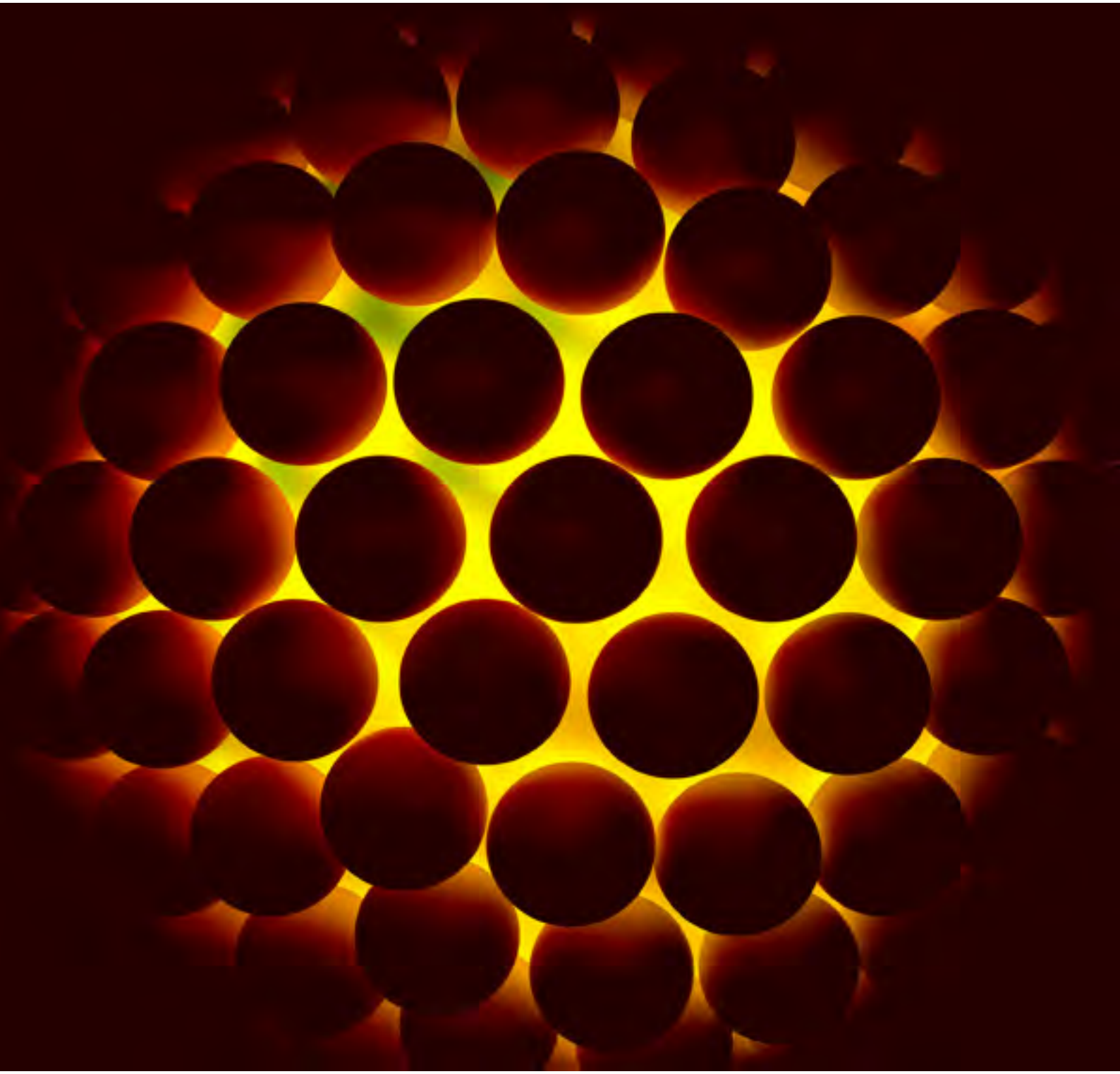
CENTRE FOR ADVANCED MOLECULAR IMAGING
AN ARC CENTRE OF EXCELLENCE



Annual Report

2015

Funding Body

Australian Government
Australian Research Council

Administrating Organisation

MONASH University

Collaborating Organisations

THE UNIVERSITY OF MELBOURNE

LA TROBE UNIVERSITY

UNSW AUSTRALIA

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Partner Organisations

ansto

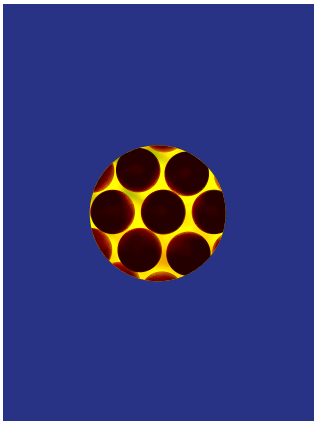
Australian Synchrotron

THE UNIVERSITY OF WARWICK

ZEISS

DESY

Leica MICROSYSTEMS



ARC Centre of Excellence in Advanced Molecular Imaging Annual Report 2015

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Design and production

Research Media Ltd

www.researchmedia.com

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Vision and Objectives

Mission

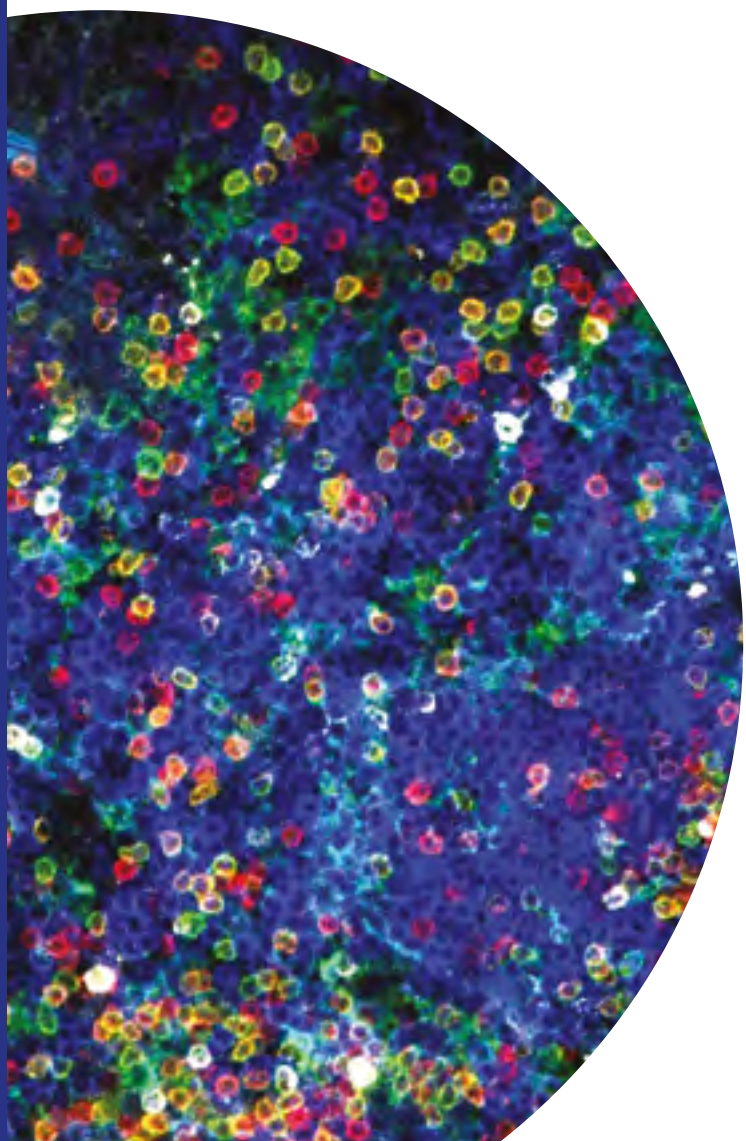
The Australian Research Council (ARC) Centre of Excellence in Advanced Molecular Imaging aims to visualise and interpret the atomic, molecular and cellular interactions involved in our immune response. The Centre will achieve this by developing and using a wide range of existing and novel imaging techniques.

The Imaging Centre's objectives are driven by three key guiding principles – excellence, engagement and translational impact.

Excellence

The Centre will achieve excellence in terms of the quality of scientific outcomes generated, and the quality of the next generation of scientists we mentor, train and inspire.

These goals are underpinned by world-class research infrastructure and the strategic partnerships the Centre has developed with the Australian Synchrotron, the Australian Nuclear Science and Technology Organisation (ANSTO), the Deutsches Elektronen Synchrotron (DESY) and the Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy.



Engagement

The Centre is focussed on fostering new, cross-disciplinary collaborations and improving communications across our diverse range of scientists. Such multi-disciplinary collaborations deliver truly groundbreaking discoveries, and also provide well-rounded training to the next generation of scientists.

Externally, the Centre is passionate about engaging with our peers internationally, in government, as well as budding scientists and the wider public to:

- form global research collaborations that deliver cutting-edge science, and
- raise public awareness and enthusiasm about the exciting and impactful discoveries our scientists are making.

Translational Impact

The Centre will maximise the impact of our discoveries through pursuing translational outcomes to benefit society. The Centre is working proactively with world leading companies to achieve these outcomes.

About us

The $39 million ARC-funded Imaging Centre develops and uses innovative imaging technologies to visualise the molecular interactions that underpin the immune system. Featuring an internationally renowned team of lead scientists across five major Australian Universities and academic and commercial partners globally, the Centre uses a truly multi-scale and programmatic approach to imaging to deliver maximum impact.

The Imaging Centre is headquartered at Monash University with four collaborating organisations – La Trobe University, the University of Melbourne, University of New South Wales and the University of Queensland.

2015 Highlights

100 scientists

48 students

9 world class Chief Investigators across physics, chemistry and biology

89 publications

353 citations

104 conference presentations in 12 countries

104 media articles

2 new linkages made with external organisations

$28.4 million attracted in additional funding and grants

Director's Message

A very warm welcome to our 2015 annual report.

It has been an exceptionally exciting year with over 89 papers describing Centre discoveries. Much of this work was published in leading generalist journals and was further highlighted in the national and international media.

It is not possible to detail all of the science taking place in the Centre in this short introduction. I would, however, like to make special mention of some of the major discoveries we made this year. In the physics arena, our Associate Investigator Hans Elmlund reported in the journal Science details of near-atomic resoluton structure of platinum nanocrystals. The approaches that he pioneered in this work are now being applied in the field of biological electron microscopy.

Our immunologists have made major leaps forward in understanding immune recognition. For example, in work published in Nature Immunology Jamie Rossjohn and his colleagues have found that a dramatically different "reversed" type of interaction between a T cell receptor and a major histocompatibility complex. This challenges the dogma with respect to how T cell signalling is achieved. This work could eventually lead to new approaches to prevent the development of Type 1 diabetes.

Our scientific program has been further boosted through a major $25 million recruitment drive. This year saw eight new group leaders, including four new EMBL Australia group leaders join the Centre (two at Monash and two at UNSW). The majority of these talented scientists were recruited from overseas. Their research skills include crystallography, EM, optical microscopy and single molecule imaging. Our Associate Investigator team, which includes talented young early career researchers, has grown to over 40. We were delighted that many of our ECRs also enjoyed spectacular success in winning funding from NHMRC and ARC grant and fellowship programs.

The core strength of our Centre is our outstanding people, and as 2015 drew to a close we received the wonderful news that Jamie Rossjohn, together with his longstanding collaborator Jim McCluskey, had jointly won the 2015 GSK award for their research around metabolite recognition by mucosal associated invariant T (MAIT) cells.

2015 saw the opening of the Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy. At the centrepiece of this platform is Australia's first 300keV FEI Titan KRIOS. This instrument is transforming the detailed study of large dynamic biological macromolecules and cellular ultrastructure. Its capability will be further boosted in 2016 with the addition of a new Gatan K2 Camera coupled with a Quantum Energy Filter. This equipment will provide researchers around Australia with a scientific edge.

In another key development, Centre Partner Investigator Andrew Peele led a successful $2 million bid to the Australian Cancer Research Foundation to equip the Crystallography MX-2 beamline with an Eiger detector. In addition to greatly increasing the capacity of MX-2, this detector will be crucial for the La Trobe University Experimental Physics team in developing approaches for efficient sample delivery at X-ray Free Electron Lasers.

Our industry linkages continue to develop, with new support for the perforin program from the Wellcome Trust Seeding Drug Discovery Program, and a new partnership signed between the Centre and FEI Inc.

We finished the year with the International Science Students Fair (ISSF), hosted by the John Monash Science School. The Centre was a proud sponsor of the ISSF and Centre CI Harry Quiney led our involvement. On a personal note, speaking in front of a lecture theatre packed with incredibly talented schoolchildren from around the world was a fantastic experience.

Looking ahead, I am really excited by what we can achieve in 2016. The Australian Government's National Innovation and Science Agenda, announced late last year, set out a number of exciting, new measures to harness the power of science and technology to drive economic growth. Two of the four key areas of the agenda were increasing collaboration between industry and researchers, and developing and attracting world-class talent – areas which are key focus areas of our Centre.

Included as part of this agenda were measures to ensure the long-term sustainability and operations of the Australian Synchrotron, and the National Collaborative Infrastructure Strategy (NCRIS) as part of the Government's National Innovation and Science Agenda. We are delighted by these measures because the Synchrotron and large-scale, open-access infrastructure are key tools for us that enable our scientists to make scientific breakthroughs.

Last but not least, I would like to thank all members of the Centre for making the year such as success. I hope you enjoy reading our report.

Prof. James Whisstock

Director, Imaging Centre
NHMRC Senior Principal Research Fellow
Department of Biochemistry & Molecular Biology
Monash University

Governing Board Message

My Governing Board colleagues and I are delighted to see the wonderful progress made by the Centre in 2015 in all key aspects – research, outreach and education and commercialisation. Prof. James Whisstock and his outstanding team of Chief Investigators have built upon a solid foundation in 2014 and have achieved a number of remarkable achievements that you will see highlighted throughout this annual report.

Some of the Centre's key highlights of 2015, in addition include:

- The launch of the Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy, which provides the Centre with world-class infrastructure that enables cutting edge structural biology,
- Recruitment of talented young scientists through the EMBL Group Leader Program and other avenues,
- The establishment of several strategic R&D collaborations with world-leading companies in the imaging technology and drug discovery arenas.

As a board, we are here to ensure that the that the Centre reaches the amazing potential that it holds; that it operates in a way that fulfills all the obligations of its agreement with the ARC; that it maintains its finances well and reports appropriately; and that it maintains a system for controlling risk.

The board is thrilled to work with the International Scientific Advisory Committee, which steers the Centre's scientific direction, to continue to expand our Centre's global collaborative networks and position ourselves as a hub for imaging research and development.

The board congratulates Prof. Whisstock and his team, as well as all the researchers and students, who have made 2015 a very successful year for the Centre and we look forward to more exciting discoveries in 2016.

On behalf of the Imaging Centre Governing Board,

Prof. Frances Shannon

Governing Board Chair
Deputy Vice Chancellor, Research
University of Canberra

ISAC Chair Message

I am delighted to serve as the Chair of the Imaging Centre International Scientific Advisory Committee (ISAC). My fellow committee members and I are thrilled by the level of achievement attained by the Centre in 2015 – its first full year of operation.

In addition to producing fantastic scientific outcomes – highlighted throughout this report – the Centre has begun forming a global network of excellence through its relationships with the Australian node of the European Molecular Biology Laboratory (EMBL), global imaging technology and pharmaceutical companies and academic institutions.

The Centre's reputation and quality on a global scale is growing as evidenced by the number of early career researchers that have been attracted to the Centre in 2015. The establishment of cutting edge research facilities and infrastructure, such as the Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy at Monash University and the Single Molecule Science initiative at University of New South Wales, provides these young and talented scientists with the tools to investigate and solve challenging biological problems.

During the Centre's annual summit in November, my colleagues and I were extremely impressed with the quality of the presentations and posters, largely by young postdoctoral researchers, PhD and masters students. Training the next generation of scientists is a key goal for our community as a whole and we are glad that the Centre is playing a leading role in this effort.

ISAC looks forward to an exciting 2016 ahead as the Centre continues to produce outstanding scientific research, expands upon its global footprint and drives impact internationally.

Best Wishes,

Prof. Volker Saile

Chair, International Scientific Advisory Committee, Karlsruhe Institute of Technology

Governance

The Imaging Centre is administered by Monash University with day-to-day operations managed by the core administrative team including the Director, Professor James Whisstock, Chief Operating Officer, Dr Manoj Sridhar, Centre Coordinator, Chantelle Linnett and Media and Communications Manager, Stephanie Pradier.

The Governing Board is at the pinnacle of the Centre's governance structure. Meeting on a biannual basis, the board's role is to ensure fiscal compliance, good research practice, and alignment of activities with respect to the goals of the Centre. The board also provides strategic advice with regards to scientific research directions, commercialisation and industry linkage opportunities, and outreach and advocacy issues.

The International Scientific Advisory Committee gives independent advice to the director on the positioning of the Centre with respect to new research directions, international outreach and industry linkage opportunities.

The committe conveys its findings to the governing board for consideration and action.

The Centre Executive oversees the general management and operations of the Centre across the five collaborating nodes. Meeting on a monthly basis the executive has a proactive approach to discussing and solving issues arising on scientific, financial and commercial fronts.

Chief Investigaters (CIs) meet on a quarterly basis to discuss their research projects, key milestones and achievements, as well as to discuss potential opportunities for collaboration and problem solving. These meetings have a strong focus on research progress, key barriers to progress and opportunities for interdisciplinary collaboration. They are a vital part of the Centre's operations as they present the opportunity for all CIs and relevant project members to meet with other staff from different nodes to share ideas and explore new opportunities for growth and development.

Imaging CoE Chief Investigators

Prof. James Whisstock
Centre Director
Monash University

Prof. Katharina (Kat) Gaus
Deputy Director
University of New South Wales

Assoc. Prof. Brian Abbey
La Trobe University

Prof. David Fairlie
The University of Queensland

Prof. Dale Godfrey
The University of Melbourne

Prof. William (Bill) Heath
The University of Melbourne

Prof. Keith Nugent
La Trobe University

Prof. Jamie Rossjohn
Monash University

Assoc. Prof. Harry Quiney
The University of Melbourne

ISAC MEMBERS

Prof. Volker Saile

Chair, International Scientific Advisory Committee
Karlsruhe Institute of Technology, Germany

Volker is Chair of the ISAC and boasts a long and distinguished career in physics. He is a member of several German and international science and technology committees and also serves as the President of the Micro, Nano and Emerging Technology Commercialisation Education Foundation (MANCEF) – initiated by global leaders in the small technology community in the early 1990s. In addition to his vast network across Europe and the United States, Volker brings to the Centre extensive experience in the areas of: synchrotron science; microstructures and devices; and mechanical engineering.

Prof. Jose-Maria Carazo

Head, Biocomputing Unit
National Center for Biotechnology, Spain

Jose-Maria is a world-renowned expert in three-dimensional electron microscopy. His particular focus is on image processing methods for the experimental determination of the structures of large biological macromolecules. With his unique background in both physics and molecular biology, Jose-Maria brings to the ISAC his perspective on how the various imaging modalities (X-ray, electron microscopy and optical/confocal microscopy) can be harnessed to solve challenging problems in biology. Jose-Maria also brings with him expertise in translating research to industry. He established a successful spin-out company, Integromics, in 2003.

Prof. Jeff Errington

Director, Centre for Bacterial Cell Biology
University of Newcastle, UK

Jeff is an eminent cell and molecular biologist with an interest in fundamental biological problems, especially the cell cycle and cell morphogenesis in bacteria. He has a strong record in the commercialisation of basic science and has served on the boards of several companies. In addition to his commercial insights, Jeff brings to the Centre scientific knowledge in optical, confocal and fluorescence microscopy.

Prof. Thomas Kay

Director, St Vincent's Institute of Medical Research

Thomas is a renowned Melbourne-based clinician-scientist with particular interest in studying the immunopathogenesis of Type 1 (juvenile) diabetes. He also leads a Melbourne-wide clinical islet transplant program that began treating diabetic patients by infusion of isolated islet cells in 2006. He brings to the Centre his expertise in immunology, clinical trials and translational biomedical research.

Governing Board Members

Prof. Frances Shannon

Chair, Governing Board
Deputy Vice Chancellor, University of Canberra

Frances is the Chair of the Governing Board and has had a long and successful career in biomedical research. Her particular interest is in how proteins of the immune system are encoded in DNA and she led the Gene Expression and Epigenomics Laboratory at John Curtin School of Medical Research at the Australian National University. She brings to the Centre her vast expertise in managing large, complex, multi-disciplinary, multi-institution projects such as the Murray-Darling Basin Futures project.

Prof. Ian Smith

Vice Provost (Research & Research Infrastructure), Monash University

Ian has been the driver at Monash University for centralised platform technology facilities to provide high quality infrastructure and the experts to operate them at the highest level. In addition, Ian has also driven numerous industry partnerships at Monash University with large multinational companies such as Siemens and Perkin Elmer. He brings to the Centre in-depth knowledge of harnessing cutting-edge research infrastructure to generate outstanding biomedical research outcomes and his experience in building strategic relationships with major industry partners.

Dr Erol Harvey

CEO, MiniFAB Pty Ltd

Erol is the CEO of MiniFAB Pty Ltd, a high tech company that specialises in producing microfluidic devices for biomedical diagnostic applications. Having moved from the academic to the commercial arena, he brings to the Centre his expertise in commercialising scientific research as well as his scientific knowledge in Laser Physics and microtechnology. Erol is also passionate about encouraging researchers to try out new ways of engaging with people outside their sphere of expertise and driving new models of collaboration.

Ben Apted

Partner, Strategic Project Partners (SPP)

Ben is a Partner of SPP. He leads SPP's Government, Education, Research and Digital Practices. Ben is a thought leader and contributor nationally and internationally on higher education strategy, engagement and operations. He brings to the Centre his expertise in developing and applying a structured and strategic approach to research to deliver maximum value for stakeholders.

Dr Kees Eijkel

CEO, Kennispark, Twente (Netherlands)

Kees is CEO of Kennispark Twente, the shell for commercialisation in and around the University of Twente and Saxion University, in co-operation with the province of Overijssel and the city of Enschede on behalf of the cities in the region. He is passionate about encouraging and supporting the entrepreneurial spirit, particularly among university students, and brings to the Centre his experience in supporting a number of new start-up firms in the Netherlands.

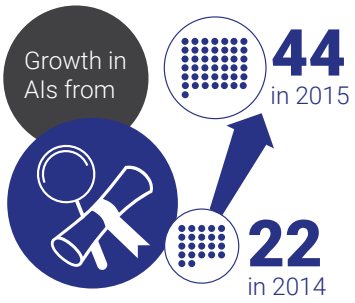
Growth of the Centre

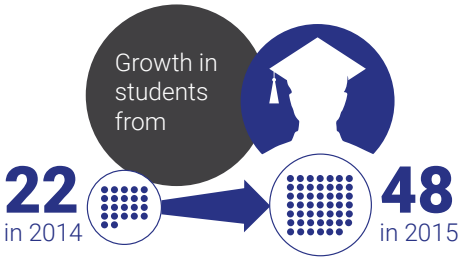
As a fledgling Centre of Excellence in our first full year of operations, building up capacity in our two key resources – people and infrastructure – was a key focal point for us.

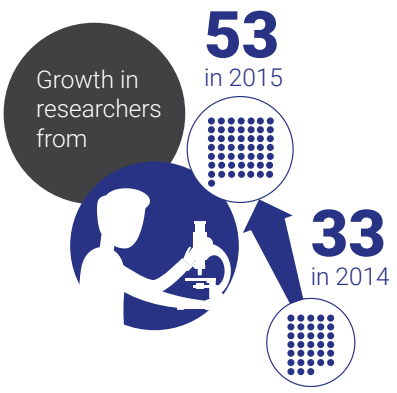
We have significantly expanded our base of Associate Investigators (AIs), researchers and students in 2015 across all our nodes. Specifically, our AI network has grown from 22 at the end of 2014 to 44 in 2015, the number of researchers in the Centre has risen from 33 in 2014 to 53 in 2015 and we now have 48 PhD/masters/honours students in the Centre compared with 22 in 2014.

A highlight of our recruitment in 2015 was the partnership of the Centre with EMBL Australia to lead the recruitment of four EMBL Australia Group Leaders, a very prestigious fellowship awarded to outstanding early career researchers.

Over a week in February the Imaging Centre's Monash University node played host to nine EMBL Australia Group Leader applicants. Of these candidates three were offered positions at Monash University and subsequently, as AIs with the Centre. Forming this strategic partnership, to recruit talented group leaders in the imaging space, is mutually beneficial and contributes to internationalising Australian research.







EMBL Group Leaders

Chen Davidovich started with the Centre in October. He brings with him a wealth of knowledge in structural and molecular biology. Chen is interested in chromatin remodelling and epigenetics. He is using a combination of optical, electron microscopy and crystallography to tackle this problem in a truly multi-scale approach. The selection committee were impressed by Chen's wide ranging and innovative experimental vision, they believe that he will flourish under the EMBL Group Leader scheme and that his future interdisciplinary discoveries align with the Centre mission.

Max Cryle's expertise lies in understanding protein machines for antibiotic synthesis. His future plans include combining EM, crystallography and structure guided chemistry to understand and harness major protein machines used to catalyse antibiotic production. Max has a strong track record of collaboration and his ability to utilise different skills when attacking complex problems will be an asset to the interdisciplinary research of the Centre.

The newly formed Centre for Single Molecule Science were looking to fill two open positions. From this recruitment drive Yann Gambin, Lawrence Lee and Maté Biro were appointed at UNSW and strategically within the Centre as AIs.

Yann Gambin is a biophysicist and molecular biologist, he joined UNSW in July. Yann has been combining single molecule detection and microfluidics to develop a microscopy based pipeline for studying protein-protein interactions at high resolution. Yann came across as a real team player and his inventiveness and energy were exactly what we were looking for. With several high profile technical papers and other publications describing interacting protein networks, Yann's expertise brings great potential to the Australian EMBL node and the Centre.

The final recruit, Maté Biro, will start with the Centre in early 2016. In his interview Maté presented novel imaging and image analysis approaches to classify cell migration modes based on the cortical actin organisation. His past accomplishments, together with the originality of his research plan, his personal drive and potential for collaborative interactions are hallmarks of EMBL scientists. Maté's focus on cell biology will complement the technology focus that Yann brings.

This partnership adds to the Centre's global and national links, adds value and diversity to our research program and ensures we continue to build capacity – both with people and with infrastructure.

New Lab Leaders

In addition, Alex de Marco was also offered a joint position at Monash University and the University of Warwick as part of the Monash-Warwick Alliance. He will develop and optimise hardware and software technologies with a particular focus on correlative light and electron microscopy. Alex is also an AI on the Centre and came to us from FEI Company – one of the Centre's strategic industry partners.

Lawrence Lee also joined the Centre in this recruitment round. His interests in artificial synthesis of biomolecular systems has led him to develop new nanotechnologies and his track record in structural biology will help him to cross Centre disciplines and establish new Centre collaborations.

Emma Sierecki also moved Down Under and with Yann Gambin maps protein interactions to solve mysteries that have so far eluded researchers. Her strategy – combining cell-free protein expression with AlphaScreen and single molecule fluorescence spectroscopy – allows them to rapidly screen a huge number of protein binding partners.

"So much of the bigger picture has been previously missed. Protein networks play a major role in gene regulation and immunity," says Emma.

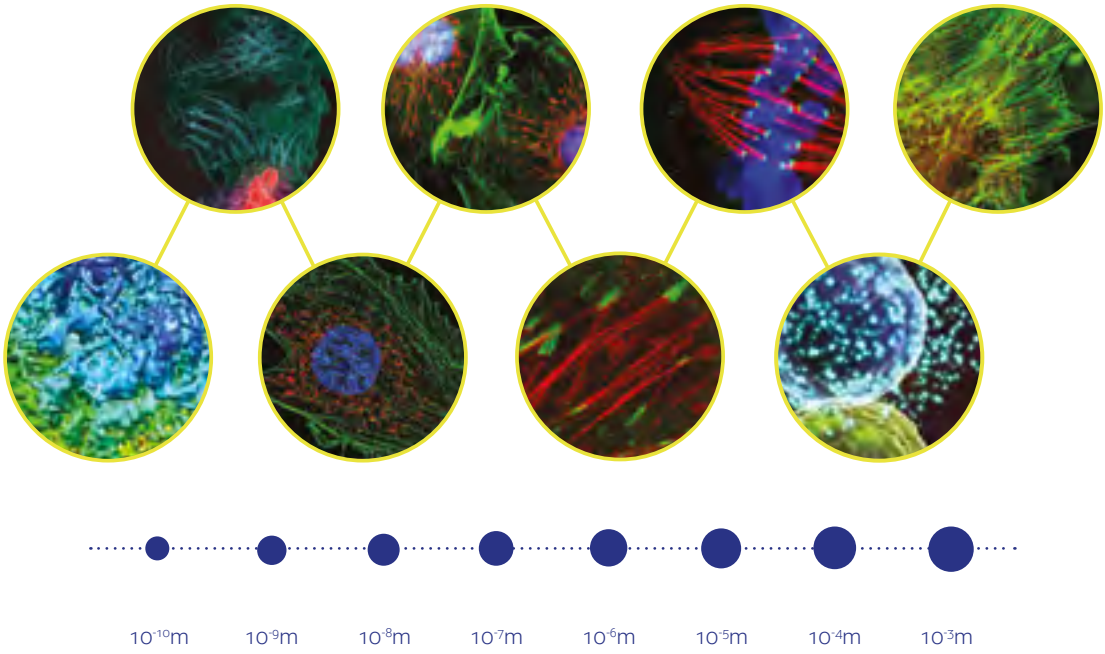
By figuring out which proteins bind together, Emma and Yann have so far identified how 25 subunits come together to form the Mediator – the biggest adapter protein complex regulating gene transcription.

Technology Infrastructure

The Imaging Centre combines world-class expertise with capabilities across all the key imaging workflow elements – sample preparation and optimisation, imaging/data acquisition, data analysis and visualisation. Our cutting edge imaging capabilities span a wide range of length scales.

In particular, the Australian Synchrotron, X-ray Free Electron Laser facilities at Stanford (LCLS), Japan (SACLA) and Hamburg (DESY), the Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy at Monash University and the Single Molecule Science laboratories at the University of New South Wales are key facilities that each provide imaging capabilities in different spatio-temporal domain.

Core Capabilities:



- X-Ray Free Electron Laser (XFEL) Nanocrystallography
- Synchrotron Macromolecular Crystallography
- Cryo-Electron Microscopy
- Single Molecule Localisation Microscopy
- Super-Resolution Microscopy
- Adaptive Microendoscopy
- Confocal Microscopy
- Two-photon Microscopy
- Fluorescence Microscopy

Enabling/Auxiliary Capabilities:

- Sample Preparation/ Anaylsis
- Protein Production Unit
- Protein Crystallisation
- Custom Fluorophore & Ligand Production
- Custom Antibody Production
- Data Analysis & Visualisation
- Supercomputing Cluster (Massive)
- Bioinformatics
- Programming Expertise
- Immersive Visualisation (CAVE2)

X-ray Crystallography

Imaging Centre physicists are actively engaged in the use of new large international X-ray Free Electron Laser facilities (XFEL) at Stanford (LCLS), Japan (SACLA) and Germany (European XFEL). The ultrahigh energy, femtosecond pulses of X-rays generated at these facilities could potentially be a revolutionary technique for protein crystallography by enabling structure determination of very small crystals.

These combine large scale accelerator technology with sophisticated detector systems and huge computer farms for data collection and handling.

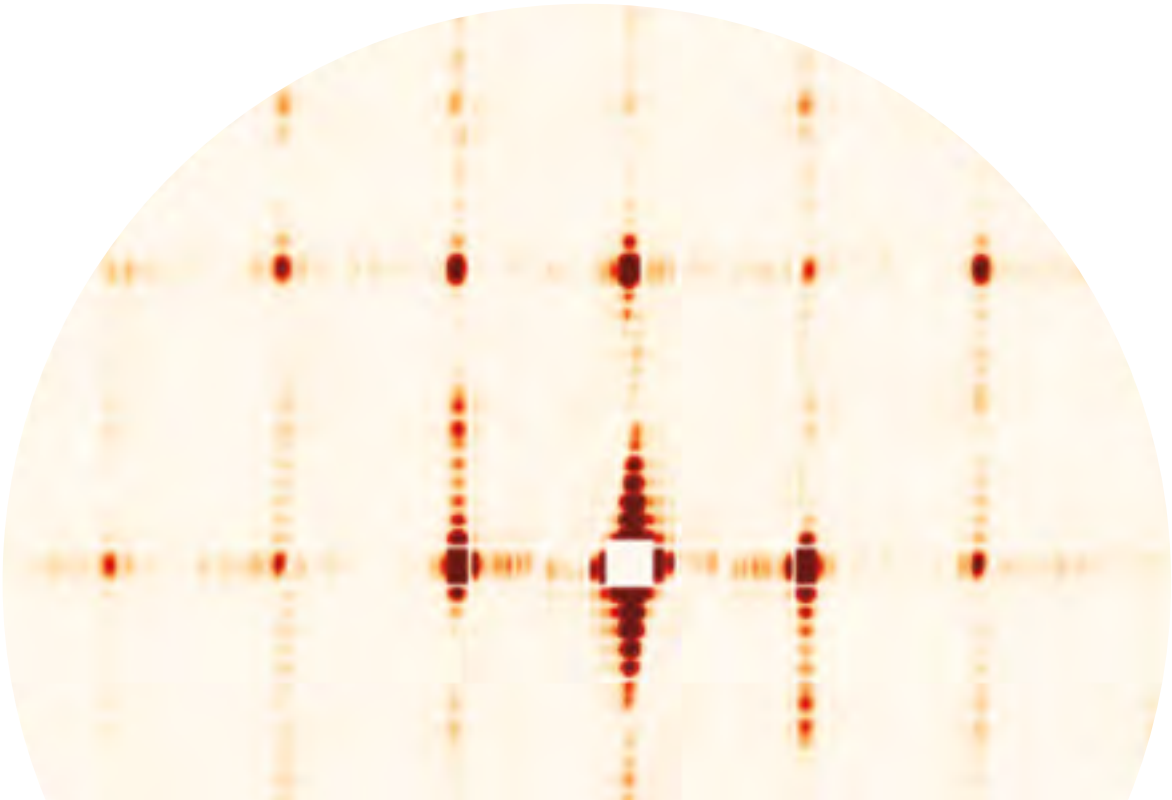
Light sources: XFEL sources are able to produce incredibly bright pulses of X-rays with wavelengths ranging from 1keV-10keV and with pulse durations ranging from a few femtoseconds to 100 femtoseconds. These light sources are tunable, can be operated in two colour mode and have a repetition rate ranging from a few Hz to a few kHz. These light sources are unique because they offer the possibility of capturing chemical and biological processes in a snapshot revealing critical information about dynamical processes.

In particular, these facilities have been developed to realise the long held ambition of imaging the structures of biomolecules in close to their native state without the need to form crystalline samples.

Detectors: Enormous investment has gone into the development of detection systems which are able to capture and read out the scattered signal generated by diffraction experiments using XFEL sources. The detectors are constructed from panels that are configured in such a way to maximise their ability to record scattered photons while allowing unscattered photons to pass through a central hole. The unscattered photons can be recycled in further experiments directly downstream.

Data collection and handling: Each femtosecond pulse scatters photons into a large detector array and at atomic resolution over a large angle. Each pulse therefore consists of an array of data involving several mega-words of information. Experiments typically run for more than a day and generate many terabytes of data. In order to maintain the flow of information from the detectors large processing farms are attached to these facilities to collect, store and process the data. Then use of an XFEL more closely resembles experiments in particle or astrophysics than conventional laboratory based imaging techniques.

Australian Synchrotron: The Centre's researchers are heavy users of the Australian Synchrotron, particularly the Macromolecular Crystallography (MX) beamlines, which are crucial and routine instruments used to determine structures of microcrystals. The Centre's formal partnership with the Australian Synchrotron allows us to embed researchers at the Synchrotron itself. This enables us deeper insight into the design and operations of these instruments as well as provide the Synchrotron with closer access to key users and their research outputs and needs. Centre CIs Jamie Rossjohn and James Whisstock were part of a team of researchers who won a $2million grant to upgrade and install a new state-of-the-art detector on the MX beamline that will enable faster and higher resolution image acquisition.



Cryo-Electron Microscopy

The Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy at Monash University was launched in February 2015. This facility enables Centre researchers to access world-class biological electron microscopy facilities and expertise in a burgeoning field that has just recently been declared Method of the Year 2015 by Nature Methods.

Imaging CoE Affiliate Partnership in MASSIVE

MASSIVE works closely with the Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy to support processing of cryo-EM data.

Throughout 2015, Imaging Centre AIs, postdocs and PhD students had access to 5.2 per cent of the M1 and M2 MASSIVE high-performance computers – this accounts for approximately 1,090,000 CPU-core hours per year. Eleven of our projects were allocated time on MASSIVE throughout 2015.

In late 2015, through funding made available by Monash University, the Imaging Centre became an affiliate partner of MASSIVE (Multi-modal Australian Science Imaging and Visualisation Environment) (www.massive.org.au). This allowed us to participate in the design and specification of M3, a new computer for data-centric science which will be online in April 2016.

Using M3, researchers will know within hours whether their cryo-Em sample was a success. MASSIVE's intent is to allow researchers the ability to quickly make decisions on whether to head back to the laboratory or keep collecting and data processing. This workflow, coupled with novel algorithms (such as PRIME) will significantly increase the return on investment of the Titan Krios microscope.

Optical Microscopy

Single Molecule Science—the ability to observe and track individual molecules and monitor molecular interactions in living cells—heralds a revolution in biology. It's a collaboration between biologists, physicists and engineers that feeds off the capacity of new microscopes and other technology to identify single molecules and analyse their behaviour in intact samples. It has emerged from developing, using and combining technologies such as single-molecule fluorescence and super resolution microscopy, atomic force microscopy, optical and magnetic tweezers, new sensors and more sophisticated computing and mathematical techniques. Single Molecule Science presents us with a new way of understanding life processes from the bottom up, following the paths and changes of many different molecules as they move through the cell, form complexes with other molecules, and influence cell function.

Data collection and handling: Researchers are developing novel algorithms that will extend the Centre's capabilities in quantitative super-resolution imaging. Some of the tools under development are: molecular counting, stoichiometric analysis, cluster analysis, filament tracking, mapping dynamic molecular interactions, 3D membrane topography analysis, 3D organelle and cell morphology analysis. For example, the questions with respect to the 3D membrane topography analysis relate to how extra optics can be used to establish 3D maps of the cell membrane at nanometre resolution. The aim is to create a membrane landscape in order to view whether or not this will correlate to protein function and to see if the distribution of TCRs is correlated with the surface topology of the membrane. The research will also solve fundamental questions in signal transduction such as signal integration and signal amplification.

Through working on both hardware and software solutions we hope to optimise and develop novel single molecule and super-resolution fluorescence microscopy approaches.

Advanced hardware: Imaging Centre single molecule scientists focus on transforming medicine by providing a molecular perspective on complex biological systems and processes, encompassing biophysics, biochemistry and cell biology as well as nanotechnology and nanofabrication. They are building cutting-edge instruments by gaining access to pre-commercial equipment and designing and building new microscopes. There are currently over ten different microscopes in operation at the UNSW node with five planned for 2016.

Each microscope contributes to the goals of the Centre by being optimised for different applications: speed, resolution, imaging depth or multi-colour imaging.

A unique $5m electron microscope launched today at Monash University, Melbourne, will transform the way we view the human immune system, and advance Australian research towards better treatment for diseases from cancer and malaria to diabetes, rheumatism and multiple sclerosis.

The FEI Titan Krios cryo-electron microscope is the centrepiece of the $20 million Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy. Standing 3m tall, weighing around a tonne, and with a powerful 300kV electron gun, it's a true giant of a machine.

The Ramaciotti Centre and its new microscope are central to the work of the Imaging Centre, of which Monash University is a lead partner.

"We want to transform our understanding of the human immune system," says James Whisstock, the director of the Imaging Centre. "To achieve this, we need to be able to observe the molecular structures at the heart of immune response.

"Our immune system, and thus our health, is ultimately driven by the interactions of these large biological molecules. And those interactions depend on the 3D shapes and structures of the molecules involved.

"The Titan Krios is powerful enough to resolve those intricate 3D shapes, identifying the position of individual atoms within a biological molecule and creating exquisitely detailed models including the molecules' loops and side chains, James says. "It fills a gap, seeing things that X-ray crystallography and the Synchrotron can't see. And Australian scientists have been queuing up to get time on Titans in Europe and America. Now they can do the job in Australia."

Projects that will use the Titan include studies of:

- a drug that can prevent the spread of the malaria, a disease that still infects hundreds of millions of people and causes more than 600,000 deaths a year—Dr Wilson Wong, Walter and Eliza Hall Institute of Medical Research (WEHI),
- key molecules which help infective bacteria acquire resistance to front-line drugs—Prof. Trevor Lithgow, Microbiology, Monash University,
- mitochondria, fundamental research into the energy powerhouses of all cells—Prof. Michael Ryan, Monash University,
- insulin and its receptor, the key to diabetes—Assoc. Prof. Mike Lawrence, WEHI,
- perforins, molecules that form pores in membranes of infected cells, as a precursor to their elimination—Prof. James Whisstock, Imaging Centre, Monash University,
- receptors that trigger the T cells of the immune system—Prof. James McCluskey, the University of Melbourne and Prof. Jamie Rossjohn, Imaging Centre, Monash University, and
- transcription, the first step in the process by which genetic material is transcribed by giant enzymes called polymerases — Assoc. Prof. Hans Elmlund and Assoc. Prof. Dominika Elmlund, Imaging Centre, Monash University.

The new microscope facility has been funded with support from the Ramaciotti Foundations, the Australian Research Council (ARC), Monash University, the Walter and Eliza Hall Institute of Medical Research (WEHI), La Trobe University and the National Health and Medical Research Council of Australia.

How it works

The Titan Krios electron microscope fires a stream of high-energy electrons through a thin sample that's frozen in a pool of liquid ethane at 200°C below zero. Some of the electrons in the beam are deflected or absorbed by the molecules in the sample when they pass through it, and these deflected rays can be used to create a two-dimensional image of the sample. Multiple two-dimensional images obtained by passing the electron beam through many hundreds of samples can then be automatically pieced together to determine the three-dimensional shapes.

Use of an electron beam allows much greater magnification than in visible-light microscopes, and the Titan Krios can achieve magnification of several billion times, resolving the positions of individual atoms in an immune-system molecule.

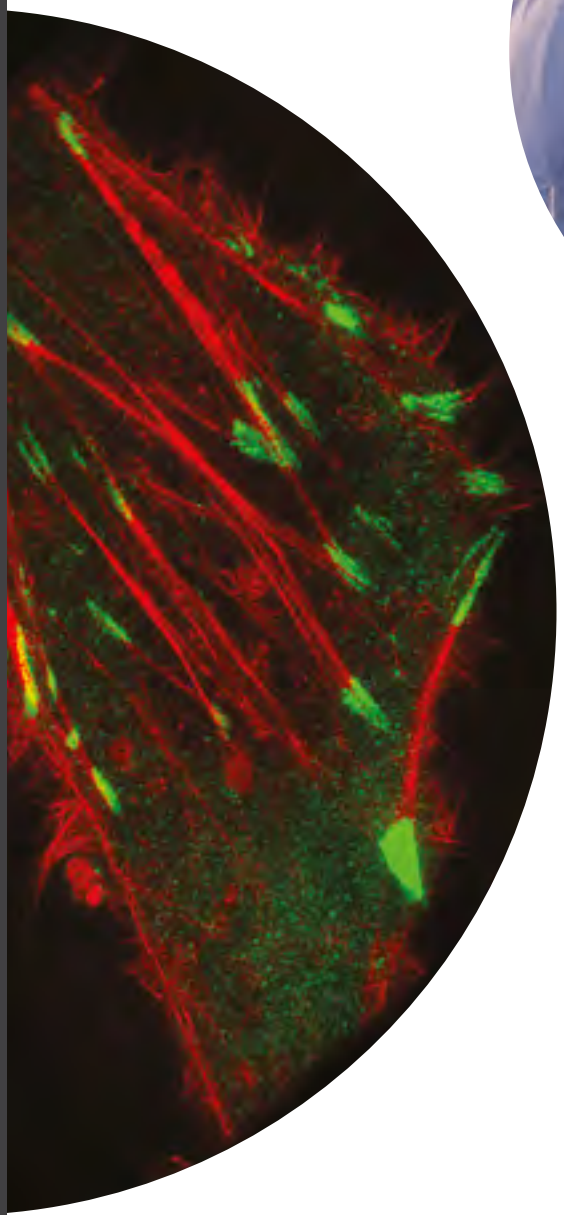
Snap-freezing the cells allows researchers to look at immune molecules in a more natural state: as close as practical to living cells.

About Ramaciotti

The Ramaciotti Foundations were established by siblings Vera and Clive Ramaciotti in 1970 with $6.7 million in funds, proceeds from the sale of the Theatre Royal in King Street, Sydney. In the four decades since their first major seeding donation to found a new research laboratory at the Walter and Eliza Hall Institute of Medical Research in 1971, Ramaciotti has donated close to $55 million to biomedical research. They are one of Australia's largest private contributors in the field. The Ramaciotti Foundations are managed by Perpetual.

Research program

The research program of the Imaging Centre is broadly organised into two key themes - imaging and immunology. The imaging research themes aim to develop new microscopy and visualisation techniques that further the state-of-the-art technology available commercially. The immunology research themes aim to understand the various processes and interactions that underpin immunity by utilising a broad range of imaging techniques and a multi-scale approach to imaging.



89
publications

353
citations

104
media articles

104
conference presentations in 12 countries

$28.4 million
grants won

Atomic Imaging

Theme Leaders: Brian Abbey, Keith Nugent and Harry Quiney

Linking atomic structure to function is the key to understanding the molecular interactions and cellular responses that underpin immunity. There are several major technical difficulties in doing this. For instance, traditionally the principal technique for determining the atomic structure of proteins has been X-ray crystallography. It demands large crystals, which diffract light well, however, preparing large crystals of certain functionally important proteins is not practically possible.

In recent years, unprecedented advances in cryogenic electron microscopy (cryo-EM) technology have enabled near-atomic resolution transmission electron microscopy that allows us to determine the atomic structure of proteins at an equal, if not better resolution than traditional X-ray crystallography. Cryo-EM allows scientists to image single protein particles, thus eliminating the need for preparing protein crystals altogether. However, this technique introduces its own set of challenges such as preparing vitrified protein samples on EM grids, and analysis and processing of large data sets in a timely fashion.

In addition, the development of X-ray free electron laser (XFEL) beamlines internationally at the Linear Coherent Light Source (LCLS) at Stanford University and DESY at Hamburg raises the possibility of studying the dynamics of proteins at the atomic level as these X-ray pulses are so fast that we could visualise the movement of protein substructures.

We believe that the three technologies – X-ray crystallography, cryo-EM and XFEL – will all eventually prove to be complementary technologies that have particular advantages and disadvantages. Hence, our strategy is to utilise and develop our expertise in all three key techniques used to study atomic structures of proteins:

- exceptionally intense micro-focused beamlines at 3rd and 4th generation synchrotron facilities in Australia and at our international partners in Germany and the US;
- X-ray free electron laser (XFEL) beamlines at our international partners in Germany and the US, and
- state-of-the-art cryogenic transmission electron microscopy and cryogenic focused ion beam scanning electron microscopy.

Using these techniques and theoretical modelling of relevant light-matter interactions, we focus on two specific outcomes obtaining :

- structural information on challenging proteins using single particle or crystallisation approaches, and
- dynamic insights or “molecular movies” that allow us to visualise how proteins change in shape during biological function.

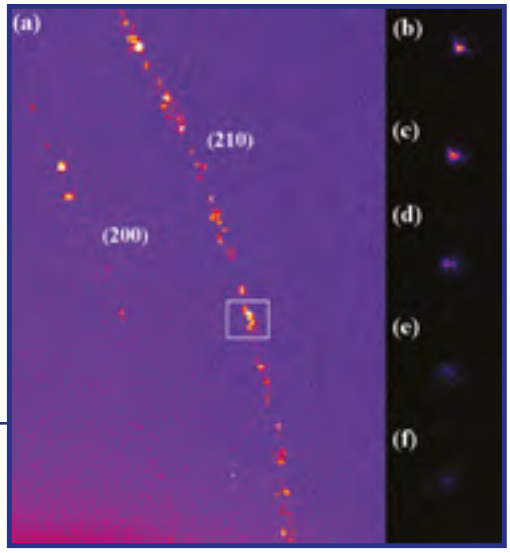
The Centre continues to build strong inter-disciplinary collaborations leading to important new discoveries and examples of joint publications between Physics and Biology include two papers published this year in PNAS. The first paper describes and demonstrates a new method for correlative X-ray imaging and fluoresce measurements: fly-scanning ptychography. The technique permits the rapid phase imaging of large sample areas paving the way to nanoscale X-ray tomography of whole intact organisms (Deng et al., PNAS, 2015). The second paper describes the use of the La Trobe X-ray microtomography facility for studying heart valve disease in collaboration with the Walter and Eliza Hall Institute (Lacey et al. PNAS, 2015).

Highlights

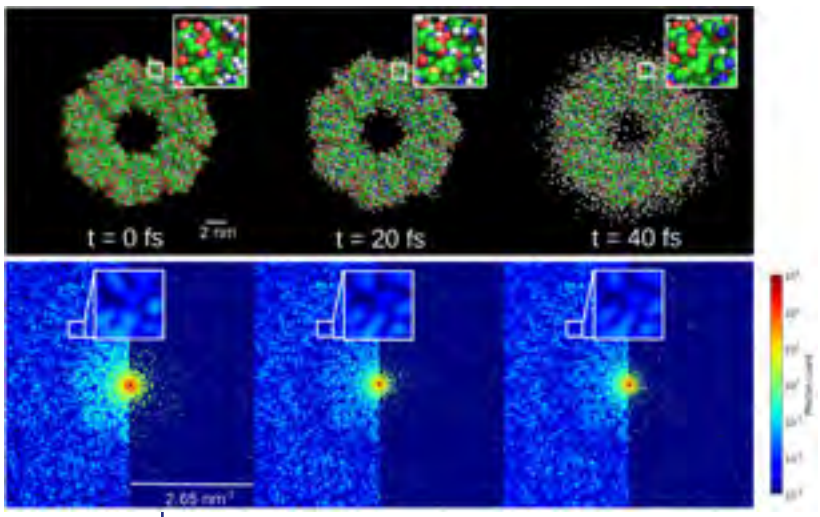
Radiation damage in a micron-sized protein crystal studied via reciprocal space mapping and Bragg coherent diffractive imaging (ACA Structural Dynamics, Vol 2, article 041704)

The Experimental Physics Group at La Trobe University have investigated the phenomenon of radiation damage in micron-sized protein crystals using highly coherent synchrotron X-rays. Previous studies have shown that the use of tightly focused X-ray beams with larger crystals alters their damage behaviour. The group used a combination of crystallography and the recently developed technique of Bragg Coherent Diffractive Imaging to observe what happens as extremely small crystals are exposed to X-rays.

Authors: Coughlan HD, Darmanin C, Phillips NW, Hofmann F, Clark JN, Harder RJ, Vine DJ and Abbey B



Single-molecule imaging with longer X-ray laser pulses (International Union of Crystallography Journal, Vol 2, pg 661-674)



The Group found that in XFEL single molecule imaging damage can act like a gate on the x-ray pulse. This makes the pulse's duration appear shorter, but produces data rich in information about the biomolecule's structure. A similar damage-gating effect is already known in XFEL crystallography and shown to be essential to its success so far. This is the first time such an effect has been predicted and understood for XFEL single molecule imaging, which brightens the future prospects for this technique.

Authors: Martin AV, Corso JK, Caleman C, Timneanu N and Quiney HM

Molecular Imaging

Theme Leader: Katharina Gaus

Understanding molecular interactions and how this translates to cellular activity represents a monumental unmet need in the biological sciences. Hence, it is imperative that structural information is linked to the movements and interactions of single molecules in intact and live immune cells.

Near-atomic resolution imaging techniques such as X-ray crystallography and cryo-EM give us precise structural information down to a few angstroms in a static system, and conventional optical and fluorescence microscopy techniques give us dynamic information but are limited in resolution to around a micron.

Single molecule and super-resolution fluorescence microscopy have a unique combination of spatial and temporal resolution that enables us to follow the dynamics of single protein molecules and/or complexes in living cells and systems.

We develop and use novel single molecule and super-resolution fluorescence microscopy hardware and software tools to bridge this gap between structural biology and cellular function.

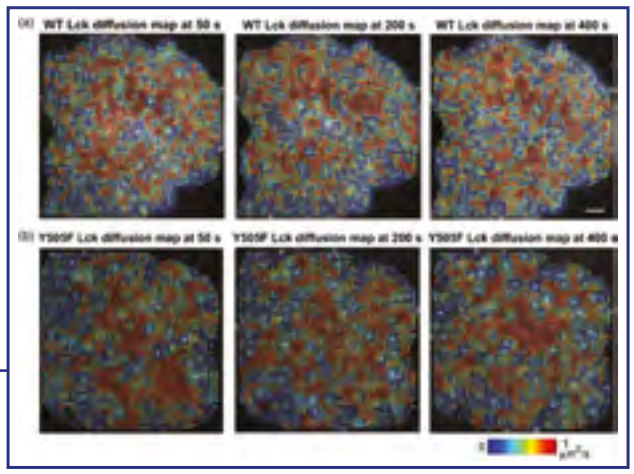
In 2015, we made significant strides towards establishing a core facility dedicated to this goal (as mentioned in the Technology Infrastructure section). This facility, combined with our recent recruitment of EMBL Group Leaders and postdoctoral researchers in this area are steps we have taken to build a critical mass of expertise that will help us drive the development of these imaging techniques and apply them to challenging biological problems.

Highlights

Tracking molecular dynamics without tracking: image correlation of photo-activation microscopy (Methods and Application of Fluroescence, Vol 3, article 014006)

In this paper, Kat and her team reported the ability to analyse the molecular dynamics of fluorescent particles with intermittent excitation and low signal-to-noise ratio present at high particle densities. They collected a series of fluorescence images of biomolecules tagged with photo-activated fluorescent molecules and then applied a spatio-temporal image correlation technique to quantify the movements of single proteins in space and time. They demonstrated the utility of their techniques by studying the diffusion of wild-type and mutant Lck, a protein present in T cells and showed that the time-dependent diffusion maps of the two different types of Lck were different.

Authors: Pandžić E, Rossy J and Gaus K



Cryo-electron microscopy and single molecule fluorescent microscopy detect CD4 receptor induced HIV size expansion prior to cell entry (Virology, Vol 486, pg 121-133)

Kat Gaus and collaborators at the CSIRO Australian Animal Health Laboratory and Deakin University discovered a previously unknown phenomenon in the process of HIV infection. Utilising atomic resolution imaging enabled by cryo-EM and the dynamic and live cell capabilities of single molecule fluorescence imaging, they were able to detect a size expansion of the HIV virus particle prior to the virus entering target cells to facilitate infection. Furthermore, they were also able to identify that the size expansion is facilitated by a particular protein called HIV-1 envelope protein (Env) and occurs when HIV binds to a receptor on the cell membrane. This is information not previously known to scientists and is vital to understanding the process by which HIV infects cells and can play a key role in designing suitable drugs to inhibit this infection process.

This work is a clear illustration of the complementary nature of atomic and molecular imaging techniques and the Centre is excited to be driving such collaborative, multi-scale imaging experiments aimed at elucidating key structures and dynamics of biological processes.

Authors: Pham S, Tabarin T, Garvey M, Pade C, Rossy J, Monaghan P, Hyatt A, Böcking T, Leis A, Gaus K and Mak J

Good things come in small packages – and metallic nanoparticles are some of the smallest. Although their dimensions are measured in nanometres, with each nanometre being one millionth of a millimetre, scientists believe that these tiny particles could be used to fight cancer, collect renewable energy and mitigate pollution. The problem is that it is difficult to know how they work, since they are so small that their structure is impossible to see.

Until now, that is.

An international team featuring contributors from leading institutions in the US and Korea and co-led by an Imaging Centre scientist has recently discovered a solution to this problem. Their discoveries will allow researchers to investigate the 3D structure of these miniscule particles for the first time.

In a new paper published in Science, Monash Associate Professor Hans Elmlund and collaborators from Princeton, Berkeley and Harvard reveal the details of a novel imaging method and show how it can be used to characterise the 3D structures of platinum nanoparticles.

The new method, which is called 3D Structure Identification of Nanoparticles by Graphene Liquid Cell EM (SINGLE), exceeds previous techniques by combining three recently-developed components. The first is the graphene liquid cell, a bag one molecule thick that can hold liquid inside it without obscuring it from the electron microscope. The second is the direct electron detector, which is even more sensitive than traditional camera film and can be used to capture movies of the nanoparticles as they spin around in solution. Finally, a 3D modelling approach known as PRIME allows the scientists to use the movies to create three-dimensional computer-models of individual nanoparticles.

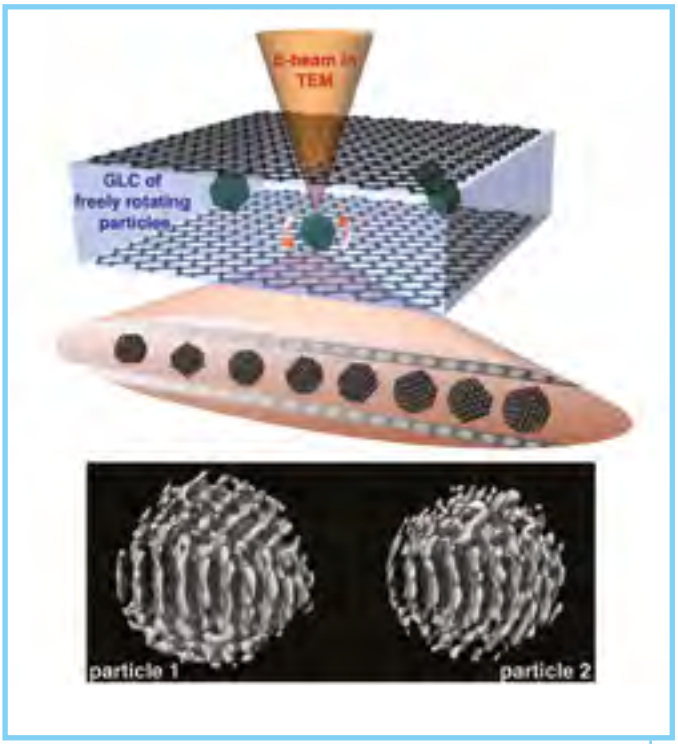
Although platinum nanocrystals have many different applications, they are mostly based on one attribute of the material: it is an excellent catalyst. This is part of the reason that Elmlund and his colleagues chose to work with platinum nanocrystals in particular; the detailed atomic structure of each particle determines, to a large degree, how effective it is as a catalyst.

The differences in structure between individual nanocrystals are pronounced, because the crystals are created by aggregation. They are effectively built up atom by atom, leading to highly complex and unpredictable structures that could not be determined – until now.

In their new article, Elmlund and his collaborators demonstrate the power of their innovative system by describing in detail the structure of two platinum nanoparticles, which were also captured in the movie clips that accompany the publication. "It was very exciting, because seeing the movie I knew that there was a possibility that we could extract 3D information from the image series," says Elmlund.

But the value of the paper extends beyond the demonstration of a novel method. Because the platinum nanoparticles described have never been seen in such detail before, at the level of individual atoms, Elmlund and his colleagues got the opportunity to draw new conclusions about how these highly useful particles grow – and their discoveries have surprised the scientific community.

"I think everybody in the field had anticipated cubical or at least highly symmetrical platinum nanocrystals," says Elmlund. "It was surprising to learn that they form asymmetrical multi-domain structures."



For the imaging scientists involved, next steps will include investigating the formation and evolution of nanoparticles and characterising the transitions they go through to reach their final form.

"It is important for us to understand this, so that we can design new materials, for example, to build better or more efficient solar cells, or make better and more economical use of fossil fuels," says Elmlund. Their new method will undoubtedly help them to shed new light on these areas, and may lead to further revelations; after all, as Elmlund reflects, "Making discoveries is one of the great privileges of being a scientist."

The new SINGLE method devised by Elmlund and his collaborators relies, in part, on the recently-discovered wonder material graphene. First isolated in the laboratory in 2003, this strong but light substance has many intriguing properties.

Each sheet of graphene is only one atom thick, and is made up of carbon atoms with bonds linking them to three of their neighbours. Seen under a microscope, the atoms and their bonds form a honeycomb lattice that resembles chickenwire.

Most of graphene's exciting properties are derived from these extraordinary proportions. For Elmlund's purposes, what was required was a material envelope to hold a liquid as it was examined by a microscope. Graphene, being extremely thin and disproportionately strong, fit the bill perfectly.

Authors: Park J, Elmlund H, Ercius P, Yuk JM, Limmer DT, Chen Q, Kim K, Han SH, Weitz DA, Zettl A, Alivisatos AP

Cellular Imaging

Theme Leader: William Heath

To understand how molecular mechanisms result in co-ordinated immune responses, it is essential to image and quantify cellular behaviour in living animals. We delve into the pathological consequences of disease and mechanisms of immune protection, and bridge the divide between animal models and imaging experiments. This will ultimately transform the fundamental understanding of how different components of the immune system interact with each other in health and disease.

The two main threads in this theme are in-vivo imaging and single cell to animal imaging. In-vivo imaging aims to visualise immune cell trafficking, antigen presentation and immune responses in organs and skin and the interplay of innate and T cell immunity.

Single cell to animal imaging aims to develop protocols that allow immunologically relevant cells to be tagged for X-ray imaging, other methods that can track clusters of cells in whole animal imaging experiments, and greater resolution of tissue structure in intravital microscopy.

To achieve these goals, we utilise intravital and in-vivo imaging facilities developed at our University of Melbourne node and at the Australian National University as well as X-ray imaging facilities available at the Australian Synchrotron.

Highlights

Clinical application of low-dose phase contrast breast CT: methods for the optimization of the reconstruction workflow (Biomedical Optics Express, Vol 6, pg 3099-3112)

Dr Timur Gureyev, University of Melbourne, is working on maximising the benefits and minimising the harms of breast screening technology. "Up to 76 per cent of women experience pain or discomfort during, and up to four days after, a mammographic procedure," explains Dr Gureyev. "Couple this with a 30 per cent chance of cancers being missed (false negatives) and many women receiving false positives, it is little wonder Australian attendance rates do not compare favourably to elsewhere."

One of the other concerns raised with regular screening is the high radiation dose. Some studies even say the harm from screening could outweigh the benefit. This is due to breast tissue being recognised as the most radiosensitive tissue in the body; it is most likely to respond adversely to radiation.

Dr Gureyev and a group of colleagues have been working on an alternative pain free 3D X-ray breast imaging technology with lower radiation doses and increased sensitivity and specificity.

"The project will result in the establishment of a new technique to detect breast cancer more effectively, at significantly reduced radiation dose and minimum patient discomfort compared with current techniques," says Dr Gureyev. "Our proposal to the National Breast Cancer Foundation will be a multinational and multi-institute project with the world's first patient trial of inline phase-contrast computed tomography (PCT)."

At least five world-expert radiologists will use the new image evaluation platform and assign diagnostic scores to the PCT mammograms. They will then compare the relative sensitivity and specificity of the same tissue samples screened with the previous standard digital mammograms (and any available tomosynthesis images). From this evaluation study, evidence to develop a comprehensive and formal clinical trial of PCT mammography will be developed.

During the trial, involving 100 women, patient satisfaction will be gauged through customer surveys. "The bulk of the work will be performed in Australia using the Imaging and Medical beamline at the Australia Synchrotron," says Dr Gureyev.

The technique of PCT mammography requires a spatially coherent X-ray beam with sufficient intensity to perform CT scans within a reasonable time. This is currently possible only at synchrotrons. Imaging and Medical Beamline (IMBL) at the Australian Synchrotron in Clayton, Victoria, has provisions for PCT imaging with variable sample-to-detector distances which can be extended to several meters, as well as the largest coherent beam in the world allowing whole-chest imaging without the need for scanning. Due to the tunability of the synchrotron radiation sources, it is also possible to perform pilot experiments at several different X-ray energies.

Finding breast cancer early before any symptoms are noticed, and when treatment is most likely to be successful, gives women the best chance of survival. And regular breast screens – every two years as recommended by the Cancer Council of Australia – is the best way to find cancer early.

"By improving the safety and comfort levels during these procedures we hope to raise attendance from less than 55 per cent to close to 100 per cent," says Dr Gureyev. "Reducing compression and dosage should, in theory, have a knock on effect for the numbers of early diagnosis."

Authors: Pacile S, Brun F, Dullin C, Nesterest YI, Dreossi D, Mohammadi S, Tonutti M, Stacul F, Lockie D, Zanconati F, Accardo A, Tromba G and Gureyev TE

Imaging Centre scientists have successfully imaged the immune response at the cellular level, laying the groundwork for significant medical advances.

For the first time, a group of researchers have been able to visualise how immune cells are activated and work together to fight off a virus infection. The new study, based at the University of Melbourne and co-authored by Imaging Centre scientists, has revealed the interactions involved in priming the immune response. Excitingly, the findings could be used to improve current vaccines, bringing hope to thousands of people at risk of chronic and deadly diseases.

Comprised of a network of organs, cells and tissues, the immune system is incredibly complex. Although many studies have examined how an immune response is initiated, very little is known about the way individual cells in the immune system coordinate themselves to fight off infections. This is because no-one has ever been able to see this phenomenon occurring – until now, that is.

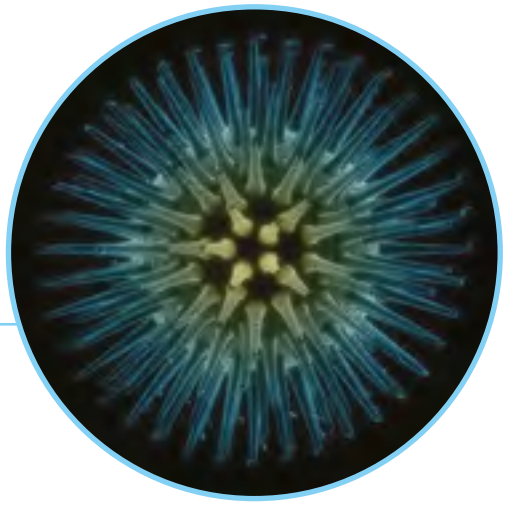
Using highly sophisticated microscope technology, the team imaged the cells of the immune system in real time within the tissues of mice. They made movies of the three major white blood cell players involved in initiating the immune response to Herpes Simplex virus infection – dendritic cells, killer T cells and helper T cells – and observed the intricate interactions that took place.

"We discovered that the immune cells make a series of interactions, like a tag team, with the helper T cells first responding and then assisting the killer T cells," says the University of Melbourne's Dr Scott Mueller, co-senior author of the study and an Associate Investigator at the Imaging Centre. "Revealing this dynamic immune cell dance for the first time explains how the immune system can respond so quickly to an infection on the skin." The study also highlighted a previously unidentified level of control of T cell activation to peripheral infection.

The scientists are now planning to dig more deeply into the mechanisms of the immune system, and explore how helper T cells actually go about delivering their help to killer T cells via dendritic cells. They will also explore how the dynamic interactions they observed in this study affect the immune response as a whole.

By showing us how immune cells behave, and providing an insight into the critical steps required to stimulate immunity, the team's discovery could lead to a range of useful applications in medicine. "Armed with knowledge of how the immune cells behave, we may be able to improve responses to diseases such as HIV, or alternately disrupt immune cell interactions where they are not wanted, such as during autoimmune diseases," Mueller says.

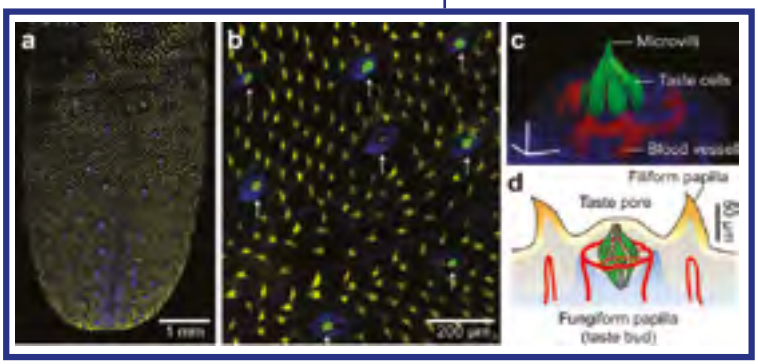
Authors: Hor JL, Whitney PG, Zaid A, Brooks AG, Heath WR and Mueller SN



Intravital microscopic interrogation of peripheral taste sensation. (Nature Scientific Reports, Vol 5, article 08661)

ANU-based Imaging Centre Associate Investigator Steve Lee co-authored a study with colleagues at Massachusetts General Hospital and Harvard Medical School that achieved real-time microscopic monitoring of taste responses from the tongue of a living mouse using specially designed tongue-imaging devices. Imaging and quantifying cellular behaviour in living animals is essential to understand how molecular mechanisms result in coordinated immune responses. The paper, Intravital Microscopic Interrogation of Peripheral Taste Sensation, was published in Scientific Reports in March.

Authors: Choi M, Lee WM and Yun SH



Recognition

Theme Leaders: Dale Godfrey and Jamie Rossjohn

Recognising a foreign invader is one of the key functions of our immune system. This role is typically performed by a variety of T cells in our body that are capable of recognising different kinds of antigens. Primarily utilising atomic and molecular imaging techniques, we focus on understanding,

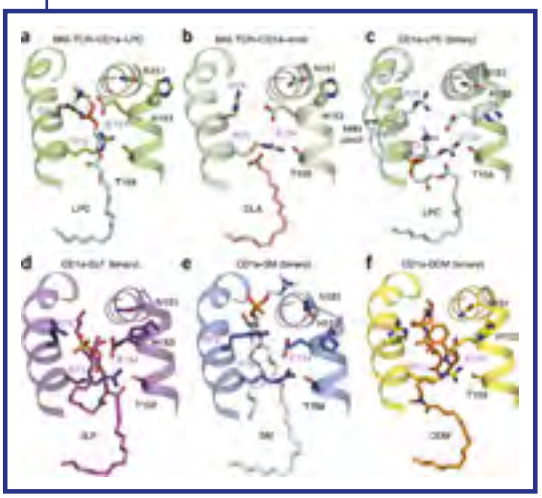
- how peptides are captured and presented to the immune system and aberrant T cell reactivity (peptide-mediated immunity),
- what specific antigens do lipid-reactive T cells see, and how are they mobilised during infection/disease (lipid-mediated immunity) and,
- how metabolites are presented to and detected by our immune system and how this triggers subsequent activation of an immune response (metabolite-mediated immunity).

Highlights

αβ T cell antigen receptor recognition of CD1a presenting self lipid ligands (Nature Immunology, Vol 16, pg 258-266)

Imaging Centre scientists reported a previously unknown mechanism whereby a class of T cells known as αβ T cells indirectly sense self antigens that are bound to an antigen-presenting molecule called CD1a. The work, led by CIs Dale Godfrey and Jamie Rossjohn in close collaboration with Prof. Branch Moody from the Harvard Medical School, showed that the T cell receptor bound in a specific configuration that only allowed binding to happen when self antigens were presented on the CD1a molecule and inhibited binding if other antigens were presented. The X-ray crystal structures reported by the scientists clearly showed the binding configuration that allowed and inhibited binding based on the type of antigens presented.

Authors: Birkinshaw RW, Pellicci PG, Cheng TY, Keller AN, Sandoval-Romero M, Gras S, de Jong A, Uldrich AP, Moody DB, Godfrey DI and Rossjohn J



Determinants of Gliadin-Specific T Cell Selection in Celiac Disease (Journal of Immunology, Vol 194, pg 6112-2122)

New findings suggest that a specific group of T cells are likely to contribute significantly to the symptoms associated with gluten intolerance.

An international research team has discovered a group of T cell receptors present in the disease-affected tissue of one of the two primary genotypes associated with celiac disease. Led by scientists at Monash University and Leiden University Medical Centre, the team found two populations of T cells that were undetectable in samples from patients on a gluten-free diet but that expanded rapidly following antigenic stimulation.

By identifying and characterising the relevant antigen-specific T cells in biopsy samples from celiac patients, the researchers have started to prepare the groundwork for future prophylactic or therapeutic interventions for this common disease of the small intestine.

The team obtained polyclonal gluten-specific T cell lines from the small intestines of four adult patients with celiac disease, from which they generated clones. They then procured the crystal structures of the antigens bound to the T cell receptors.

The results indicate that the emergence and proliferation of these specific T cells are implicated in the onset of celiac disease – and they may also explain variations in the symptoms experienced by patients. Analysis of the crystal structures also revealed the vital role of an amino acid called arginine in the region where T cell receptors bind to the antigen. The work could eventually contribute to the development of novel compounds that target the T cell receptors described in the study.

"Our group is focused on understanding a disease of direct human relevance that ultimately may lead to translational outcomes," says Professor Jamie Rossjohn, an Imaging Centre researcher and one of the study's authors. "Our next steps are to continue our work understanding the basic biomedical mechanisms underpinning celiac disease."

Challenging a universally accepted, longstanding consensus in the field of immunity requires hard evidence. New research has shown the proof is in the picture. And this proof may have implications for type 1 diabetes.

Type 1 diabetes is an autoimmune disease – the body's immune system mistakenly attacks its own cells, leading to the inability to produce enough insulin to regulate glucose levels in the blood. Now, an unexpected discovery about how these immune cells work at the atomic level may provide avenues to investigate new mechanisms able to short-circuit the inappropriate immune response in patients with type 1 diabetes.

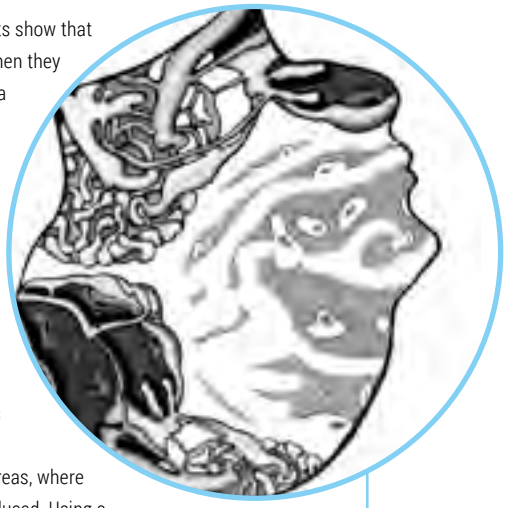
When microorganisms such as bacteria and viruses invade the body, the immune system elicits a response that ensures they are engulfed and destroyed. Central to this response is the molecular-level interaction between the surface receptors of white blood cells (T cells) and immune molecules known as the major histocompatibility complex (MHC). Basically, a cell signals to a T cell that it is infected and the T cells mount a broad immune attack in the area of the infection.

Until now, the assumption has been that the receptors on the T cells (TCRs) must bind to MHC in a specific orientation in order to trigger a signal to the immune system.

A team of researchers, led by Professor Jamie Rossjohn at Monash University, has succeeded in turning current immunology on its head, demonstrating for the first time that TCRs can bind with a completely reversed orientation – compared to all previously studied receptors.

Using the National Synchrotron, the team has investigated TCRs associated with a particular type of T cell – a regulatory T cell (Treg) – that prevents the body from attacking its own insulin-producing cells. "We like to call Treg cells 'peacekeeping' cells. They come about to stop the inflammatory response (once infections have been cleared) and false alarms that occur in autoimmune diseases.

In type 1 diabetes there are not enough of these peacekeeping cells and so the immune system continues to attack and destroy insulin-secreting cells," says Dr Hugh Reid, a co-author of the paper published in Nature Immunology.



"Our atomic snapshots show that TCRs still function when they interact with MHC in a completely different orientation."

Individuals with type 1 diabetes are thought to have a reduced number of the peacekeeping cells. This subsequently triggers an unhelpful immune response in the pancreas, where insulin protein is produced. Using a fragment of this protein and an MHC molecule, the researchers stimulated the production of the peacekeeping cells needed by patients with type 1 diabetes, and they discovered – along with collaborators Tony Tiganis, Monash University and Bart Roep, Leiden University- that despite the reversed mode of connection, the cell still suppressed the attacking response in the presence of insulin.

This 'fixed' orientation of TCR recognition has always been put down to natural selection within the immune system's evolution. And immunologists have strongly believed for T cells to be activated they must 'dock' in this fashion. Challenging this conventional understanding of the fixed orientation of TCRs suggests that all types of T cells could be capable of connecting with MHC in completely different ways.

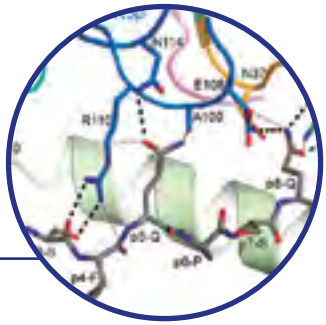
Their findings challenge established views and open up many exciting opportunities for further research. Of particular interest is that, despite the TCRs' reversed orientation, the Treg cells are still functional, suppressing the immune response when necessary.

"We will now set out to determine more TCR-MHC interactions of the same regulatory T cell subset and compare them to the other T cell TCR-MHC interactions derived from the inflammatory T cells," reveals Reid.

Authors: Beringer DX, Kleijwegt FS, Wiede F, van der Slik AR, Loh KL, Petersen J, Dudek NL, Duinkerken G, Laban S, Joosten A, Vivian JP, Chen Z, Uldrich AP, Godfrey DI, McCluskey J, Price DA, Radford KJ, Purcell AW, Nikolic T, Reid HH, Tiganis T, Roep BO and Rossjohn J

The paper was published in June 2015 in the Journal of Immunology. In a notable accolade, it featured in the 'In this Issue' section, which highlights articles considered to be among the top 10 per cent of those published in the journal.

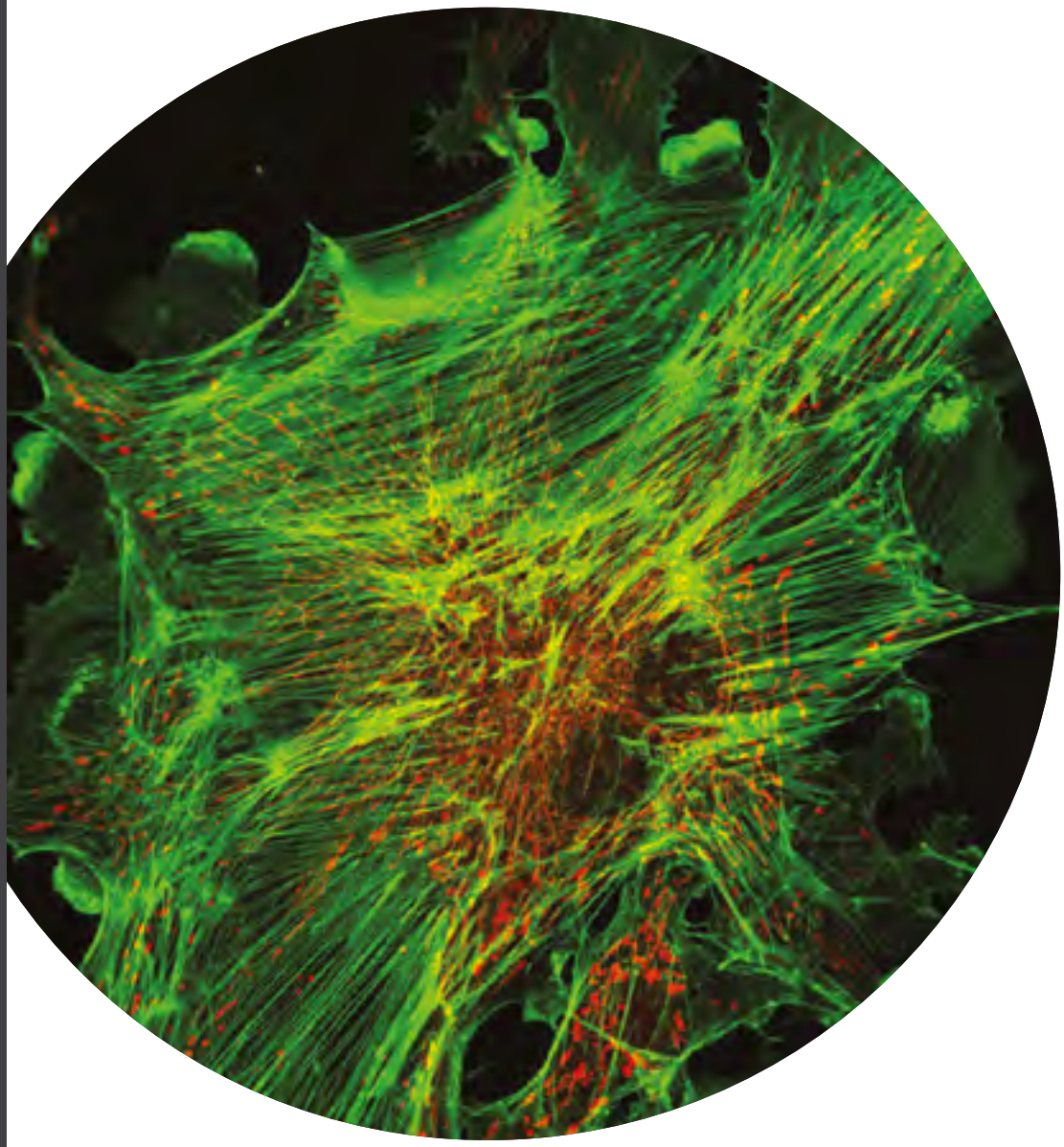
Authors: Petersen J, van Bergen J, Loh KL, Kooy-Winkelaar Y, Beringer DX, Thompson A, Bakker SF, Mulder CJJ, Ladell K, McLaren JE, Price DA, Rossjohn J, Reid HH and Koning F



Activation

Theme Leader: Katharina Gaus

Once a foreign invader is recognised by our immune system, the next stage is the activation of an appropriate response to deal with the threat. After a T cell receptor detects an antigen, multi-subunit, membrane signalling complexes translate this antigen recognition into T cell signalling and activation through a signalling apparatus known as the CD3 complex. Using specialised fluorescent T cells and single molecule and super-resolution microscopy techniques, we aim to determine the dynamic spatial organisations of signalling complexes, clusters and vesicles, and link these signalling patterns to downstream activation responses (imaging of T cell activation networks).



Effector Function

Theme Leaders: James Whisstock and David Fairlie

The final step in the process of dealing with a foreign invader is effecting an appropriate lethal response to deal with the threat. How immune recognition events translate into cell fate decisions and the dynamics of the movement of various immune cells in response to "danger" signals within the body are key areas of investigation in this research theme. Specifically, we look at:

- how the innate immune system responds to the detection of pathogens, and ways to target and selectively modulate the response of specific innate immune cells (imaging of innate immune responses) tracking,
- different innate immune cells during different stages of the immune response (imaging innate immune cells) and,
- the weaponry associated with immune killing, and the roles for complement proteins in immune signalling (imaging of immune effectors).

The immune response to infection or injury is augmented by a network of "Complement" proteins in blood and on cell surfaces. These proteins recognise infected cells and release fragments such as C3a and C5a that stimulate new immune cells to migrate to the site of infection. In 2015, we downsized the C3a protein to small molecules of similar potency but much greater stability. We labelled these compounds with fluorophores for tracking their binding to their unique receptor, and developed small molecules for blocking their actions. These compounds are being used to study the relative actions of innate immune cells in vitro (mast cells, macrophages, neutrophils). We have been tracking their actions on C3a receptors at different stages of the immune response in mice subjected to an inflammatory insult. These studies are helping us understand molecular mechanisms that initiate, sustain and terminate the acute immune response."

Following this recognition and recruitment process, pathogens & infected cells are tagged for destruction and lysed by the Membrane Attack Complex.

In 2015, we have used a combination of cryo-Electron Microscopy, Nuclear Magnetic Resonance spectroscopy and X-ray crystallography to gain a comprehensive understanding of how perforin-like immune effectors first interact with the membrane and start to assemble into pores.

Our team initially performed a comprehensive mutagenesis study to understand how perforin interacts with the membrane. Then, using NMR we directly identified the key amino acids that initially bind to lipids, locking the perforin monomer onto the membrane surface.

Next, using protein crystallography, we made the unexpected s discovery that the venom of the Australian stonefish contains a soluble assembly of two perforin-like proteins in an early pre-pore complex. Our findings further highlighted a new and extensive branch of the perforin like superfamily in fish and reptiles that likely play general roles in combatting bacterial and viral infection.

Finally, we used cryo-EM to study the conformational changes that perforin-like proteins move through en route to forming a pore. To achieve this we studied a model perforin-like protein present in the oyster mushroom and that forms unusually homogenous pores. Using protein engineering we introduced mutations that "locked-up" the perforin machinery at discrete intermediate steps. The resulting EM structures, reported at between 11-16Å resolution and interpreted using the crystal structure of individual components provide the most detailed picture to date of how these remarkable molecular machines punch holes in cells.

Highlights

Nutrient and immune sensing are obligate pathways in metabolism, immunity, and disease. (FASEB Journal, Vol 29, pg 3612-3625)

Historically, inflammation has been viewed as a coordinated response to infection. However, many of the signalling molecules produced or activated during the innate immune response to infection are also observed in the absence of any infectious stimulus. An alternative view for some immunological responses is that they are triggered by disrupted homeostasis and their purpose is to restore normal homeostasis. Imaging Centre researchers have recognised important molecular links between innate immune responses and chemical, genetic and environmental disruption to homeostasis and are working to better understand the molecular basis of these links and the roles of these common signalling pathways, signalling molecules and effector functions. This article described some novel mechanistic links between innate immunity and metabolism that underlie metabolic function and dysfunction, providing a different context to the importance of the molecular experiments being conducted within the Centre to identify and understand the molecular basis of innate immunity.

Authors: Iyer A, Brown L, Whitehead JP, Prins JB and Fairlie DP

Media Release | Torso-like mediates extracellular accumulation of Furin-cleaved Trunk to pattern the Drosophila embryo termini (Nature Communications, Vol 6, article 8759)

A member of a protein family that is usually associated with immune destruction of virally infected or cancerous cells has been found to control the release from cells of a critical growth factor governing head and tail development in fruit flies (Drosophila melanogaster). This may help explain how these perforin-like proteins function in human brain development and neurodevelopmental disorders such as Autism Spectrum Disorder.

The team believes their findings may provide new opportunities for the generation of novel therapeutics – for example, in the treatment of brain developmental disorders and conditions such as Autism Spectrum Disorder.

The research published today in Nature Communications was carried out at Monash University by postdoctoral researcher Dr Michelle Henstridge, Australian Research Council DECRA Fellow Dr Travis Johnson, and co-led by Associate Professor Coral Warr in the School of Biological Sciences and Professor James Whisstock in the Department of Biochemistry and Molecular Biology. Their research solves a long-standing question in developmental biology: how is the growth factor in the fly embryo controlled in order to determine where the head and tail form?

"These findings are significant and exciting as they suggest a completely new mechanism for how growth factor activity can be controlled," Dr Johnson say.

Dr Henstridge adds: "Understanding how growth factor activity is controlled is vital because loss of control of growth factors underlies many of the major diseases that afflict society, such as cancer and obesity."

The perforin-like protein in the fruit fly is called 'Torso-like' because female flies lacking this protein produce embryos lacking heads and tails.

"The fruit fly Drosophila is a fantastic organism for investigating the question of how these perforin-like proteins act in embryo development; most of our knowledge of how human development and growth is regulated started with studies in the fruit fly. This is because most human genes controlling development and growth act in the same way in fruit flies," Associate Professor Warr says.

Professor James Whisstock, highlights the significance of discovering that a protein related to the human immunity protein perforin – which punches holes in and kills foreign pathogen cells – is used to release a growth factor only at each end of the fly embryo.

"What's exciting about our research is the discovery that a protein related to perforin – which usually functions to kill cells – is actually helping cells develop and differentiate in fly embryos. This is important because a group of perforin-like proteins found in the human brain have, in previous research, been shown to be associated with proper brain development," Professor Whisstock say.

Associate Professor Warr concludes: "While we don't yet know how these proteins work, we suspect they may also be involved in controlling growth factor release from cells."

With support from a Monash University grant, they plan to continue to study fruit flies to explore the functions of important mammalian proteins on a much larger scale.

Authors: Johnson TK, Henstridge MA, Herr A, Moore KA, Whisstock JC and Warr CG

Downsizing Proteins Without Losing Potency or Function (Proceedings of the 24th American Peptide Symposium, Vol 24 , pg 16-20)

Human complement protein C3a is a 77-residue protein produced on the cell surface after activation of a complex network of plasma and membrane proteins that constitute the complement system, named for its role in complementing antibody-mediated immune defence. C3a is best known for its ability to attract (chemotaxis) and activate (degranulate) innate immune cells such as mast cells and neutrophils which contain granules that release inflammatory stimuli like histamine, tryptase, heparin and other enzymes often associated with allergies, asthma and acute inflammatory responses. In recent years, innate immune cells have been more strongly associated with chronic inflammatory diseases. This study reported the successful downsizing of the complement C3a protein, which is rapidly deactivated in plasma through carboxypeptidase-mediated removal of its C-terminal arginine. We have shown that the smaller protein still has the same potent and selective functional responses as the original one. Furthermore, through subtle chemical changes these small molecule 'agonists' have been successfully converted into the first potent and selective small molecule 'antagonists' that block or inhibit all of these functions caused in vitro by C3a and small molecule agonists.

Media Release | Stonefish toxin defines an ancient branch of the perforin-like superfamily (PNAS, Vol 112, pg 15360, 15365)

The stonefish is one of the world's ugliest and deadliest fish. You'll know if you step on one; the fish protects itself using 13 razor sharp venom filled spines capable of slicing through reef shoes. The resulting pain is crippling, can last for days and may result in amputation of a limb or death – a torturous venom worth avoiding.

Monash University researchers have solved the X-ray crystal structure of the lethal factor present in stonefish venom. Their discoveries have provided unexpected insight into a crucial human immune response that is responsible for the failure of up to 30 per cent of bone marrow transplant therapies for treating leukaemia.

The structural insights obtained from stonefish venom are now being used to develop immunosuppressants to improve the success rate of transplant therapies.

The work, published today in PNAS (Proceedings of the National Academy of Sciences of the United States of America), reveals that the lethal component of stonefish venom, a protein called Stonustoxin, is an ancient relative of the human immune protein perforin.

In humans, perforin is an essential weapon unleashed to destroy virally infected and cancerous cells.

Perforin proteins attach themselves to a diseased cell and assemble to form giant ring shaped holes, or pores, on the cell surface. Each pore contains around 20 perforin proteins that stick together in a symmetrical fashion. The pores are big enough to allow toxins to enter the cell, killing it from within.

How these pores form is a mystery but the work on stonustoxin has revealed a key part of the pore assembly mechanism.

To make their discovery, the team used powerful synchrotron radiation to visualise the atomic structure of stonustoxin. Crucially, they found that the toxin contains two perforin-like proteins stuck together. By seeing how two of the proteins first interact, the researchers can build on this to understand how the full assembly of 20 perforin molecules forms a complete pore.

Unravelling the structure of the stonefish's lethal toxin was carried out at Monash University and the Imaging Centre. The leading authors of the study were Dr Andrew Ellisdon, Dr Sheena McGowan and Professor James Whisstock.

"The lethal factor in stonefish venom is like a loaded gun: ready to fire as soon as it is injected into the foot of an unsuspecting victim," says co-lead author Dr Sheena McGowan.

In humans, unwanted or excessive perforin activity is responsible for a range of medical problems including pancreatic cell destruction in Type 1 diabetes and the rejection of bone marrow transplants in the treatment of leukaemia.

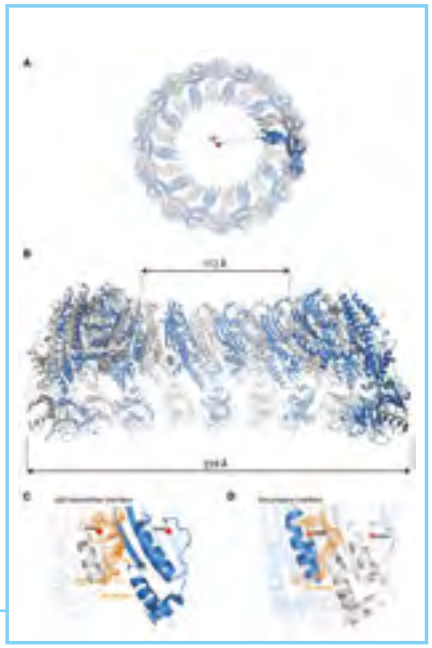
Accordingly, an international group of researchers, led by the Peter MacCallum Cancer Institute and including Monash based Professor Whisstock and his team, are working to develop perforin inhibitors.

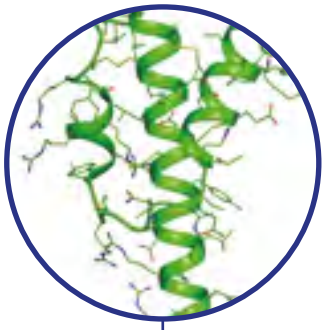
"Already the structure of stonustoxin is starting to inform our drug development program," says co-lead author Professor Whisstock. "Now we understand the very first stages of perforin pore formation. This type of mechanistic information is extremely useful in developing new strategies to inhibit perforin itself.

"People who step on a stonefish suffer agonising pain because the lethal stonustoxin protein attacks nerves. The treatment for envenomation includes an antivenom together with soaking the wound in non-scolding hot water – the latter treatment unravels the venom and stops it punching holes," he says.

The work conducted at the Imaging Centre used major national research platforms, including the Australian Synchrotron, and Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy.

Authors: Ellisdon AM, Reboul CF, Panjikar S, Huynh K, Oellig CA, Winter KL, Dunstone MA, Hodgson WC, Seymour J, Dearden PK, Tweten RK, Whisstock JC and McGowan S





Our objective of creating small molecules was aimed at producing a more stable form of C3 that could be used to identify the true functional roles of C3a in innate immunity. CoE scientists are now labelling and using these powerful small molecule probes to interrogate C3a-mediated activities in innate immune cells and in rodent models of inflammatory conditions towards better understanding the molecular basis of this axis of innate immunity.

Authors: Fairlie DP, Yau MK, Hamidon JK, Singh R, Lim J, Suen JY, Rowley JA, Lohman RJ, Stoermer MJ, Iyer A and Reid RC

Media and Outreach

When the Clive and Vera Ramaciotti Centre for Structural Cryo-Electron Microscopy was launched in early February we knew 2015 was going to be a big year for not just for science but for our role as science communicators.

As a Centre we have a broad target audience and a responsibility to effectively communicate our science to this audience. This is not always an easy feat, but something the Centre aims to continue improving. Communicating the impact of our research and raising awareness amongst our key stakeholders and partners, state and federal governments and their agencies, the broader scientific community and the general public forms a major part of our strategy.

We are currently engaged with Research Media, an international communications agency, who provide us with support across all our communications channels: newsletters, image creation, media releases and the website redesign. Research Media are not a typical agency; their expertise lies in their niche understanding of the problems faced by their as they have a background ranging across scholarly publishing, academia and science communication.

Our media communications efforts have been extremely productive to date; we have attracted TV, radio and print coverage for some of the outstanding research being done in our Centre.

Media Coverage

There were a total of eight media releases produced during 2015. These resulted in 4 television, 14 radio and 53 newspaper articles with another 33 occurrences online publications.

The media coverage received for our Centre research has given our researchers a vital platform to explain the relevance and significance of their work to both the broader scientific community and the general public.

This coverage has given our researchers a platform to explain their work to both the broader scientific community and the general public. It also helps them to look at their research from the eyes of this wider audience, provides them with experience communicating in lay terms as well as adding to national conversation about the importance of fundamental science for innovation.

Website and Social Media

The Imaging Centre's interactive website acts as a central hub for our community. The website is updated regularly with news and events relevant for Centre staff, media releases, as well as an easily navigable publications tab. In 2015, our website attracted 9,418 unique visitors, up from 3,113 in 2014. Collectively, these visitors contributed 27,586 pageviews in 2015 compared with 15,670 in 2014. Of all visits to the website in 2015 71 per cent were new, a statistic that reflects our growing online community. In fact, our online community was also largely international – 60 per cent of our website visitors were based outside Australia with the United States, United Kingdom, the Netherlands and Germany bringing in the most guests.

Our newsletter subscribers and social media presence steadily increased throughout 2015 – effectively growing our impact and our ability to stay connected with students, the media, members and the scientific community. Our Twitter followers almost doubled, 192 at the end of 2014 to 396 at the end of 205.

We also boasted an extremely high open rate (47 per cent) for our newsletter compared to the education sector average open rate (19 per cent) – testament to our reputation of providing quality, timely information regarding Centre research and activities.

Newsletter

Each month we put together a newsletter that is distributed to approximately 600 people – with open and click rates well above industry standard. The newsletter forms an important medium for us to communicate with key stakeholders, all Centre staff, government officials as well as interested public who subscribe from the website.

We rebranded and refined our newsletter mid-year; we have found the short form is more appealing to our readers. With a dedicated media and communications manager on board we have been able to incorporate alternative media into the newsletters. Short video interviews about recent publications have been popular with our audience and have given valuable media training to our researchers.

Public Outreach

In addition to reaching the broader scientific community and general public via our media opportunities, our researchers are also proactive in taking steps to communicate their work and key insights via public lectures, outreach in schools programs and targeted talks and workshops.

During June we took part in the *Light in Winter*, an annual program held in Melbourne's Federation Square.

This year, the celebration was part of a bigger picture as 2015 was proclaimed the International Year of Light and Light-based Technologies by the UN General Assembly – and the Light in Winter was one of many global efforts to boost public and political understanding of the vital role of light in the modern world.

We seized the opportunity proffered by this event to educate the public about lasers capable of printing jet engines, boring holes in the hardest of diamonds and performing complex surgical procedures. Two of our PhD candidates – Hannah Coughlan and Nicholas Anthony both from our La Trobe University node – participated in the creation of a video.

Entitled 'This is Laser', the video was projected across Federation Square and gave a fascinating insight into how laser technologies work. The exhibition further showcased Molecule of Light, a dramatic laser installation created especially for the Melbourne-based festival by the world-renowned UK artist Chris Levine. Finally, Professor Whisstock spoke in an evening educational forum that highlighted the importance and utility of all wavelengths of light in understanding biological processes.

In August 2015, Monash hosted the first *STEM Talks*® giving the public an opportunity to hear from leading scientists from Monash University. Our director shared insights into the challenges he faces when undertaking cutting edge STEM (Science Technology Engineering and Maths) research.

James told a story about immune killing, his aim was to persuade the audience that a little bit of killing is good for you but too much is not. And to highlight how structural biology is tackling how the immune system kills. The Monash *STEM Talks*® reveal how leading scientists undertake their research and explore the unforeseen challenges and successes of cutting edge science the Centre is actively looking to be included in further events of this kind.

Public lecture: The technical advance
ANZAC Centenary Lecture, Museum of Victoria, 11 June 2015

The Great War (1914-1918) may be regarded as the first modern war; soldiers wore camouflage green to escape detection rather than red or blue uniforms to attract attention; technology played a leading role in warfare. The aeroplane, the tank, the submarine and the machine gun all developed rapidly as modern science played an increasingly important part in the struggle for supremacy by both sides. The University of Melbourne presented a series of "ANZAC Centenary Lectures" in 2015 to commemorate the Australia's participation in the Battle of Gallipoli and to echo a series of public lectures delivered in 1915 that communicated the role that the University was playing in the conflict. These complemented an exhibition at the Museum of Victoria on loan from the Imperial War Museum in London and were presented in partnership with the Shrine of Remembrance and the National Gallery of Victoria.

The lecture "The Technical Advance" on 11 June 2015 at the Museum of Victoria was moderated by Maxine McKew and presented by Professor Iven Mareels (Dean of Engineering), Professor Tom Spurling (CSIRO Board Member), Dr Charlie Day (Carlton Connect) and Assoc. Prof. Harry Quiney (Imaging Centre CI). CI Quiney recalled the contributions and the sacrifices made by physicists in the Great War and, in particular the work of Harry Moseley and Lawrence Bragg. Both had connections to Australia and both have left a legacy that continues as part of the active research of the Imaging centre. Moseley had been in Australia at the outbreak of the Great War as part of a travelling science fair organized by the British Association for the Advancement of Science and presented his research in Melbourne and Sydney on the X-ray physics that forms the basis of the modern understanding of the order of the elements in the Periodic Table. Tragically, Moseley was killed by a sniper's bullet at Gallipoli in 1915; there seems little doubt that he would have been awarded the Nobel Prize for Physics for his discovery of Moseley's Law. Lawrence Bragg, who was born in Adelaide, was awarded the 1915 Nobel Prize in Physics for the development of crystallography with his father, Sir William Bragg. Bragg was recruited by the British Army to develop methods of acoustic detection of artillery. An inventive experimentalist, he developed an acoustic detector crafted out of old ammunition boxes that worked by measuring the cooling effect on the resistance of a current carrying wire caused by the shockwave from the distant gunfire. His detectors continued in use throughout both world wars and were credited with turning the tide of several battles in The Great War, for which Bragg was decorated with military and civilian medals. His father, William Bragg, contributed to the development of an early form of sonar for the British Admiralty in response to attacks by U-boats.

CI Quiney also noted that fundamental science continued throughout the Great War, despite the dire situation on both sides of the trenches. Albert Einstein, for example, published many of the significant articles on the General Theory of Relativity in these years. Despite the prevailing antipathy to the Germans, Sir Arthur Eddington, a leading Cambridge astronomer, Quaker and pacifist, promoted the scientific work of Einstein to the British public throughout the Great War and organized the expedition to observe a total eclipse of the sun in order to verify Einstein's predictions about the curvature of space around massive bodies. It was Eddington, a popular and effective communicator of physics, who created the popular mystique that surrounded Einstein in the first half of the twentieth century and which put the experimental confirmation of the General Theory of Relativity on the front page of many leading newspapers.

2015 International Student Science Fair

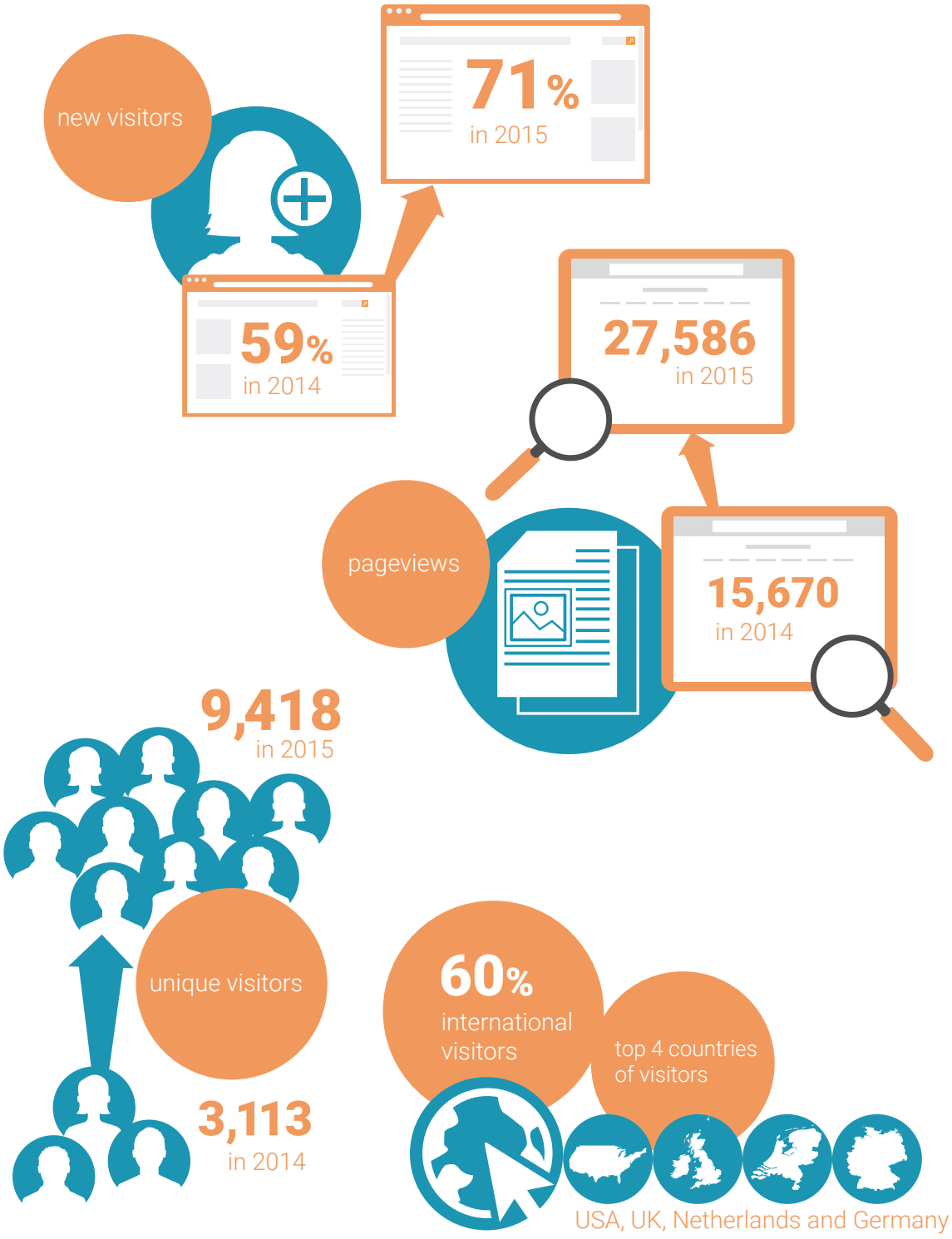
John Monash Science School hosted the 2015 International Science Students Fair from 7-11 December. The Imaging CoE was a proud sponsor of the event and six of our researchers took 40 ISSF students through a workshop in either immunology, X-ray physics, optical imaging or image processing – one of these was the DIY Lens Workshop devised by AI Steve Lee.

Developed by CI Harry Quiney, the short scientific workshops illustrated the interdisciplinary work being done across the Centre's five nodes. At the end workshop the students and mentors held a facilitated discussion about the important features of each of the four projects. The students gained a lot from this experience and realised that while the Centre's quest is to understand the mechanisms that drive the immune system, this research also drives knowledge in new and unexpected directions.

The workshops were so successful and inspiring, Imaging Centre CI Harry Quiney has been asked to come back and deliver the program as part of the John Monash Science School regular curriculum.

Media and Outreach

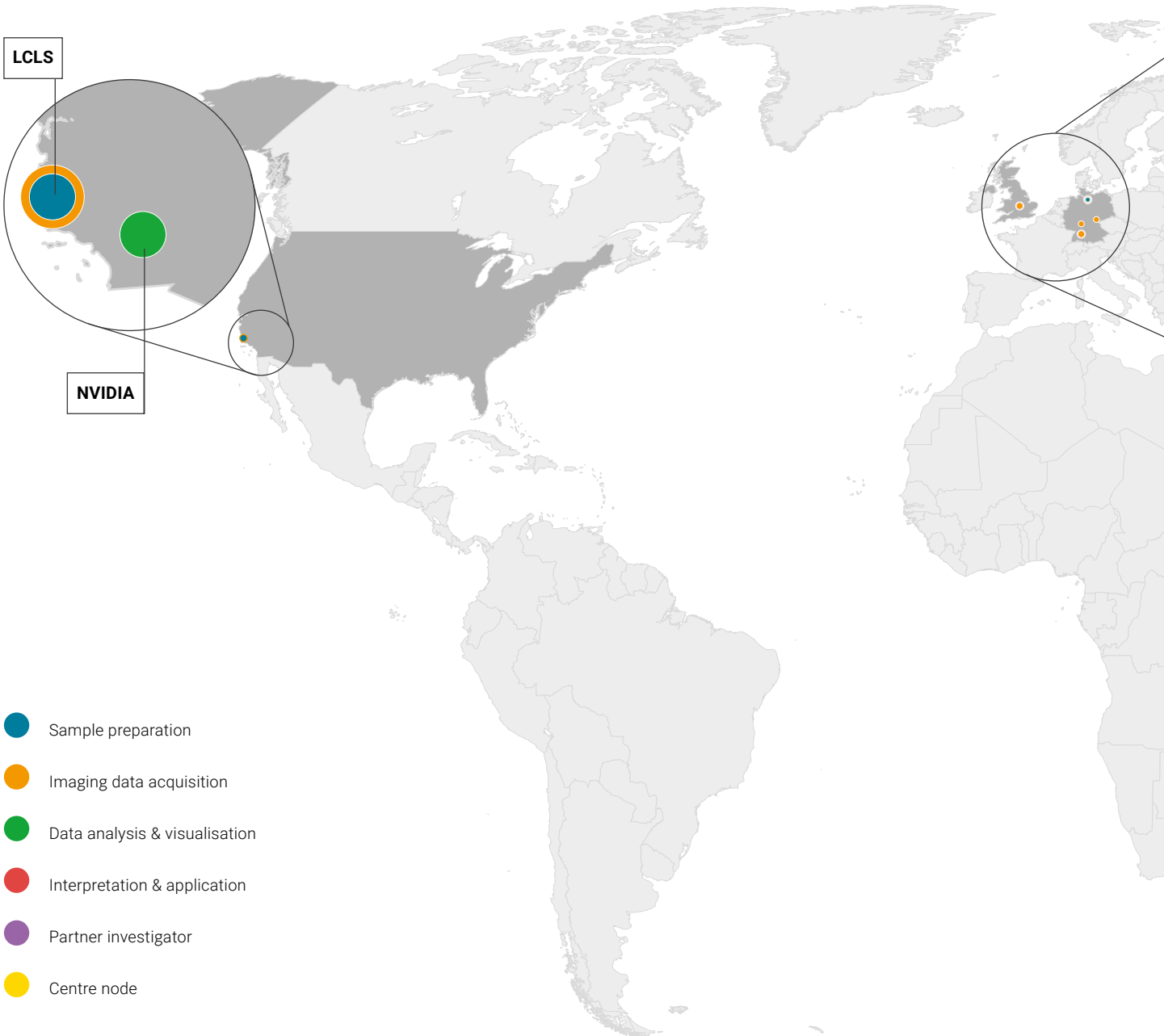
Website stats



National and International Linkages

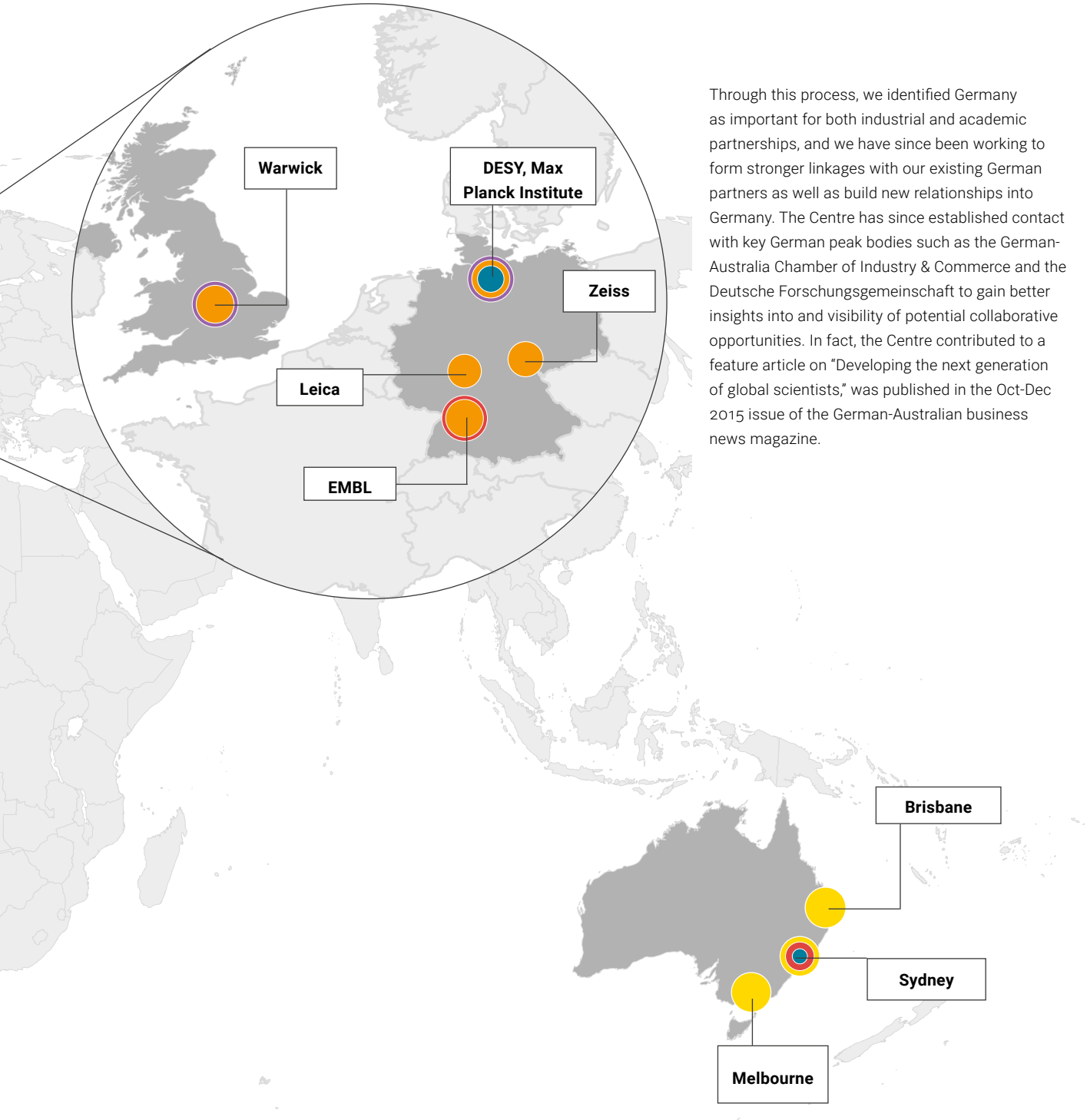
A Strategic Approach

The Centre took a very strategic approach to developing national and international linkages in 2015. Working together with colleagues at Monash University's Office of Global Engagement, we developed a value chain framework to better focus our research themes to build a global network of excellence in imaging.



Capabilities

Sample Preparation	Imaging Data Acquisition	Data Analysis & Visulisation	Interpretation & Application
• Protein production	• Atomic imaging (XFEL, CryoEM)	• Supercomputing (MASSIVE)	• Multi-scale imaging (single molecule to whole animal)
• Crystallisation	• Molecular imaging (single molecule, lattice sheet)	• Structure determination (PRIME/SIMPLE)	• Custom antibody development (MATF)
• Synthesize fluorophores and ligands	• Cellular imaging (intravital imaging, adaptive optics)	• Programming expertise	• Proteomics
• Integration with hardware		• Integration with imaging hardware/workflow	• Bioinformatics



Through this process, we identified Germany as important for both industrial and academic partnerships, and we have since been working to form stronger linkages with our existing German partners as well as build new relationships into Germany. The Centre has since established contact with key German peak bodies such as the German-Australia Chamber of Industry & Commerce and the Deutsche Forschungsgemeinschaft to gain better insights into and visibility of potential collaborative opportunities. In fact, the Centre contributed to a feature article on "Developing the next generation of global scientists," was published in the Oct-Dec 2015 issue of the German-Australian business news magazine.

National Linkages

In 2015, the Centre has continued building its linkages with key national partners – the Australian Synchrotron and the Australian Nuclear Science and Technology Organisation (ANSTO). For instance, in collaboration with the Australian Synchrotron, the Centre has hired Dr Jun Aishima, a postdoctoral research fellow who joins us from the Diamond Light Source (UK) and will boost efforts in developing automation systems of the crystallography beamlines at the Synchrotron utilising the Multi-modal Australian ScienceS Imaging and Visualisation Environment (MASSIVE).

The Centre also played an important role in advocating and delivering a much-needed upgrade to the MASSIVE hardware that will enable greater capacity and throughput to be handled on the platform.

In partnership with ANSTO and FEI Company, the Centre has also appointed a new postdoctoral research fellow (Chris Lupton) who will be investigating novel approaches for the application of electron sources to solve problems in protein nanocrystallography (see boxout for more details). The Centre is also currently working in partnership with ANSTO and the Deutsches Elektronen Synchrotron (DESY) to recruit a second postdoctoral fellow to work on X-ray Free Electron Laser (XFEL) approaches to protein nanocrystallography.

The Imaging CoE also collaborated with the ARC Centre of Excellence for Integrative Brain Function, the ARC Centre of Excellence in Convergent Bio-Nano Science & Technology and the BioMelbourne Network to organise a BioBriefing seminar session and networking event called "Seeing is believing: Advances in imaging technology R&D". The aim of the event was to raise awareness around the imaging technologies, capabilities and expertise available within the three Centres and to showcase some of the commercial successes that have been enabled by these imaging-based Centres of Excellence. The event, attended by over 60 members of the BioMelbourne Network, was held at the Australian Synchrotron, featured talks by Prof. Tom Davis, Prof. Gary Egan and Dr Michael Bettess, followed by a networking session and a tour of the Synchrotron's imaging facilities.

International Linkages

Our international linkages have primarily been focused on industry partnerships. In 2015, we had a number of successes in partnering with world-class companies to delivery R&D outcomes that will have real impact on society.

In January, CI Jamie Rossjohn and colleagues finalised an agreement with Janssen-Cilag, one of the Janssen Pharmaceutical companies of Johnson & Johnson. Johnson & Johnson Innovation facilitated this research

Engaging with the global biotechnology industry

The Imaging Centre Chief Operating Officer, Dr Manoj Sridhar, and Commercialisation Officer, Dr Michael Bettess attended the 2015 Biotechnology Industry Organization (BIO) International Convention in Philadelphia, USA, in June. Armed with a broad portfolio of exciting, cutting-edge projects, their primary aim was to explore and develop potential relationships with international pharmaceutical and platform technology companies.

A strong Australian delegation attended the event, coordinated by Australia's Biotechnology Organisation - AusBiotech. Based in Philadelphia, Pennsylvania, the conference was perfectly placed at the heart of the US biopharma industry; combined with New Jersey and Delaware, the tri-state region comprises 80% of the country's pharmaceutical industries.

Exhibiting our projects in the 'Australia Pavilion' over the course of four days, Manoj and Mike met with over 40 companies, which included major global pharmaceutical corporations such as GlaxoSmithKline and Novartis. The feedback we received from these world-class representatives was extremely positive, and clearly indicated the global competitiveness of our research; companies were truly impressed by the quality and breadth of the research conducted within the Imaging Centre.

The key outcome of the trip was the establishment of regular communication lines between the Centre and these companies, which enables relationship building and discussion of potential opportunities in a timely and effective manner.

collaboration that unravels that molecular mechanisms that underlie automimmune diseases. The research could lead to new medicines to treat autoimmune diseases and disorders such as rheumatoid arthritis and psoriasis.

The Centre also established collaborative R&D links with another major global pharmaceutical company around cryo-electron microscopy for biological molecules. Scientists from the pharmaceutical company's R&D division spent two weeks with our Centre's cryo-electron microscopy experts to carry out experiments at our facilities at Monash University.

The Imaging Centre is the only Australian institution to be member of the international Single Particle Imaging (SPI) initiative at the LCLS (Stanford). In 2015 the initiative collected the highest ever resolution X-ray diffraction data from a single particle (the rice-dwarf virus). Though there is still a lot of work to be done, the XFEL data (which was measured out to 4Å) is an important first step towards realising high-resolution single molecule imaging using ultrafast X-ray sources. The SPI initiative also brings together major international centres in XFEL science which includes the BioXFEL (whose science director is Prof. John Spence FRS) and the Centre for Free Electron Laser science (CFEL) lead by PI Chapman.

Researchers at La Trobe participated in a number of collaborative experiments at the LCLS with PI Chapman's CFEL group in 2015. In all there were 4 experiments performed involving 4 researchers from La Trobe and 9 from CFEL. These experiments build on existing collaborations with PI Chapman and will contribute to outcomes within the serial femtosecond nanocrystallography (SFX) and single molecule imaging themes. In addition a new collaboration between La trobe and Richard Neutze's group at Uppsala University in Sweden was established in 2015 within the molecular movies theme; two experiments have been performed so far studying the protein dynamics associated with Photosystem I an integral membrane protein complex involved in light-harvesting processes within plants.

Future Research & Development with FEI

In November, Monash University Vice-Provost (Research & Research Infrastructure), Professor Ian Smith, along with Dr Jens Greiser, Vice President and CTO and Dr Frank de Jong, Director of Strategic Collaborations at FEI Company, signed the dotted line on an umbrella framework for all future R&D projects and collaborations between the Imaging Centre and FEI Company.

"Collaborative work with multinationals is a step towards the federal government's current agenda on the commercialisation of publicly funded research and has benefits for the community at large," says Professor Ian Smith.

This new agreement will see Monash build on its existing relationship with FEI, who are one of the major suppliers of electron microscopes to the university.

FEI have recently collaborated with the Imaging Centre to test a new approach to optimise samples prior to preparing them for vitrification and subsequent cryo-transmission electron microscopy (cryo-TEM).

Dr Marc Storms, Product Marketing Manager of the FEI Business Unit Life Sciences, says many strategic benefits and scientific insights have been gained and learnt through the collaboration.

"Monash University is a strategically important site for FEI. As one of the leading centres for a wide variation of imaging technologies, the Imaging Centre is also spearheading in the adoption and developments of cryo-TEM. We would like to adopt as much hands-on knowledge in the areas of both sample preparation and image handling and processing: Monash is the perfect incubator for this," says Dr Storms.

Professor James Whisstock, says the collaboration framework agreement paves the way for the Centre and Monash University to work on technology development projects with FEI through the exchange of researchers and expertise between the organisations on a project-by-project basis.

"This agreement is just one example of how Monash University and the Centre are committed to helping translate research into solutions that make a difference. And that ongoing partnerships with companies like FEI help us fulfil this commitment as well as provides further evidence of the value in, and to, Australian research institutions through industry engagement," says Professor Whisstock.

Graduate Training

The Imaging Centre's overall training mission is to provide our graduate students and postdoctoral researchers with a well rounded experience that enables them to develop their scientific expertise and deliver maximum impact for themselves and to the Centre's broader goals. In particular, the Centre will target three key training areas — technical skills in imaging and immunology and science communication — that will achieve our mission.

In 2015, we continued to focus on ensuring Centre staff had (a) the necessary capabilities to carry out leading edge science, and (b) awareness of the breadth of scientific research that was being carried out across the Centre's nodes.

Our annual Imaging Summit was held at the National Synchrotron Science Building in November. The motivation for the summit was to expose Centre staff and researchers to areas of inquiry outside their specialty – to promote cross-disciplinary collaborations.

This year we ran the summit more like a conference and sent out a call for abstracts. With over 50 abstracts submitted and only time for 13 talks our Centre executive were hard pressed to choose. We extended the poster sessions to accommodate all abstracts. The talks covered the breadth of expertise present in our Centre, from physics and modelling of molecular interaction with X-ray free electron laser beams to chemistry and targeting immune cells with small molecules to biology and understanding the regulation of T cell immunity after viral infection of the skin.

All attendees had the chance to interact with speakers and poster presenters both immediately after each talk, during discussion breaks and after the event. Feedback collected indicated that attendees found the talks, posters and format of the event conducive to gaining a greater understanding of the work being done across the Centre, which has sparked collaborative ideas and potential projects.

This year also marked the first in person meeting of our ISAC. We were delighted that they were able to attend the summit and provide constructive criticism of to the science being done at our Centre.

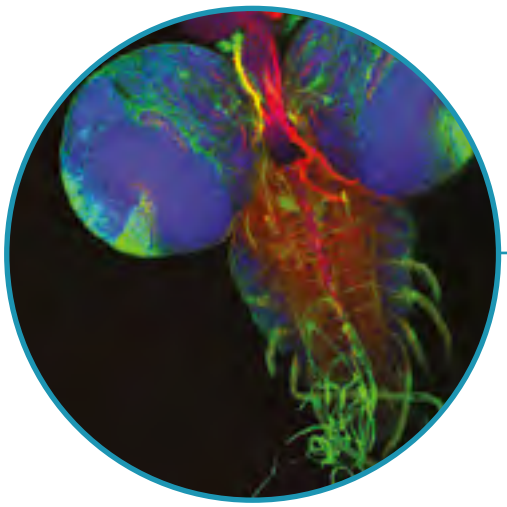
Highlights

The 3rd Prato Conference On Pore Forming Proteins

The 3rd Prato Conference On Pore Forming Proteins addressed a wide spectrum of research on proteins that self-assemble into trans-membrane pores. Many of these toxins are virulence factors used by pathogens. At the same time, the mammalian immune system has turned pore-forming proteins to its advantage to clear viral and bacterial infections.

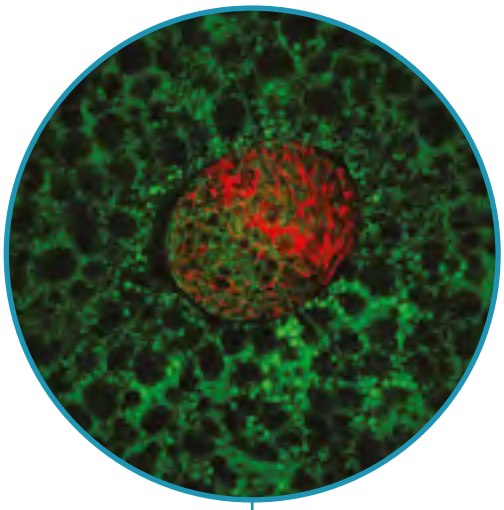
The meeting brought together experts in structural and cellular biology, immunology and microbiology, to discuss pore-forming toxins, with a particular focus on similarities in their structures, function and role in disease. Furthermore, the meeting explored the role of these proteins in non-immune processes, such as development and neurobiology.

Australian Society of Immunology IgV Masterclass



The Australian Society of Immunology IgV Masterclass was held in May. Over 80 delegates were treated to talks from Jenny Stow, Scott Mueller, James Whisstock, Jeremie Rossy, Justine Mintern, Kate Lawlor, Kelly Rogers and Georg Ramm on a wide range of exciting new techniques on the theme of Visualising the Immune System.

Deep Sequencing Meets Structural Biology



The Deep Sequencing Meets Structural Biology was the theme of the 2015 International Conference on Structural Genomics – hosted by the Weismann Institute of Science and sponsored by our partner Field Emission Inc. (FEI).

Speakers at the workshop included Centre Director, Professor James Whisstock, and Professor Patrick Cramer from the Max Planck Institute for Biophysical Chemistry in Germany. The talks focused on the new technical challenges facing crystallographers using Electron Microscopy (EM) in structural studies, and sparked lively discussion and debate. The serious shortage of EM experts was mooted – an issue that we are aiming to tackle head on at the Imaging CoE over the coming years.

Do-It-Yourself Lens Workshop

The summit also featured a Do-It-Yourself Lens Workshop where Centre AI's, Dr Steve Lee, and his group led a hands-on workshop on making your own simple, plastic droplet-based lenses that can transform your smartphone cameras into portable microscope. The workshop was extremely well-received by an excited audience of over 50 students, researchers and professors who thoroughly enjoyed the opportunity to make their own lenses and test their image quality.

2016 Activity Plan

Research

Theme	Activity
Atomic Imaging	Prepare for the installation of the Eiger detector at the Australian Synchrotron
	Study protein structure/dynamics using selective deuteration
	Develop theoretical models for photoionization in biomolecules
	Obtain high resolution diffraction data from protein nanocrystals using XFEL
	Collaborate on international femtosecond pump-probe "molecular movie" experiments at the XFEL
	Develop analysis tools for nanocrystallography that incorporate disorder and multiple scattering
	Collaborate in the Single Particle Initiative (SPI) with researchers from Hamburg and LCLS
	Develop Micro-Electron Diffraction (MED) techniques for protein crystallography
Molecular Imaging	Collect proof-of-principle data for sub-5nm localisation of fluorophores
	Collect proof-of-principle data for molecular counting algorithms in single molecule experiments
	Install and test single objective light-sheet microscope
	Fabricate and test prototype 3D printed microscope components
	Determine near-atomic resolution structure of a biological macromolecule using cryo-EM
	Initiate correlative light and electron microscopy program
Cellular Imaging	Measure CD4, CD8 and dendritic cell interactions during initiation of immune response
	Develop multi-colour histocytometry for various tissues
	Develop capacity for multi-cell type imaging in the liver and brain
	Test algorithms and clearing protocols for imaging through complex tissues
	Develop labelling strategies for immune cells in intact tissue
	Map the consequences of immune receptor interactions via mutations and receptor deficiency

Theme	Activity
Recognition	Conduct pilot time-resolved experiments using antigen presenting molecules
	Investigate reversed polarity TCR-pMHC recognition
	Use MHC-II tetramers to study celiac disease and rheumatoid arthritis
	Conduct initial T-cell activation studies by lipids presented by CD1
	Investigate MR1 presentation of vitamin B metabolites
	Develop histocytometry technique to image and monitor T cell populations
	Determine how T cell receptors recognise peptides, metabolites and lipids
	Identify new MAIT cell antigens
	Identify novel MR1 restricted T cells
	Investigate MAIT cell development
Activation	Collect proof-of-principle data regarding dynamic spatial organisation of signalling complexes
	Assess signal integration and propagation across surface receptors using nano/micro-patterned surfaces
	Collect proof-of-principle data on the biophysical properties of plasma membranes
	Develop new statistical framework for predicting signalling patterns
	Develop labelling approach for studying assembly of immune effectors
	Undertake imaging on T-cell signalling machines
Effector Function	Determine near atomic resolution structure of pore-forming immune effectors using cryo-EM
	Conduct initial EM experiments on protease-related immune complexes
	Discover new inhibitors of complement and related cascades
	Optimise targeting and delivery of ligands to macrophages
	Develop small molecules that specifically target complement GPCRs
	Undertake cryo-EM experiments of an innate receptor
	Image mast cells in acute and chronic inflammatory conditions
	Investigate impact of KIR polymorphism on HLA recognition
	Investigate the role of the perforin-like protein BRINP1 in an autism spectrum-like disorder phenotype

2016 Activity Plan

Training & Outreach

Focus area	Activity
Technical skills of Centre students/ postdocs	Conduct a series of workshops around cryo-EM, crystallography, chemistry, light sheet microscopy and crystallisation robotics
Scientific writing	Three workshops planned aimed at developing the scientific writing skills of Centre students and postdocs, particularly with respect to writing journal articles and grant proposals
Science communication	PhD students and postdocs to run a symposium entirely by themselves to encourage interdisciplinary and internode collaborations Publish 100 word layman summaries to be compiled for every Centre publication Presentation skills workshop to be held at annual summit Short YouTube video interview will be created for major Centre publications.
Commercialisation	IP workshop/entrepreneurs roundtable to be held at annual summit
Events Media and Outreach	Launch of Single Molecule Science Lab at UNSW Launch of Formulatrix Crystallisation Facility at Monash University A number of high profile public lectures by Nobel Laureates and high-profile scientists planned Melbourne Knowledge Week seminar
Secondary school students	Develop educational program with John Monash Science School involving Centre PhD students Host Growing Tall Poppies programs across Centre nodes

Key Performance Indicators

Research findings

Performance Measure	Target 2015	Actual 2015
Number of publications	50	89
Number of citations	300	353
Number of invited talks	20	104
Number of media releases	2	7
Number of media articles	2	104

Research Training and Professional Education

Performance Measure	Target 2015	Actual 2015
Number of professional training courses	2	9
Number of Centre attendees	20	320
Number of new postgraduate students	8	21
Number of new postdoctoral researchers recruited	4	17
Number of new Honours students	9	8
Number of early career researchers	2	12
Number of students mentored	20	85
Number of mentoring programs	4	9

International, National and Regional Links and Networks

Performance Measure	Target 2015	Actual 2015
Number of international visitors and visiting fellows	10	20
Number of national and international workshops held/organised by the Centre	1	2
Number of visits to overseas laboratories and facilities	5	45
Examples of relevant interdisciplinary research supported by the Centre	4	7

End-user Links

Performance Measure	Target 2015	Actual 2015
Number of government, industry and business community briefings	3	57
Number and nature of public awareness/ outreach programs	2	2
Number of website hits	5,000	27,586
Number of talks given by Centre staff open to public	3	14

Organisational Support

Performance Measure	Target 2015	Actual 2015
Annual cash contributions from Administering and Collaborating Organisations	$1,333,334	$1,399,334
Annual in-kind contributions from Collaborating Organisations	$2,684,041	$3,501,025
Annual cash contributions from Partner Organisations	$195,000	$140,000
Annual in-kind contributions from Partner Organisations	$1,518,572	$1,050,024
ARC grants secured by Centre staff	$250,000	$3,260,960
Other Australian competitive grants secured by Centre staff	$250,000	$16,273,509
Number of new organisations collaborating with, or involved in, the Centre	1	2

Publications

January 2015

GlycoMine: a machine learning-based approach for predicting N-, C- and O-linked glycosylation in the human proteome. (Bioinformatics, Vol 31, pg 1411-1419)
Authors: Li F, Li C¬, Wang M, Webb GI, Zhang Y, Whisstock JC and Song J

Understanding the complexity and malleability of T-cell recognition. (Nature Immunology and Cell Biology, Vol 93, pg 433-411)
Authors: Miles JJ, McCluskey J, Rossjohn J and Gras S

Helix-Constrained Nociceptin Peptides Are Potent Agonists and Antagonists of ORL-1 and Nociception. (Vitamin and Hormones, Vol 97, pg 1-55)
Authors: Lohman RJ, Harrison RS, Ruiz-Gómez G, Hoang HN, Shepherd NE, Chow S, Hill TA, Madala PK and Fairlie DP

Regulatory iNKT cells lack expression of the transcription factor PLZF and control the homeostasis of T(reg) cells and macrophages in adipose tissue. (Nature Immunology, Vol 16, pg 89-95)
Authors: Lynch L, Michelet X, Zhang S, Brennan PJ, Moseman A, Lester C, Besra G, Vomhof-Dekrey EE, Tighe M, Koay HF, Godfrey DI, Leadbetter EA, Sant'Angelo DB, von Andrian U and Brenner MB

MR1 presentation of vitamin B-based metabolite ligands (Current Opinon on Immunology, Vol 34, pg 28-34)
Authors: McWilliam HE, Birkinshaw RW, Villadangos JA, McCluskey J and Rossjohn J

Ultrafast self-gating Bragg diffraction of exploding nanocrystals in an X-ray laser (Optics Express, Vol 23, pg 1213-1231)
Authors: Caleman C, Tîmneanu N, Martin AV, Jönsson HO, Aquila A, Barty A, Scott HA, White TA, and Chapman HN

An RPTPα/Src Family Kinase /Rap1 signaling module recruits Myosin IIB to support contractile tension at apical E-cadherin junctions. (Molecular Biology of the Cell, Vol 14, pg 1223)
Authors: Gomez GA, McLachlan RW, Wu SK, Caldwell BJ, Moussa E, Verma S, Bastiani M, Priya R, Parton RG, Gaus K, Sap J, and Yap AS

Tropomyosin isoforms support actomyosin biogenesis to generate contractile tension at the epithelial zonula adherens (Cytoskeleton, Vol 71, pg 663-676)
Authors: Caldwell BJ, Lucas C, Kee AJ, Gaus K, Gunning PW, Hardeman EC, Yap AS, and Gomez G

February 2015

Comparing sixteen scoring functions for predicting biological activities of ligands for protein targets (Journal of Molecular Graphics and Modelling, Vol 57, pg 76-88)
Authors: Xu W, Lucke AJ and Fairlie DP

Self-Calibrated Line-Scan STED-FCS to Quantify Lipid Dynamics in Model and Cell Membranes (Cell Biophysical Journal, Vol 108, pg 596-609)
Authors: Benda, A; Ma, YQ; Gaus, K

αβ T cell antigen receptor recognition of CD1a presenting self lipid ligands (Nature Immunology, Vol 16, pg 258-266)
Authors: Birkinshaw RW, Pellicci PG, Cheng TY, Keller AN, Sandoval-Romero M, Gras S, de Jong A, Uldrich AP, Moody DB, Godfrey DI and Rossjohn J

Conformational Changes during Pore Formation by the Perforin-Related Protein Pleurotolysin (Plos Biology, Vol 13 e1002049)
Authors: NLukoyanova N, Kondos SC, Farabella I, Law RHP, Reboul CF, Caradoc-Davies TT, Spicer BA, Kleifeld O, Traore DAK, Ekkel SM, Voskoboinik I, Trapani JA, Hatfaludi T, Oliver K, Hotze EM, Tweten RK, Whisstock JC, Topf M, Saibil HR, Dunstone MA

CD3(bright) signals on γδ T cells identify IL-17A-producing Vγ6Vδ1(+) T cells. (Nature Immunology and Cell Biology, Vol 93, pg 198-212)
Authors: Paget C, Chow MT, Gherardin NA, Beavis PA, Uldrich AP, Duret H, Hassane M, Souza-Fonseca-Guimaraes F, Mogilenko DA, Staumont-Sallé D, Escalante NK, Hill GR, Neeson P, Ritchie DS, Dombrowicz D, Mallevaey T, Trottein F, Belz GT, Godfrey DI and Smyth MJ

MAIT cells are depleted early but retain functional cytokine expression in HIV infection. (Nature Immunology and Cell Biology, Vol 93, pg 177-188)
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Simultaneous cryo X-ray ptychographic and fluorescence microscopy of a marine algae (PNAS, Vol 112, pg 2314-2319)
Authors: Deng J, Vine DJ, Chen S, Nashed YSG, Jin Q, Phillips NW, Peterka T, Ross R, Vogt S and Jacobsen C

Continuous motion scan ptychography : characterization for increased speed in coherent x-ray imaging (Optics Express, Vol 23, pg 5438-5451)
Authors: Deng J, Nashed YSG, Chen S, Phillips W, Peterka T, Ross R, Vogt S, Jacobsen C and Vine DJ

Facile synthesis of mono- and bis-methylated Fmoc-Dap, -Dab and -Orn amino acids. (Chemical Communications, Vol 51, pg 4496-4498)
Authors: Lindahl F, Hoang HN, Fairlie DP and Cooper MA.

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IL-37 requires the receptors IL-18Rα and IL-1R8 (SIGIRR) to carry out its multifaceted anti-inflammatory program upon innate signal transduction (Nature Immunology, Vol 16, pg 354-365)
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X-Ray Imaging of a Single Virus in 3D (APS Physics, Vol 8, pg 19)
Authors: Nugent KA

Intravital microscopic interrogation of peripheral taste sensation. (Nature Scientific Reports, Vol 5, article 08661)
Authors: Choi M, Lee WM and Yun SH

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Authors: O'Connor GM, Vivian JP, Gostick E, Pymm P, Lafont BA, Price DA, Rossjohn J, Brooks AG and McVicar DW

Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients (Journal of Clinical Investigation, Vol 125, pg 1752-1762)
Authors: Magalhaes I, Pingris K, Poitou C, Bessoles S, Venteclef N, Kiaf B, Beaudoin L, Da Silva J, Allatif O, Rossjohn J, Kjer-Nielsen L, McCluskey J, Ledoux S, Genser L, Torcivia A, Soudais C, Lantz O, Boitard C, Aron-Wisnewsk y J, Larger E, Clément K and Lehuen A

Tracking molecular dynamics without tracking: image correlation of photo-activation microscopy (Methods and Application of Fluroescence, Vol 3, article 014006)
Authors: Pandžić E, Rossy J and Gaus K

The structure of the atypical Killer Cell Immunoglobulin-like Receptor, KIR2DL4. (Journal of Biological Chemistry, Vol 290, pg 10460-10471)
Authors: Moradi S, Berry R, Pymm P, Hitchen C, Beckham SA, Wilce MC, Walpole NG, Clements CS, Reid HH, Perugini MA, Brooks AG, Rossjohn J and Vivian JP

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Authors: Cork AJ, Ericsson DJ, Law RH, Casey LW, Valkov E, Bertozzi C, Stamp A, Jovcevski B, Aquilina JA, Whisstock JC, Walker M Jand Kobe B

Inhibiting histone deacetylase 1 suppresses both inflammation and bone loss in arthritis (Rheumatology, Vol 54, pg 1713-1723)
Authors: Cantley MD, Fairlie DP, Bartold PM, Marino V, Gupta PK and Haynes DR

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Authors: Aquila A, Barty A, Bostedt C, Boutet S, Carini G, dePonte D, Drell P, Doniach S, Downing SKH, Earnest T, Elmlund H, Elser V, Gühr M, Hajdu J, Hastings J, Hau-Riege SP, Huang Z, Lattman EE, Maia FRNC, Marchesini S, Ourmazd A, Pellegrini C, Santra R, Schlichting I, Schroer C, Spence JCH, Vartanyants IA, Wakatsuki S, Weis WI and Williams GJ

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Authors: Cukalac T, Kan WT, Dash P, Guan J, Quinn KM, Gras S, Thomas PG and La Gruta NL

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Authors: Coughlan HD, Darmanin C, Phillips NW, Hofmann F, Clark JN, Harder RJ, Vine DJ and Abbey B

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Authors: Bedoui S and Heath WR

Perforin and granzymes: function, dysfunction and human pathology (Nature Reviews Immunology, Vol 15, pg 388-400)
Authors: Voskoboinik I, Whisstock JC and Trapani JA

The myelin proteolipid plasmolipin forms oligomers and induces liquid-ordered membranes in the Golgi complex (Journal of Cell Science, Vol 128, pg 2293-2302)
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Three Homology Models of PAR2 Derived from Different Templates: Application to Antagonist Discovery (Journal of Chemical Information and Modeling, Vol 55, pg 1181-1191)
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Authors: Sakala IG, Kjer-Nielsen L, Eickhoff CS, Wang X, Blazevic A, Liu L, Fairlie DP, Rossjohn J, McCluskey J, Fremont DH, Hansen TH and Hoft DF

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Authors: Engel JA, Jones A, Avery VM, Sumanadasa SD, Ng SS, Fairlie DP, Adams TS and Andrews KT

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Authors: Lucato CM, Halls ML, Ooms LM, Liu HJ, Mitchell CA, Whisstock JC and Ellisdon AM

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July 2015

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Authors: Jones MW, de Jonge MD, James SA and Burke R

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Authors: Pacile S, Brun F, Dullin C, Nesterest YI, Dreossi D, Mohammadi S, Tonutti M, Stacul F, Lockie D, Zanconati F, Accardo A, Tromba G and Gureyev TE

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Mechanical forces regulate the interactions of fibronectin and collagen I in extracellular matrix (Nature Communications, Vol 6, article 8026)
Authors: Kubow KE, Vukmirovic R, Zhe L, Klotzsch E, Smith ML, Gourdon D, Luna S and Vogel V

A bird's eye view of NK, cell receptor interactions with their MHC class I ligands. (Immunological Review, Vol 267, pg 148-166)
Authors: Saunders PM, Vivian JP, O'Connor G1, Sullivan LC, Pymm P, Rossjohn J and Brooks AG

Spatiotemporally Distinct Interactions with Dendritic Cell Subsets Facilitates CD4+ and CD8+ T Cell Activation to Localized Viral Infection (Immunity, Vol 43, pg 554-565)
Authors: Hor JL, Whitney PG, Zaid A, Brooks AG, Heath WR and Mueller SN

Structural basis for Ca2+-mediated interaction of the perforin C2 domain with lipid membranes (Journal of Biological Chemistry, Vol 290, pg 25213-25226)
Authors: Yagi H, Conroy PJ, Leung EWW, Law RHP, Trapani JA, Voskoboinik I, Whisstock JC and Norton RS

Ultrasensitive and Specific Measurement of Protease Activity Using Functionalized Photonic Crystals (Analytical Chemistry, Vol 87, pg 9946-9953)
Authors: Gupta B, Mai K, Lowe SB, Wakefield D, Girolamo ND, Gaus K, Reece PJ and Gooding JJ

Cyclic alpha-conotoxin peptidomimetic chimeras as potent GLP-1R agonists (European Journal of Medicinal Chemistry, Vol 103, pg 175-184)
Authors: Swedberg JE, Schroeder CI, Mitchell JM, Durek T, Fairlie DP, Edmonds DJ, Griffith DA, Ruggeri RB, Derksen DR, Loria PM, Liras S, Price DA and Craik DJ

Enhancing quantum dots for bioimaging using advanced surface chemistry and advanced optical microscopy: application to silicon quantum dots (SiQDs) (Advanced Materials, Vol 27, pg 6614-6150)
Authors: Cheng X, Hinde E, Owen DM, Lowe SB, Reece PJ, Gaus K and Gooding JJ

September 2015

Lipid and small-molecule display by CD1 and MR1 (Nature Reviews Immunology, Vol 15, pg 643-654)
Authors: Van Rhijn I, Godfrey DI, Rossjohn J & Moody DB

Cryo-electron microscopy and single molecule fluorescent microscopy detect CD4 receptor induced HIV size expansion prior to cell entry (Virology, Vol 486, pg 121-133)
Authors: Pham S, Tabarin T, Garvey M, Pade C, Rossy J, Monaghan P, Hyatt A, Böcking T, Leis A, Gaus K and Mak J

Antigen Specificity of Type I NKT Cells Is Governed by TCR β-Chain Diversity. (Journal of Immunology, Vol 195, pg 4604-4614)
Authors: Cameron G, Pellicci DG, Uldrich AP, Besra GS, Illarionov P, Williams SJ, La Gruta NL, Rossjohn J and Godfrey DI

October 2015

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Authors: Beringer DX, Kleijwegt FS, Wiede F, van der Slik AR, Loh KL, Petersen J, Dudek NL, Duinkerken G, Laban S, Joosten A, Vivian JP, Chen Z, Uldrich AP, Godfrey DI, McCluskey J, Price DA, Radford KJ, Purcell AW, Nikolic T, Reid HH, Tiganis T, Roep BO and Rossjohn J

Flexibility versus Rigidity for Orally Bioavailable Cyclic Hexapeptides (Chembiochem, Vol 16, pg 2289-2293)
Authors: Nielsen DS, Lohman RJ, Hoang HN, Hill TA, Jones A, Lucke AJ and Fairlie DP

Repurposing Registered Drugs as Antagonists for Protease-Activated Receptor 2 (Journal of Chemical Information and Modeling, Vol 55, pg 2079-2084)
Authors: Xu W, Lim J, Goh CY, Suen JY, Jiang Y, Yau MK, Wu KC, Liu L and Fairlie DP

The aPKC/Par3/Par6 polarity complex and membrane order are functionally inter-dependent in epithelia during vertebrate organogenesis (Traffic, VOL 17, PG 66-79)
Authors: Abu-Siniyeh A, Owen DM, Benzing C, Rinkwitz S, Becker TS, Majumdar A and Gaus K

Recognition of Vitamin B precursors and byproducts by Mucosal Associated Invariant T cells. (Journal of Biological Chemistry, Vol 290, pg 30204-30211)
Authors: Eckle SB, Corbett AJ, Keller A, Chen Z, Godfrey DI, Liu L, Mak JY, Fairlie DP, Rossjohn J and McCluskey J

The burgeoning family of unconventional T cells (Nature Immunology, Vol 16, pg 1114-1123)
Authors: Godfrey DI, Uldrich AP, McCluskey J, Rossjohn J and Moody DB

Single-molecule imaging with longer X-ray laser pulses (International Union of Crystallography Journal, Vol 2, pg 661-674)
Authors: Martin AV, Corso JK, Caleman C, Timneanu N and Quiney HM

On-chip photonic Fourier transform with surface plasmon polaritons (Light-Science and Applications, Vol 5, e16034)
Authors: Lin J, Kou S, Yuan G, Wang Q, Du L, Balaur E, Zhang DH, Tang D, Abbey B, and Yuan XC

Potent complement C3a receptor agonists derived from oxazole amino acids: Structure-activity relationships (Bioorganic & Medicinal Chemistry Letters, Vol 25, pg 5604-5608)
Authors: Singh R, Reed AN, Chu P, Scully CC, Yau MK, Suen JY, Durek T, Reid RC and Fairlie DP

Torso-like mediates extracellular accumulation of Furin-cleaved Trunk to pattern the Drosophila embryo termini (Nature Communications, Vol 6, article 8759)
Authors: Johnson TK, Henstridge MA, Herr A, Moore KA, Whisstock JC and Warr CG

Toward peptide-based inhibitors as therapies for Parkinson's disease (Future Medicinal Chemistry, Vol 7, pg 2103-2105)
Authors: Mason JM and Fairlie DP

November 2015

Plasmon-Enhanced Sensing: Current Status and Prospects (Journal of Nanomaterials, Vol 2015, article 474730)
Authors: Lv J, Leong ESP, Jiang X, Kou S, Dai H, Lin J, Liu YJ, and Si G

High-resolution complementary chemical imaging of bio-elements in Caenorhabditis elegans (Metallomics, VOl 8, pg 156-160)
Authors: Hare DJ, Jones MWM, Wimmer VC, Jenkins NL, de Jonge MD, Bushb AI and McColl G

Polyalanine expansions drive a shift into α-helical clusters without amyloid-fibril formation (Nature Structural and Molecular Biology, Vol 22, pg 1008-1015)
Authors: Polling S, Ormsby AR, Wood RJ, Lee K, Shoubridge C, Hughes JN, Thomas PQ, Griffin MDW, Hill AF, Bowden Q, Böcking T and Hatters DM

Towards identification of immune and genetic correlates of severe influenza disease in Indigenous Australians. (Nature Immunology and Cell Biology, Vol 93)
Authors: Bridie Clemens E, Grant EJ, Wang Z, Gras S, Tipping P, Rossjohn J, Miller A, Tong SY and Kedzierska K

Membrane-anchored Serine Protease Matriptase is a Trigger of Pulmonary Fibrogenesis (American Journal of Respiratory and Critical Care Medicine, Vol 2015)
Authors: Bardou O, Menou A, François C, Duitman JW, von der Thüsen JH, Borie R, Sales KU, Mutze K, Castier Y, Sage E, Liu L, Bugge TH, Fairlie DP, Königshoff M, Crestani B and Borensztajn KS

Giant MACPF/CDC pore forming toxins: A class of their own (Biochimica Et BioPhysica Acta-Biomembranes, Vol 1858, pg 475-486)
Authors: Reboul CF, Whisstock JC and Dunstone MA

A feasibility study of X-ray phase-contrast mammographic tomography at the Imaging and Medical beamline of the Australian Synchrotron (Journal of Synchrotron Radiation, Vol 2015, article 38)
Authors: Nesterets Y,Gureyev T, Tromba G, Mayo S, Stevenson, A, Thompson D, Jeremy B, Kitchen M, Pavlov K, Lockie D and Brun F

Human autoreactive T cells recognize CD1b and phospholipids (PNAS, Vol 113, pg 380-385)
Authors: Van Rhijn I, van Berlo T, Hilmeny T, Cheng TY, Wolf BJ, Tatituri RVV, Uldrich AP, Napolitani G, Cerundolo V, Altman JD, Willemsen P, Huang S, Rossjohn J, Besra GS, Brenner MB, Godfrey DI and Moody DB

December 2015

Broadband chirality-coded meta-aperture for photon-spin resolving (Nature Communications, Vol 6, article 10051)
Authors: Lin J, Du L, Kou S, Balaur E, Cadusch J, Roberts A, Abbey B, Yuan XC, and Tang D

Stonefish toxin defines an ancient branch of the perforin-like superfamily (PNAS, Vol 112, pg 15360, 15365)
Authors: Ellisdon AM, Reboul CF, Panjikar S, Huynh K, Oellig CA, Winter KL, Dunstone MA, Hodgson WC, Seymour J, Dearden PK, Tweten RK, Whisstock JC and McGowan S

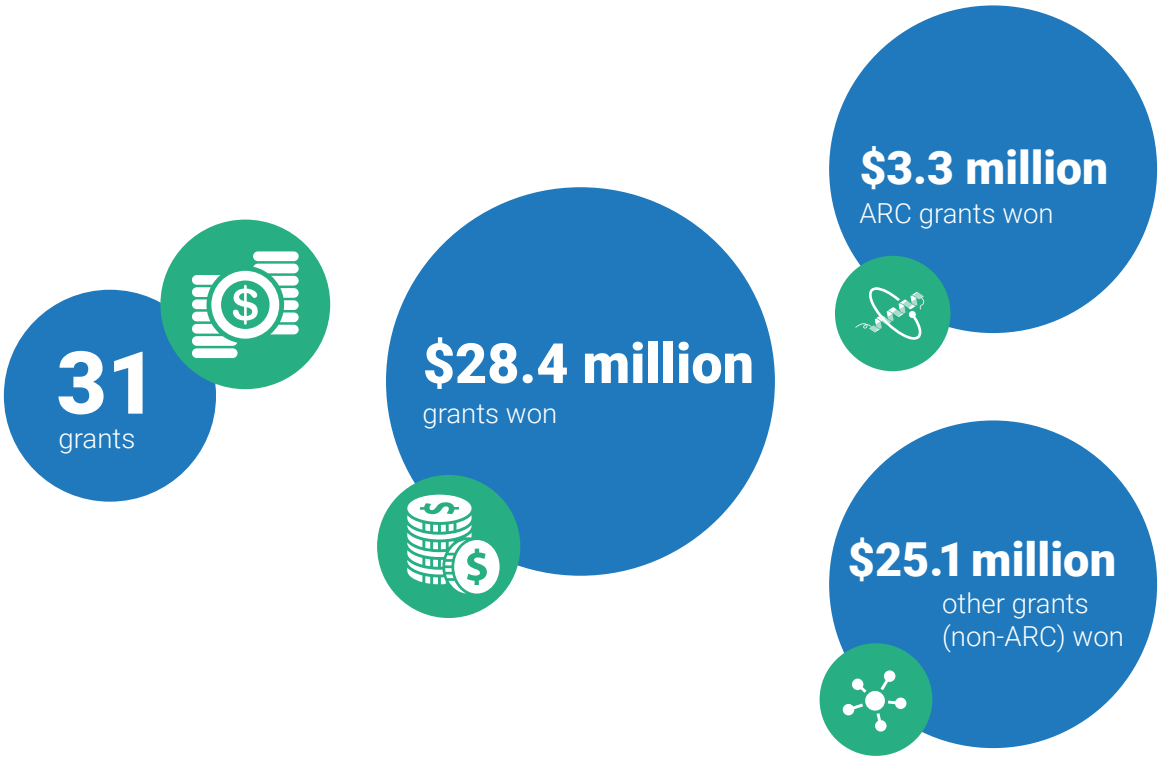
Reconstitution of GPCRs in Lipidic Cubic Phase (LCP):Comparison between human Histamine 1 and Dopamine 2 Long receptor reconstitution into five different self-assembly lipids (Journal of Cytology and Molecular Biology, Vol 2015)
Authors: Darmanin C and Liang YL

T-box Transcription Factors Combine with the Cytokines TGF-β and IL-15 to Control Tissue-Resident Memory T Cell Fate (Immunity, Vol 43, pg 1101-1111)
Authors: Mackay LK, Wynne-Jones E, Freestone D, Pellicci DG, Mielke LA, Newman DM, Braun A, Masson F, Kallies A, Belz GT and Carbone FR

Tissue-resident memory T cells: local specialists in immune defence (Nature Reviews Immunology, Vol 16, pg 79-89)
Authors: Mueller SN and Mackay LK.

Grants

Imaging Centre researchers were successful in obtaining a number of competitive grants in 2015. The total amount of funding obtained by our researchers in 2015 is $28.4 million. This includes grants from the Australian Research Council, (ARC) National Health & Medical Research Council (NHMRC) and other sources.



ARC Grants

Centre Researcher(s)	Project description
David Fairlie	A nuclear magnetic resonance facility for modern molecular analysis
Jamie Rossjohn, Hans Elmlund	Next generation mass spectrometry for analysis of biomolecules
Jamie Rossjohn, Dale Godfrey, Keith Nugent, Stephanie Gras	An automated protein nano-crystallisation facility
Antoine van Oijen, Till Boecking	Superresolution fluorescence imaging in microbiology
Enrico Klotzsch	Advanced microscopy to study the forces involved in T-cell activation leading to an immune response
Woei Ming (Steve) Lee	Develop new multimodality microscopy to investigate and optimise light delivery of macromolecules into living cells
Kate Schroder	Characterise novel molecular timer that dictates the co-ordinated timing of immune responses and immune cell death
Coral Warr	Understanding Torso-like functions in growth regulation
Spencer Williams	Develop new approaches to chemically synthesise bacterial and fungal glycolipids
Michelle Dunstone	Future Fellowship: Membrane Attack Complex (MAC)

NHMRC Grants

Centre Researcher(s)	Project description
Till Boecking, Antoine van Oijen, Mate Biro	Formin' actin filaments associated with cancer
Richard Berry	The structure and composition of T-cell receptor-CD3 complex
Julian Vivian	Structural and functional investigation of Killer-Cell Immunoglobulin-like receptors
Spencer Williams	Targeting carbohydrate metabolism in Leishmania
Till Boecking, Elizabeth Hinde	Regulation of ERK-driven cell proliferation by the actin cytoskeleton
James Whisstock	Structural studies on the immune effector perforin: developing mechanism-based inhibitors
Till Boecking, Yann Gambin	Discovery and mechanisms of host cell factors in HIV uncoating
Matthew Sweet	A new master adaptor protein for Toll-like receptor signalling
Jeremie Rossy	A signalling endosomal network in T cell activation
James Whisstock	Molecular basis for conjugative transfer of antibiotic resistance genes in gram positive pathogens
Andrew Ellisdon	Characterisation of a novel oncogene in breast cancer
Mate Biro	The role of the actomyosin cytoskeleton in T cell-mediated anti-tumour immunity
Kate Schroder	Autophagic suppression of ASC inflammasomes
Stephanie Gras	Defining the molecular and functional features of protective HIV-specific T cells
Marcel Nold	Characterising the role of IL-37 in the development of H. pylori infection
Daniel Hatters	Pathogenic and adaptive molecular interactions with mutant huntingtin exon 1
Elizabeth Hinde	The role of nuclear architecture in the DNA damage response
Yann Gambin, Jeremie Rossy	Prion-like behaviour in immunity: super-sized signalling platforms

Other grants

Centre Researcher(s)	Project description
James Whisstock	Wellcome Trust Seeding Drug Discovery program
James Whisstock, Jamie Rossjohn, Andrew Peele	Australian Cancer Research Foundation Detector for Micro Crystallography (MX-2) beamline, Australian Synchrotron
Timur Gureyev	National Breast Cancer Foundation Grant to develop new imaging diagnostic technique for breast cancer
Elizabeth Hinde	Cancer Institute (NSW) Early Career fellowship

Imaging Centre Staff

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Prof. Keith Nugent	La Trobe University
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Prof. James Whisstock	Monash University
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Prof. William Heath	The University of Melbourne
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Prof. David Fairlie	The University of Queensland
Prof. Katharina Gaus	University of New South Wales

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Assoc. Prof. Matt Sweet	The University of Queensland
Dr Ranjeny Thomas	The University of Queensland
Prof. Antoine van Oijen	University of Wollongong
Dr Lawrence Lee	Victor Chang Cardiac Research Institute

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Dr Andrew Keller	Monash University
Mr Gordon Lloyd	Monash University
Mr Christopher Lupton	Monash University
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Mr Henry Kirkwood	La Trobe University
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Mr Hugh Marman	La Trobe University
Mr Nicholas Phillips	La Trobe University
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Mr Blake Mazzitelli	Monash University
Mr Shoeib Moradi	Monash University
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Ms Virginia Richichi	Monash University
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Mr Ronal Rai	Monash University
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Mr Michael Souter	The University of Melbourne
Mr Rory Van Geleuken	The University of Melbourne
Mr Robin Wang	The University of Melbourne
Mr Daniel Wells	The University of Melbourne
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Ms Jessica Rowley	The University of Queensland
Ms Kai-chen Wu	The University of Queensland
Mr Weijun Xu	The University of Queensland

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Ms Lyn Fairlie	The University of Queensland

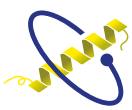
Financial Statement

Statement of Operating Income and Expenditure for the calendar year ended 31 December 2015

Income	2015 Budget $	2015 Actual $
ARC Centre Grant	4,000,000	4,194,688
Administering Organisation Cash Support	400,000	399,334
Collaborating Organisations Cash Support	933,333	1,000,000
Partner Organisations Cash Support	195,000	140,000
Other income	0	7,600
Total	5,528,333	5,741,622

Expenditure	2015 Budget $	2015 Actual $
Salaries	3,932,414	3,312,385
Research Support (incl. equipment, access, consumables)	843,693	724,319
Scholarships	102,142	47,194
Travel & Meetings	56,781	182,347
Outreach	140,387	139,128
EMBL Australia Recruitment Expenses[1]	0	63,853
Centre Administration	202,980	49,360
Total	5,278,397	4,518,587
Surplus	249,936	1,223,035

[1] EMBL Australia recruitment expenses will be recovered in 2016 through the EMBL Group Leader program



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