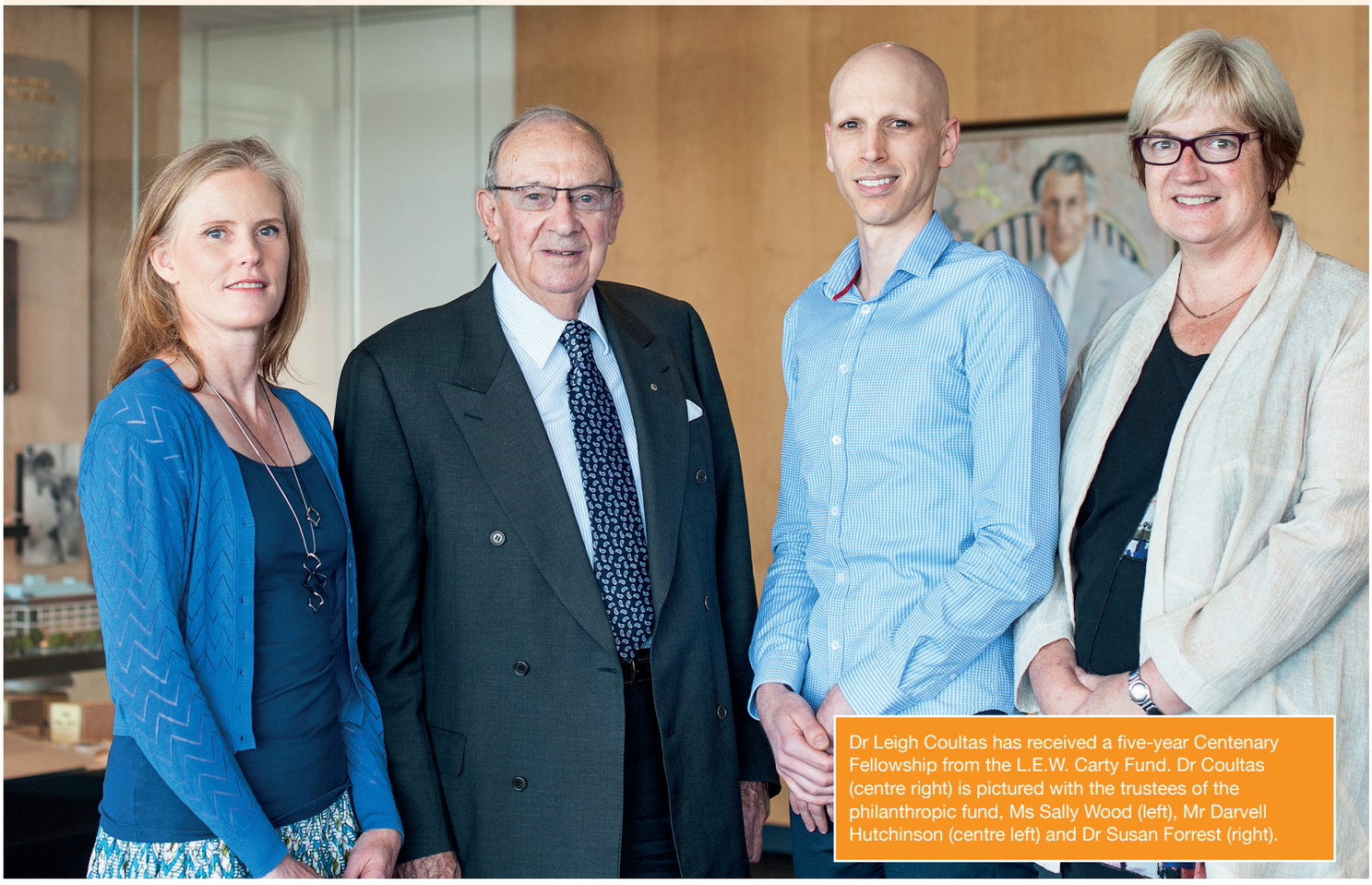
"Treating cancer by starving tumours of their blood supply is an appealing concept, but thus far this approach has been largely ineffective due to high rates of drug resistance."

Dr Coultas has already made a major step forward in understanding how new blood vessels form. "Endothelial cells are the building blocks used to make new blood vessels," he said. "We discovered that a protein called MCL1 was required for endothelial cells to survive during angiogenesis. This means that a drug that inhibits the function of MCL1 might prevent angiogenesis and starve a growing tumour."

The L.E.W. Carty Charitable Fund was established by Mrs Olive Carty in tribute to her late husband Mr Leslie Ernest William Carty, who died from cancer.

Dr Susan Forrest, one of the L.E.W. Carty Charitable Fund's three trustees, said they were very pleased to support Dr Coultas' research. "It is important to be able to give bright young scientists a degree of security in the early stages of their career so that they can focus on being innovative and make major discoveries," she said. "Dr Coultas is indeed taking an exciting approach to developing urgently needed new treatments for cancer."

Dr Coultas said he was grateful for the ongoing support he received from the philanthropic fund. "Receiving a five-year fellowship allows me to focus on making discoveries that could improve treatments for people with cancer in the future."



Dr Leigh Coultas has received a five-year Centenary Fellowship from the L.E.W. Carty Fund. Dr Coultas (centre right) is pictured with the trustees of the philanthropic fund, Ms Sally Wood (left), Mr Darvell Hutchinson (centre left) and Dr Susan Forrest (right).

POPULATION HEALTH AND IMMUNITY

The Population Health and Immunity division uses population-based studies to investigate the basic biology of diseases. We have a strong focus on the epidemiology of infectious diseases such as malaria, and understanding the causes of complex diseases including diabetes and brain disorders.

Enhanced sequencing of circulating DNA

Cell-free DNA is DNA released from cells – such as normal cells, a developing embryo or cancerous tissues – that circulates in the blood. Sequencing of cell-free DNA has recently gained significant interest for its potential as a non-invasive test for detecting foetal abnormalities, and detecting cancer and monitoring its spread and response to treatment.

Dr Dineika Chandrananda, Dr Natalie Thorne and Associate Professor Melanie Bahlo have described distinctive DNA patterns found in cell-free DNA. These patterns could be harnessed to improve algorithms and analysis, enabling scientists to identify and develop biomarkers that monitor changes that occur in disease, including cancer.

Funding for malaria vaccine

Researchers received a $2.8M grant from the Bill & Melinda Gates Foundation to pursue the preclinical development of a vaccine aimed at eradicating malaria. The funding will enable the team of researchers to develop a broad-spectrum vaccine effective against most species of the parasite that causes human malaria.

The research will be led by Professor Louis Schofield, laboratory head at the institute and director of the Australian Institute of Tropical Health and Medicine, Queensland, with colleagues at the institute and collaborators and institutions in the US.

Pinpointing faulty genes

Associate Professor Melanie Bahlo won the 2015 Ross Crozier Medal from the Genetics Society of Australasia for her contributions to pinpointing faulty genes involved in human diseases.

Associate Professor Bahlo has made fundamental contributions to population genetics, genetics and bioinformatics. Her work has found the genes responsible for illnesses such as epilepsy, ataxia – a neurological disorder that affects muscle control, and mitochondrial disease – a debilitating condition culminating in organ failure. She has directly contributed to discovering 22 genes that are involved in human disease, particularly genetic brain disorders.

Health impact

Immune disorders: type 1 diabetes, type 2 diabetes

Infectious disease: filariasis, malaria, tuberculosis, vaccines

Other areas: brain disorders, congenital disease

Division heads

Associate Professor Melanie Bahlo

Professor Ivo Mueller

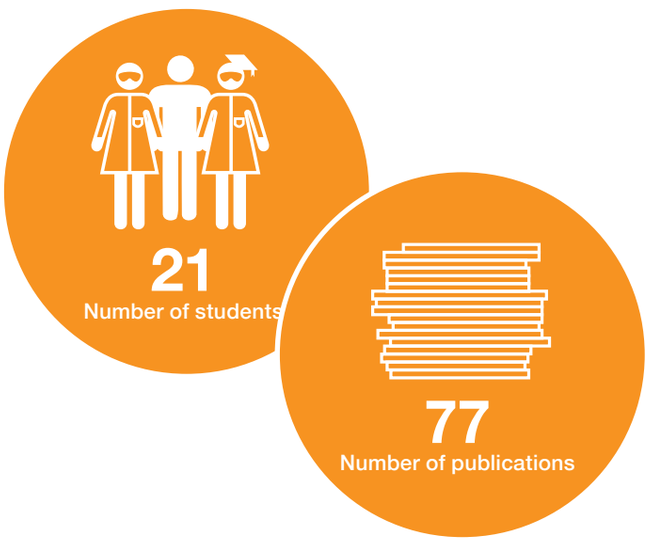
Laboratory heads

Dr Alyssa Barry

Professor Len Harrison

Dr Leanne Robinson

Professor Louis Schofield



New challenges for malaria eradication

An international study led by institute scientists has shown that childhood malaria infections are the result of relapsed – not new – infections. The finding means that eradicating malaria could be more challenging than previously thought, and further advances are needed in current malaria control programs.

The study was led by Dr Leanne Robinson from the Walter and Eliza Hall Institute and Papua New Guinea Institute of Medical Research and Professor Ivo Mueller from the Walter and Eliza Hall Institute and Barcelona Centre for International Health Research, Spain.

The team investigated malaria caused by the parasite *Plasmodium vivax*, which is responsible for most malaria cases outside of Africa and is a major cause of infection and illness in young children in the Asia-Pacific and Americas.

"RELAPSING INFECTIONS WITH *P.VIVAX* WERE RESPONSIBLE FOR 80 PER CENT OF INFECTIONS CHILDREN IN PAPUA NEW GUINEA"

They found that relapsing *P.vivax* infections were one of the biggest problems in achieving malaria eradication.

"*P. vivax* parasites are able to hide in the liver for long periods of time before 'reawakening' to cause disease and continue the transmission cycle," Dr Robinson said. "Relapsing infections with *P.vivax* were responsible for 80 per cent of infections in five to 10 year old children in Papua New Guinea."

The finding has significant repercussions for malaria control programs worldwide.

Professor Mueller said current programs would be unable to achieve elimination because they failed to identify and treat children with dormant liver infections.

The team is now working with international collaborators to develop a test that identifies children with dormant malaria parasites in their liver. These children could then be treated with a drug that kills dormant parasites, a strategy that would be key to the successful elimination of *P.vivax*.

"This is the only way to stop the malaria transmission cycle in PNG and in other parts of the Asia-Pacific and Americas where *P. vivax* is a significant cause of disease," Professor Mueller said.

Collaborating organisations:

Papua New Guinea Institute of Medical Research, Barcelona Centre for International Health Research (Spain)

Funding partners:

TransEPI consortium (funded by The Bill & Melinda Gates Foundation, US), Australian National Health and Medical Research Council, Swiss National Science Foundation, Cellex Foundation (Spain), International Centers of Excellence in Malaria Research (US), the Victorian Government Operational Infrastructure Support Scheme

More information:

Robinson LJ *et al*. Strategies for understanding and reducing the *Plasmodium vivax* and *Plasmodium ovale* hypnozoite reservoir in Papua New Guinean children: a randomised placebo-controlled trial and mathematical model. *PLoS Med.* 2015 Oct 27;12(10):e1001891

Global malaria control efforts depend on detecting and treating people infected with the parasite to prevent its spread. Dr Leanne Robinson and colleagues have revealed that most childhood malaria cases in Papua New Guinea arise from dormant liver parasites. This finding indicates that a new approach to malaria elimination will be needed.

A transformational gift for type 1 diabetes research

Type 1 diabetes is the most common chronic (long-term) childhood illness in Australia. More than 120,000 Australians have type 1 diabetes, yet the triggers of this immune disorder are still poorly understood.

Funding from an international donor and a local foundation is supporting Professor Len Harrison's quest to discover why some people's immune system mistakenly destroys the insulin-producing cells in their pancreas, causing type 1 diabetes.

"THE REMARKABLE SUPPORT WE'VE RECEIVED ACCELERATES THE EFFORTS OF OUR MEDICAL RESEARCHERS AND OFFERS HOPE TO THOSE IN AUSTRALIA AND AROUND THE WORLD WHO ARE STRUGGLING WITH THIS DEBILITATING AND LIFE-THREATENING DISORDER"

The donor's $5 million commitment is being made in conjunction with a $3 million grant from JDRF Australia, an organisation working towards a cure for type 1 diabetes and its complications through supporting research.

This funding is supporting the Environmental Determinants of Islet Autoimmunity (ENDIA) program, a study that links environment and gene expression to understand the determinants of type 1 diabetes from pregnancy through early life. With an aim of following 1400 pregnant women and their children, ENDIA is the largest ever study of its type in the world.

The Walter and Eliza Hall Institute is responsible for performing analyses of the ENDIA participants' immune system, epigenetic changes to their DNA, resident bacteria (microbiome) and metabolic state.

Professor Harrison, who is one of the lead investigators of ENDIA, said the $8 million in funding was already having a transformational impact on the scope and outcomes of the program.

"We've been able to expand the study to five Australian states, employ more research nurses and increase recruitment of scientists, including bioinformaticians, to carry out important basic scientific work," Professor Harrison said.

"The remarkable support we've received accelerates the efforts of our medical researchers and offers hope to those in Australia and around the world who are struggling with this debilitating and life-threatening disorder," Professor Harrison said.

New funding is supporting a study, jointly led by clinician scientist Professor Len Harrison, that is investigating how environmental factors interact with genes to influence the development of type 1 diabetes.

TRANSLATION

A major goal for the institute is to harness and translate basic research discoveries into the clinic, delivering real patient benefits. To achieve this, we embed translation into many aspects of our research.

The institute's Clinical Translation Centre provides strong links between clinicians, research and hospital partners, and supports highly skilled clinician-scientists who are helping to translate fundamental discoveries into treatments that will improve patient outcomes.

The institute also supports the involvement of consumers – people who have experienced a disease – in research, overseen by the Consumer Advisory Panel. This year saw the growth of our consumer buddy program, and the development of new initiatives to enhance consumer-researcher relationships.

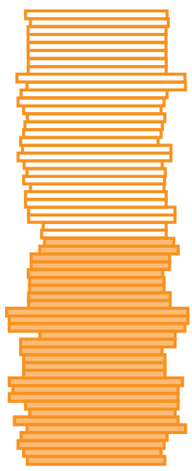
The Business Development Office initiates start-up ventures, partnerships and collaborative projects with the public and private sectors to help achieve translation of discoveries to the clinic.

28
Consumer buddies paired with research groups

21
PhD students with medical training

22
Clinician researchers

>30 million patients benefited worldwide



>50%
of publications relate to clinical translation

37
Patents granted in 2015

CANCER

One in two Australians will be diagnosed with a cancer by the age of 85. The institute has clinical and translational research programs focused on blood, breast, bowel, lung, ovarian and stomach cancers.

World first clinical trials give hope for new leukaemia treatment

The institute has collaborated in the first clinical trials of a potent new anti-cancer drug that is showing promise for treating people with advanced forms of chronic lymphocytic leukaemia (CLL).

The novel tablet treatment, venetoclax, was developed based on a landmark discovery made in the 1980s by Walter and Eliza Hall Institute scientists that a protein called BCL-2 promoted cancer cell survival.

"THIS IS A VERY EXCITING RESULT FOR A GROUP OF PEOPLE WHO OFTEN HAD NO OTHER TREATMENT OPTIONS AVAILABLE"

Professor Andrew Roberts, head of clinical translation at the institute and a clinical haematologist at The Royal Melbourne Hospital, said 79 per cent of patients in the phase 1 trial responded positively to the therapy, showing substantial reductions in the number of leukaemia cells in their body.

"Many patients have maintained this response more than a year after their treatment began, and some patients remain in remission more than four years on," Professor Roberts said.

"This is a very exciting result for a group of people who often had no other treatment options available."

The trials were conducted at the institute's Victorian Comprehensive Cancer Centre partners, The Royal Melbourne Hospital and the Peter MacCallum Cancer Centre, as well as at trial sites in the US, in collaboration with the Walter and Eliza Hall Institute.

Phase 2 and phase 3 studies are currently being undertaken to test venetoclax across a range of blood cancers globally, including at many sites in Australia.

Venetoclax was co-developed for clinical use by US pharmaceutical companies AbbVie and Genentech, and was discovered by AbbVie scientists as part of a joint research collaboration that involved Walter and Eliza Hall Institute scientists.

In 2015 the drug was granted Priority Review status by the US Federal Drug Agency (FDA) for treating some types of CLL that have a poor response to current therapies. The designation is granted to medicines that the FDA has determined to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a disease.

Promising cancer drug enters trial for breast cancer

Breast cancer is the most common cancer in Australian women, affecting one in eight women throughout their lifetime.

The majority of breast cancers are 'oestrogen receptor (ER)-positive' and many can be treated with hormone therapies such as tamoxifen. For some people with ER-positive breast cancer, however, hormone therapies are not effective, and chemotherapy is also required – often with serious side effects.

"WE ARE EXCITED THAT A DISCOVERY IN OUR LAB HAS GROWN INTO A TRIAL THAT COULD IMPROVE TREATMENT FOR BREAST CANCER PATIENTS"

Professor Geoff Lindeman, Professor Jane Visvader, Dr François Vaillant and Dr Delphine Merino are leading research to find new treatments for ER-positive breast cancer. The team has focused on the role of the protein BCL-2 in helping ER-positive breast cancers to resist treatment.

Venetoclax is a new anti-cancer agent that inhibits BCL-2, and has shown promise in phase 1 and 2 clinical trials for the treatment of advanced leukaemia.

Professor Lindeman and his colleagues are investigating whether venetoclax could also help people with ER-positive breast cancer.

The team showed that combining venetoclax and tamoxifen reduced tumour growth and improved survival in pre-clinical models, in some cases even leading to complete remission. The treatment was well tolerated, suggesting it may have fewer side effects than chemotherapy.

Professor Lindeman, who is a medical oncologist, is now leading a clinical trial at The Royal Melbourne Hospital and the Peter MacCallum Cancer Centre to determine the safest dose of venetoclax and tamoxifen in breast cancer patients before expanding to a larger cohort of patients and investigating how well the combination works.

"This is the first study in the world to evaluate venetoclax in a solid tumour," Professor Lindeman said. "We are excited that a discovery in our lab has grown into a trial that could improve treatment for breast cancer patients."

The trial is being delivered through a National Health and Medical Research Council Centre of Excellence in Translational Breast Cancer Research, with the help of medical oncologist Dr Sheau Wen Lok and centre coordinator Ms Kylie Shackleton.

The trial is supported by the Victorian Cancer Agency, the National Breast Cancer Foundation and AbbVie, the US pharmaceutical company that discovered venetoclax as part of a joint research collaboration that involved Walter and Eliza Hall Institute scientists.

Cancer research collaboration leads to landmark licensing agreement

The institute is a significant partner and contributor to the Cancer Therapeutics Cooperative Research Centre (CTx). Collaborative research at CTx has led to the development of a new class of drugs with potential for treating cancer and blood disorders.

Using the institute's high throughput screening and medicinal chemistry facilities over five years, Associate Professor Ian Street and Dr Hendrik Falk from the Systems Biology and Personalised Medicine division, working with Monash University and Alfred Health researchers, developed and tested new agents that inhibit a protein called PRMT5.

PRMT5 controls how genes are switched on or off in cells. High levels of PRMT5 are found in human cancers, including certain blood cancers, and are associated with a poor response to treatment. The CTx team's research suggested the newly developed PRMT5 inhibitors may have applications for treating cancer and blood disorders such as beta thalassemia and sickle cell anaemia.

In one of the largest preclinical biotech deals to arise from Australian research, CTx through one of its commercialisation partners, CRT UK, has licensed the rights to research and development of PRMT5 inhibitors to global healthcare company MSD, known as Merck in North America. The agreement includes an initial payment of $US15 million, future milestone payments, royalties, and support for further research into new treatments for blood disorders by CTx. A significant majority of the revenue will be returned to CTx and its partners.

"WE HAVE BEEN ABLE TO TAKE A LABORATORY DISCOVERY THROUGH TO A POINT THAT IT CAN BE LICENSED TO A GLOBAL COMPANY"

Associate Professor Street, who is the chief scientific officer of CTx, said the licensing deal with MSD was an important milestone for CTx and the Australian biotech sector. "We have been able to take a laboratory discovery through to a point that it can be licensed to a global company," he said. "As well as being an exciting development for healthcare, it has also put CTx, and Australian medical research, on the global biotech landscape."

Associate Professor Ian Street (right) and Dr Hendrik Falk (left) led the development of a new class of drugs with potential for treating cancer and blood disorders.

IMMUNE DISORDERS

Immune disorders, or chronic inflammatory diseases, are caused by an inappropriate immune response that attacks the body's own tissues. The institute has clinical and translational research programs focused on immune disorders including coeliac disease, rheumatoid arthritis, rheumatic fever and type 1 and 2 diabetes.

Unravelling the causes of immune deficiency

A healthy immune system works to protect the body against infection. Primary immunodeficiencies occur when part of the immune system is missing, leaving the body vulnerable to infections with common bacteria and viruses.

People with primary immunodeficiencies require life-long treatment to supplement their immune system. They suffer regularly from infections, and are also at a greater risk of developing autoimmune diseases and cancer.

Institute researchers Dr Vanessa Bryant and Dr Charlotte Slade, together with Professor Jo Douglass, head of immunology and allergy at The Royal Melbourne Hospital, are investigating the genetic causes of primary immunodeficiency. The research could lead to improved diagnosis and treatments for the condition.

The team recently made an important breakthrough, identifying a previously unrecognised genetic change that causes common variable immune deficiency (CVID), one of the most common forms of primary immunodeficiency.

By sequencing the genomes of people with CVID and their family members, the researchers were able to uncover gene variants associated with disease. They identified a fault in a gene encoding NF kappa B1, a protein involved in immune cell function, which had not previously been implicated in CVID.

The research was part of an international collaboration, with the faulty gene discovered in families from Australia, the Netherlands, Germany and New Zealand.

Dr Slade, who is a PhD student at the institute as well as a clinical immunologist at The Royal Melbourne Hospital, said that knowing the causative gene would have a great impact on management and treatment of primary immunodeficiencies.

"We are now one step closer to finding new treatments for CVID, which will be life changing for people whose immune system cannot defend the body from infections," she said.

Primary immunodeficiencies are caused by problems with immune function. Many are hereditary, yet for many families affected by primary immunodeficiencies, the genetic cause is not known. Dr Vanessa Bryant (left) and PhD student Dr Charlotte Slade (right) are investigating the genetic changes linked to a common form of inherited immunodeficiency.

Bringing hope to children with coeliac disease

Coeliac disease is a common autoimmune disorder causing digestive symptoms such as bloating, abdominal pain and diarrhoea, as well as fatigue, anaemia and nutrient deficiencies. People with coeliac disease are at elevated risk of osteoporosis, other autoimmune diseases, infertility and cancer.

The disease is caused by an inappropriate immune response to gluten, a protein found in wheat, barley and rye. Currently, the only treatment for coeliac disease is a lifelong gluten-free diet – which is restrictive and challenging to maintain, particularly for children.

"THERE IS A REAL NEED FOR BETTER DIAGNOSIS AND TREATMENT OF COELIAC DISEASE FOR ALL AGES"

Institute researcher and gastroenterologist at The Royal Melbourne Hospital Dr Jason Tye-Din and colleagues have performed a landmark study on childhood coeliac disease.

They discovered that the immune system of children with coeliac disease reacted to the same key toxic proteins in gluten that cause the disease in adults. This overturns the previously held view that coeliac disease was fundamentally different between children and adults.

The research offers hope for people with coeliac disease and their families, as it suggests new treatments and diagnostic tests under development for adults with coeliac disease could also benefit children with the condition.

One potential new treatment, called Nexvax2®, is an immunotherapy that aims to teach the immune system to tolerate gluten, which would allow patients to reintroduce gluten to their diets.

Nexvax2® is based on research from the Walter and Eliza Hall Institute and is being developed by US biotechnology company ImmusanT Inc. The treatment will soon enter phase 2 clinical trials for people with coeliac disease.

"There is a real need for better diagnosis and treatment of coeliac disease for all ages," Dr Tye-Din said. "Our findings are exciting as they suggest that new treatments such as Nexvax2® could help children as well as adults with the disease."

Finding the immune culprit in food allergy

Childhood food allergies are common in Australia, affecting up to one in every 10 babies in Melbourne during their first year of life.

The incidence of food allergies is rising, mostly among children under five years of age. In some people, food allergies can cause a severe, life-threatening immune reaction called anaphylaxis.

Institute researchers Professor Len Harrison, Dr Yuxia Zhang and colleagues are investigating childhood food allergies in the hope of guiding future treatments for babies and infants to prevent allergies developing.

They analysed the state of a baby's immune system at birth and linked this to data on food allergy collected by a large-scale infant health study called the Barwon Infant Study (BIS).

The BIS, led by paediatrician Associate Professor Peter Vuillermin, is a collaboration between Barwon Health, Deakin University, Murdoch Childrens Research Institute and the Walter and Eliza Hall Institute. The study collects health data from more than 1000 pregnant women and their babies from the Barwon region of Victoria.

The team discovered that babies with hyperactive immune cells at birth, detected in umbilical cord blood, were more likely to develop food allergies.

"We found a link between children who had hyperactive immune cells at birth and the development of allergies to milk, eggs, peanuts, wheat and other common foods in their first years of life," Professor Harrison said.

The next step for the research team is to identify why some babies have hyperactive immune cells.

"This study emphasises how critical it is to look at pregnancy and early life to really understand why chronic immune and inflammatory disorders such as allergies develop in childhood and later," he said.

Clinician scientist Dr Jason Tye-Din leads the institute's coeliac disease research program.

Dr Tye-Din's team has revealed significant similarities between coeliac disease in adults and children.

INFECTIOUS DISEASES

Infectious diseases continue to be a significant burden of disease globally, causing many millions of deaths. The institute has clinical and translational research focused on global health problems such as malaria, hepatitis B, HIV and tuberculosis.

Cancer drug shows promise as cure for hepatitis B

One-third of the world's population has been infected with the hepatitis B virus (HBV). Most people can suppress and control the virus, but approximately 400 million people worldwide have an incurable lifelong 'chronic' infection that causes persistent liver inflammation and puts them at risk of complications including liver disease and cancer.

Professor Marc Pellegrini, Dr Greg Ebert and colleagues have found a potential cure for HBV infections that proved 100 per cent successful in eliminating HBV infection in preclinical models.

The treatment combines a current antiviral treatment, entecavir, with birinapant, a drug that was developed by US biotech company TetraLogic Pharmaceuticals for treating cancer. The company is currently undergoing regulatory review in Asia to perform a clinical trial in hepatitis B patients.

Dr Ebert said birinapant targets the cell signalling pathways that HBV uses to keep host liver cells alive, enabling it to persist in the body for many years.

"Normally, liver cells would respond to infection by switching on a signal that tells the cell to destroy itself 'for the greater good', preventing further infection," he said.

"Our research showed that the virus commandeers the liver cells' internal communications, telling the cells to ignore the infection and stay alive. Birinapant flips the cell survival 'switch' used by the virus, causing the infected cell to die."

"WE ARE HOPEFUL THESE PROMISING RESULTS WILL BE AS SUCCESSFUL IN HUMAN CLINICAL TRIALS"

Professor Pellegrini said birinapant enabled the destruction of hepatitis B-infected liver cells while leaving normal cells unharmed. "Excitingly, the combination of entecavir and birinapant cleared the infection twice as fast compared with birinapant alone," he said. "We are hopeful these promising results will be as successful in human clinical trials."

Professor Pellegrini and his team are also investigating whether the same strategy could be applied to other chronic infectious diseases. "Pathogens that infect and reside inside host cells, including viral diseases such as HIV, herpes simplex and dengue fever, and bacterial infections such as tuberculosis, could all potentially be cured in a similar way," he said.

Dr Greg Ebert (left) and Professor Marc Pellegrini (right) are leading studies of a potential new treatment for hepatitis B. This discovery could help hundreds of millions of people worldwide with chronic hepatitis B virus infections.

Accelerating efforts to eradicate malaria

Malaria is a deadly disease caused by parasites transmitted via infected mosquitoes. Young children are particularly vulnerable to the disease, which causes more than 400,000 deaths worldwide each year.

The parasite *Plasmodium vivax* is responsible for most malaria cases outside of Africa, particularly in the Asia-Pacific and Americas. *P.vivax* can lie dormant in the liver for long periods of time, later reawakening to cause disease relapse.

> "THE FUNDING WILL SUPPORT DEVELOPMENT OF A DIAGNOSTIC TEST TO IDENTIFY PEOPLE WITH CHRONIC MALARIA INFECTIONS SO THAT WE CAN EFFECTIVELY TREAT THEM"

A team of researchers led by Dr Leanne Robinson and Professor Ivo Mueller recently discovered that most childhood cases of *P.vivax* malaria are the result of relapsing, not new infections. This poses a major challenge for malaria eradication efforts, as current programs cannot identify and treat children with dormant liver infections.

The research team is now using a AUD$1.15 million grant through the Global Health Innovative Technology (GHIT) Fund to accelerate development of a test that identifies people with dormant malaria parasites in the liver.

Professor Mueller said the GHIT grant was crucial for stopping the malaria transmission cycle.

"The funding will support development of a diagnostic test to identify people with chronic malaria infections so that we can effectively treat them, which will be critical for achieving malaria eradication in areas where *P.vivax* is a significant cause of disease," he said.

GHIT is a public-private partnership between Japanese pharmaceutical companies, the Japanese government and the Bill & Melinda Gates Foundation to leverage Japanese biotechnology capabilities to fight neglected diseases.

The research team will work with Japan's Ehime University, Switzerland's Foundation for Innovative New Diagnostics and Japanese biotech CellFree Sciences Co. Ltd. to develop biomarkers for *P.vivax* malaria that could drive the development of new diagnostic tools.

This is only the second diagnostic project supported by the GHIT Fund and the first to be led by an Australian research institute.

Attracting investment in tropical medicine

Forty per cent of the world's population, including around one million Australians, live in tropical regions, where they are exposed to significant health challenges.

In 2015 the Northern Australia Investment Forum was held in Darwin, hosted by the Australian Government in conjunction with the state governments of Queensland, the Northern Territory and Western Australia.

> "FOR MORE THAN 30 YEARS, THE INSTITUTE HAS BUILT ITS RESEARCH EXPERTISE IN INFECTIOUS DISEASES"

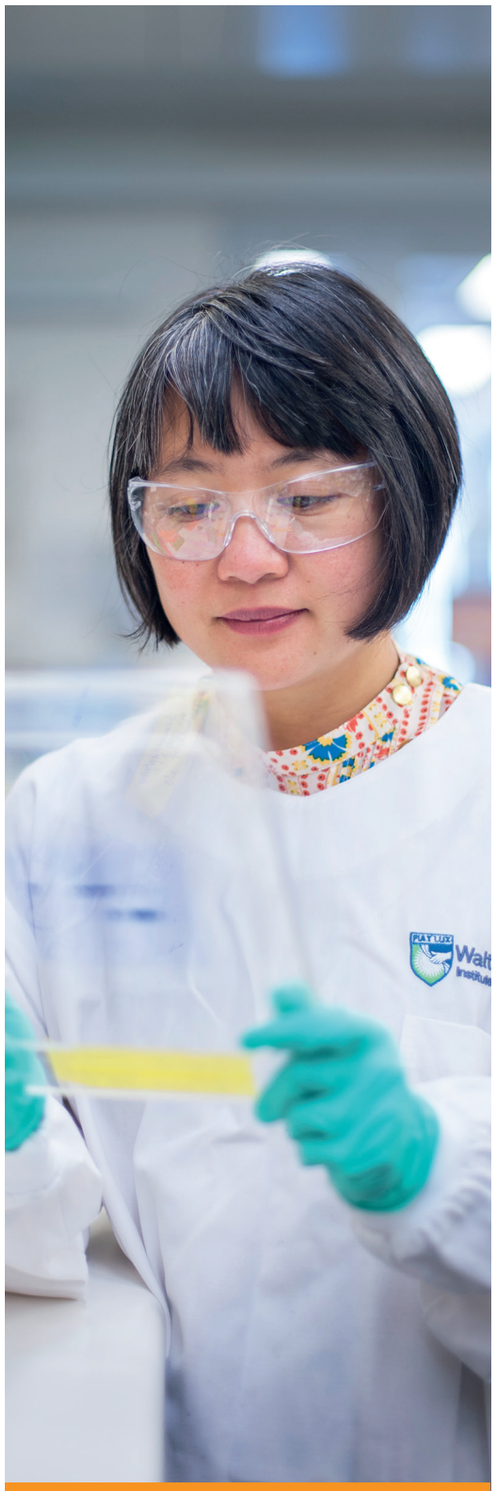
One of the focuses of the forum was investment in tropical medicine, and the institute was one of the Australian organisations invited to discuss potential opportunities with more than 350 business leaders from 20 countries.

Dr Julian Clark, Head of Business Development, said the forum provided the institute with the opportunity to present more than 20 investment-ready medical research projects to an international audience of investors.

"For more than 30 years, the institute has built its research expertise in infectious diseases," he said. "Recently our research has tackled some of the biggest tropical health challenges including malaria, drug-resistant tuberculosis, dengue fever and meliodosis."

At the forum, the Australian Department of Industry, Innovation and Science launched the Australian Tropical Medicine Commercialisation Grants program, which will allocate $8.5 million in funding to support commercialisation of Australian tropical medicine research.

"The Australian Government's commitment to boosting the economic growth of Northern Australia, and enabling investment in tropical health research will not only benefit Australians, but also has the potential to improve the health of billions of people around the world," Dr Clark said. "The institute is in an outstanding position to contribute to these advances."



In 2015 there were more than 200 million cases of malaria worldwide, causing more than 400,000 deaths.

Dr Wai-Hong Tham's research team is investigating how malaria parasites evade our immune system and penetrate red blood cells. Their goal is to identify new ways to block the malaria life cycle, thereby preventing disease.

PARTNERSHIPS

The institute is involved in a number of national and international partnerships to drive research and translation forward and deliver health benefits to the community.

Powerful partnership to improve cancer care

The Walter and Eliza Hall Institute is proud to be the research powerhouse of the Victorian Comprehensive Cancer Centre (VCCC), with scientists at the forefront of research into cancers of the blood, bowel, brain, breast, ovary, pancreas, prostate, skin and stomach.

"THE STRENGTH OF THE VCCC LIES IN THE CLOSE TIES IT FOSTERS BETWEEN THE LABORATORY-BASED, CLINICAL AND OTHER RESEARCHERS IN ITS PARTNER ORGANISATIONS"

The VCCC aims to improve health through an integrated approach to cancer prevention, detection and treatment.

The VCCC is a partnership of major Melbourne health organisations: the Walter and Eliza Hall Institute, Peter MacCallum Cancer Centre, Melbourne Health, The University of Melbourne, The Royal Women's Hospital, Royal Children's Hospital, Western Health, St Vincent's Hospital Melbourne, Austin Health and Murdoch Childrens Research Institute.

The institute has a strong track record of translating our research into clinical benefits for patients, with discoveries such as the colony stimulating factors improving the lives of millions of cancer patients worldwide.

Professor Jim Bishop, Executive Director of the VCCC, said the institute was an important contributor to Victoria's cancer research capabilities.

"The strength of the VCCC lies in the close ties it fosters between the laboratory-based, clinical and other researchers in its partner organisations," he said. "This means that discoveries made in basic science at the Walter and Eliza Hall Institute will be translated into new treatments for cancer as rapidly in Melbourne as anywhere in the world. Similarly, clinical problems can be more quickly solved by engaged laboratory researchers at the institute."

Professor Andrew Roberts, who heads the institute's Clinical Translation Centre, as well as being the VCCC's education and research lead in haematology, said the institute's cancer researchers were excited to be founding members of the VCCC workforce. "Now that the VCCC is underway, we're looking forward to driving the next generation of improvement in cancer care," he said.

Alliance opens the door to the genomic medicine era for Victorian patients

The institute is a founding member of a Victorian alliance evaluating the usefulness of genomic sequencing in providing better diagnosis and care for patients with cancers and rare diseases.

During 2015, the Melbourne Genomics Health Alliance evaluated how genomic information might provide more personalised care for patients with medical conditions including hereditary neuropathy, acute myeloid leukaemia, colorectal cancer, focal epilepsy and genetic conditions of childhood.

To best understand genomics' impact, the alliance has developed a model in which targeted groups of patients are offered genomic sequencing alongside usual approaches to diagnosis and care. Outcomes of each approach can then be compared and evaluated.

Early evaluation of the alliance's 2014-2015 phase of work involving more than 300 patients has found that genomic sequencing is a far superior test for some conditions, providing quicker and more accurate diagnosis and improved patient care. The alliance has also been investigating how genomics might best be supported within Victoria's healthcare system.

Institute researchers involved include clinician-scientist Professor Andrew Roberts, who led the project on acute myeloid leukaemia, clinician-scientist Dr Charlotte Slade, Associate Professor Melanie Bahlo and Dr Ian Majewski.

The Victorian Government has now committed $25 million in funding over four years (2016-2019), to support an expanded phase of alliance activity, involving up to 2000 patients.

The institute is one of seven founding alliance members, with The Royal Melbourne Hospital, The Royal Children's Hospital, The University of Melbourne, Murdoch Childrens Research Institute, CSIRO and the Australian Genome Research Facility – with Peter MacCallum Cancer Centre, Austin Health and Monash Health joining from 2016.

TECHNOLOGY

Crunch time for high-performance computing

In laboratories throughout the Walter and Eliza Hall Institute a growing brigade of bioinformaticians and computational biologists plays a vital role analysing data generated on high-performance computing equipment. But the rapidly increasing volume of data has risked outpacing the institute's computing resources. A more centralised approach to high-performance computing and the creation of a new centre to coordinate this are tackling the problem.

The Centre for Computational Biology, led by Associate Professor Tony Papenfuss, is now poised to oversee a big leap forward in high-throughput computing.

Associate Professor Papenfuss said the institute had implemented a plan for the purchase and roll out of equipment that would expand research computing four-fold.

"The new capacity in high-performance computing will make a massive difference," Associate Professor Papenfuss said. "It's going to enable lots of new techniques not only in data analysis but also mathematical modelling.

"In the past it had become challenging to analyse even a single whole genome sequencing data set at the institute; the new equipment will make analysis of multiple whole genome sequencing datasets possible," he said.

"THE NEW CAPACITY IN HIGH-PERFORMANCE COMPUTING WILL MAKE A MASSIVE DIFFERENCE"

Whole genome data is used, for example, to understand the formation and evolution of complex genomic arrangements in cancer, which can shed light on the genesis of some types of cancers and how they evolve, as well as revealing new targets for therapy.

Associate Professor Papenfuss said the new equipment would accelerate his laboratory's research analysing the entire DNA sequence of the scabies mite. Skin scabies infections are a significant health problem in Aboriginal communities, and are associated with bacterial infections that lead to rheumatic heart disease and chronic kidney disease.

The institute's microscopy and imaging capabilities are other areas that will benefit from improved research computing, Associate Professor Papenfuss said.

Under the new plan, 'cloud' computing – offsite, online computing – will eventually be made available to researchers, and a research computing scientist recruited to work within the Centre for Computational Biology will help laboratories access internal and external computing resources.

"What's made it easier to get this far is the amazing, collaborative effort of the many people in the institute's Information Technology Services and the computational biologists who contributed their ideas," Associate Professor Papenfuss said.

Breakthrough cancer research technologies to advance treatments

A partnership between the Australian Cancer Research Foundation (ACRF) and Melbourne's Walter and Eliza Hall Institute has led to the establishment of an Australian-first facility to research and develop new treatments for cancer.

The $2.5 million ACRF Breakthrough Technologies Laboratory is giving researchers new insights into how cancer develops, and how it can be more effectively treated.

"THE FACILITY WILL HELP TO ACCELERATE NEW TREATMENTS FOR PEOPLE WITH CANCER IN AUSTRALIA AND WORLDWIDE"

The facility is Australia's first dedicated cancer laboratory to use 'CRISPR/Cas9' technology to target and directly manipulate genes in cancer cells. This will be used by researchers from the Walter and Eliza Hall Institute and its Victorian Comprehensive Cancer Centre partners to enhance and accelerate research into many of Australia's most common, and most deadly, cancers including cancers of the blood (leukaemia, lymphoma), breast, ovary, lung and bowel.

The director of the Walter and Eliza Hall Institute, Professor Doug Hilton, said the ACRF Breakthrough Technologies Laboratory would provide an enormous boost to Australia's cancer research efforts. "It has become clear that technologies such as CRISPR/Cas9 can accelerate new breakthroughs in understanding cancer and developing new treatments," he said.

"The generosity of ACRF and its donors has allowed us to equip our research teams with precisely the technologies they need to advance their research," Professor Hilton said.

Mr Tom Dery AO, chairman of the ACRF board, said the contributions Australian researchers were making to improving the prevention, diagnosis and treatment of cancer were very significant.

"More than 14 million people around the world were diagnosed with cancer last year, including more than 125,000 Australians," he said.

"We are proud to enable the groundbreaking research conducted at the ACRF Breakthrough Technologies Laboratory. The facility will help to accelerate new treatments for people with cancer in Australia and worldwide," Mr Dery said.

A $2.5 million grant from the Australian Cancer Research Foundation has enabled the institute to establish the ACRF Breakthrough Technologies Laboratory, providing institute researchers with new insights into how cancer develops and how it can be more effectively treated.

A centrepiece of the facility is 'CRISPR/Cas9' gene editing technology, the first such application in a dedicated cancer research laboratory in Australia.

PATENTS GRANTED IN 2015

Apoptosis-inducing agents for the treatment of cancer and immune and autoimmune diseases
Inventors: P Colman, P Czabotar, G Lessene
Japan, Mexico, Peru, South Africa, Ukraine, US

Barley with low levels of hordeins
Inventor: G Tanner
Mexico, Japan, US

Modified cells and methods of using same
Inventors: L Corcoran, A Kallies, P Hodgkin, S Nutt
Canada

Compounds and methods of use
Inventors: P Czabotar, P Colman, B Sleebs, G Lessene
France, Germany, Hong Kong Italy, Japan, Mexico, Russian Federation Spain, Turkey, UK, US

Dendritic cell marker and uses thereof
Inventors: A Lew, K Shortman
Australia

Immunogenic compositions and uses thereof
Inventor: L Schofield
Denmark, Germany, France, Hungary, Ireland, Switzerland, UK

Methods and compositions for treating and preventing malaria using an invasion ligand directed to a protease-resistant receptor
Inventor: A Cowman
US

Methods of detecting cells with a disrupted cell membrane, cells infected with a pathogen, dying cells or dead cells
Inventors: D Huang, K Shortman
Australia

Protein kinase inhibitors and methods of treatment
Inventors: G Lessene, T Burgess
Australia, Japan, US

Soluble CD52
Inventor: L Harrison
Singapore

Structure of the C-terminal region of the insulin receptor alpha chain and the insulin-like growth factor receptor alpha chain
Inventor: M Lawrence
Denmark, Germany, France, Ireland, Netherlands, Sweden, Switzerland, UK

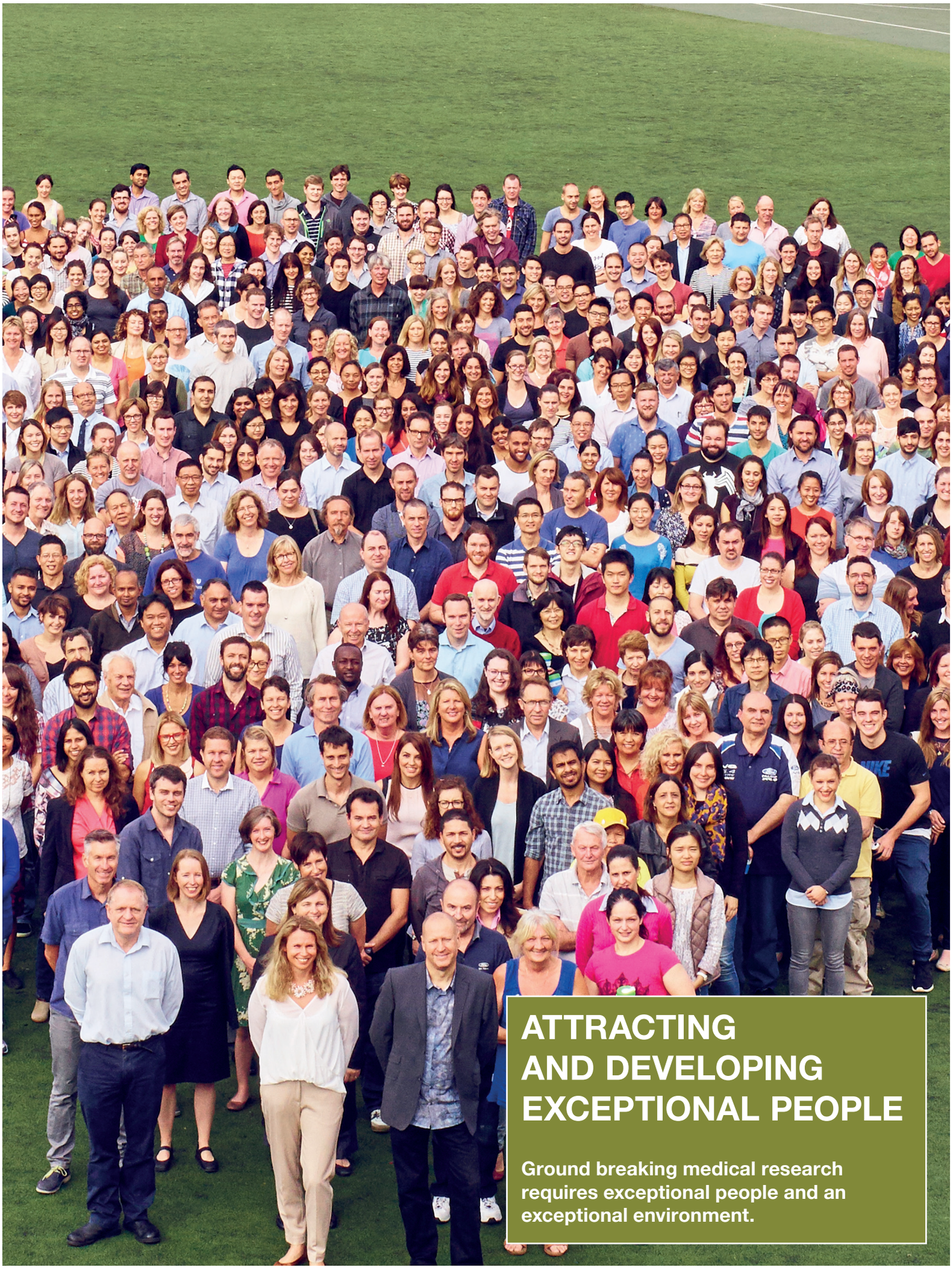
Structure of the C-terminal region of the insulin receptor alpha chain and the insulin-like growth factor receptor alpha chain
Inventor: M Lawrence
Australia

Structure of the insulin receptor ectodomain
Inventor: M Lawrence
Belgium, France, Germany, Ireland, Italy, Netherlands, Sweden, Switzerland, UK

Therapeutic molecules and methods for generating and/or selecting same
Inventor: D Fairlie
Canada

Treatment and prevention of malaria
Inventor: A Cowman
China, US

Triazine compound
Inventors: G Lessene, T Burgess
Australia, New Zealand, US



ATTRACTING AND DEVELOPING EXCEPTIONAL PEOPLE

Ground breaking medical research requires exceptional people and an exceptional environment.

EDUCATING THE NEXT GENERATION

Metcalf Scholarships support our brightest young minds

Established in honour of the remarkable contributions of Professor Don Metcalf, who passed away on 19 December 2014, the Metcalf Scholarships support undergraduate students to get hands-on lab experience while still at university.

Three undergraduate students, Mr Adam Lipszyc, Ms Madeleine Dawson and Ms Kimberley Callaghan were our inaugural Metcalf Scholars. The students are some of the youngest researchers at the institute, supported by the scholarships to work in the laboratory with institute research teams.

Institute director Professor Doug Hilton said that involving aspiring scientists in the reality of life in the lab was the best way to ignite their passion for a research career. "These bright young scientists are the ones who'll be making key discoveries in the years to come," he said. "We need to support and nurture them from the very start of their careers."

Professor Metcalf worked at the Walter and Eliza Hall Institute for an impressive six decades and made an outstanding contribution not just to medical science, but also to the careers of many young researchers.

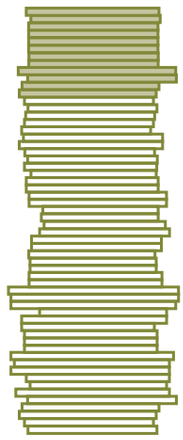
More than 200 people, including patients who had benefited from Professor Metcalf's research, scientists and colleagues, contributed more than $525,000 to establish the Metcalf Scholarship Fund as a permanent tribute to Professor Metcalf.

Professor Hilton said the community would remember and pay tribute to Professor Metcalf's legacy for many decades to come. "Don was an inspiration to us all at the institute and we miss him," he said.

"I am overwhelmed by the community's generosity in remembering Professor Metcalf, and I know Don would be excited about the opportunities that young researchers will receive through this fund, just as he was supported as a young researcher," Professor Hilton said.

Metcalf Scholars will be announced each year at the institute's Annual General Meeting.

166
number of students



19
publications with student authors with impact factor >10

78
publications with student authors

Metcalf Scholarships have enabled undergraduate students Ms Madeleine Dawson (left), Mr Adam Lipszyc (centre right) and Ms Kimberley Callaghan (right) to gain experience of working in a research laboratory. The scholars are pictured with institute director Professor Doug Hilton (centre left).

A pathway to new anti-inflammatory drug targets

A recently described cell death pathway called necroptosis has been implicated in a variety of inflammatory diseases, including psoriasis, rheumatoid arthritis and Crohn's disease.

Necroptosis occurs when damaged or infected cells are programmed to die, and as well as eliminating the problematic cell, the process alerts the immune system to a potential threat.

Ms Catia Pierotti received the Colman Speed Honours Award as the top honours student at the institute in 2015. Her honours research project, supervised by Associate Professor Guillaume Lessene and Dr Jean-Marc Garnier, focused on characterising novel inhibitors of necroptosis. This was supported by a scholarship from the Strathmore Community Bank.

Ms Pierotti's interest in necroptosis arose during her undergraduate studies, when she completed an Undergraduate Research Opportunity Program (UROP) placement in Associate Professor Lessene's laboratory.

This work led to her being an author on a research paper published in the *Proceedings of the National Academy of Sciences* in 2014, and encouraged her to continue in this research field.

"I was really interested in the work I was doing in my UROP placement and decided that I wanted to continue investigating necroptosis in my honours year," she said.

Her honours project involved identifying the biological targets of a panel of small molecule necroptosis inhibitors. She hopes that validation of the targets she identified – the proteins MLKL and RIPK1 – may improve our understanding of necroptosis and contribute to the development of new drugs to treat inflammatory diseases.

> "I MET MANY HIGHLY MOTIVATED AND INSPIRATIONAL PEOPLE WHO WERE INCREDIBLY SUPPORTIVE AND ENCOURAGING OF STUDENTS,"

Ms Pierotti said she found her honours year challenging and rewarding. "It was a wonderful experience to work among the institute's world-class scientists in an environment with outstanding facilities, a strong culture of learning, a high standard of research and fantastic academic and social support for students."

A highlight of her honours year was the opportunity to collaborate with many scientists throughout the institute.

"I met many highly motivated and inspirational people who were incredibly supportive and encouraging of students," Ms Pierotti said.

She also enjoyed attending conferences, including the Japan Australia Meeting on Cell Death.

Ms Pierotti will continue her investigations of necroptosis for her PhD studies at the institute.

Ms Catia Pierotti received the Colman Speed Honours Award as the top honours student at the institute in 2015, for her research into new approaches to prevent a form of cell death called necroptosis.

Contributing to science and society

Apoptosis, or programmed cell death, is a natural process that eliminates damaged cells or those that are no longer required by the body. Defects in apoptosis can lead to cancer and may also play a role in neurodegenerative diseases.

Dr Jason Brouwer's PhD research examined the proteins that trigger apoptosis. Using the Australian Synchrotron, he visualised for the first time how a protein called Bak is activated, leading to cell death. The research was published in *Molecular Cell*.

"I ORIGINALLY GOT INTO SCIENCE TO CONTRIBUTE SOMETHING POSITIVE TO SOCIETY"

Dr Brouwer, who graduated in 2015, said his research revealed that Bak takes on two different forms. "In normal circumstances, Bak sits in an inert way and can't kill the cell," he said.

"When a cell experiences stress or danger, Bak undergoes structural changes that open up the protein, allowing it to interact with other activated Bak proteins and trigger cell death."

Dr Brouwer said it was amazing to see how the protein underwent its transition from inert protein to killing machine.

"Driving home from the synchrotron after seeing the first images, I felt like I was flying in my car!"

During his PhD, Dr Brouwer also contributed to a publication in the journal *Cell Death and Disease* describing new tools for analysing cell death.

He hopes that understanding how apoptosis is triggered could lead to new drugs for diseases where apoptosis goes awry, such as neurodegeneration, cancer or stroke.

But science isn't Dr Brouwer's only passion. Coming from a small country town, Dr Brouwer also has a keen interest in Aboriginal and Torres Strait Islander health and reconciliation.

He is an active member of the institute's Reconciliation Committee and has played a key role in developing and promoting our Reconciliation Action Plan (RAP). He has also volunteered as a teacher in a remote Aboriginal community through the Teachabout program and tutored Aboriginal and Torres Strait Islander high school students through the Yalari initiative.

"I originally got into science to contribute something positive to society," Dr Brouwer said. "During my PhD I realised I could contribute in other areas as well. I hope that through my involvement in establishing the RAP at the institute I can have a lasting impact on reconciliation."

Dr Brouwer's dedication to both his research at the institute and the broader community was recognised by the Rotary Club of Melbourne, which presented him with a Young Achiever Award in 2015.

Aberrant cell death is an important contributor to diseases including cancer, neurodegenerative diseases and stroke. Dr Jason Brouwer's PhD studies focused on understanding the molecular detail of how cell death is regulated.

Turning the tables on chronic infections

Our immune system protects us against diverse infectious diseases, but some organisms have evolved to evade our immune defenses. One common strategy is for microbes to hide out within cells, allowing the infection to persist in our body long term and avoiding immune clearance.

Treating these chronic infections by manipulating the immune system has been the focus of Dr Samar Ojaimi's PhD studies with Professor Marc Pellegrini.

"IT MAY BE TIME WE CHANGE FOCUS TO TARGET THE HOST RATHER THAN THE MICROBE"

Dr Ojaimi, who is also a clinician specialising in immunology and infectious diseases, said chronic infections such as HIV, hepatitis B and multidrug resistant strains of tuberculosis were an enormous global health burden.

"We're clearly not winning with our current approaches to treating chronic infections, that target the microbe," she said. "For many infections we are seeing growing rates of resistance to conventional treatments. It may be time we change focus to target the host rather than the microbe."

Dr Ojaimi's research has focused on manipulating cell death signalling in cells infected with the bacterium that causes tuberculosis, an infection found in more than one-third of the world's population.

"We found that by using new classes of medications that activate cell death, we could reduce the burden of tuberculosis infection," Dr Ojaimi said. "The development of antibiotic resistance has been an enormous challenge to treating tuberculosis, but we are hopeful that by directing our treatments at the host cell rather than the microbe - and killing the infected host cell - the bacteria won't be able to grow as effectively".

"My research aims to provide new insights into the complex interactions between tuberculosis bacteria and their host cell. These are key to enabling a chronic infection. The next step will be to see how these new treatments can be combined with antibiotics or immune-boosting medications to further enhance the clearance of tuberculosis infections," she said.

Tuberculosis is not the only chronic infection in Dr Ojaimi's sights. She hopes that the new medication classes she is investigating might also be effective in treating the neglected tropical disease leishmaniasis, a parasitic infection that affects approximately 12 million people worldwide.

Immune cells key to good digestive health

Innate lymphoid cells (ILCs) are a family of immune cells found in the lining of body surfaces including the digestive system.

ILCs play a crucial role in regulating the immune system, helping prevent diseases such as asthma, inflammatory bowel disease and psoriasis.

"I ENJOYED ENGAGING WITH MY COLLEAGUES AT ALL LEVELS, WHICH ALLOWED FOR THE FLOWING OF IDEAS AND RESOURCES."

Dr Lucille Rankin, who completed her PhD at the institute in 2015, was part of a research team that revealed how ILCs act in concert with other immune cells for proper digestive health. Dr Rankin was the first author on a research publication describing this in *Nature Immunology*.

Using a model of gastrointestinal infection that is localised to the intestine, Dr Rankin showed that ILCs were an important component of the body's defences.

"The intestinal immune system consists of a diverse array of cell types," she said. "Some, like ILCs, respond early during infection, while others, like T cells, are recruited later and are highly specific for particular types of bacteria.

"These multiple layers of the immune system provide a failsafe mechanism for protection from disease – even when one layer of defence is depleted, the body has 'back ups' that can fight infection."

Dr Rankin's supervisor Professor Gabrielle Belz said the study also showed ILCs helped the appendix maintain digestive health. "ILCs protect the gut during an infection, allowing specialised organs such as the appendix to reseed 'good' bacteria throughout the body and restore digestive balance," she said.

The study was performed in collaboration with colleagues at the Centre d'Immunologie de Marseille-Luminy, France.

Dr Rankin said the success of the study was a testament to the collaborative environment at the institute. "I enjoyed engaging with my colleagues at all levels, which allowed for the flowing of ideas and resources."

Dr Rankin previously discovered the genes required for development of ILCs, in a study that led to another first author *Nature Immunology* paper in 2013.

Dr Rankin's success during her PhD studies led to her receiving a commendation in the Victorian Premier's Award for Health and Medical Research in 2015.

Dr Rankin is now undertaking postdoctoral studies at Weill Cornell Medicine, New York, US, where she is investigating how interactions between bacteria and diet may influence the immune system.

Collaborating divisions:

Molecular Immunology, Bioinformatics, Inflammation

Collaborating partners:

Centre d'Immunologie de Marseille-Luminy, France

Funding partners:

Australian National Health and Medical Research Council, Australian Research Council, European Research Council, Ligue Nationale contre le Cancer (France), IINSERM (France), CNRS (France), Agence Nationale pour la Recherche (France), Aix-Marseille University to Centre d'Immunologie de Marseille-Luminy (France), Institut Universitaire de France, the Victorian Government Operational Infrastructure Support Program

More information:

Rankin LC *et al*. Complementarity and redundancy of IL-22-producing innate lymphoid cells. *Nature Immunology*. 2016 Feb;17(2):179-86

2015 GRADUATES

Congratulations to the following students who successfully completed their studies this year.

Doctor of Philosophy, The University of Melbourne

Dr Fiona Angrisano
Dissecting the molecular basis of malaria parasite movement and host cell traversal in the mosquito midgut
Associate Professor Jake Baum, Professor Alan Cowman, Dr Geoffrey McFadden

Dr Natasha Anstee
Studies of the role of Mcl-1 in haemopoiesis and leukaemia
Professor Suzanne Cory, Dr Cassandra Vandenberg

Dr Priscilla Auyeung
Autoreactive T cells in chronic idiopathic urticaria
Professor Len Harrison, Professor Phil Hodgkin, Dr Diana Mittag

Dr Julian Bosco
Investigations of CD52-mediated immune regulation in the mouse
Professor Len Harrison, Dr Bandala Sanchez, Dr Yuxia Zhang

Dr Jason Brouwer
Structural transitions during cell death: Bak activation and oligomerisation
Dr Peter Czabotar, Professor Peter Colman

Dr Sandunie Dineika Chandrananda
Analysis of whole-genome sequencing data from cell-free DNA in maternal plasma to detect fetal aneuploidy
Associate Professor Melanie Bahlo, Professor Terry Speed, Dr Natalie Thorne

Dr Kelan Chen
Mechanistic and structure-function characterisation of the epigenetic regulator Smchd1
Dr Marnie Blewitt, Dr James Murphy

Dr Nima Etemadi
Investigating the roles of activators, inhibitors and regulators of tumour necrosis factor receptor-1 signalling
Professor John Silke, Professor David Vaux, Dr Ueli Nachbur

Dr Danika Hill
Merozoite antigens of *P. falciparum* elicit strain-transcending opsonising immunity
Professor Louis Schofield, Professor Alan Cowman

Dr Colin Hockings
The Bcl-2 apoptotic switch – clarifying the functions of proapoptotic and prosurvival players
Dr Ruth Kluck, Professor Jerry Adams, Dr Grant Dewson

Dr Sweta Iyer
Bak (and Bax) activation and apoptotic pore formation: roles for the a1-a2 loop and C terminus
Dr Ruth Kluck, Professor Peter Colman, Dr Brian Smith

Dr Timothy Johanson
The role of Drosha, Dicer and microRNAs in the development of dendritic cells
Associate Professor Andrew Lew, Dr Mark Chong, Dr Yifan Zhan

Dr Grace Liu
Investigating the role of Pax5 hypomorphism in B-progenitor acute lymphoblastic leukaemia
Associate Professor Ross Dickins

Dr Kevin Man
Regulation of CD8 T cell differentiation and metabolic reprogramming by the T cell receptor dependent transcription factor IRF4
Dr Axel Kallies, Professor Stephen Nutt

Dr Julia Marchingo
A quantitative analysis of T cell responses to stimulatory inputs
Professor Phil Hodgkin, Dr Susanne Heinzel

Dr James McCoy
The role of calcium dependent protein kinases in *Toxoplasma gondii* cell signalling
Dr Chris Tonkin, Professor Alan Cowman

Dr Darcy Moore
Identification of epigenetic modifiers involved in neural stem cell function
Dr Marnie Blewitt, Professor Douglas Hilton, Dr Clare Parish

Dr Maya Olshina
Actin regulation in *Plasmodium falciparum*: towards understanding the elusive nature of malarial actin filaments
Associate Professor Jake Baum, Dr Jacqui Gulbis, Dr Wilson Wong

Dr Lucille Rankin
Distinct requirements of T-bet and Nfil3 for the generation of innate lymphoid cell populations
Professor Gabrielle Belz, Professor Stephen Nutt

Dr Maryam Rashidi
Soluble CD52 inhibits innate immune signalling and is a potential therapeutic for inflammatory diseases
Professor Len Harrison, Dr John Wentworth, Dr James Vince

Dr Leona Rohrbeck
Regulation of the pro-apoptotic BH3-only protein BIM
Dr Marco Herold, Professor Andreas Strasser

Dr Victoria Ryg-Cornejo
B cell responses during severe malaria: the impact of inflammation on T follicular helper cell and germinal centre responses
Dr Diana Hansen, Professor Ivo Mueller

Dr Tana Taechalertpaisarn
Analysis of 6-cys proteins and calcium fluxes during erythrocyte invasion by *Plasmodium falciparum* parasites
Professor Brendan Crabb, Professor Alan Cowman, Dr Tony Hodder, Dr Paul Gilson

Dr Jesse Toe
Manipulation of apoptotic signaling promotes cell-mediated immunity and death of infected cells during chronic viral infection
Professor Marc Pellegrini, Professor Gabrielle Belz

Dr Hannah Vanyai
The molecular and germ layer-specific functions of the histone acetyltransferase MOZ in embryonic development
Associate Professor Anne Voss, Associate Professor Tim Thomas

Dr Matthew Witkowski
Reversible tumour suppression by Ikaros in mouse models of acute lymphoblastic leukaemia
Associate Professor Ross Dickins, Dr Mark McKenzie

Dr Alan Yap
Function of ligands in *Plasmodium falciparum* invasion of human erythrocytes
Professor Alan Cowman, Dr Paul Gilson, Dr Diana Hansen

Dr Janet Yeo
Characterisation of the putative RNase III enzyme Mrpl44: investigations into Mrpl44's role in RNA processing and the regulation of the mitochondrial OXPHOS system
Dr Mark Chong, Professor Gabrielle Belz

Dr Kelvin Yip
Niche factors stimulate the formation of colon crypts in vitro
Professor Tony Burgess, Dr Jonathan McQualter

Dr Elizabeth Zuccala
Cell-cell interactions during malaria parasite invasion of the human erythrocyte
Associate Professor Jake Baum, Professor Alan Cowman, Professor Ivo Mueller, Dr Silvia Haase

Bachelor of Science (Honours), The University of Melbourne

Ms Maria Bergamasco
The role of MYST4 in the regulation of neural stem cells and inner ear development
Associate Professor Anne Voss, Associate Professor Tim Thomas

Mr Mario Tirta Djajawi
Investigating the mechanism of Noxa-mediated MCL1 degradation
Dr Mark van Delft, Professor David Huang

Ms Qiutong (Angela) Huang
Immune regulation of intestinal inflammation and colon cancer
Dr Lisa Mielke, Dr Tracy Putoczki, Professor Gabrielle Belz

Ms Stephanie Hyslop
The role of platelets in lung cancer
Dr Emma Josefsson, Professor Warren Alexander

Ms Annette Jacobsen
Cell-based approaches to unveil necroptosis effectors downstream of MLKL activation
Dr James Murphy, Professor John Silke

Mr Isa Khan
Role of unkempt and ZC3H10 in TNF-Regulation
Dr Philippe Bouillet, Dr Derek Lacey

Ms Isabella Yingjia Kong
PRC2 regulates division destiny of CD4+ T lymphocytes
Dr Susanne Heinzel, Dr Rhys Allan

Ms Ranit Lahmy
Design of fluorescent probes for studying the malarial protease plasmepsin V
Dr Justin Boddey, Dr Brad Sleebs, Professor Alan Cowman

Mr Indiana Matti
Investigating orthologues of the pseudokinase, mixed lineage kinase domain-like (MLKL) and its molecular mechanism of action
Dr James Murphy, Dr Peter Czabotar

Ms Kimberly Morgan
Manipulating cancer in zebrafish model
Associate Professor Joan K Heath, Dr Karen Doggett

Ms Catia Pierotti
Chemical probes for target identification of necroptosis inhibitors
Associate Professor Guillaume Lessene, Dr Jean-Marc Garnier

Ms Catherine Pitt
The role of the histone acetyltransferase TIP60 during early embyonic development
Associate Professor Anne Voss, Associate Professor Tim Thomas

Mr Richard Sun
Elucidating the link between caspases, interferons and platelet biogenesis
Professor Ben Kile, Dr Stephane Chappaz

Ms Leisa-Rebecca Watson
Investigating the role of CXCR3 in CD4+ T cell responses to influenza virus
Dr Joanna Groom, Professor Gabrielle Belz

VISIBLE AND INSPIRING LEADERS

Researchers join new Academy of Health and Medical Sciences

Seven institute researchers were recognised in 2015 for their contributions to medical research, with their election as fellows of the newly established Australian Academy of Health and Medical Sciences.

The academy promotes medical research and its translation to enable a healthier community both in Australia and globally. Fellows are elected for outstanding leadership and distinguished professional achievement in their field.

Institute clinician-scientists Professor Len Harrison, Professor Geoff Lindeman and Professor Andrew Roberts, institute director Professor Doug Hilton, and cancer researchers Professor Nick Nicola, Professor Warren Alexander and Professor David Vaux were among almost 200 eminent Australians appointed as fellows of the Australian Academy of Health and Medical Sciences.

Walter and Eliza Hall Institute patron and former director Sir Gustav Nossal has also been named an honorary fellow and patron of the academy.

New laboratory heads boost institute research

Eight new laboratory heads were appointed in 2015, bringing a range of new research skills and disease interests to the institute. Our new faculty members were:

Dr Rhys Allan, whose research is focused on understanding the causes of allergic diseases such as asthma and food allergy, and autoimmune conditions such as lupus.

Dr Joanna Groom, studying how the function of the immune system is influenced by the movement of immune cells around the body, and interactions between immune cells.

Dr Edwin Hawkins, discovering how immune cells that protect us from infection function efficiently and keep us healthy, and how defects in immune cells contribute to autoimmune disease and cancer.

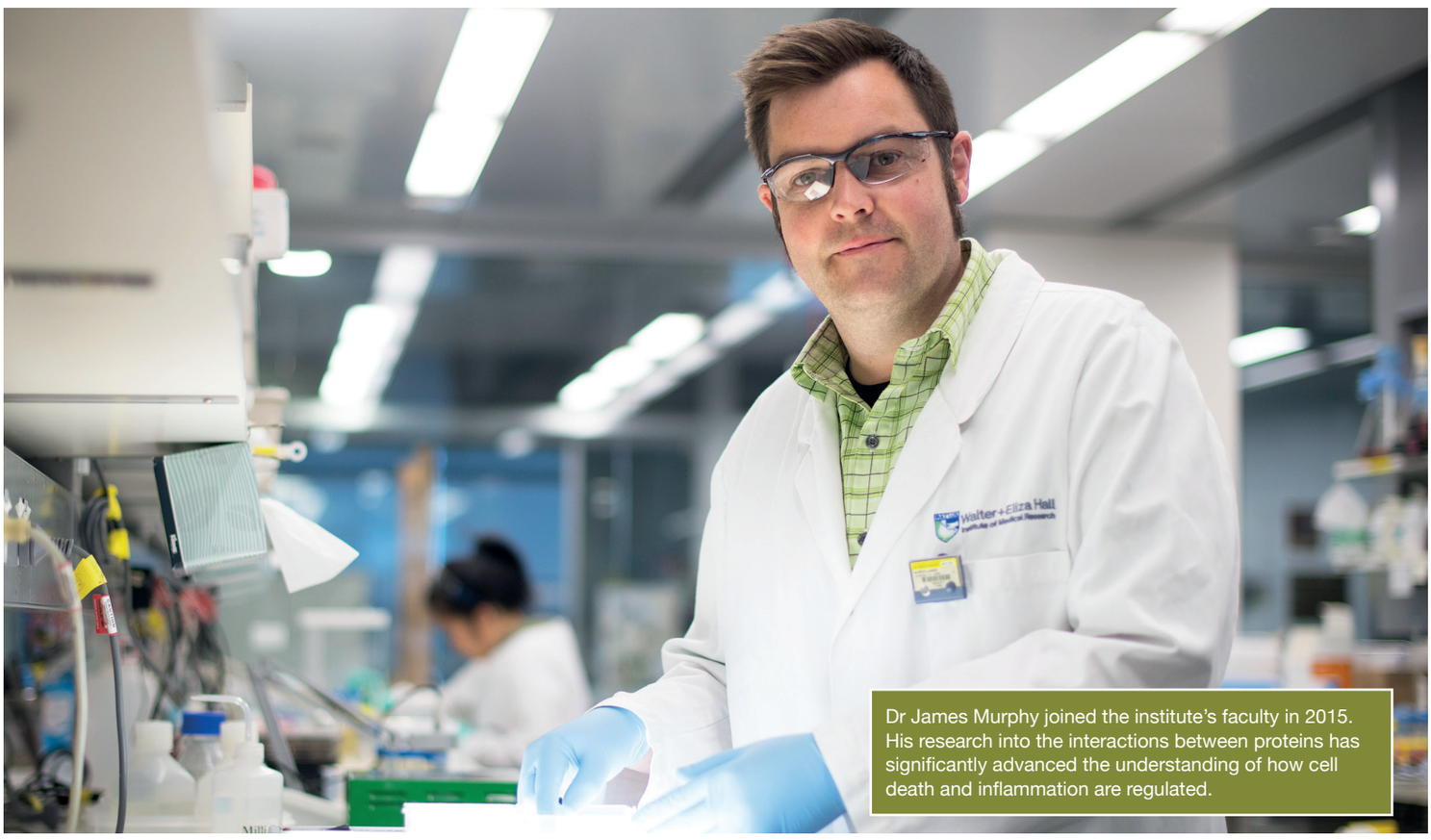
Dr Aaron Jex, who investigates the biology of gastrointestinal parasites, including worms and agents of diarrhoeal disease, with the goal of developing approaches to better control these infections.

Dr Ian Majewski, investigating why there is large variation in how cancer patients respond to anti-cancer therapy, and defining genetic mutations that contribute to the development of leukaemia.

Dr James Murphy, whose research is focused on understanding how proteins within cells interact, and how genetic mutations that perturb these interactions can cause human disease.

Dr Leanne Robinson, based at the Papua New Guinea Institute of Medical Research, where she leads a program aimed at improving the prevention, diagnosis and treatment of mosquito-borne parasitic diseases, particularly malaria and filariasis.

Dr Andrew Webb, whose laboratory applies the latest proteomics methods to understand how changes in proteins in our body influence health and disease, and develops new techniques to advance basic and clinical research.



Dr James Murphy joined the institute's faculty in 2015. His research into the interactions between proteins has significantly advanced the understanding of how cell death and inflammation are regulated.

DIVERSITY AND INCLUSION

Driving innovation and a positive workplace culture

We embrace and celebrate diversity amongst our people and know the importance of a positive workplace culture to the success of our organisation.

We are working hard to create a fully inclusive workplace and to ensure that the diverse voices of our staff and students are heard and can influence policy, practice and decision-making at the institute. This is guided by the key diversity principle, "nothing about us, without us".

We know we must attract and retain the most talented people from the broadest talent pool to achieve our goals.

We strive for equity so all our people have equal access to employment opportunities and we have diversity of representation at senior levels. We know we still have work to do and we will continue to tackle the barriers that stand in the way of our people reaching their full potential.

CONTINUING ON OUR RECONCILIATION JOURNEY

Delivery of our first Reconciliation Action Plan

We are proud to report the successful implementation of our first Reconciliation Action Plan (RAP). The RAP enabled the institute to build a strong foundation under the areas of *Respect, Relationships* and *Opportunities*, that are necessary to take us on the next stage of our reconciliation journey.

It is testament to the success of the institute's RAP program and the organisation's long-term commitment to reconciliation, that Aboriginal and Torres Strait Islander people are a key focus in the institute's *Strategic Plan 2015-2020*. The institute has committed to increasing its work on diseases that disproportionately affect Aboriginal and Torres Strait Islander people, to better involve Aboriginal and Torres Strait Islander people in broader medical and clinical research conversations and create meaningful and sustainable training and employment opportunities for Aboriginal and Torres Strait Islander people.

Key achievements towards reconciliation in 2015 included:

- strengthening our partnership with the CareerTrackers Indigenous Internship program;
- building strong relationships with Aboriginal and Torres Strait Islander leaders and organisations;
- obtaining membership of Supply Nation, an Indigenous supplier diversity organisation;
- holding reconciliation seminars on Aboriginal and Torres Strait Islander health;
- capacity building with local organisations working to improve Indigenous health and education outcomes;
- cultural awareness-raising activities for staff and students including guided walks led by the Koorie Heritage Trust;
- celebrating NAIDOC week with an exhibition of the institute's Aboriginal art collection; and
- hosting a Parkville Community Leaders Breakfast with the theme 'taking action to improve Indigenous health outcomes'.

We commenced development of our second RAP in 2015, with a comprehensive consultation process with internal and external stakeholders. The new RAP will outline our actions to deliver on reconciliation aligned to the goals in the *Strategic Plan 2015-2020*.

Nurturing the next generation of Indigenous scientific leaders

The institute is committed to playing a leading role in growing the next generation of Aboriginal and Torres Strait Islander health and medical researchers.

We are proud to be entering the third year of a partnership with CareerTrackers, a national non-profit organisation offering internships and work experience opportunities for talented Aboriginal and Torres Strait Islander undergraduate students.

To date, five Aboriginal and Torres Strait Islander students, Ms Kristy Meiselbach, Ms Nancy Fintic, Mr Dylan Lester, Ms Lilly Backshell and Ms Keisha Nash, have undertaken internships in our laboratories, enabling them to gain invaluable experience working with some of Australia's leading scientific minds and put their university theory into practice. All our interns have displayed a real aptitude and enthusiasm for a career in science.

Ms Meiselbach and her supervisor, Dr Tracy Putoczki, were awarded the CareerTrackers 2015/2016 Project of the Year, selected from a pool of more than 1000 participants.

The program is already realising its potential to create meaningful pathways into the scientific workforce. Ms Meiselbach, who will commence Honours at the institute in 2016, said her experience as a CareerTrackers intern was life-changing. "Winning the award with Tracy was just icing on the cake for what has been an unbelievable experience," she said. "I'm excited about my next chapter here and seeing where that takes me."

5
Aboriginal and Torres Strait Islander interns

35
Staff and students attended cultural learning activities

3
Supported organisations working to improve Indigenous health and education outcomes

5
Reconciliation-focussed seminars and events

GENDER EQUITY IN ACTION

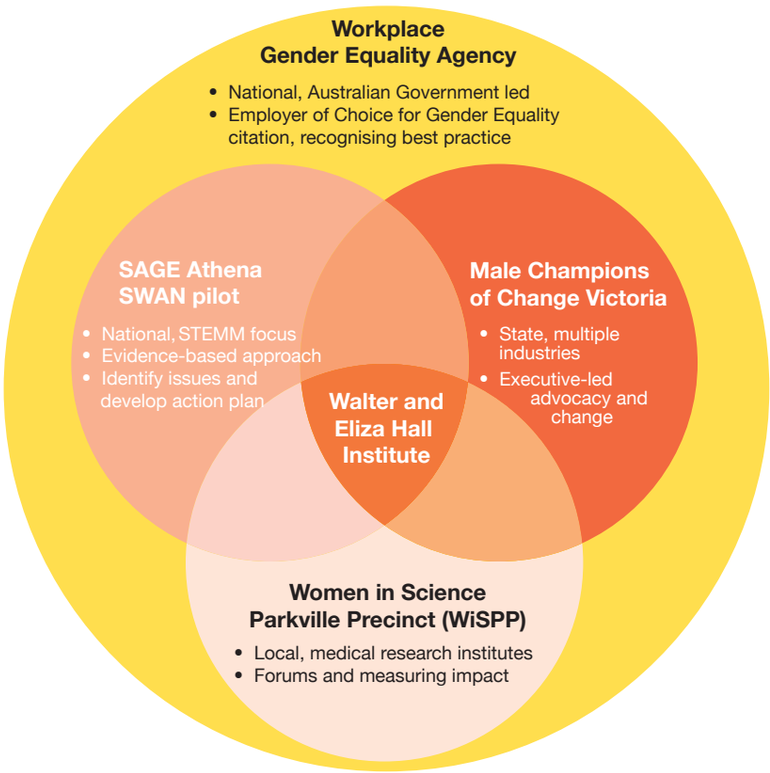
Our institute is acutely aware of the challenges experienced by women in the scientific workforce. Although women have made up the majority of biology undergraduates in Australia for decades, progress towards parity at senior levels has been slow. This loss and under-utilisation of half our talent pool is something we cannot afford to let continue.

The institute is a leader in Australia's scientific sector. With this comes a responsibility to show leadership in achieving workplace gender equity; and we still have some way to go.

Although there has been some increase in numbers over time – 31 per cent of our laboratory heads and 14 per cent of our division heads are women – around half of institute postdoctoral researchers are women. Addressing the barriers to career advancement for women scientists is therefore a significant focus of the institute's gender equity activities.

Tackling gender inequity ultimately improves conditions for all. Access to flexible working can provide benefits to both women and men in achieving work:life balance and enable a sharing of caring responsibilities.

The institute has committed to programs to achieve gender equity across our institute, our sector and our community. These initiatives complement each other in several areas such as measurement and accountability, flexibility in the workplace and raising the profile of women in science.



SAGE pilot of the Athena SWAN Charter

The institute joined more than half of Australia's universities and science organisations in a pilot program to improve the promotion and retention of women and gender minorities in science, technology, engineering, mathematics and medicine (STEMM).

The Athena SWAN (Scientific Women's Academic Network) charter evolved in the UK to advance the representation of women in STEMM. Australia's Athena SWAN pilot is a two-year program established by the Science in Australia Gender Equity (SAGE) program, an initiative of the Australian Academy of Science and the Australian Academy of Technological Sciences and Engineering.

As part of the pilot, the institute will collect and analyse data and other evidence to understand gender equity across a range of indicators, using workshops, surveys, interviews, policy review and analysis, and database interrogation. This will guide an action plan to address the issues and gaps found.

Male Champions of Change Victoria

Institute director Professor Doug Hilton was named as one of 20 inaugural 'Male Champions of Change' by the Victorian Equal Opportunity and Human Rights Commission, for his work to improve the representation of women at senior levels of medical research.

The Male Champions of Change is a state-based, high profile coalition across multiple industries and is part of a national initiative. It aims to enhance collaborations and resource development to enact high-impact change that will improve gender equity in workplaces and communities. The champions are influential male corporate, government and community leaders leading on gender equity through action and advocacy.

Women in Science Parkville Precinct (WiSPP)

This local initiative involves five medical research institutes in Parkville, promoting the maintenance of an environment that enables more women in science to lead and excel. WiSPP also provides a platform for change and empowerment, challenging the *status quo*, through increasing the profile of women in key roles.

Along with regular seminars and discussion forums promoting women in science, WiSPP is collating data across the five participating institutes to measure the impact of gender equity activities.

Strengthening research links with Asia

With the ongoing transformation of the global economy, the past 25 years have seen a significant growth in biomedical research capacity in Asia, particularly in China.

The Walter and Eliza Hall Institute has been home to many researchers from Asia, including Professor Li Wu, a medical graduate from Peking University, China, who undertook a PhD at the institute in the 1980s. Professor Wu now holds a joint appointment at the institute and at Tsinghua University, China.

> "WE HOPE IT WILL FOSTER NEW AND LONG-TERM SCIENTIFIC COLLABORATIONS, AND STRENGTHEN EXISTING TIES WITH TOP CHINESE UNIVERSITIES"

Because of the institute's strong research track record, especially in translating basic research to the clinic, we have developed a strategic approach to engaging with researchers and leading research organisations in Asian countries.

A major focus of our current efforts is Tsinghua University, widely considered to be one of the top two Chinese universities. Visiting students from Tsinghua are undertaking two years of research training at the institute, before returning to Beijing to complete their graduate studies. Such student exchanges and visits by Walter and Eliza Hall Institute faculty to top institutions such as Tsinghua are establishing long-term research collaborations and strengthening our ties with these institutions in China.

Professor David Huang, who oversees the institute's relationships with China, said the institute had also established an exciting new program, InSPIRE (International Student Program in Research Experience), to commence in 2016. "The institute will host internship students from four of China's top universities, Fudan, Nanjing, Nankai and Tsinghua," he said. "The students will participate in a 10-week research experience program at the institute, which will involve rotations though different laboratories and weekly seminars from leading institute researchers.

"The InSPIRE program aims to provide talented visiting students with an experience of biomedical research in Australia, promoting the institute as an attractive destination for biomedical research. We hope it will foster new and long-term scientific collaborations, and strengthen existing ties with top Chinese universities," Professor Huang said. The institute will also host trainee clinician scientists from the Shanghai General Hospital, part of the School of Medicine at Shanghai Jiao Tong University.

In addition to current activities that are building links with China, the institute is also developing links with researchers in India and exploring new opportunities in Vietnam.

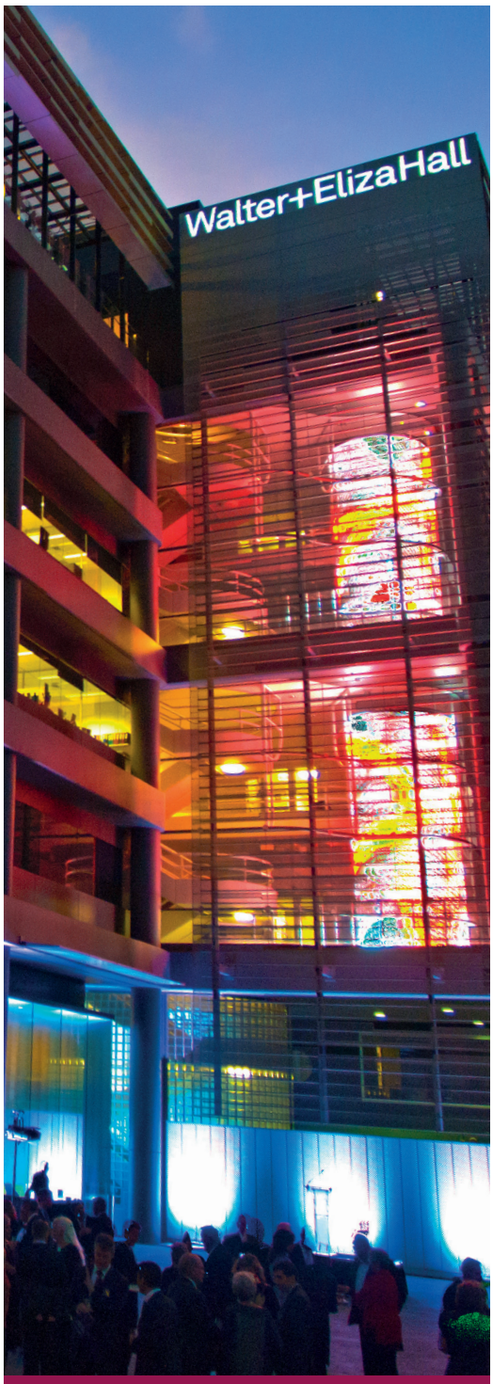
"We see these strategic engagement efforts as essential if we wish to draw on the widest pool of research talent possible, and maximize our investments in translational research as we head into the so-called Asian century," Professor Huang said.

Ms Yao Yuan (left) is a medical student from Tsinghua University, China, who is undertaking Masters research with Professor David Huang (right) and Professor Andrew Roberts. Ms Yao's research focuses on understanding how cell death proteins influence cancer cells' response to treatment.

SECURING THE SUPPORT WE NEED

The institute does not exist in isolation. To achieve our goals, we rely on productive partnerships with external organisations, and on the support of the community.

CELEBRATING OUR CENTENARY



The Illuminarium, an impressive LED light installation was designed by award-winning biomedical animator Mr Drew Berry, in celebration of the institute's centenary.

Biomedical animations displayed on the installation can be seen by people on the streets adjacent to the Parkville campus, generating a new interest in the institute.

To mark our centenary year, the institute hosted a diverse program of events and activities at its Parkville campus, elsewhere in Melbourne including Federation Square and Government House, and at Parliament House, Canberra.

Carefully designed to engage a range of valued members of the institute community, the events and activities successfully attracted staff, students, donors, alumni, collaborators, peers and government representatives, as well as many members of the broader community who had not previously heard of the institute.

Our centenary activity was programmed to collectively pay homage to a rich century of discoveries for humanity, explore health challenges our researchers are tackling today, and look ahead to what might be in store for the next 100 years.

Within the institute, a series of Centenary Games promoted team building and a sense of shared history. Staff and students came together to represent their areas of expertise and participate in friendly competitions, building and strengthening friendships. Scientific seminars attracted people to our Parkville campus, where a new sculpture commemorating our first director designate was also unveiled.

For the broader community, science was brought to life through art, theatre, film and public talks in a lively civic celebration of the Walter and Eliza Hall Institute's biomedical research. The release of a commemorative Australia Post stamp issue and new website dedicated to the institute's history were also launched for the momentous occasion.

Prime minister launches centenary

Prime Minister the Honourable Tony Abbott officially launched the institute's centenary celebrations on 12 March, delivering a speech to more than 250 guests gathered on the institute's Parkville forecourt.

The Prime Minister congratulated the institute on its significant history of discoveries. "You have every reason to savour your first 100 years, and I look forward to seeing the advances that will come from the institute in its next 100 years," he said.

An a cappella blessing from Torres Strait Islanders was followed by the unveiling of the *Illuminarium*, an impressive 25-metre-tall LED installation by award-winning institute animator Mr Drew Berry. As dusk set in, the *Illuminarium* came to life with glowing, revolving biomedical animations revealing the beautiful imagery found in scientific research.

Also in attendance at the cocktail event was the original 1912 Silver Ghost Rolls Royce that Mr Walter Hall had purchased for Eliza. The antique car was marveled at by guests and made a popular addition to photographs captured at the event.

Governor hosts celebrations

A formal reception was hosted at Government House by His Excellency the Honourable Alex Chernov AC QC, Governor of Victoria. In recognition of the institute's contribution to society, more than 150 Walter and Eliza Hall Institute staff and supporters, including alumni and donors, were welcomed to the residence to reflect upon an amazing history of discoveries and celebrate the people behind the science.

Science comes to life at Federation Square

The primary public engagement event of the institute's centenary year was the Science in the Square Festival, held in August at Federation Square in Melbourne's city centre.

Institute director Professor Doug Hilton said the festival encouraged new audiences of all ages and backgrounds to engage with the wonders of science. "Science in the Square was all about exploring science in a way that everyone can be part of," he said.

Presented as part of National Science Week 2015 and the Melbourne Writers' Festival, Science in the Square attracted thousands to have fun with science and learn how current work and past discoveries from the institute benefit the lives of tens of millions of people.

The festival was launched by Ms Esther Anatolitis, director of Regional Arts Victoria, and institute deputy director Professor David Vaux in the Atrium at Federation Square.

Talking Science

In a free public forum at Deakin Edge, clinicians and scientists Dr Jayesh Desai, Dr Kylie Mason, Professor Grant McArthur, Dr Kate Sutherland and Associate Professor Clara Gaff came together to discuss the future of cancer research. Posed with the question: 'Will there ever be a cure for cancer?' the panelists delivered insightful presentations, which were followed by an audience Q & A session.

Art of Science exhibition

The Atrium at Federation Square was the site of a free admission, pop-up exhibition showcasing the beautiful imagery created and captured by institute scientists. Over the course of 12 days, more than 1000 people admired the 15 shortlisted works from the institute's 2015 Art of Science competition.

Walter and Eliza's Big Night Out

On 15 August, a full house at Deakin Edge roared with laughter as science and comedy collided in a stage show with a twist. Host Mr Paul McDermott led an all-star cast of Melbourne comedians including Ms Anne Edmonds and Mr Rod Quantock OAM. Written and directed by Mr Matt Parkinson, the trivia night both educated and delighted the crowd.

Silver Screen Science

Hollywood loves a good science fiction film... but what are the facts among the fiction? A free three-night science fiction film festival held at the Australian Centre for the Moving Image, in conjunction with the Melbourne Writers' Festival, delivered entertainment and education to hundreds of film buffs and science-lovers alike. Popular sci-fi titles *Contagion*, *Gattaca* and *Outbreak* were screened and followed by an illuminating discussion between the audience and a panel of researchers, science writers and artists.

Audience members enjoyed a live demonstration of 'elephant toothpaste' at the Science in the Square festival's headline event, Walter and Eliza's Big Night Out.

Centenary stamp issue released

Australia Post celebrated the centenary of the Walter and Eliza Hall Institute with the release of a stamp issue. The gold-coloured stamp was released on 30 June and featured institute cancer researcher Dr Tracy Putoczki.

Philatelic Manager of Australia Post Mr Michael Zsolt said the institute was an icon of Australian innovation, knowledge and service to the community. "This stamp issue highlights a centenary of achievements which we trust will resonate with all Australians," he said.

Scientific Symposium

A three-day scientific symposium featured presentations from 20 world-renowned scientists, including Nobel Laureates Professor Elizabeth Blackburn and Professor Tom Steitz.

Scientific Seminar Series

Hosted at the institute by director Professor Doug Hilton, a scientific seminar series featured internationally renowned scientists for a series of keynote presentations:

- **Professor Brenda Schulman**
  St Jude's Children's Research Hospital, US
  Dynamic mechanisms in ubiquitin-like protein conjugation cascades
- **Dr Eric Betzig**
  Howard Hughes Medical Institute, US
  Imaging life at high spatiotemporal resolution
- **Dr David Williams**
  Boston Children's Hospital, US
  Successes in gene therapy for monogenic diseases: a platform for future genome editing in the clinic
- **Dr Vishva Dixit**
  Genentech, US
  Lessons from death: the inflammasome and beyond

Dr Tracy Putoczki featured on the Walter and Eliza Hall Institute's centenary stamp issue, alongside images relating to current research.

A centenary of discoveries showcased online

The award-winning Discovery Timeline is a dynamic and immersive website dedicated to celebrating the institute's scientific journey in achieving real outcomes for health.

Through an engaging presentation of text, photographs and video, the site is a rich tapestry of stories capturing the milestone moments of discovery, key contributions to society, hard work and people – our staff, students, donors and alumni – who have made our institute the world-class powerhouse it is today.

The site preserves all that we have celebrated throughout our centenary year, and is an ever-growing resource for audiences to learn about the institute and become inspired by what medical research can offer humanity.

Through easily searchable pathways including time and themes such as 'conquering cancer' and 'treating immune disorders', the sheer impact that the institute's research has had within Australia and around the world is understood.

The Discovery Timeline received a 2015 Melbourne Design Award for its unique interface, combination of multimedia, cross-device responsiveness, and the careful consideration given to matching information and communication style with audience needs.

The inspirational journey begins at: discovery.wehi.edu.au

Commemorating Dr Gordon Clunes McKay Mathison

Special events were held on 18 May 2015 to commemorate the Walter and Eliza Hall Institute's first director designate, Dr Gordon Clunes McKay Mathison, marking the 100th anniversary of his death at Gallipoli during World War I. Historian and author Dr Ross McMullin delivered a moving historical lecture about Dr Mathison, a man of incredible potential whose untimely loss was felt by friends and colleagues around the world.

Dr Mathison is permanently commemorated in the institute forecourt by a two metre bronze memorial sculpture, *Irreparable Loss of Potential*, which was unveiled in a candle-lit ceremony. The memorial was created by local artist Mr Michael Meszaros and generously funded by the Dyson Bequest.

The institute's 100 years of contributions to Australia were celebrated at the Walter and Eliza Hall Institute of Medical Research Centenary Reception in the Mural Hall, Parliament House, Canberra. Pictured (left to right) are Opposition Leader the Hon Bill Shorten MP, institute director Professor Doug Hilton, Health Minister the Hon Sussan Ley MP and institute board president Mr Chris Thomas.

Building the teams that will make tomorrow's discoveries

Investing in the next generation of scientists is vital if we are to continue to tackle the significant and complex health challenges facing humanity.

In our centenary year we launched a campaign with the ambitious five-year aim of securing 100 fellowships for our most promising young researchers.

"OVER THE NEXT FIVE YEARS, WE WILL BE ABLE TO SELECT FROM AN IMPRESSIVE POOL OF TALENT AS WE BUILD THE RESEARCH TEAMS THAT WILL DRIVE THE DISCOVERIES IN THE COMING DECADE"

The centenary campaign reflects our increasing concern at the difficulties faced by early-career researchers, and our commitment to providing our most promising young scientists with the support and security they need to continue their vital work.

We are grateful to our founding centenary donors for sharing our vision and making an investment in the future health of all Australians by supporting our early-career researchers.

As a result of these centenary gifts and pledges, we have already been able to strengthen our research into diseases as diverse as multiple sclerosis, pancreatic cancer, childhood leukaemia, rare cancers and immune disorders. Many of our founding centenary donors generously provided funds for equipment and laboratory costs in addition to fellowship funding.

Our centenary fellowship donors are helping us to assemble the world-class research teams that will make discoveries in the next decades. More than 240 postgraduates from 39 countries applied for the first of the advertised five-year centenary fellowships.

Institute director Professor Doug Hilton said research was a global enterprise that drew together teams of people from around the world who are inspired to tackle the toughest health challenges facing humanity.

"We want the institute to be a dynamic hub for Australian and international researchers. We want to attract the best and the brightest to Australia, to Melbourne and to the institute so that Australian patients will be among the first to benefit from breakthroughs," he said.

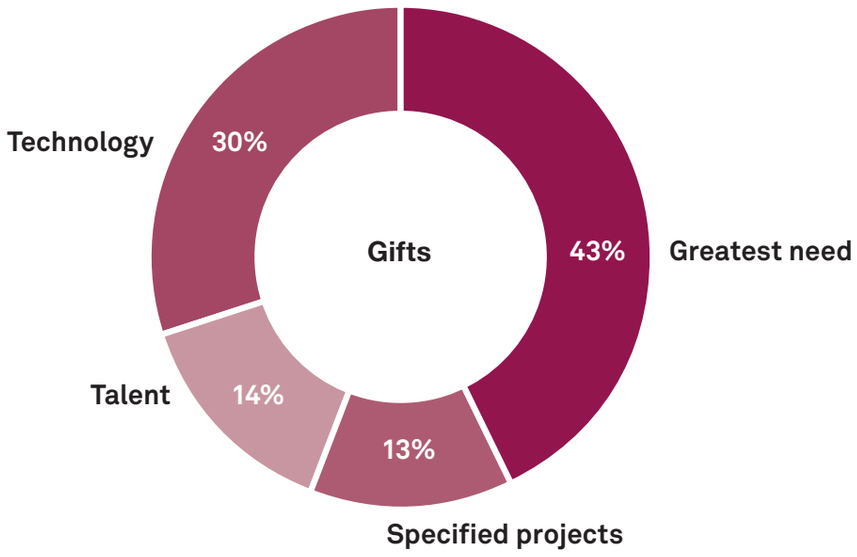
"The commitment by our centenary donors to support five-year fellowships has attracted high-quality candidates. Over the next five years, we will be able to select from an impressive pool of talent as we build the research teams that will drive the discoveries in the coming decade."

The centenary campaign secured more than $13 million in gifts and pledges in 2015. In addition, the institute received a record $16.36 million in philanthropic gifts. For the full year, the return on fundraising investment was $15 for every $1 invested. The institute's fundraising and marketing and communications teams received a national award for the centenary campaign from the Fundraising Institute of Australia.

Warmest thanks to our founding centenary fellowship donors:

- Mr Malcolm Broomhead
- Mrs Jane Hemstritch
- CSL Limited
- L.E.W. Carty Charitable Fund
- The Dyson Bequest
- The Alfred Felton Bequest
- The Stafford Fox Medical Research Foundation
- The Walter & Eliza Hall Trust
- Ormond College (co-funding the Thwaites Gutch Fellowship)
- The University of Melbourne

How your gifts made a difference



OUR SUPPORTERS

The supporters who make our discoveries possible

The advances in medical science at the Walter and Eliza Hall Institute are made possible by our generous supporters. We are proud to acknowledge these gifts, grants and bequests received from 1 January to 31 December 2015. Gifts of $1000 or more are acknowledged, unless otherwise requested by our donors.

The institute acknowledges the support of the Australian Government through funding from schemes including National Health and Medical Research Council and the Australian Research Council, and from the Victorian Government through schemes including the Operational Infrastructure Support (OIS) Program.

International grants

Grants of more than $500,000

Foundation for Innovative New Diagnostics, Switzerland
The Leukemia & Lymphoma Society, US
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Grants up to $500,000

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Grants up to $100,000

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Gifts up to $1,000,000

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Gifts up to $500,000

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Gifts up to $50,000

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Gifts up to $10,000

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Gifts up to $5000

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Estate of Sheila Jessie Thompson
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Estate of the late Mary Annie Shearer
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(listed by grant amount)

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The institute remembers those members who have passed away since 2014

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Mr Ronald Diamond
Mr Terry Flanagan
Mr John Gough AO OBE
Professor Emeritus Priscilla Kincaid-Smith AC OBE
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MAINTAINING A SUSTAINABLE ORGANISATION

Achieving outstanding scientific results over the long term requires a sustainable funding base and efficient and effective enablers of a creative and productive environment.

OPERATIONAL OVERVIEW

The institute experienced significant growth over the past five years, enabled by the completion of our building and renovation project in 2012. The next five years provide us with an opportunity to consolidate the benefits of this growth and capitalise on improved economies of scale.

Planning for success

Our *Strategic Plan 2015-2020* provides a compass that guides the institute's activities over this period, both in our scientific priorities as well as the professional services that maximise the opportunities for our researchers to continue to do great science.

"AN IMPORTANT ASPECT OF THE STRATEGIC PLAN WAS TO GUIDE A TRANSFORMATIONAL JOURNEY THAT WILL ENHANCE OUR PROFESSIONAL SERVICES, ENSURING THEY ARE EFFECTIVE, YET STREAMLINED AND EFFICIENT"

The management systems and business processes that were fit for purpose when the institute was considerably smaller are not scalable to the doubling in size of the institute. Thus, an important aspect of the strategic plan was to guide a transformational journey that will enhance our professional services, ensuring they are effective, yet streamlined and efficient – providing the best support for the institute's research missions, through optimised capability and cost effectiveness, while minimising administrative burden.

To support the deployment and implementation of the *Strategic Plan 2015-2020*, a comprehensive annual planning framework has been developed. A project management office and project governance framework have also been created to oversee the successful delivery of key projects across the institute. Improving the institute's capabilities in risk management has also been an important focus, ensuring the institute can sustain its growth, development and achievement without concomitant risks.

Enhanced financial processes

We continued to streamline the institute's financial management in 2015. Central to this was the shift in financial reporting to a calendar year that aligns with the funding grant cycle, an important measure for grant reporting and budget planning. A new e-procurement system has also been implemented to realise cost savings and minimise administrative burden on researchers – providing more money and time to do great science.

Institute Chief Operating Officer
Ms Samantha Ludolf

Building IT capacity

In recent years, the need for information technology support across all areas of the institute has rapidly grown in volume and significance. The rapid growth of scientific data requirements and the greater volumes of information sharing with collaborators have placed new demands on our IT services and systems. In 2015, under the stewardship of our newly appointed Chief Information Officer, Mr Michael Carolan, a plan for modernising our IT services has been created and implementation begun. One important aspect of this has been the enhancement of our high throughput computing capacity (see page 59). A new bioservices management system is also streamlining our research, compliance and budgeting capacities.

Growing and supporting our workforce

The institute's centenary celebrations highlighted the fact that groundbreaking medical research requires exceptional people. The *Strategic Plan 2015-2020* created a framework for continuing to attract the best people to join the institute, and nurture their careers. Our People and Culture review in 2015 has provided guidance for future enhancement of the institute's capabilities in recruitment, as well as career development, training and talent management. The institute has also continued to build on its commitment to diversity and inclusion, with key programs implemented to improve gender equity and reconciliation (see page 68).

"EXCEPTIONAL PEOPLE DESERVE AN EXCEPTIONAL ENVIRONMENT IN WHICH TO WORK"

Exceptional people deserve an exceptional environment in which to work. Since the expansion of our Parkville campus, our needs for our Bundoora campus have changed. In 2015 we completed a campus consolidation plan that saw redeployment of a number of staff from Bundoora to Parkville and Kew, with significant and timely renovations commenced at our Kew campus.

Access to childcare close to the workplace has also been identified as a significant barrier to career development of our researchers, particularly women. In December 2015, the institute board endorsed a proposal for a new early childhood education centre to be constructed on the institute forecourt. We are grateful to the Dyson Bequest and Professor Terry Speed and Mrs Sally Speed who have pledged generous gifts towards the centre.

Ms Samantha Ludolf
Chief Operating Officer
Walter and Eliza Hall Institute

Vale Mr Terry Flanagan

It was with sadness that the institute community farewelled Mr Terry Flanagan, an institute member who had served as a community representative on the institute's Animal Ethics Committee from 1997 to 2014.

Mr Flanagan made an enormous contribution to the institute's Animal Ethics Committee. Dr Catheryn O'Brien, Head of Bioservices, said: "He was diligent in his preparation for committee meetings, and in the 17 years of membership I only remember him missing a couple of meetings.

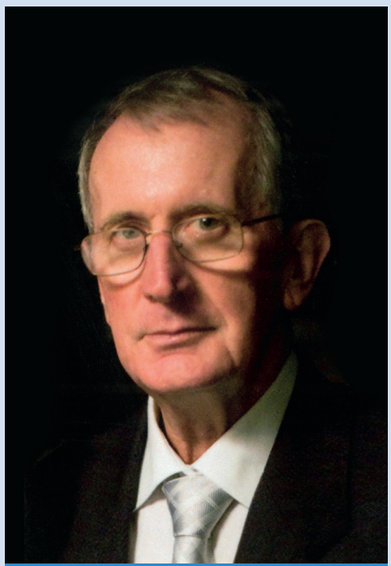
"Terry had great regard for the work of the institute and the importance of medical research generally, as well as having personally experienced the impact of serious health conditions in his family.

"I think that participating in the committee gave him a sense of contributing in some way to facilitate the work of our scientists, and he was always keen to hear of any research breakthroughs."

After Mr Flanagan's involvement in the Animal Ethics Committee concluded, he stayed in contact with the institute, becoming an institute member in 2014 and participating in the institute's centenary celebrations.

"Terry's wife Pauline told me that his involvement with the institute gave him a great deal of pleasure," Dr O'Brien said. "Terry was unfailingly courteous and kind, an erudite man who read widely and was interested in contributing to the wider community. I think he would have been pleased that he was able to contribute to his family and community right up until the end of his life.

"The members of the Animal Ethics Committee remember Terry fondly and still miss his company and contributions," she said.



Mr Terry Flanagan

WALTER AND ELIZA HALL INSTITUTE BOARD

The directors of the Walter and Eliza Hall Institute of Medical Research board
31 December 2015

Mr Christopher W Thomas

BCom (Hons) MBA *Melbourne* FAICD
Appointed: February 2001
Appointed President: February 2013

Mr Thomas joined executive search firm Egon Zehnder International in 1979 and was managing partner of the Melbourne office from 1986 to 2003. He was also leader of the firm's global Board Consulting Practice Group (1998-2006) and chaired the firm's twice-yearly international partners' meetings from 1997 to 2007.

Mr Thomas is a fellow of the Australian Institute of Company Directors, and is currently a member of the National Gallery of Victoria's Remuneration and Nomination Committee. He has served on the board of the Corps of Commissionaires (Victoria) and the Council of the Australian Film, Television and Radio School. He was a board member of the Heide Museum of Modern Art for nine years (and its chairman for three years), chairman of the Victorian Community Foundation and president of the Melbourne Business School Alumni.

Mr Steven Skala AO

BA LLB (Hons) *Qld* BCL *Oxon*
Appointed: June 1999
Appointed Vice President: March 2004

Mr Skala is vice chairman, Australia and New Zealand, of Deutsche Bank and a former senior partner of Arnold Bloch Leibler.

He is chairman of Blue Chilli Technology Pty Ltd and a director of Wilson HTM Investment Group Ltd. Active beyond banking and commerce, Mr Skala is chairman of the Heide Museum of Modern Art, is a director of the Centre for Independent Studies and The General Sir John Monash Foundation and is a member of the International Council of New York's Museum of Modern Art. Mr Skala is a former chairman of Film Australia Limited and the Australian Centre for Contemporary Art, and recently retired from the board of the Australian Broadcasting Corporation where he served as a director for 10 years.

Mr Robert Wylie

FCA FAICD
Appointed: April 2014
Appointed Honorary Treasurer: April 2014

Mr Wylie is a fellow of the Australian Institute of Company Directors, a fellow and past president of the Institute of Chartered Accountants in Australia and a member of the Institute of Chartered Accountants in Scotland. He is a non-executive director of Maxitrans Industries Limited.

Mr Wylie joined Deloitte in 1973 in the United Kingdom, transferring to Australia in 1976. He was national chairman of Deloitte Australia from 1993 to 2001. He was deputy managing Partner Asia Pacific from 2001 before joining Deloitte & Touche USA as a senior executive partner in 2002 to 2006. He was also a member of The Deloitte Global Board and Global Governance Committee as well as The Deloitte Consulting Global Board.

Associate Professor Rufus Black

BA LLB (Hons) *Melbourne* MPhil DPhil *Oxon*
Appointed: August 2013

Associate Professor Rufus Black has extensive private, public and social sectors experience at both management and governance levels with a deep academic background in ethics. He is master of Ormond College at The University of Melbourne, deputy chancellor of Victoria University, a director of the law firm Corrs Chambers Westgarth, and a principal fellow in both the Department of Philosophy and the Department of Management and Marketing at The University of Melbourne. He also chairs the Teach for Australia board and is a director emeritus of the New York-based Teach for All.

Associate Professor Black has previously worked as a partner at McKinsey & Company and has made many contributions to public policy. He holds degrees in law and politics from The University of Melbourne and graduate degrees in moral theology from the University of Oxford, where he was a Rhodes Scholar.

Mr Malcolm Broomhead

BE (Civil), MBA *UQ*, FIE (Aus), FAusIMM, FAIM, MICE (UK), FAICD

Appointed: July 2014

Mr Broomhead is a professional non-executive director. His directorships include BHP Billiton Limited and Plc and Asciano Limited (where he is also chairman) and Orica Limited (chairman).

Mr Broomhead was formerly managing director and CEO of Orica Limited from 2001 until September 2005. Prior to Orica, he was managing director and CEO of the global diversified resources company North Limited. Mr Broomhead has had extensive experience in the resources industry, as well as in finance, investment and construction activities. He has worked in management positions with Halcrow (UK), MIM Holdings, Peko Wallsend and Industrial Equity.

Mr Michael C Fitzpatrick

BA (Hons) *Oxon* BEng (Hons) *UWA*

Appointed: February 2001

Mr Fitzpatrick is chairman of the Australian Football League and Treasury Group Limited, a director of Infrastructure Capital Group, and a former director of Rio Tinto plc.

He is the founder and former managing director of Hastings Funds Management Limited. In that role, Mr Fitzpatrick was a director of a number of Hastings-managed investments including Pacific Hydro Limited, Global Renewables Limited, Utilities of Australia, Australian Infrastructure Fund and Airstralia Development Group Pty Ltd (Perth Airport).

Mr Fitzpatrick was a premiership captain (1981, 1982) with the Carlton Football Club in the Australian Football League and a first-grade cricketer. He was formerly a member of the Melbourne Park Tennis Centre Trust, a director of the Carlton Football Club, chairman of the Australian Sports Commission and, in the early 1980s, vice-president of the AFL Players' Association.

Dr Gareth Goodier

MB ChB *Sheffield* MHA *NSW* DHSc *Anglian Ruskin University* FRACMA FAFPHM

Appointed: August 2012

Dr Goodier commenced in the role as chief executive for Melbourne Health in June 2012. He qualified as a medical practitioner in 1974, and practiced as a clinician in the United Kingdom, Australia and Saudi Arabia before moving into management.

Over the past 23 years, Dr Goodier has worked as the chief executive for a number of academic teaching hospitals and health authorities. In addition, he has worked as a management consultant for the World Bank and Arthur Andersen.

Dr Goodier returned to the United Kingdom as the CEO of the Royal Brompton and Harefield NHS Trust in 2003 and was later appointed as the CEO of North West London Strategic Health Authority. In September 2006, he was appointed as the CEO of Cambridge University Hospitals NHS Foundation Trust.

Mrs Jane Hemstritch

BSc (Hons) *London University* FICAEW FICAA FAICD

Appointed: October 2013

Mrs Hemstritch was managing director Asia Pacific for Accenture Limited from 2004 until her retirement in February 2007. In this role, Mrs Hemstritch was a member of Accenture's global executive leadership team and oversaw the management of Accenture's business portfolio in Asia Pacific.

She holds a Bachelor of Science with honours in Biochemistry and Physiology and has professional expertise in technology, communications, change management and accounting.

Mrs Hemstritch is a member of the Council of The National Library of Australia, the Global Council of Herbert Smith Freehills, the Council of Governing Members of The Smith Family and Chief Executive Women. She is an independent non-executive director of Lend Lease Corporation Limited, Tabcorp Holdings Ltd, and Victorian Opera Company Ltd (chairman from February 2013).

Professor James McCluskey

BMedSc MB BS MD *UWA* FRACP FRCPA FAA FAHMS

Appointed: April 2011

Professor James McCluskey has been the deputy vice-chancellor (research) at The University of Melbourne since 2011. He is also a Redmond Barry Distinguished Professor in Microbiology and Immunology.

Professor McCluskey is known for his research in basic and clinical immunology in the area of genetic control of specific immunity. He has consulted for the Australian Red Cross in the area of transplantation matching for more than 25 years.

He is a member of the board of directors of the Bionics Institute, Australian Friends of Asha Slums and UoM Commercial. He is Chair of Nossal Institue Ltd. He has previously been a director of the Florey Institute of Neuroscience and Mental Health, St Vincent's Institute and the Burnet Institute. He led the development of the Peter Doherty Institute for Infection and Immunity, a joint venture between The University of Melbourne and Melbourne Health.

Dr Graham Mitchell AO

RDA BVSc *Sydney* FACVSc PhD *Melbourne* FTSE FAA

Appointed: July 2007

Dr Mitchell completed his PhD at the Walter and Eliza Hall Institute in the late 1960s, where he contributed to the discovery of T and B cells.

In 1973, after postdoctoral experience in the United States, United Kingdom and Switzerland, Dr Mitchell returned to the institute and established a program on the immunology of parasitism. He was also a previous director of research in the R&D Division of CSL Limited.

Dr Mitchell is an adviser on science and innovation to the Victorian Government and jointly acts as chief scientist for Victorian departments. He is a non-executive director of Antisense Therapeutics Limited and Avipep Pty Ltd and has a detailed knowledge of the academia-industry interface.

Mr Terry Moran AC

BA (Hons) *LaTrobe*

Appointed: November 2013

Mr Terry Moran is the former secretary of the Department of Prime Minister and Cabinet and former secretary of the Victorian Department of Premier and Cabinet.

Mr Moran's involvement in the public service has resulted in the establishment of institutions that have made important contributions to Australia's cultural and educational landscape, such as the Wheeler Centre, the Grattan Institute, Opera Victoria, the Melbourne Recital Centre, the Australian and New Zealand School of Government and the National Institute of Public Policy.

He is the board chair for both the Barangaroo Delivery Authority and Melbourne Theatre Company, and holds the position of senior advisor at the Boston Consulting Group.

Ms Catherine M Walter AM

LLB (Hons) LLM MBA *Melbourne* FAICD

Appointed: February 2001

Ms Walter is deputy chair of Victorian Funds Management Corporation, a non-executive director of Australian Foundation Investment Company, the Reserve Bank's Payment Systems Board and Victorian Opera.

She practised law for 20 years as a commercial lawyer, which included a term as managing partner of Clayton Utz in Melbourne. Ms Walter is a former Commissioner of the City of Melbourne.

In 2003, Ms Walter was appointed a Member of the Order of Australia for her service to business, particularly as a director of a number of public companies, to the arts, to the law, and to the community through the City of Melbourne. She was awarded a Centenary Medal in the same year.

Professor Ingrid M Winship

MB ChB MD *Cape Town* FRACP FACD

Appointed: June 2007

Professor Winship is the inaugural chair of adult clinical genetics at The University of Melbourne and executive director of research for Melbourne Health.

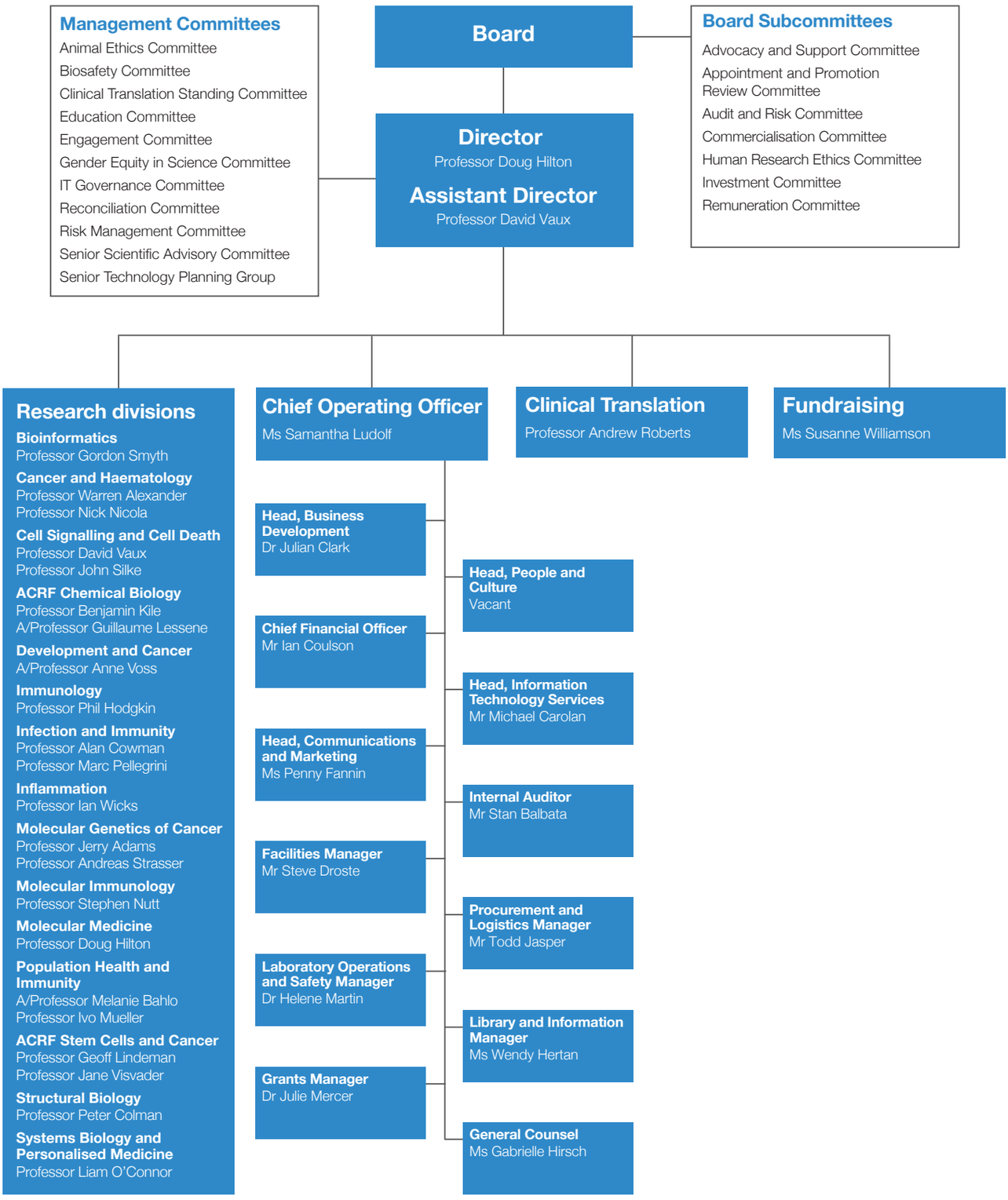
A medical graduate of the University of Cape Town, she completed postgraduate training in genetics and dermatology before combining an academic position at the university with a clinical position.

In 1994, Professor Winship took up an academic position at the University of Auckland where she later became Professor of Clinical Genetics, clinical director of the Northern Regional Genetic Service and associate dean for research in the Faculty of Medicine and Health Sciences (1999-2003).

She is currently a member of the Australian Health Ethics Committee and the Victorian Cancer Agency. She is on the Executive Management Committee of the Melbourne Genomic Health Alliance.

INSTITUTE ORGANISATION

31 December 2015



The Walter and Eliza Hall Institute acknowledges the support of these organisations

Australian Government

VICTORIA State Government

The Walter and Eliza Hall Trust
Helping Australians in need since 1912

American Asthma Foundation

The Atlantic Philanthropies

Australian Cancer Research Foundation

Bill & Melinda Gates foundation

Bionomics

Cancer Council NSW

Cancer Council Victoria

Coeliac Australia

Coeliac Victoria and Tasmania

CSL

Cure Cancer Australia Foundation

diabetes australia

Donald Cant Watts Corke

Felton Bequest 1904

Gandel Philanthropy

HFSP

The Ian Potter Foundation

JDRF Improving lives. Curing Type 1 diabetes.

Leukaemia Foundation

Leukemia & Lymphoma Society fighting blood cancers

Ludwig Cancer Research

MM RF Multiple Myeloma Research Foundation

National Breast Cancer Foundation

mvi PATH Malaria Vaccine Initiative

Ramaciotti Supporting Biomedical Research

Rotary International

snowdome Foundation

Therapeutic Innovation Australia

veski

In kind support was received from these organisations

Deloitte.

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Fed Square

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JBWere

SPP

The Walter and Eliza Hall Institute is associated with the following organisations

The Royal Melbourne Hospital

The University of Melbourne

agrf

Athena SWAN Member

Biomedical Research Victoria
Innovating for Health

BioGrid Australia
Health through information

Cancer Therapeutics CRC

Cancer Trials Australia

CareerTrackers Indigenous Internship Program

CART-WHEEL
Centre for Analysis of Rare Tumours

CATALYST therapeutics

GTAC
Gene Technology Access Centre

The HEARing CRC

Male Champions of Change Victoria

MRCF
Medical Research Commercialisation Fund

Melbourne Genomics Health Alliance

Ormond College
The University of Melbourne

Type 1 Diabetes TrialNet

SupplyNation MEMBER

Victorian Breast Cancer Research Consortium Inc

Victorian Cancer Biobank

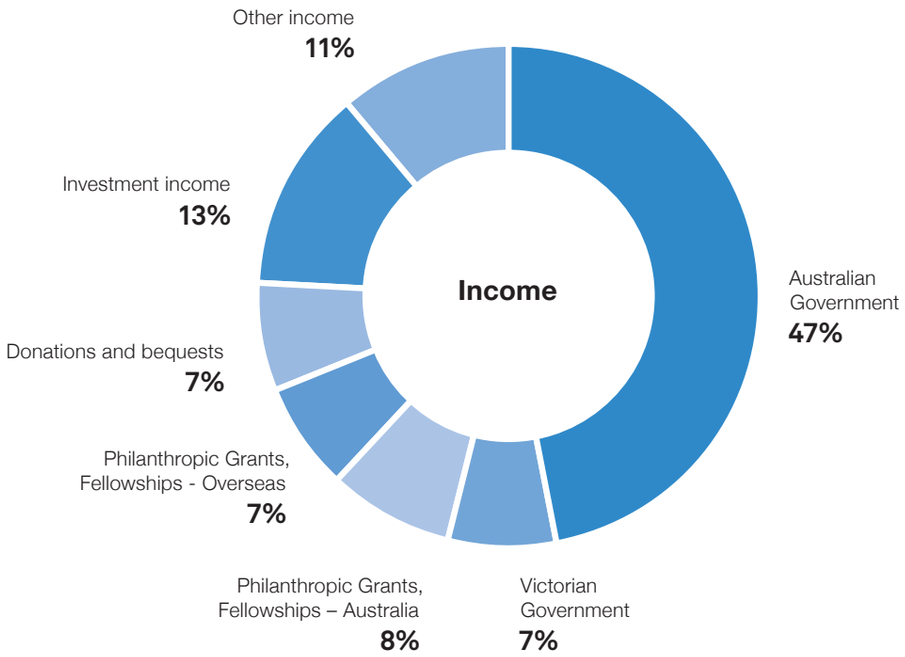
Victorian Comprehensive Cancer Centre

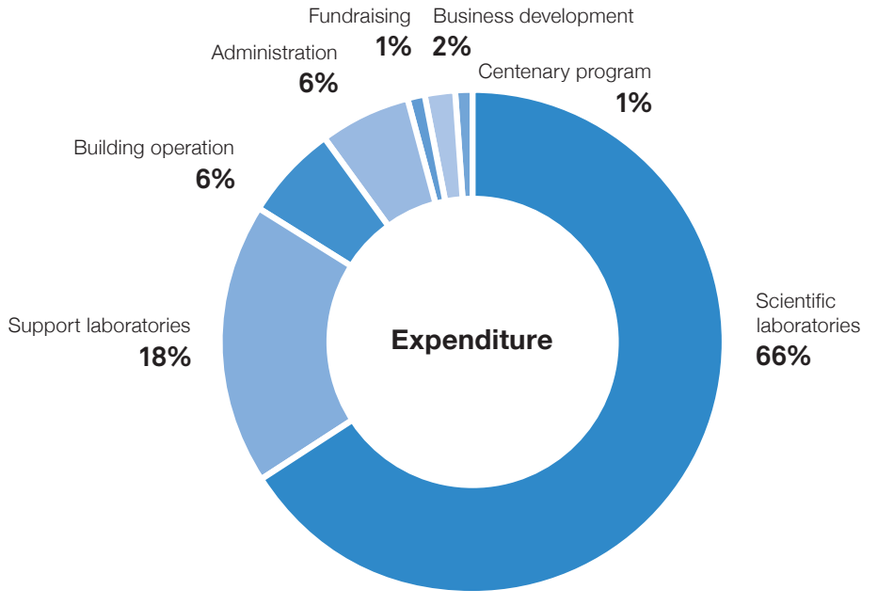
Statistical summary for the year ended 31 December 2015

	2015	6 months to 31 December 2014	12 months to 30 June 2014	2013	2012
	$'000s	$'000s	$'000s	$'000s	$'000s
Research revenue					
Australian Government	48,492	25,569	51,512	52,995	49,962
Victorian Government	7,419	3,078	6,936	6,771	7,074
Foreign governments	495	47	506	472	359
Government revenue	**56,406**	**28,694**	**58,954**	**60,238**	**57,395**
Industrial grants and contracts	4,691	1,058	1,696	1,482	1,114
Philanthropic grants and fellowships – Australia	8,062	4,659	9,024	6,971	5,285
Philanthropic grants and fellowships – international	7,386	4,056	6,355	5,376	2,180
Investment income	13,172	7,074	12,925	13,146	11,280
Royalty income	2,262	4,727	3,119	828	810
General revenue	4,430	1,077	3,369	2,819	3,054
Donations and bequests	7,297	4,126	6,678	4,402	3,043
Non-government revenue	**47,300**	**26,773**	**43,166**	**35,024**	**26,766**
Total revenue for research	**103,706**	**55,467**	**102,120**	**95,262**	**84,161**
Research expenditure					
Staff costs	76,570	38,544	75,027	69,339	61,559
Laboratory operating costs	18,327	9,326	17,841	17,650	16,452
Laboratory equipment	2,284	1,105	2,538	3,487	4,119
Building operations	4,712	2,424	5,171	5,307	4,746
Administration	2,501	1,451	1,985	1,162	1,203
Fundraising	219	106	-	-	-
Business development	825	390	849	815	899
Doubtful debts expense	-	201	-	-	-
Total research expenditure	**105,438**	**53,547**	**103,411**	**97,760**	**88,978**
Results from research activities	**(1,732)**	**1,920**	**(1,291)**	**(2,498)**	**(4,817)**
Other income					
Profit and loss on sale of long-term assets	9,512	2,170	5,324	21,600	746
Contribution income for recognition of land lease	-	-	-	-	12,782
Donations and bequests capitalised to Permanent Funds	719	137	1,581	219	3,461
Grants and donations for capital works	6,071	870	3,204	2,105	906
Total other income	**16,302**	**3,177**	**10,109**	**23,924**	**17,895**
Other expenses					
Loss on impairment write down of long-term investments	(4,808)	(391)	-	(263)	(2,333)
Depreciation and amortisation	(8,512)	(4,486)	(8,671)	(8,396)	(5,681)
Total other expenses	**(13,320)**	**(4,877)**	**(8,671)**	**(8,659)**	**(8,014)**
Net operating surplus	**1,250**	**220**	**147**	**12,767**	**5,064**
Capital funds					
Permanent invested capital funds	168,392	159,027	157,026	152,428	139,073
General funds	130,122	143,126	150,132	160,291	162,909
Royalty fund	26,169	24,387	19,994	17,551	17,079
Leadership fund	21,682	19,724	18,975	17,840	16,282
Discovery fund	2,362	2,109	2,030	-	-
Centenary fund	1,000	104	100	-	-
Investment revaluation reserve	35,305	47,755	46,763	31,165	29,086
Total funds	**385,032**	**396,232**	**395,020**	**379,275**	**364,429**
Capital expenditure					
Property, plant and equipment	**5,062**	**1,484**	**3,937**	**5,852**	**43,348**

Staff numbers: (equivalent full-time)	2015	6 months to 31 December 2014	12 months to 30 June 2014	2013	2012
Scientific research staff:					
– Senior faculty	79	77	78	76	64
– Postdoctoral scientists	176	190	197	186	160
– Visiting scientists	23	12	14	15	10
–Other laboratory research staff	238	269	265	268	252
Supporting staff:					
– Other support services	146	144	135	129	122
Total staff and visiting scientists	**662**	**692**	**689**	**674**	**608**
Students	**169**	**159**	**175**	**151**	**137**
Papers published	**410**	**167**	**381**	**298**	**284**

THE YEAR AT A GLANCE





The period in brief	2015	31 December 2014
Income for operations	**103,706**	**55,467**
Expenditure in operations	**105,438**	**53,547**
Net surplus (deficit) from operations	**(1,732)**	**1,920**
Number of staff and visiting scientists	**662**	**692**
Number of postgraduate students	**169**	**159**
Total staff and students (EFT)s	**831**	**851**

Walter+Eliza Hall
Institute of Medical Research

DISCOVERIES FOR HUMANITY

We don't want other families to suffer.

When my mum died from breast cancer, I knew that I didn't want other families to suffer the same tragic loss.

That's why our family supports the Walter and Eliza Hall Institute of Medical Research.

It is Australia's oldest medical research institute.

For more than 100 years the Walter and Eliza Hall Institute has tackled the challenging and complex diseases confronting humanity.

More than 20 million people around the world have already benefited from the institute's discoveries, including better treatments for cancer.

Right now, more than 100 clinical trials are underway based on institute discoveries, including new anti-cancer drugs to treat leukaemia, and vaccines for coeliac disease, type 1 diabetes and malaria.

When we met the scientists at the Walter and Eliza Hall Institute, we were inspired by their passionate commitment to finding better treatments for patients.

You can be assured that donations and bequests to the Walter and Eliza Hall Institute support the best research into cancer, infectious diseases and immune disorders.

– Eleni Horbury with her daughter Sophie, and cancer researcher Dr Anne Rios. August 2015.

For more information please contact Ms Susanne Williamson, Head of Fundraising, on 9345 2962 or williamson.s@wehi.edu.au

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Walter and Eliza Hall Institute

CANCER | IMMUNE DISORDERS | INFECTIOUS DISEASE