CENTRE FOR ADVANCED MOLECULAR IMAGING
AN ARC CENTRE OF EXCELLENCE

ANNUAL REPORT
2018

FUNDING BODY

Australian Government
Australian Research Council

ADMINISTERING ORGANISATION

MONASH University

COLLABORATING ORGANISATIONS

THE UNIVERSITY OF MELBOURNE

LA TROBE UNIVERSITY

UNSW SYDNEY

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

PARTNER ORGANISATIONS

Australian Government | ANSTO Science. Ingenuity. Sustainability.

THE UNIVERSITY OF WARWICK

DESY

ZEISS

Members of our Chief and Associate Investigator team closely collaborate with the following companies and organisations on projects that are relevant to Imaging CoE activities: The Janssen Pharmaceutical Companies of Johnson & Johnson, Roche, Thermo Fisher Scientific (formerly FEI), EMBL, EMBL Australia, Fraunhofer Institute for Cell Therapy and Immunology IZI and and its branch for Bioanalytics and Bioprocesses (IZI-BB), the European XFEL (EuXFEL), Linac Coherent Light Source (LCLS) and Wolf Biotherapeutics.

CONTACT INFORMATION

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@ImagingCoE

COVER IMAGE: A representation of molecules in the Imaging CoE Theme colours. Credit: Digial Image.

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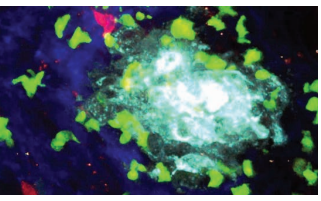
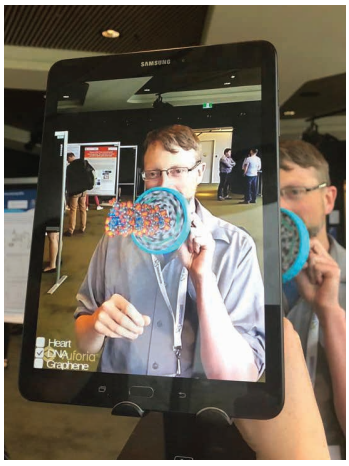




ABOUT US

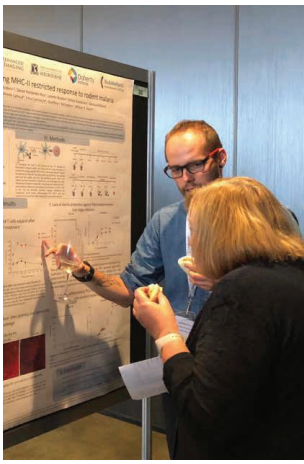
The Australian Research Council Centre of Excellence in Advanced Molecular Imaging (Imaging CoE) develops and uses innovative microscopy and imaging techniques to observe the details of how the immune system functions at the molecular level.

Funded in 2014 with more than $39 million over seven years, the Centre brings together leading biologists, chemists and physicists from five major Australian universities, as well as scientific and commercial partners globally. Collectively, the Centre uses a truly multi-scale and programmatic approach to imaging to deliver maximum impact.

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

VISION & OBJECTIVES

The Imaging CoE aims to visualise and interpret the atomic, molecular and cellular interactions involved in our immune response.
We achieve this by developing and using a wide range of tools across chemistry, biology and physics.



EXCELLENCE

We achieve excellence in terms of the quality of scientific outcomes and the quality of the next generation of scientists we mentor, train and inspire.

Underpinning these goals is world-class research infrastructure and strategic partnerships developed with the Australian Synchrotron, The Australian Nuclear Science and Technology Organisation (ANSTO), the Deutsches Elektronen-Synchrotron (DESY) and the Monash Ramaciotti Centre for Cryo-Electron Microscopy.

The Imaging CoE uses a truly multi-scale and programmatic approach to imaging to deliver maximum impact.

ENGAGEMENT

Externally, we engage with an extensive community of scientists, industry, government, and the general public. We form global research collaborations, translate our discoveries into commercial outcomes benefitting society. We raise public awareness and enthusiasm for our discoveries and build a sustainable network of peers and pipeline of future talent.

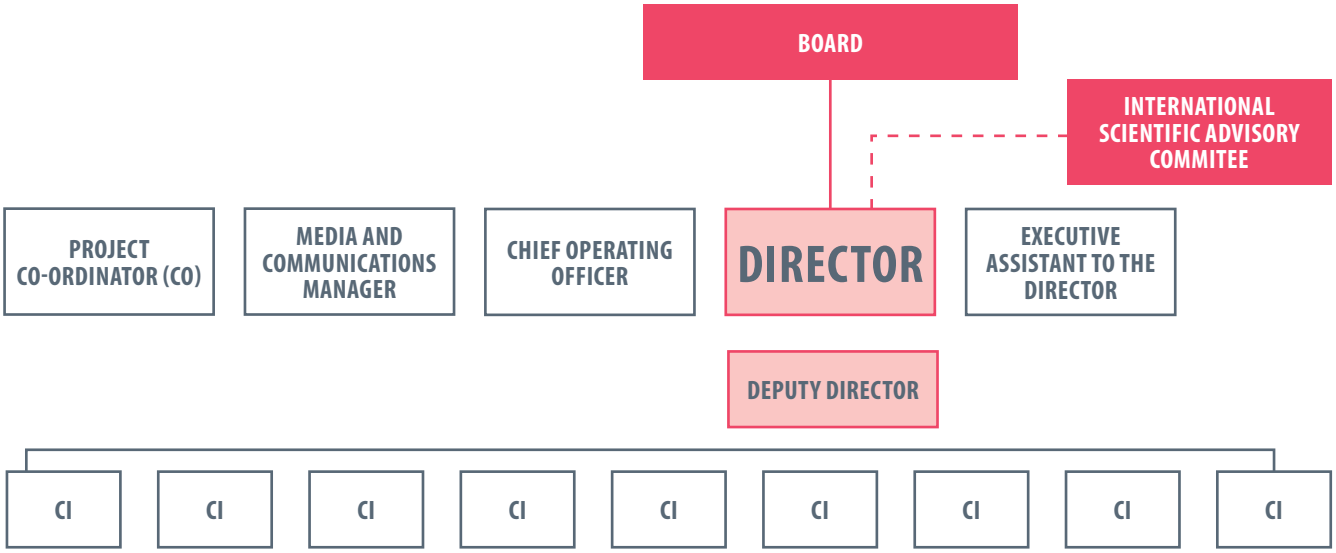
The Imaging CoE uses multi-disciplinary collaborations to deliver truly groundbreaking discoveries and provide well-rounded training to our next generation of scientists.

TRANSLATIONAL IMPACT

We will maximise the impact of our discoveries by working with companies to pursue translational outcomes. We also leverage the expertise of the commercialisation groups at our associated universities.

"We aim to foster new, cross-disciplinary collaborations and facilitate communications across our diverse range of experts."

GOVERNANCE



The Imaging CoE is administered by Monash University with day-to-day operations managed by the core administrative team including the Centre Director, Professor James Whisstock, Chief Operating Officer, Annette Wittmann, Media and Communications Manager, Haley Gyngell and Project Coordinator (Centre Operations), Juliana Villa. Operations are further supported by dedicated administrators at each node.

Our Governing Board meets twice a year and ensures the Centre's fiscal compliance, best research practice and alignment of activities and goals, while also providing advice across all facets of Centre operations.

The International Scientific Advisory Committee gives independent strategic advice to the Director on the positioning of the Centre with respect to new research directions, international outreach and industry linkage opportunities. Together, they review the research, education and outreach programs annually and convey findings to the Governing Board for consideration and action.

General management and operations of the Centre across the five nodes is overseen by the Centre Executive who meet on a monthly basis. Our executive take a proactive approach to discussing and solving issues arising on financial, operational and commercial fronts.

Centre Chief Investigators meet on a quarterly basis to discuss research projects, progress and achievements as well as scientific milestones. These meetings are a vital part of the Centre as they provide a platform for sharing ideas and exploring new interdisciplinary collaboration opportunities.

MESSAGE FROM THE CHAIR

PROF. FRANCES SHANNON
GOVERNING BOARD CHAIR
EMERITUS PROFESSOR, JOHN CURTIN SCHOOL OF MEDICAL RESEARCH, AUSTRALIAN NATIONAL UNIVERSITY

Each year as I sit down to write my report as Chair of the Governing Board of the Imaging Centre of Excellence, I am blown away by the excellence and innovative aspects of the science that is being carried out by all Centre members.

Each year the Centre grows nationally, increases its international links, secures a rising amount of additional funding at each new grant round, and the recognition (through awards and prizes) being received by Centre member increases. In this context, the job of the Governing Board is straightforward, and it is a pleasure to be associated with such a successful centre.

The 2017 midterm review provided an opportunity to assess progress and implement some changes in areas of concern. It is pleasing to see significant improvement in the integration of the physics and biology teams following the restructure of the scientific themes. New early career and PhD student programs have been initiated and centre workshops in new technology areas will be a focus in 2019. Engagement with the broader community continues to develop.

The involvement of veski in the annual centre summit this year provided opportunities for centre students to consider commercial, business and innovation approaches and learn how to engage with this world which can sometimes seem daunting for those embedded in academia.

An innovative engagement program was initiated this year by Professor Jamie Rossjohn and colleagues that brought science to the low vision and blind community. In conjunction with a legally blind artist, Dr Erica Tandori, centre researchers created tactile 3D models, 2D graphic and olfactory displays, large print and braille format posters, sculptures and conceptual works that effectively communicated key concepts in infection, immunity, and biomedicine. This program was run in both Melbourne and Sydney and attracted more than 100 people at its Melbourne launch.

I would like to congratulate all centre members who won awards, prizes and grants in 2018. There are far too many to mention them all here, and you can read the full lists throughout this report. A few highlights only:

- Professor James Whisstock was awarded an ARC Australian Laureate Fellowship in 2018
- Professor Kat Gaus was named as a laureate of the prestigious Khwarizmi International Award in the Islamic Republic of Iran
- Professors David Fairlie, Dale Godfrey, Bill Heath and Jamie Rossjohn were named in the Clarivate Analytics prestigious 2018 highly cited researchers list
- A/Professor Brian Abbey and his team were finalists in the Medtech's Got Talent program
- Dr Daniel Pellicci, won the Commonwealth Health Minister's Award for Excellence in Health and Medical Research for 2018.

Engagement with industry and opportunities for translation of research findings are also making sound progress within the centre. Three centre members (AI's Marcel Nold, Claudia Nold and Centre Director James Whisstock), together with Andrew Ellisdon and Eric Morand, recently established a startup company, Wolf Biotherapeutics to develop novel molecular treatments for inflammatory disease.

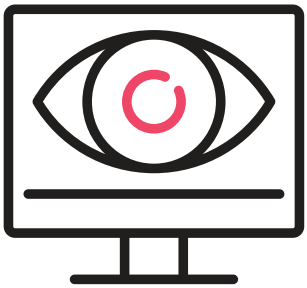
Jamie Rossjohn and colleagues continue to develop a strong relationship with Janssen Biotech Inc, extending a program of research to examine the interplay between genetic and environmental triggers of psoriasis, a disease which affects 125 million people worldwide and 300,000 Australians.

The International Scientific Advisory Committee continues to provide excellent advice and support to the centre. Professor Volker Saile (Karlsruhe Institute of Technology) has chaired ISAC since its inception until the end of this year, and I would like to thank him for his commitment to the centre. Professor Jeff Errington (University of Newcastle, UK) has now taken on the role and I am sure ISAC will continue to provide excellent advice under his leadership.

The annual Centre Summit has become an important yearly event bringing together all centre members for a three day extravaganza of some of the best imaging science in the world. The level of engagement from centre members is extraordinary and in addition to the excellent science, the Imaging CoE has placed a focus on opportunities for development of PhDs and early career scientists. I was pleased to see the provision of streamed sessions to a family room and the family friendly atmosphere created by all – including the Centre Director's children - great example to younger members of the centre wondering how to juggle a science career with a family.

Finally, thank you to the other members of the Governing Board; Ben Apted, Errol Harvey and Ian Smith for being such a great team to work with. Thank you also to James and Kat for running an excellent centre and providing us with the opportunity to glimpse some amazing science.

2018 AT A GLANCE



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RESEARCH THEMES

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AWARDS, PRIZES AND FELLOWSIPS

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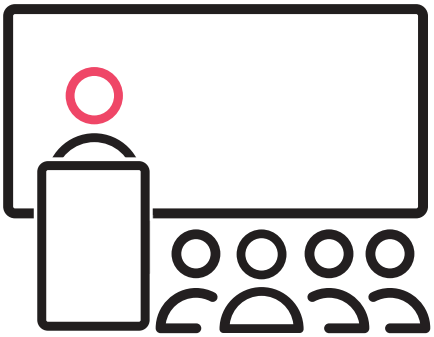
CENTRE MEMBERS



75 INVITED CONFERENCE TALKS

30 WORKSHOPS & CONFERENCES OFFERED

145
PUBLICATIONS

$32M
IN EXTERNAL FUNDING GRANTS

9
PATENTS

MESSAGE FROM THE DIRECTOR

PROF. JAMES WHISSTOCK DIRECTOR

NHMRC SENIOR PRINCIPAL RESEARCH FELLOW
DEPARTMENT OF BIOCHEMISTRY & MOLECULAR BIOLOGY, MONASH UNIVERSITY

Welcome to our 2018 annual report, a year that has seen the continued growth of the Imaging CoE. Our team now numbers over 230 scientists across five different academic institutions. Furthermore, many of the technologies that we conceptualised developing while writing the research plan of the Centre in 2012 are now firmly established within the Imaging CoE and are being used to study key immune questions.

One of the great challenges in modern biology includes how to image immunity in action in the context of a large multicellular organism or whole organs. In 2018, Professor Bill Heath (Theme 4) and colleagues were successful in using intravital two-photon microscopy to understand how immune cells in the skin and the spleen respond to viral infection (see page 31).

Our Centre also continues to respond to the rapid pace of development of exciting new imaging approaches. At Monash in 2018 we were delighted to be the first in Australia to take delivery of two different types of cryo-Focused Ion Beam Scanning Microscopes (cryo FIB-SEMs). These instruments, which are commonly used in the semi-conductor industries, are now being applied to biological problems. Both cryo-FIB-SEMs are now online, and, accordingly, in 2019 I anticipate that the first results produced by these workstations will be reported.

Imaging is not just about instrumentation – indeed some of the most significant discoveries have come from the development of new reagents designed to help report on the location and function of proteins in cells and whole organisms. In these regards our Melbourne, Monash and Queensland teams have been developing a suite of new reagents that they have subsequently applied to understand the activity and localisation of Mucosal associated invariant T cells. Their successes in these regards are reported in Theme 7 (see page 43).

Internationally, our Imaging CoE scientists are now firmly embedded in key large, multidisciplinary teams that are exploring the potential of the European XFEL to yield atomic resolution insights into how proteins move and change shape. Over the next ten years, our engagement will continue to grow as the European XFEL expands its capacity and capabilities.

In international activities our partnership with the Fraunhofer IZI-BB continues to grow, with scientific visits and technology exchanges between Australia and Germany. We are particularly excited about the application of cell-free-expression technology developed by our colleagues in the Fraunhofer to solve challenges in imaging hard-to-study membrane associated immune complexes.

Throughout the course of Imaging CoE, we have been delighted to run workshops aimed at helping to train scientists in the use and application of the latest imaging technologies. These initiatives have been enthusiastically received and, with the support of the ARC, we aim to expand these training events during the course of 2019. Our new workshops will be multi-day events, will be open to all scientists around Australia and internationally, and will also, where appropriate, permit groups to bring their own imaging data for on-site analysis.

Finally, and also from the outreach perspective, with the leadership of Jamie Rossjohn, our Centre has participated in running Sensory Scientific Exhibition and Discovery days (see Communicating our Science on page 56). These events are designed to bring the world of imaging and immunology to the low vision community. The latest such event was held at UNSW in December 2018.

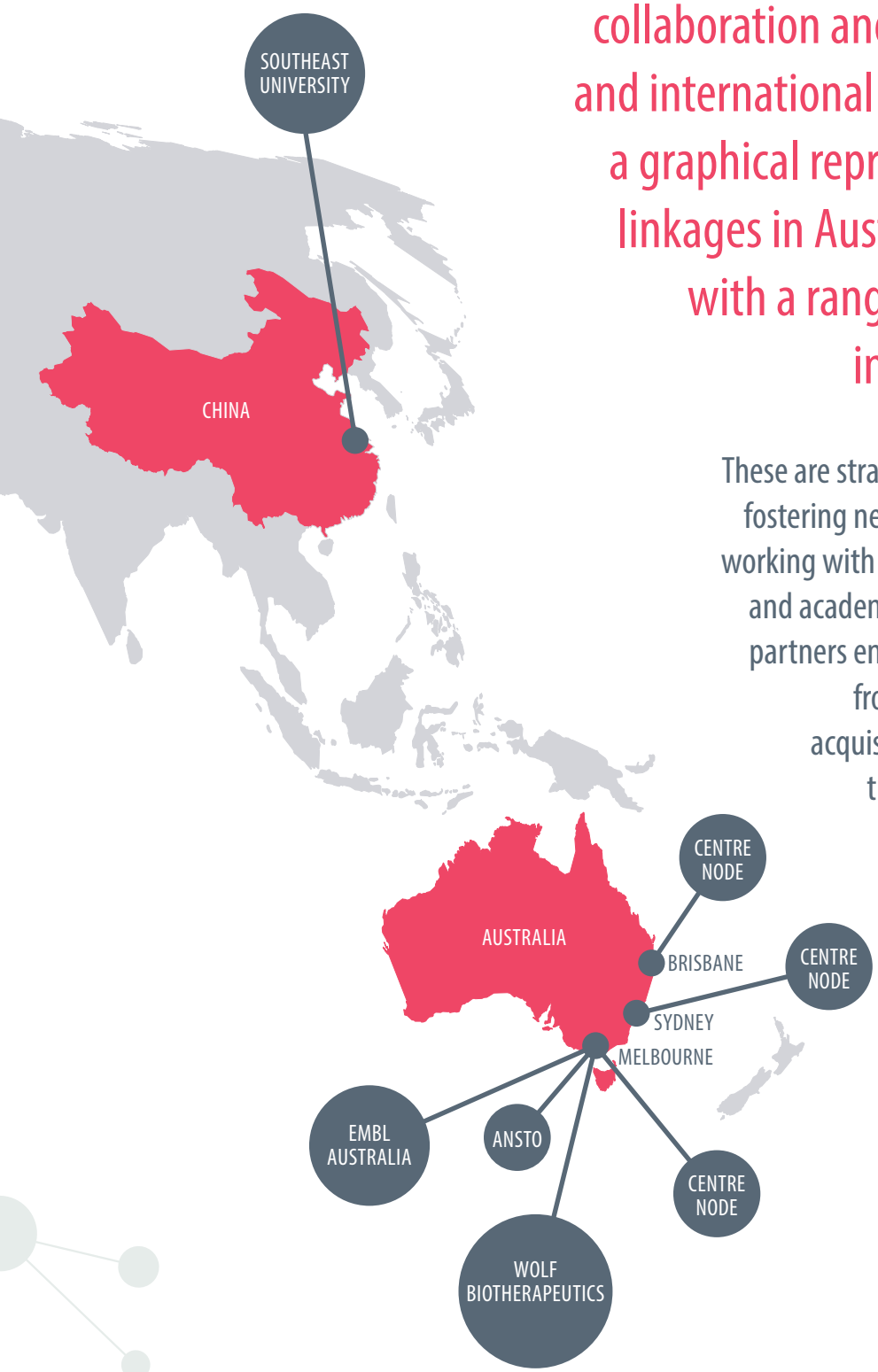
I would like to thank all our Centre scientists and supporters, our Governing Board, and our International Scientific Advisory Committee for their strong involvement and support of Centre activities.

I would also personally like to thank all our administration for their support of the Centre throughout the year, and in particular at Monash University our team of Juliana Villa (Project Coordinator – CO), Haley Gyngell (Media and Communications manager) and Nadya Glebova (Executive Officer). I would further congratulate our COO Annette Wittmann, who will return from maternity leave in mid 2019. I also congratulate Haley Gyngell on her appointment as Manager, Media and Communications in the Office of the Vice Provost (Research and Research Infrastructure).

I hope you enjoy the snapshot of 2018 provided in this annual report!

STRENGTHENING LINKAGES: INTERNATIONAL

The Imaging CoE has been growing in its collaboration and connections, nationally and internationally, every year. This map is a graphical representation of our current linkages in Australia and internationally with a range of businesses, research institutes and universities.



These are strategic relationships that work towards fostering new opportunities and ensuring we are working with the best minds possible for industrial and academic partnerships. Our work with these partners encompasses a wide range of activities, from sample preparation, imaging data acquisition, data analysis and visualisation, through to interpretation, application, and commercialisation.

STRENGTHENING LINKAGES: INTERNATIONAL CONT.

IMAGING CoE CONTINUES TO STRENGTHEN INTERNATIONAL TIES

The Imaging CoE continued its strong and collaborative research partnership, entering into the second year of a five-year collaboration with the German Fraunhofer IZI and Fraunhofer IZI-BB Institutes.

The strategic partnership focuses on accelerating the development of novel therapeutics, imaging technologies and diagnostic devices to better treat diseases such as cancer and other immune-associated disorders.

In January, the Centre was very pleased to welcome Dr Dagmar Schlenzig and Dr Doreen Wüstenhagen, from Fraunhofer in Germany, who were the first researchers to visit the Centre since the partnership began.

During the 12 week visit, Dr Schlenzig, who works in the area of Cryo Electron Microscopy, collaborated with A/Professor Alex De Marco and Dr Chris Lupton. Dr Wüstenhagen was part of a cross disciplinary collaboration with A/Professor Claudia Nold (Hudson Institute of Medical Research), Professor Marcel Nold (Department of Paediatrics Monash Health) and Dr Andrew Ellisdon (Biomedical Discovery Institute), using cell free systems to investigate receptor complex formation. As a result of this visit, these projects are ongoing.

This year, the Imaging CoE's researchers continued to support and participate in Innohealth Australia, a program led by Fraunhofer-Gesellschaft that supports German and Australian connections and collaborations in the healthcare research sector. Representatives from the Centre attended an Innovation Platform event held in Melbourne in April, which was also supported by Fraunhofer-Gesellschaft. At the event, Australian and German researchers, together with healthcare industry representatives, presented, networked and discussed healthcare research and industry linkage pathways between Australia and Germany.

L-R Dr Doreen Wüstenhagen, Dr Amanda Caples and Dr Dagmar Schlenzig

Attendees from Monash University, Fraunhofer and MiniFab come together to show International partnerships are already in motion.

L-R Dr Dagmar Schlenzig, Fraunhofer IZI, Dr Doreen Wuestenhagen, Fraunhofer IZI-BB, Dr Dirk Kuhlmeier, Fraunhofer IZI, Annette Wittmann, Monash University, Dr Chris Lupton, Monash University, Juliana Villa, Monash University, Prof Ian Smith, Monash University, Eckart Bierduempel, Fraunhofer-Gesellschaft , Carolina Wieland, Fraunhofer-Gesellschaft, Mark Buecking, Fraunhofer IME-AE, Kim Cham, Monash University, Dr Erol Harvey, MiniFAB.

MONASH-FRAUNHOFER PARTNERSHIP

In September, Centre Director Professor James Whisstock, Vice-Provost (Research and Research Infrastructure) Monash University Professor Ian Smith, and Deputy Vice-Chancellor and Vice-President (Global Engagement) Monash University Professor Abid Khan travelled to Fraunhofer IZI-BB in Berlin to discuss the development of new high throughput imaging approaches for studying integral membrane proteins that are relevant to immunity.

The visit reinforced the strong links between Monash University and the Centre with Fraunhofer IZI-BB, and was also an opportunity to discuss the pathways that Australian scientists can use to translate research into outcomes that benefit society. The German-Fruanhofer model is very successful at transforming innovation and research from universities into industry.

The Fraunhofer partnership was further showcased in October in Melbourne during a delegation visit from the Federal German Ministry of Education and Research, which included the Deputy Director General, Mr Frithjof A. Maennel.

Fraunhofer's Head of Marketing and Business Development Pierre Tangermann, and Centre Director Professor James Whisstock impressed the delegation by highlighting the collaborative relationship between the Centre and Fraunhofer Institutes and its effect on high-end research and industry partners in both Australia and Germany.

To inspire the next generation of scientists, who drive the future of Australian science and innovation, the Imaging CoE will offer Australian PhD students a placement opportunity with German researchers at the Fraunhofer Institutes next year. The international research experience will help establish connections for students at the beginning of their careers, and could have a significant impact on relationships between German and Australian researchers in the future. The Imaging CoE's researchers are also looking forward to working with the German researchers who are scheduled to visit Australia next year.

L-R Mr Frithjof A. Maennel, Prof James Whisstock and Pierre Tangermann.

STRENGTHENING LINKAGES: INTERNATIONAL CONT.

JANSSEN BIOTECH COLLABORATION CONTINUES

In January an extension of the collaboration between Janssen Biotech, Inc. (one of the Janssen Pharmaceutical Companies of Johnson & Johnson) and Monash University was announced. The collaboration centres on researchers investigating triggers of the immune-mediated disease, psoriasis, and focussing on the discovery of potential new treatment approaches to prevent psoriasis.

Imaging CoE Chief Investigator Professor Jamie Rossjohn, in his capacity as Head of the Infection and Immunity Program at the Monash Biomedicine Discovery Institute, leads the research program.

The collaboration will continue to focus on ground-breaking research to examine the interplay between genetic and environmental triggers of psoriasis, a disease which affects 125 million people worldwide and 300,000 Australians.

The collaboration is an extension of a three-year research program focused on the development of novel approaches to treat autoimmune disease through Monash University's technological capabilities and world-leading research expertise.

"We're delighted to be working alongside Janssen once again in a joint effort to broaden our knowledge around this condition and develop novel treatments for psoriasis," Professor Rossjohn said.

Both genetic and environmental factors predispose to the development of psoriasis. Despite the compelling genetic evidence for the triggers of psoriasis, the interplay between genetic and environmental factors remains unclear. Professor Rossjohn's research project aims to explore this critical interplay and develop novel treatments.

ARTICLE SOURCE: https://www.monash.edu/discovery-institute/news-and-events/news/monash-extends-collaboration-with-janssen-on-psoriasis-prevention

Prof. Jamie Rossjohn

STRENGTHENING LINKAGES: NATIONAL

PARTNERSHIP WITH ANSTO'S AUSTRALIAN SYNCHROTRON

ANSTO is the home of one of Australia's most significant landmarks and national pieces of infrastructure for research. Thousands of scientists from industry and academia benefit from gaining access to the state-of-the-art instruments every year.

ANSTO leverages great science to deliver big outcomes, partnering with scientists and engineers and applying new technologies to provide real-world benefits.

In 2018, The ARC Imaging CoE staff were involved in upgrading a key mirror system at the MX2 beamline of the Australian Synchrotron (part of ANSTO).

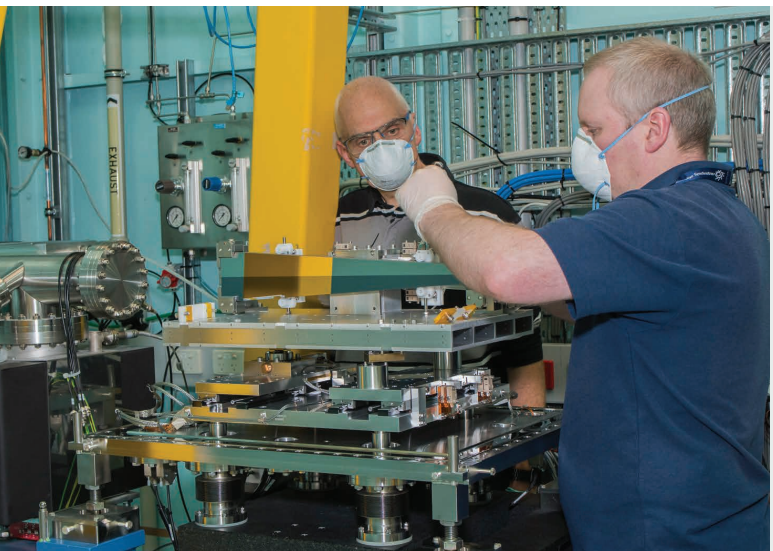
The microfocusing horizontal mirror (MHFM) is a key component of the MX2 beamline that enables the final fine horizontal focusing of the x-ray beam. Due to the size of many of the crystals studied on MX2 the focus of the beam is critical for obtaining high quality data.

The old MHFM mirror had become degraded over 10 years of beam from the intense undulator X-ray source inside the synchrotron's storage ring. In addition, the old mirror caused movement in the beam and was vulnerable to vibration.

A completely new mirror system was installed, including mirror, positioners, benders and vacuum vessel. The new mirror provides nearly twice the flux of the old mirror and horizontal vibration is less than a quarter than it was before.

Another major milestone was achieved with the installation of The Australian Cancer Research Detector was installed at the Australian Synchrotron on the MX2 beamline in February 2017. The new detector brings an unparalleled capacity to acquire user datasets in tens of seconds instead of minutes. This upgrade has been a huge gain to users but has also come with some issues. The ACRF detector counts individual photons, leading to very high data quality and low noise. However, when the rate at which photons hit a pixel becomes too fast the pixels begin to "miss" counting some of these photons. This under-counting of photons can be corrected in part by detector software. But this under counting can still lead to problems with poor data quality under some circumstances.

Dr Jun Aishima (Imaging CoE postdoctoral Fellow based at the Australian Synchrotron) is writing new code to identify data as it is being collected to prevent/minimise these potential count-rate correction issues whilst alerting the users to alter their strategy for data acquisition. This code will be deployed on the MX2 beamline in 2019 and will greatly assist users to undertake a better collection strategy which in turn will maximise their data quality.



MHFM installation.
L-R Dr Alan Riboldi-Tunnicliffe (ANSTO) and John Kendall (FMB-Oxford).

Dr Jun Aishima (Imaging CoE postdoctoral Fellow based at the Australian Synchrotron).

RESEARCH PROGRAMS

While our Centre is composed of chemists, immunologists, physicists, structural biologists, single molecule scientists and biophysicists, we break these down into nine research themes which cover three key disciplines: immunology, chemistry and physics. The researchers within these disciplines are engaged in the application and fundamental development of imaging, for the mutual benefit of all.

IMAGING

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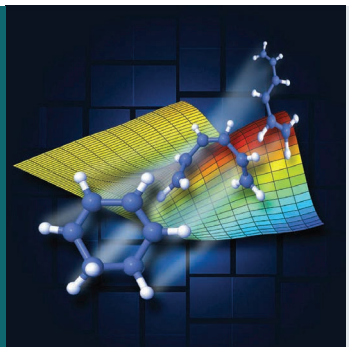

MOLECULAR MOVIES USING XFEL

We are actively working on techniques to capture real-time molecular movies using ultrafast X-ray diffraction. Molecular movies using XFELs could allow scientists to track the intricacies, nuances and detailed behaviour of molecules like never before.

HIGHLIGHT: **THE SECRET LIFE OF ATOMS** – 20

ACHIEVEMENT: **COMMERCIALISING IMAGING TECHNOLOGY** – 21

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SINGLE MOLECULE IMAGING

We are addressing the challenges associated with instrument fluctuations, electronic damage, natural conformational variability and the effects of confinement by developing new systems and tools to map the heterogeneity landscape of single molecules.

HIGHLIGHT: **DISORDERED CRYSTALS MERGE CRYSTALLOGRAPHY AND SINGLE MOLECULE IMAGING** – 24

ACHIEVEMENT: **COMMERCIALISING IMAGING TECHNOLOGY** – 25

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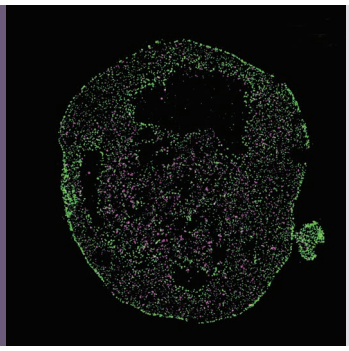

MOLECULAR IMAGING OF T CELLS

To further understand how antigens elicit an immune response, we use single molecule imaging and other fluorescence techniques to map intracellular signalling processes.

HIGHLIGHT: **SCIENCE WITHOUT SIGHT: BRINGING MEDICAL DISCOVERY TO LOW VISION COMMUNITY** – 28

ACHIEVEMENT: **KAT GAUS HONOURED WITH INTERNATIONAL SCIENCE AND TECHNOLOGY AWARD** – 29

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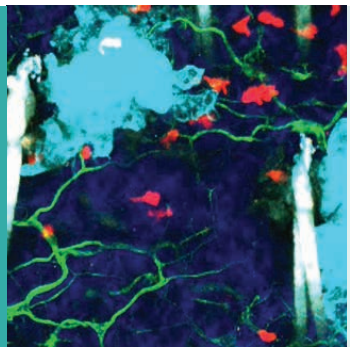

IN VIVO IMAGING

We are working to solve major questions about immune cell interactions, how responses are initiated and how various cells co-ordinate their functions. Using sophisticated imaging techniques, we enable visualization of multiple cellular interactions in real-time.

HIGHLIGHT: **TISSUE RESIDENT MEMORY T CELLS PROLIFERATE LOCALLY** – 32

ACHIEVEMENT: **DEVELOPING LIVE IMAGING OF THE LIVER AND ITS MULTIPLE IMMUNE CELL TYPES** – 33

IMMUNOLOGY

IMAGING PEPTIDE-MEDIATED IMMUNITY

By developing atomic and molecular imaging innovations, our research can further understand T cell function and dysfunction.

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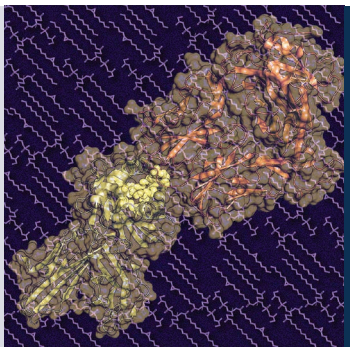
IMAGING LIPID-MEDIATED IMMUNITY

We are investigating the types of lipids that are responsible for lipid mediated immunity in the context of both foreign and self-antigens.



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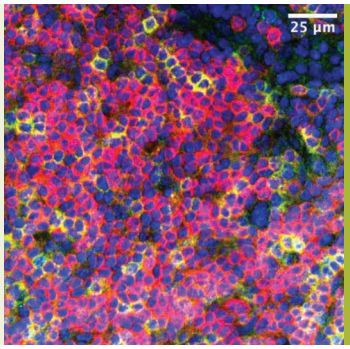
IMAGING METABOLITE-MEDIATED IMMUNITY

Using our novel imaging reagents and imaging modalities developed within this theme, we are beginning to understand MAIT cell antigen recognition, activation, development and maintenance, and how these cells traffic in the host in response to infection.



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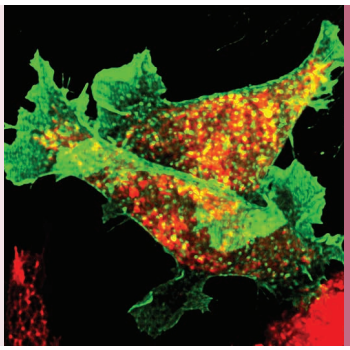
IMAGING INNATE IMMUNE RESPONSES

We are working to uncover what happens over time when cells of the innate immune system are confronted with infectious and non-infectious stimuli.



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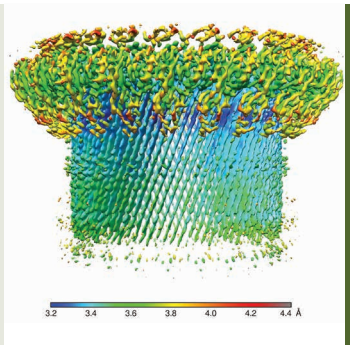
IMAGING IMMUNE EFFECTORS

We are working to gain a better understanding of the control of the immune cascades governed by the Complement system. In the longer term we hope to use this information to control Complement, in a range of different diseases.



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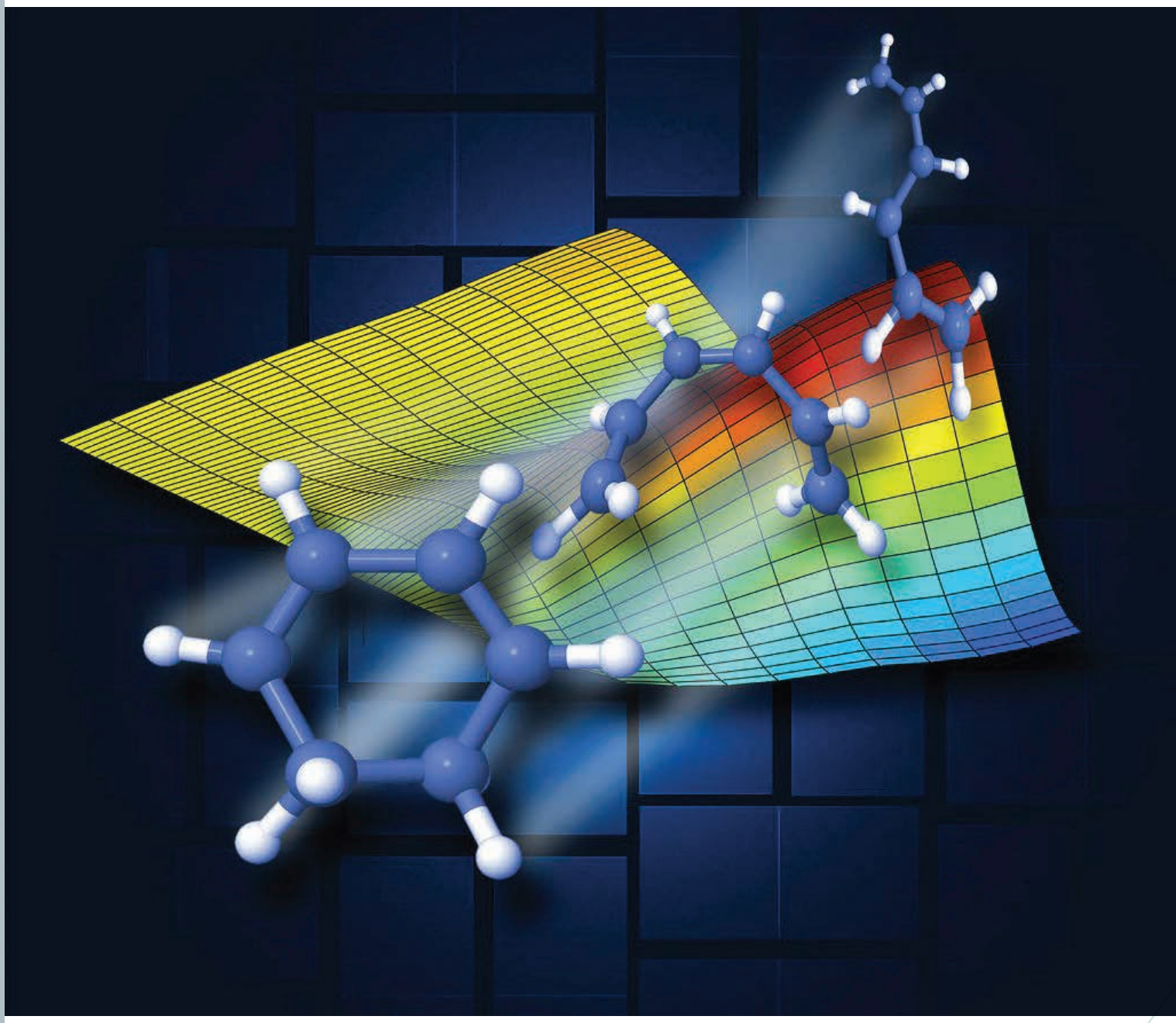
MOLECULAR MOVIES USING XFEL



"We have now developed a new platform to control and measure molecular dynamics in real-time at the atomic scale. This will provide unpresented insight into the inner workings of biomolecules."

'Molecular Movie' Reveals Ultrafast Chemistry in Motion: This illustration shows shape changes that occur in quadrillionths-of-a-second intervals in a ring-shaped molecule that was broken open by light. The molecular motion was measured using SLAC's Linac Coherent Light Source X-ray laser. The coloured chart shows a theoretical model of molecular changes that syncs well with the actual results. The squares in the background represent panels in an LCLS X-ray detector.

SLAC National Accelerator Laboratory - https://www6.slac.stanford.edu/news/2015-06-22-new-%E2%80%98molecular-movie%E2%80%99-reveals-ultrafast-chemistry-motion.aspx

Working with the Australian Synchrotron and the Melbourne Centre for Nanofabrciation (MCN), we have developed new approaches for chemically 'triggering' molecular movies using state-of-the -art nanofabrication techniques. This technique is being deployed at the XFEL and will allow us to capture the real-time dynamics of biomolecules on sub-picosecond timescales.

A/PROF. BRIAN ABBEY
PROF. KEITH NUGENT

AT A GLANCE

The ability to collect high-resolution, damage-free, molecular movie data at atomic resolution is fast becoming a reality thanks to recent availability of XFELs. Conventional synchrotron and electron-based techniques typically provide a static view of molecular structures. Through a process known as 'diffract-and-destroy' XFELs are able to take snapshots of molecular conformations prior to any significant nuclear motion occurring.

One of the major challenges with XFEL based molecular movies is the amount of data required to enable a 3D reconstruction of the relevant molecular dynamics. In December 2017 the worlds' first MHz XFEL source, the European XFEL, came online. These sources can collect orders of magnitude more data then current generation XFELs potentially solving one of the biggest problems faced by groups making these types of measurements.

Imaging CoE researchers were part of the first group in the world, and the only scientists from Australia, to use the European XFEL to collect atomic resolution data from proteins. Over the past 12 months this data has been successfully analysed to produce the worlds' first MHz X-ray structures (Wiedorn et al. Nature Comm. 2018 and Grünbein et al., Nature Comm. 2018). This result is a significant boost to efforts in generating real-time, atomic-scale molecular movies using XFELs and paves the way for Centre researchers to apply this approach to studying biomolecules. This work was also highlighted in the Herald Sun newspaper.

However, with the much faster data rates, issues around how to handle and process the more than 30,000 frames of data collected each second, become even more critical. Jointly supported by ANSTO, Imaging CoE researcher Dr Marjan Hadian has been developing algorithms for online processing of XFEL data. Her work is currently being integrated into the data analysis pipeline at the European XFEL and will benefit both Australian researchers and the international molecular movies community.

Other recent successes include the commercialisation of the La Trobe groups' molecular imaging technology as a platform for ultra-sensitive tissue imaging. In 2018 the team behind this technology won several regional and national awards (including being finalists in the Medtech's Got Talent awards) and were successful in attracting significant support to help with commercial development.

ACTIVITY PLAN

1. Work with the Australian Synchrotron and the external user community on the serial synchrotron crystallography (SSX) platform built by La Trobe University and Monash University at the MX2 beamline.
2. Analyse the molecular movies data collected from key regulators of the complement system at the Australian Synchrotron.
3. Continue to develop new approaches to extracting structural information from XFEL SAXS/WAXS data based on LCLS experiments performed in September 2018.
4. In collaboration with the theoretical physics group at University of Melbourne and Bio21 continue to work on understanding the effects of confinement in single particle imaging experiments.
5. Continue the commercialisation of our imaging technology with a view to forming a company in 2019.

HIGHLIGHT

THE SECRET LIFE OF ATOMS

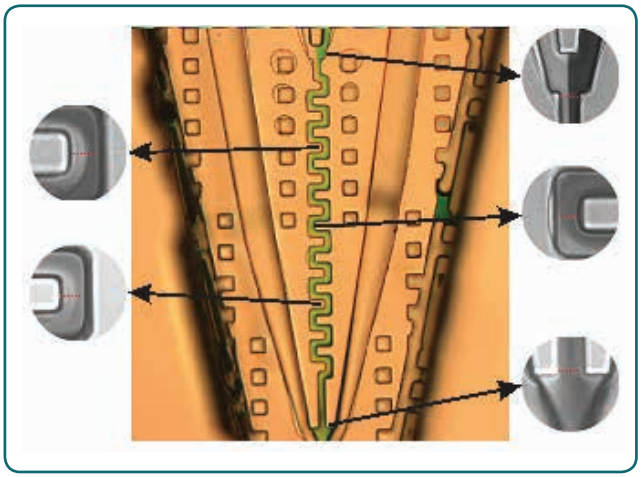
In 2018 the first protein structures measured using MHz XFEL sources were published. These experiments paved the way to performing molecular movies experiments in real-time at the atomic scale where data volumes and sample consumption are major challenges which need to be addressed. Our molecular movies program is designing methods for triggering molecular movies as well as new approaches to analysing big data and interpreting XFEL diffraction patterns.

"This is innovative science and arguably the biggest science project in the world right now," La Trobe University researcher Professor Keith Nugent said.

"It's exciting for our team to work alongside the world's best molecular scientists, as well as a number of our students who are now based at Euro XFEL."

La Trobe University's A/Professor Brian Abbey, Chief Investigator of the Imaging CoE, said the laser "allows, for the first time, snapshots of the atomic structure of molecules to be captured at a rate of up to one million images per second, allowing us to track their movements and interactions in real-time".

"This information can be used to construct 3D models of proteins as they change their shape in solution or come together and combine to form larger structures," A/Professor Abbey said.



Rapid mix-and-inject device for creating biological movies at the XFEL designed and fabricated by the La Trobe CoE node. From: Hejazian et al. Microfluidic mixing and jetting devices based on SU8 and glass for time-resolved molecular imaging experiments. SPIE, 2019 (in-press).

ACHIEVEMENT

COMMERCIALISING IMAGING TECHNOLOGY

During 2018, Chief Investigator A/Professor Brian Abbey and CoE nanofabrication expert Dr Eugeniu Balaur worked towards commercialising a new type of ultrasensitive imaging technology for characterising tissues. Initially developed as a way to track molecular dynamics in-situ their breakthrough enables stain-free, label-free, imaging of optically transparent samples providing a new approach to understanding and detecting disease.

Following a series of laboratory trials, the La Trobe group have been successful in attracting significant financial support for commercialisation of their technology and are currently working on establishing a spin-out company based on their patented devices.

The La Trobe node have won multiple awards for their technology over the past 12 months including a 2018 regional innovation award; they are also finalists in the Medtech's Got Talent program which aims to support new start-ups form long term sustainable businesses within Australia.

La Trobe University researchers were finalists in the 2018 Medtech's Got Talent award picking up a $10,000 prize. From L-R, Imaging CoE researcher Dr Eugeniu Balaur, La Trobe Senior Commercialisation Officer Dr Caroline Bathje, Chief Investigator A/Prof Brian Abbey, and Dr Richard Stevens business development manager at Hydrix.

SINGLE MOLECULE IMAGING

"We are addressing the challenges associated with instrument fluctuations, electronic damage, natural conformational variability and the effects of confinement...by developing new systems and tools to map the heterogeneity landscape of single molecules."

X-ray image of the silica shell of the diatom Actinotychus Senarius obtained at 5000-fold magnification. Fine details in the diatom are visible thanks to a powerful new X-ray lens design that is being developed for eventual application to single-molecule imaging.

Andrew Morgan, Sasa Bajt, Henry Chapman, Christian Hamm.

Single molecule imaging reveals biologically relevant heterogeneities within proteins and protein complexes. Rather than producing an average or dominant structure of a protein or complex, single molecule techniques can capture the 'heterogeneity landscape' occupied by a single particle. The details of this landscape convey information about biochemical reactions and the functionality of biomolecules within living systems.

THE UNIVERSITY OF MELBOURNE

PROF. HARRY QUINEY

AT A GLANCE

Imaging CoE scientists perform single particle experiments that encompass X-ray free-electron laser single particle imaging (XFEL-SPI), cryogenic electron microscopy (cryo-EM), micro electron diffraction (micro-ED) and fluorescence imaging. Each of these techniques faces different and significant challenges in order to achieve single molecule imaging. It is not enough merely to achieve atomic scale molecular imaging, because this has no biological value if the molecule is not in its native state. The real challenge is to adapt and develop our techniques to better accommodate the intrinsic inhomogeneity of the systems we wish to image.

Imaging CoE researchers are advancing this field by combining XFEL-SPI or cryo-EM studies with complementary experiments using crystallography and molecular fluorescence. Such advances can come only though a collaboration spanning physics, chemistry and biology and involving both experiment and theory to determine the real behaviour of the target molecules under imaging conditions.

Our Centre's expertise in single-molecule microscopy at UNSW, and a technology developed at La Trobe University to produce nano-droplets on demand, will allow us to devise protocols for the appropriate handling of samples in XFEL experiments, delivering molecules in their native states.

In 2018, we engaged with experimental work performed by Professor Ilme Schlichting, a member of our International Scientific Advisory Committee, on the effects of electronic damage on pump-probe XFEL measurements of molecular dynamics. We developed closer links with the Hamburg-based CFEL group led by Professor Henry Chapman (Imaging CoE PI) and recently recruited Dr Andrew Morgan from Hamburg to join the Melbourne node of the Centre.

ACTIVITY PLAN

1. Utilise topological data analysis to establish the "shape" of large, noisy and incomplete data sets in cryo-EM, XFEL-SPI, including the effects of damage on the efficiency of the imaging systems.
2. Explore electronic damage processes in XFEL imaging techniques.
3. Develop new sample delivery systems to improve the outcomes of XFEL-SPI experiments.
4. Explore micro electron diffraction techniques using the Imaging CoE's expertise across both theoretical analysis and experimental studies.

HIGHLIGHT

DISORDERED CRYSTALS MERGE CRYSTALLOGRAPHY AND SINGLE MOLECULE IMAGING

X-ray crystallography has been the most successful and widely used technique for imaging protein molecules, the building blocks of life. It is well known, however, that crystallography has long suffered from a basic problem: that the information provided by crystal diffraction is insufficient to determine the protein structure. To get around this problem, scientists must rely on prior assumptions about the structure of the protein or conduct further experiments to compensate for the missing information.

Another well-known problem in crystallography is that some crystals are observed to diffract "poorly". In other words, the bright Bragg spots that are emitted, when diffracting X-rays through a crystal, are only observed at shallow angles with respect to the incoming beam and this limits the resolution of the final image. Professor Henry Chapman (CFEL Hamburg, Imaging CoE PI) realised that such "poorly" diffracting crystals may actually provide more information, and at higher resolution, than their perfect counterparts due to the presence of additional diffuse diffraction.

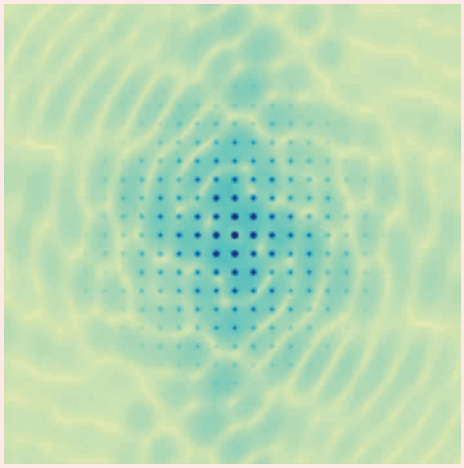
Dr Andrew Morgan joined the Imaging CoE in May 2018 from Henry Chapman's group in Germany. He has shown that such poorly diffracting crystals can provide enough information to completely determine the protein structure.

This means that many proteins can be imaged without bias and with finer detail than was previously possible at crystallographic beamlines.

A fascinating unsolved problem in science is the mystery of how the Photosystem II protein molecule can so efficiently split water in plants. Being a membrane protein, it is hard to crystallise, and researches often find that it diffracts too poorly to achieve the desired resolution. Dr Andrew Morgan and Imaging CoE physicists are collaborating with groups led by Professor Henry Chapman and Professor Petra Fromme to investigate new and existing Photosystem II datasets to see if this new approach to crystallography can unlock this outstanding mystery.

PAPER:
AB initio phasing of the diffraction of crystals with translational disorder

VOLUME:
75 PAGES, Article number: 1 (2019). Andrew J. Morgan, et al, Acta Cryst.



A disordered crystal of ducks (left) and the accompanying diffraction pattern (right) that exhibits features of both crystallography (Bragg spots) and single particle imaging (continuous diffraction).

Andrew J. Morgan

ACHIEVEMENT

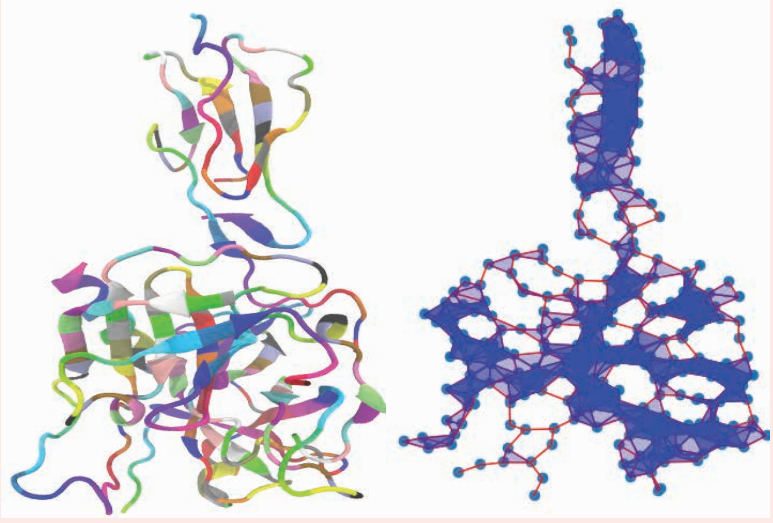
SEARCHING FOR ORDER IN HETEROGENEITY USING MATHEMATICAL TOPOLOGY

A biomolecule *in vivo* exists in a wide range of conformations. We encounter heterogeneity in many forms; in the disorder of crystals, in conformal distributions in cryo-EM and in the effects of molecular confinement in XFEL sample delivery by aerosols. We can reduce damage to the sample by rapidly freezing the samples and using weak electron probes, or we can attempt to outrun the damage by measuring structures on femtosecond timescales using brute force XFEL pulses.

Nevertheless, the signatures of high-resolution biomolecular structure are accompanied by high levels of noise in any imaging system. These are the principal challenges of Theme 2; the example below is just one example of our progress in 2018, which also includes the link between noise and resolution within a quantum mechanical formalism of imaging and the development of a hybrid scheme that merges plasma physics and molecular dynamics in describing XFEL-molecule interactions.

All forms of advanced molecular imaging are characterised by a shift to the methods driven by huge datasets. Topological data analysis (TDA) tools have been developed in the last couple of decades to analyse the multidimensional features of such datasets. These tools classify topological spaces using topological invariants such as homotopy, homology, and Euler characteristic. For example, homology can detect topological features such as connected components, holes and voids and record the evolution of these features as the parameters change. Such a feature is extremely useful to classify the data.

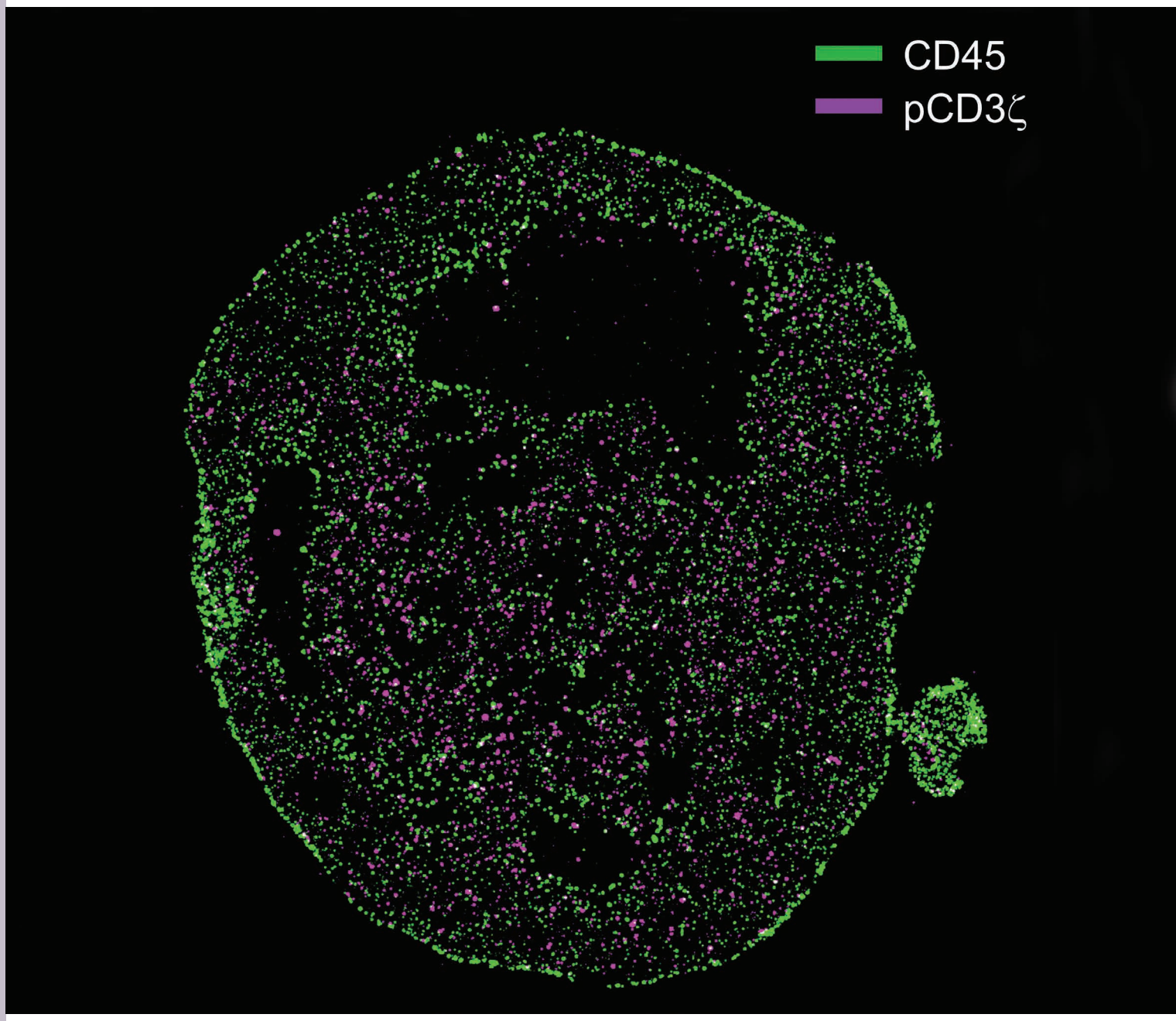
We have adapted these mathematical tools with machine-learning techniques to study the conformational space of large bio-molecules and capture their dynamical properties in a compact topological representation. Incorporation of this scheme in imaging algorithms connects heterogeneous structural datasets from distinct conformers continuously rather than classifying them as distinct instances of structure.



Persistent structural features of c1 complement protein (left) in molecular dynamics simulations represented as a vietoris-rips complex (right) of topological analysis. The analysis identifies collective motion of subunits within the atomic-scale simulation of the entire protein at varying length scales in an aqueous environment.

Saumitra Saha

MOLECULAR IMAGING OF T CELLS



"With our new single molecule microscope, we can now measure distances between molecules in intact immune cells on the biologically relevant scale."

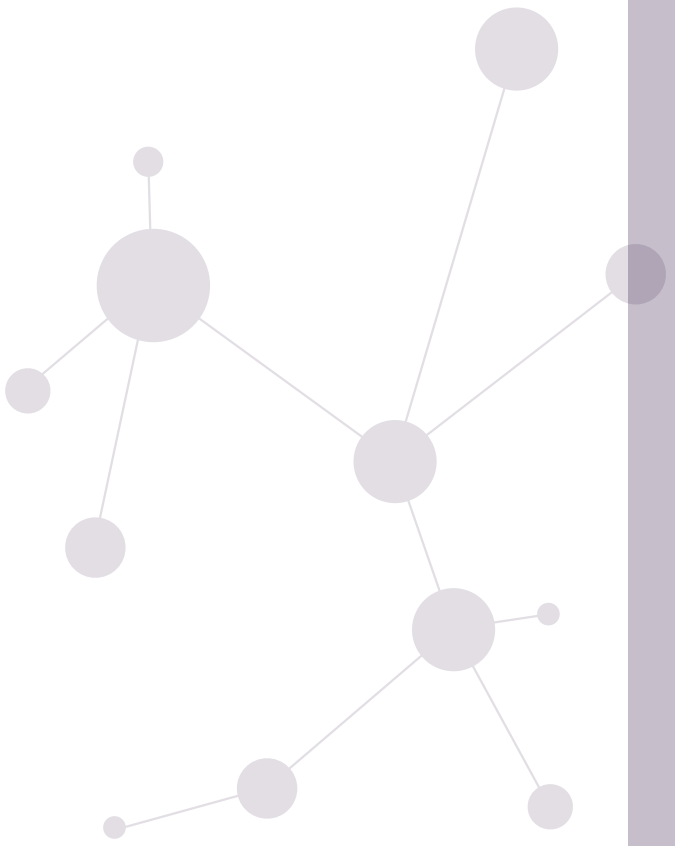
Single molecule fluorescent image of a human T lymphocyte (also called a T cell) in which each molecule is localised with a precision of 2-4 nm.

More than 30 years after the discovery of the T cell receptor, we still do not know how signalling begins. It is important that we work out how antigen binding initiates intracellular signalling because these signals shape the resulting immune response. With new super-resolution fluorescence microscopy and single molecule imaging approaches, we aim to map the molecular level while retaining the spatial organisation of intact cells. We are developing new instruments, new analysis methods and new molecular biology tools in an interdisciplinary research program that spans physics, chemistry, mathematics and biology.

PROF. KATHARINA (KAT) GAUS

AT A GLANCE

Super-resolution fluorescence microscopy promises the opportunity to place single molecules and multi-molecular complexes in the cellular context in the cellular context and in turn understand how molecular organisation of cells leads to cellular outcome. A key question in cellular immunology is how antigen recognition leads to intracellular signalling on which T cell fate decisions are based. The T cell signalling field is stymied as we do not understand how engagement of the T cell receptor (TCR) on the extracellular side initiates phosphorylation of the constitutively associated CD3 dimers on the intracellular side. Further, it is not known how diverse signalling outcomes are encoded by a common TCR-CD3 signalling transduction process. We hypothesise that the spatial organisations are key to signal initiation, integration of signals from multiple receptor, and the regulation of a highly plastic signalling network.



ACTIVITY PLAN

1. Identify subunits and subunit arrangements of protein complexes in intact cells, exploiting the photophyiscal properties of fluorophores for molecular counting.
2. Link protein localisation and spatial organisations to function, distinguishing signalling from non-signalling molecules and determine the environmental factors.
3. Combining biochemical assays with single molecule imaging to establish a conceptual and theoretical framework of signal integration at the receptor level.
4. Map signalling networks by developing new statistical analysis for single molecule data that reveals the information flow in intracellular signalling networks.
5. Disseminating microscopy hardware and software. To make a lasting impact on the scientific community and connect with end-users, we are not just developing novel microscope hardware and software but also developing avenues to cost efficiently replicate and disseminate our approaches. For example, we are exploring how 3-D printing could aid in the prototyping of hardware and collaborating with MASSIVE to develop approaches for handling and processing large imaging-based data.

HIGHLIGHT

SCIENCE WITHOUT SIGHT: BRINGING MEDICAL DISCOVERY TO LOW VISION COMMUNITY

Professors Jamie Rossjohn, Kat Gaus and the scientists at Single Molecule Science at UNSW organised and participated in an event in Sydney where the blind and low vision community experienced scientific and medical discovery through shapes, textures, sounds, spoken word, and even smells.

Rapid advances in science and technology – from AI, screen reading software and image recognition devices – has made the world a more inclusive place for people with limited vision.

But for people with impaired vision or blindness, access to the wonder and discovery behind science has been far more elusive.

Visitors explored breakthroughs in the understanding of the AIDS virus (HIV) using tactile and audio displays and models representing developments in understanding our immune system and how this has led to more advanced cancer treatments.

The event included models of the biology of the eye, tactile models of cells, bacteria and viruses that will explain infectious diseases and a lab experience will guide participants through using real lab tools.

"We know how important it is to be able to communicate science to the public. Being able to participate in an initiative like this, where we were able to reach people we might otherwise miss, was so important for my group. It was such an interesting process to try and work out how to make sure our science was accessible to everyone," said Professor Kat Gaus.

Examining the theme of the building blocks of life, presenters and researchers from the School of Medical Sciences, School of Physics, the Centre for Eye Health, the Museum of Human Disease, and Monash Biomedicine Discovery Institute also explained their research on disease agents and the structure of atoms, molecules, cells, tissues, or organs.

Sensory Scientific Exhibition & Discovery Day is supported by UNSW Disability Innovation Institute, Museum of Human Disease and the ARC Centre of Excellence in Advanced Molecular Imaging.

The Sensory Science Discovery Day was first held in Melbourne with Imaging CoE Chief Investigator Professor Jamie Rossjohn, to read more about this initiative see page 56, Communicating our Science.

ORIGINALLY PUBLISHED:
https://newsroom.unsw.edu.au/news/science-tech/science-without-sight-bringing-medical-discovery-low-vision-community

James Halstead (left) and Jesse Goyette (above), both Postdocs from the Gaus Group designed and made their own activities to demonstrate their research concepts in immune memory and recognition.

Stephen Blake

ACHIEVEMENT

KAT GAUS HONOURED WITH INTERNATIONAL SCIENCE AND TECHNOLOGY AWARD

In a mark of her contribution to the research community, this year, UNSW's Scienta Professor Kat Gaus was named as a laureate of the prestigious *Khwarizmi International Award*.

Kat received her award from his Excellency, the president of the Islamic Republic of Iran during the annual awards ceremony, Professor Gaus travelled to Tehran in February.

"This recognition is a real honour, and it's great to see science being recognised beyond boarders, cultures and languages," says Professor Gaus of her award from the Iranian Ministry of Science and Technology.

Professor Gaus was awarded the prize for her achievements in single molecule imaging to visualise how T cells initiate an immune response. A major research focus in Professor Gaus' research group is the molecular signals that determine whether or not a T cell becomes activated when it encounters foreign material.

Gaus' work has been long recognised for its outstanding contribution to science, she was previously named as one of UNSW's 15 Women Changing Our World. Along with her work with the Imaging CoE, Gaus established the EMBL Australia Node in Single Molecule Science at UNSW to create a collaborative and interdisciplinary environment supportive of conducive to cutting edge molecular biology research.

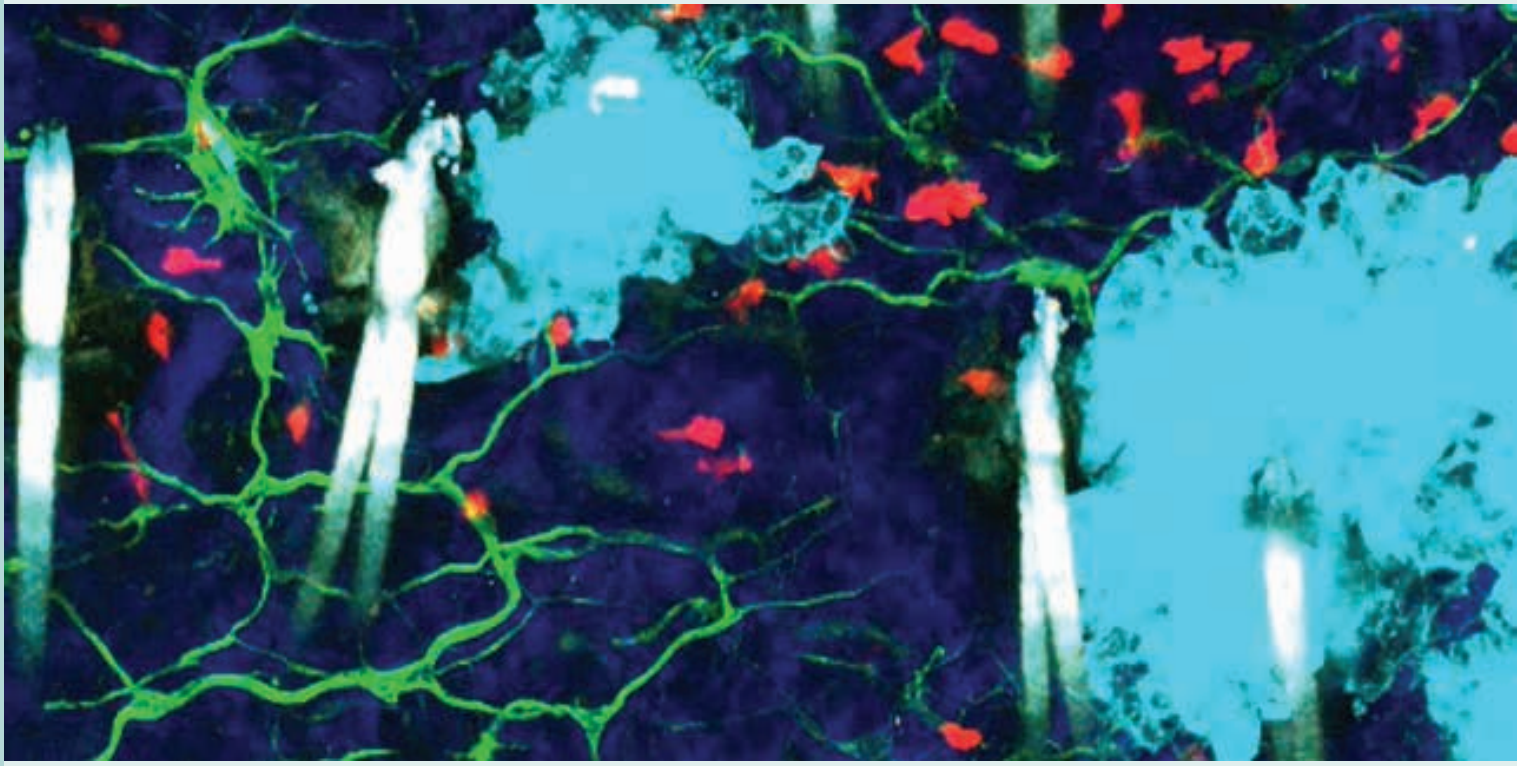
The award – named in honour of eminent Iranian mathematician and astronomer Khwarizmi – was first established in 1987, and the Foreign Section of the award was introduced in 1991 to recognize outstanding scientific achievements made by researchers from all over the world. Past recipients include distinguished scientists from Europe, UK, the Americas, Australia and Asia.

ORIGINALLY PUBLISHED:
https://sms.unsw.edu.au/news/katharina-gaus-honoured-international-science-and-technology-award

Professor Gaus receiving her Khwarizmi International Award

THEME 4

IN VIVO IMAGING



"Achieving visualisation of multiple cell types and structures by intra-vital imaging provides new insight into biology."

"Skin resident memory T cells proliferate in response to virus infection." Multi-colour imaging the skin using dual laser two-photon microscopy to identify tissue-resident T cells responding to virus infection. Image shows a single frame of a movie identifying virus-infected cells (light blue), skin collagen fibres (dark blue), nerve fibres (green), hairs (white) and tissue-resident memory T cells (red).

In this theme, we are developing microscopes with increased capacity to image at high speed deep within living animal tissues. This work is being combined with development of advanced surgical and engineering methods to enable imaging of live tissues without disturbing their function. We are developing labelling techniques and novel transgenic systems to visualise multiple cell populations and structural features in living animals or their tissues. These objectives provide highly visual, novel understanding of the biology of immune cells as they migrate, interact and function in their natural environment.

PROF. WILLIAM (BILL) HEATH

AT A GLANCE

In 2018, Imaging CoE scientists successfully used intravital two-photon microscopy to monitor the function and fate of tissue-resident memory T cells and other immune cells in skin, after viral infections or exposure to tumour cells, and in the liver during development of immunity and beyond. They also visualised B cells in lymph nodes and the spleen during the development of antibody responses.

These studies are beginning to reveal important roles for immune cells in control of infections and cancer and to outline critical factors that influenced generation and maintenance of immune populations in animal models. Our work sets the scene to enable manipulation of immunity in favour of protection from invading pathogens such as Plasmodium berghei, which causes malaria. It's our use of two-photon microscopy and novel transgenic mouse models that has achieved sophisticated imaging to enable visualisation of immune cells in complex tissue environments.

The immune system is comprised of a variety of cell types that must interact with each other during initiation of immunity and then later during the battle with invading microbes. Interactions that initiate immunity occur deep within lymphoid tissues, i.e. the spleen and lymph nodes, which are challenging organs to visualise. To address this goal, Imaging CoE scientists are creating tools to simultaneously monitor multiple populations of cells, improving microscopes for deeper penetration of vital organs, and developing methodologies for labelling cells and structures within these tissues.

In this field, our scientists are now working to solve major questions about immune cell interactions with invading pathogens, how immune responses to infections begin and how cells co-operate to fight microbes and cancer cells. We anticipate that by mapping the behaviour of various immune cell populations during the various phases of immunity, we will be able to build insight into the regulation of this complex but vital system.

ACTIVITY PLAN

1. Develop clearing techniques for spleen, liver and lymph nodes to enable whole organ imaging leading to advances in our understanding immune cell functions during immune responses.
2. Identify multiple cell types within tissues using an immunohistocytometry approach to identify and map the location of multiple different cell types simultaneously in static images.
3. Improve depth of intra-vital imaging by developing adaptive optics, rapid axial scanning and real-time image processing for 3D imaging deep in living tissues, e.g. spleen.
4. Mathematically model immune surveillance of the liver, lymph nodes and spleen by identifying and measuring immune cells subset movement and function within these tissues, mapping tissue architecture and then modelling behaviour.

HIGHLIGHT

TISSUE RESIDENT MEMORY T CELLS PROLIFERATE LOCALLY

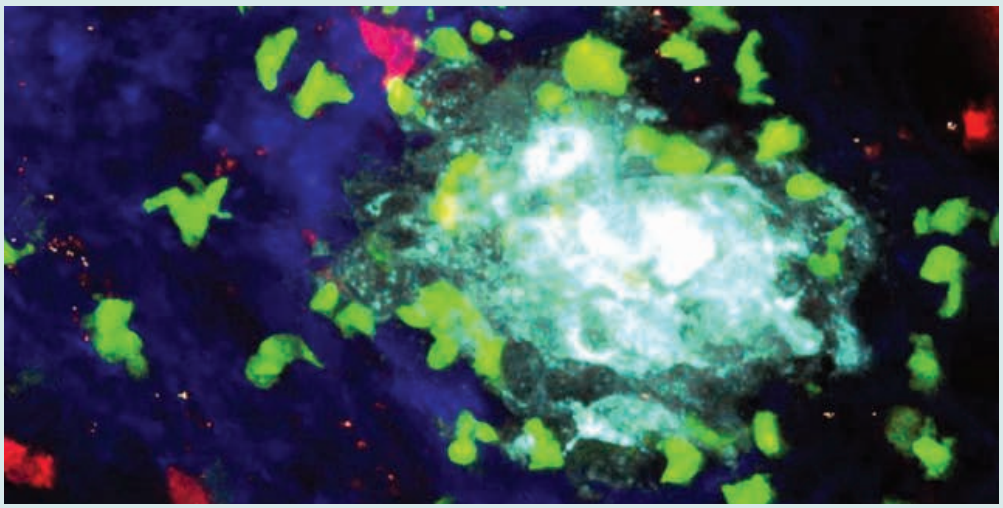
Memory T cells develop from naïve T cells after exposure to new infections or vaccines. These cells are crucial for protecting against future infections by the same organism, the basis of vaccination. There are three main types of memory T cells, central memory T cells, effector memory T cells and tissue-resident memory T cells (T_{RM} cells). While the former two populations recirculate throughout the body, T_{RM} cells remain permanently within any tissue they seed during the initial infection or vaccination. Their tissue localisation places them in the front-line for preventing future infections. While it has been clear that T_{RM} cells can survive long-term, perhaps indefinitely, in tissues such as the skin and brain in the absence of any further infections, it was unknown how they responded to re-infection or how unrelated infections affected their survival.

Imaging CoE scientists used advance two-photon imaging and flow cytometry approaches to show that upon re-infection with the same virus, skin T_{RM} cells engaged virus-infected cells, proliferated in situ in response to local antigen encounter and remained in the skin, where they exclusively reside.

As a consequence of proliferation, new secondary T_{RM} cells formed from pre-existing primary T_{RM} cells. In addition to this source, new primary T_{RM} cells could develop, recruited from precursors in the circulating memory T cell pool.

By examining responses to multiple different antigens in the one animal, we showed that new antigens could recruit new waves of T_{RM} cells and that these new waves did not displace cells of the pre-existing T_{RM} cell pool. Our studies revealed that multiple T_{RM} cell specificities could be stably maintained within the skin.

Our results reveal the complexity of T_{RM} cell maintenance (in the skin) and provide insight into how we can maintain immunity to multiple infective agents without diminishing individual responses.



Specific T_{RM} cells (green) attacking virus-infected skin cells (light blue), while non-specific T_{RM} cells (red) ignore infection

ACHIEVEMENT

DEVELOPING LIVE IMAGING OF THE LIVER AND ITS MULTIPLE IMMUNE CELL TYPES

In 2018, work in this Imaging CoE research theme has focused on improving liver imaging. We have developed imaging surgery and engineering to reduce image artefacts and improve tissue stability. This has led to unprecedented quality of live-cell multi-photon imaging of this tissue (see image below).

Our investigations have revealed that during most immune responses, activated killer T lymphocytes enter the liver and convert into a liver-resident population that are stably maintained in this organ. These cells are important for fighting intracellular infections of the liver, such as pre-erythrocytic malaria, and can be visualised migrating around the liver in the small blood vessels called sinusoid (see accompanying image).

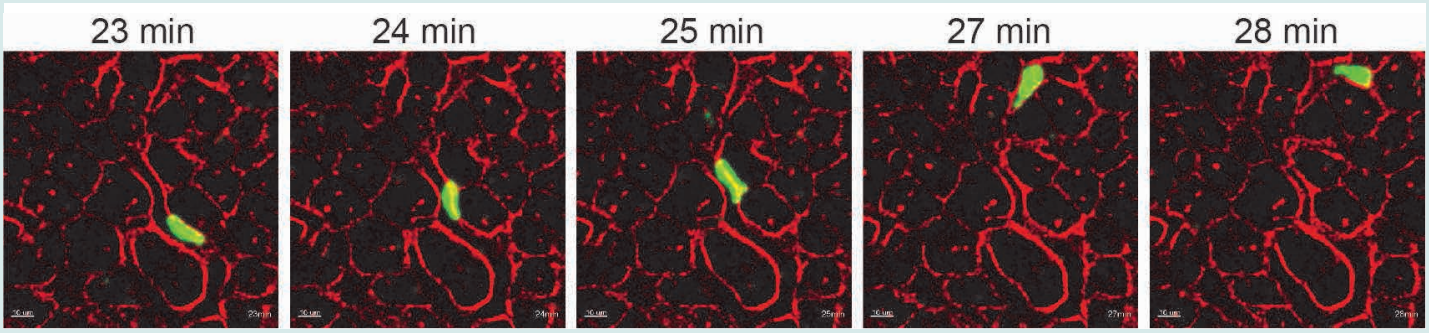
By studying multiple waves of T cells entering the liver, Imaging CoE investigators revealed that individual populations decayed in number over time, but that new populations did not displace older populations, enabling large numbers of T cells with multiple specificities to inhabit the liver over time.

This is likely important to maintain immunity to the variety of parasites, viruses and bacteria that may infect the liver over a life-time under natural conditions.

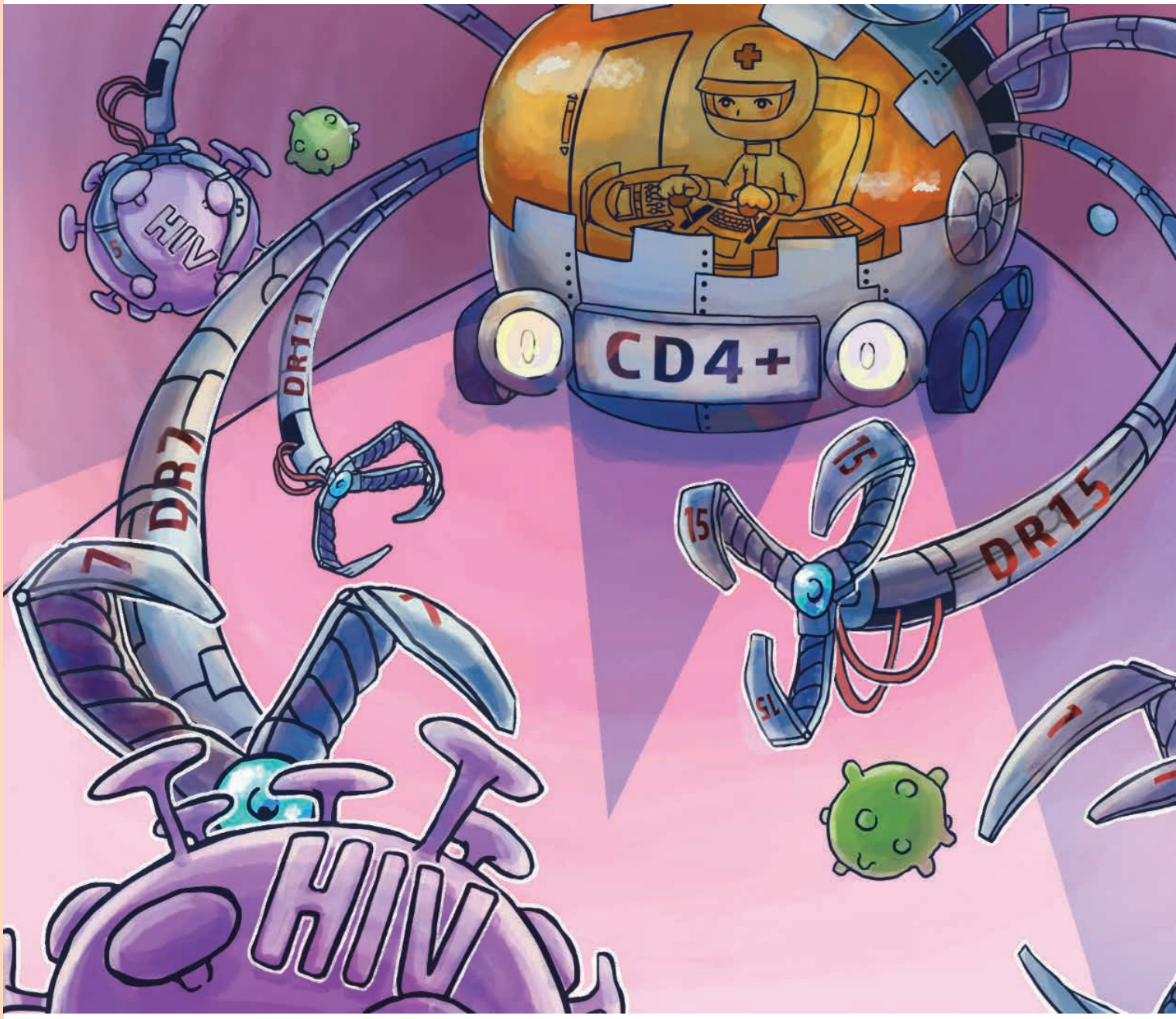
This research theme has also enabled visualisation of another population of T lymphocytes within the liver, i.e. the helper T lymphocytes. Like killer T lymphocytes, they can be seen migrating within the sinusoids in an ameboid-like patrolling manner. We have revealed that upon infection with malaria parasites, these cells form clusters throughout the liver, presumably to attack the invading pathogen. We are currently developing tools and reagents for imaging multiple components of this response.

In collaboration with associate investigator Professor Steve Lee (ANU), we have obtained images of the spleen and other tissues with the newly-developed multi-photon system, revealing detailed cellular images at unprecedented speed.

Migration of killer T lymphocyte (green) through liver sinusoid (red).



IMAGING PEPTIDE-MEDIATED IMMUNITY



"We are using a technology to produce stable, antigen-specific MHC- class II tetramers that has permitted our team to track auto-reactive T cells relevant to disease."

"Super" receptor that helps kill HIV infected cells.

Vanette Tran

Within this theme, conceptual challenges lie in understanding how the T cell antigen receptor co-recognises peptide determinants while being presented by molecules encoded by the Major Histocompatibility Complex (MHC) – both in the context of protective immunity (e.g. to viruses) and aberrant immunity (eg autoimmunity). The Imaging CoE's strategy is to develop reagents to characterise peptide-specific T-cells ex vivo and then use atomic and molecular imaging-based techniques to investigate the structural basis underpinning the interactions by the TCR.

PROF. JAMIE ROSSJOHN

AT A GLANCE

This theme has continued a series of structural studies in the TCR-peptide-MHC axis central to protective and aberrant immunity, principally using protein chemistry and X-ray crystallography as the main experimental tools.

Concomitantly, we are using a technology to produce stable, antigen-specific MHC- class II tetramers that has permitted our team to track auto-reactive T cells relevant to disease.

This has led to:

1. An increased understanding of the mechanisms of post-translational modifications of peptides and MHC presentation (JBC, Science Immunology and Proteomics).

2. An understanding of how HLA polymorphism leads to protective immune responses in HIV elite controllers (Science Immunology).

3. How TCRs can interact with tumour-derived epitopes via previously unknown mechanisms (Nature Communications). Collectively our work in the axis has led to some important basic insights into peptide-mediated immunity. Highlighting the standing of Imaging CoE investigators in the field, two authoritative reviews in MHC-restricted immunity were published in 2018. (Nature Reviews Immunology).

ACTIVITY PLAN

1. Explore protective immune responses to lipid antigens.

2. Examine CD1 auto reactivity in the context of health and autoimmunity.

HIGHLIGHT

A "SUPER" RECEPTOR THAT HELPS KILL HIV INFECTED CELLS

While treatments for HIV mean that the disease is no longer largely fatal, the world still lacks a true therapy that can eradicate the virus across a globally – and genetically different – population.

Imaging CoE researchers, together with colleagues from the Pasteur Institute in Paris, have discovered a unique set of "super" receptors on immune cells capable of killing HIV across genetically diverse populations, making them a potential candidate for immunotherapy treatments. The work was published in *Science Immunology*

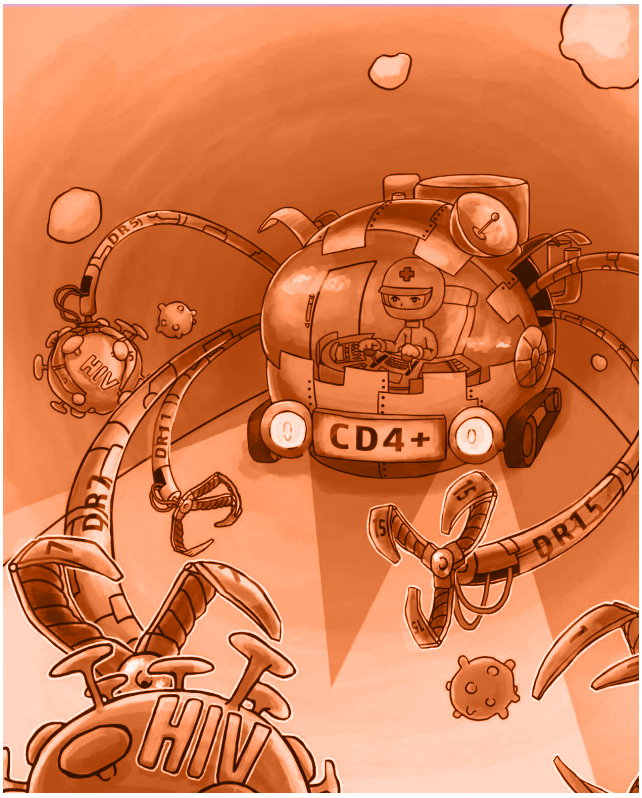
Professor Jamie Rossjohn, A/Professor Stephanie Gras from Monash University and ARC Centre of Advanced Molecular Imaging, and colleagues from the Pasteur Institute in Paris, studied fifteen unique individuals who all had been infected with HIV (ANRS CO21 CODEX cohort), but have immune systems that protect them from AIDs progression. These rare individuals, called HIV controllers, could hold clues to the cure for the disease.

Upon HIV infection, CD4 T cells, which are an important part of our protective immune system, can be depleted and drop dramatically in numbers, leading to a weak immune system with the progression of the disease to AIDs. These CD4 T cells can remain low even when the disease is kept in check with anti-retroviral therapy (ART), which is currently provided to more than half of people living with HIV globally. ART lowers the risk of mortality but does not eradicate the virus.

Rossjohn and his colleagues found that HIV controllers are able to retain CD4 T cells of a higher quality, able to detect and react to minute amounts of virus, therefore representing a great opportunity to study their potential role in HIV infection.

We discovered that those CD4 T cells, usually viewed as helper cells for the killer CD8 T cells that destroy infected cells, could be turned into killer cells themselves in HIV controllers. These killer CD4+ T cells could recognize very low amounts of HIV thanks to the expression of "super" T cell receptors on their surface. Importantly when they studied these receptors – they found identical receptors across multiple HIV controllers. "The likelihood of finding the exact same T cell receptor in different individuals is extremely low, like winning the lottery, and is likely linked to the control of HIV", said Carine Farenc, a lead author of the study said.

T cell receptors recognises virus or bacteria fragments bound to specialised molecule called HLA (Human Leukocyte Antigen). HLA molecules are like fingerprints: every person has a specific combination of HLA molecules, which help the immune system recognize foreign invaders like bacteria or viruses. Monash University researchers used the Australian Synchrotron, effectively a giant microscope the size of a football field, to study the binding of this super T cell receptor in complex with the HIV antigen. This revealed another remarkable feature of those killer CD4 T cells: their ability to recognise HIV fragment in genetically diverse individuals (with different HLA molecules). The Gras team and her colleagues found that these killer CD4 T cells can bind with HLA molecules shared by a quarter of world population, a figure that is likely to increase as studies progress.



Vanette Tran

ACHIEVEMENT

PROFESSOR JAMIE ROSSJOHN RECEIVES 2018 ASBMB LEMBERG MEDAL

Professor Jamie Rossjohn was announced as the 2018 Australian Society for Biochemistry and Molecular Biology (ASBMB) Lemberg Medal recipient.

This prestigious medal honours Professor Rossjohn's significant and sustained contributions to the understanding of the molecular basis underpinning immunity.

Awarded annually, the Lemberg medal is presented in memory of Emeritus Professor M.R. Lemberg, who was the Society's first President and Honorary Member. Only three other scientists from Monash University have won this Medal. Professor Rossjohn joins the esteemed company of Professor Anthony Linnane (1973), Emeritus Professor Phillip Nagley (2001) and the Dean of the Faculty of Medicine, Nursing and Health Sciences and Academic Vice-President, Professor Christina Mitchell (2015).

"An outstanding team of researchers who work alongside me, coupled with the continuous and strong support of Monash University, have enabled numerous exciting finds in the area of immunity to be made over the last 15 years," Professor Rossjohn said

Professor Rossjohn's research on the immune system, how the body reacts to infection and what happens when the immune system fails has led to a sustained advancement of knowledge in the field of immunity. His work has been generously supported by the Anti-Cancer Council, the NHMRC, and the ARC, including the Imaging CoE.

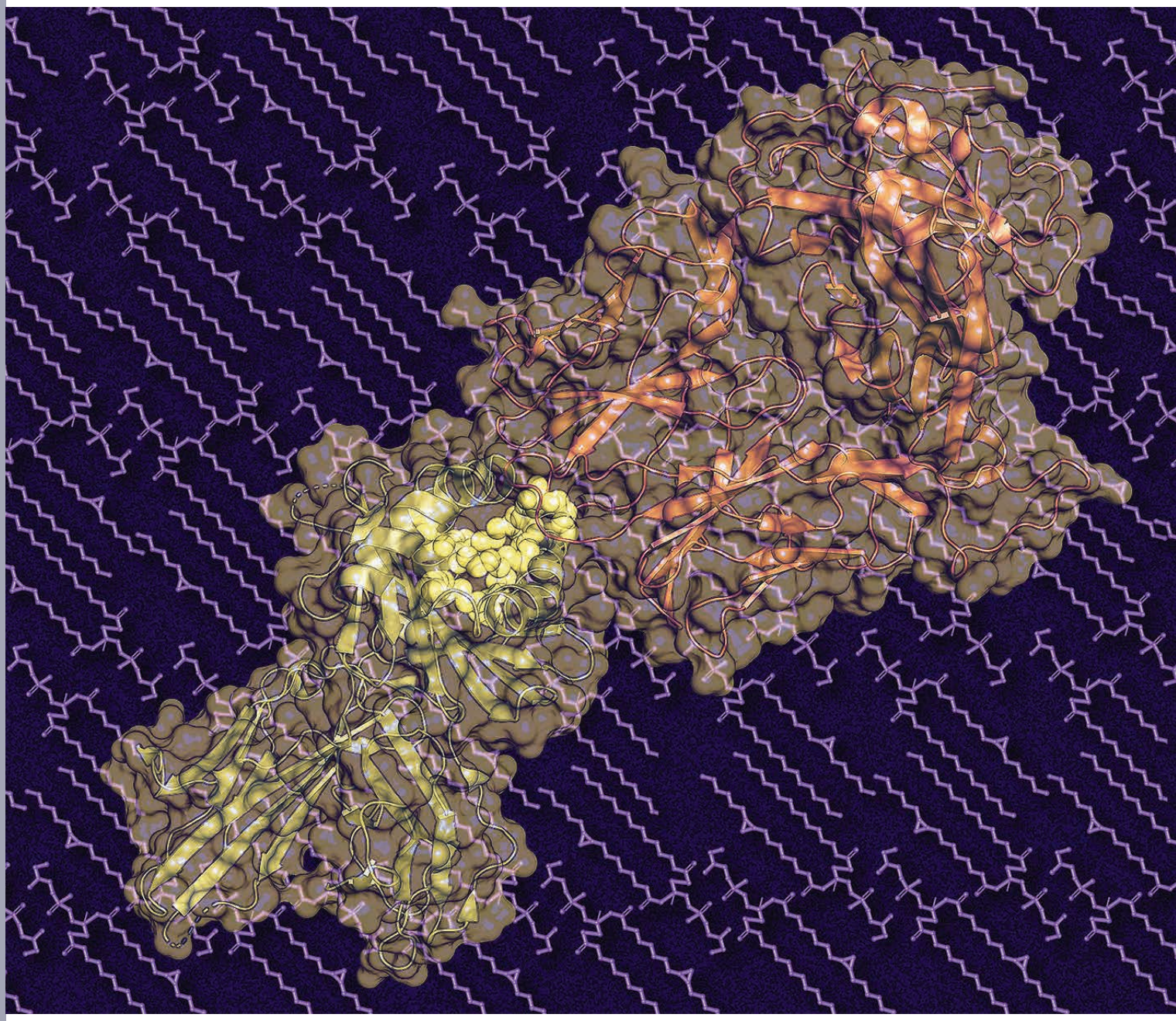
As the recipient of the 2018 ASBMB Lemberg Medal, Professor Rossjohn also attended the ComBio2018 conference in September to give the Lemberg Medal Lecture.

ARTICLE SOURCE:
https://www.monash.edu/discovery-institute/news-and-events/news/professor-jamie-rossjohn-receives-2018-asbmb-lemberg-medal

Professor Jamie Rossjohn

THEME 6

IMAGING LIPID-MEDIATED IMMUNITY



"It is now becoming evident that the CD1 family can play an important role in both protective immunity and immunopathology."

Lipids in Immunity: Presentation of lipid antigens (yellow) by lipid antigen presenting molecules (gold) for recognition by T cell receptors (orange) is a critical first step in lipid mediated T cell immunity.

As well as T cells sensing peptides presented by MHC molecules (Theme 5), they can also respond to lipids (this theme) and metabolites (Theme 7). In the context of lipid-mediated immunity, TCRs recognise lipids that are presented by MHC-I like molecules, namely the CD1 family.

There are four members of the CD1 family of antigen-presenting molecules expressed on the cell surface (CD1a,b,c,d), each one of which possesses unique structural and biochemical/cellular features that indicates distinct roles in immunity. Indeed, it is now becoming evident – in part due to the contributions of Imaging CoE scientists, that the CD1 family can play an important role in both protective immunity (e.g. response to Mycobacterium tuberculosis) and immunopathology. Imaging CoE scientists continue to pioneer this aspect of immunity.

PROF. JAMIE ROSSJOHN
PROF. DALE GODFREY

AT A GLANCE

While most studies into lipid mediated immunity have centred on understanding how Natural Killer T (NKT) cells respond to lipids presented by the CD1d member, there is a major lack of understanding of T cell responses to the other CD1 family members (CD1a-c). The Imaging CoE is focused on bridging this basic knowledge gap.

Collectively, findings in this area has led to:

1. Understanding of how TCRs recognise CD1c via a previously undescribed mechanism (Nature Immunology).
2. How the different isoforms of CD1d play a key role in immunity (PNAS).
3. How the fine chemical structure of lipid antigens modulate the immune response to NKT cells (Cell Chemical Biology).
4. How lipid antigen recognition by NKT cells in liver can lead to enhanced CD8 T cell resident memory cells in liver (Cell Reports).
5. How CD1d-lipid antigen reactive NKT cells are functionally diverse and how this response is shaped by the inflammatory environment at the time of activation (Immunol. Cell Biol.).

ACTIVITY PLAN

1. Explore protective immune responses to lipid antigens.
2. Examine CD1 auto reactivity in the context of health and autoimmunity.

HIGHLIGHT

T CELL AUTOREACTIVITY DIRECTED TOWARD CD1C ITSELF RATHER THAN TOWARD CARRIED SELF LIPIDS

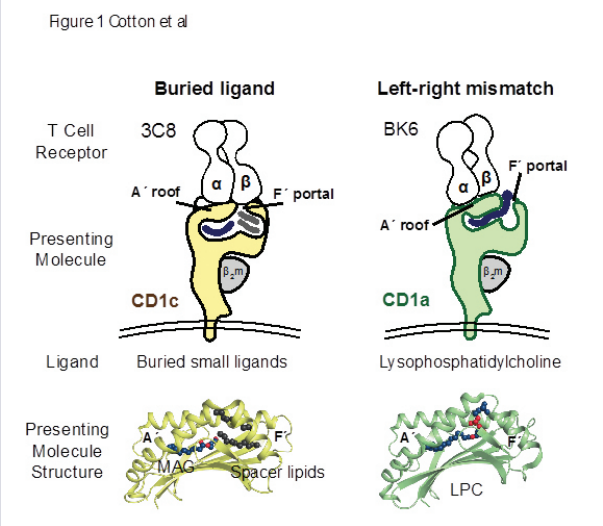
There are 4 CD1 isoforms – CD1a, CD1b, CD1c and CD1d. Imaging CoE scientists have pioneered our understanding of how TCRs recognise CD1d (Borg, Nature 2007), CD1a (Birkinshaw, Nature Immunology 2015) and CD1b (Nature Comms 2016 & Science Immunology 2017).

A last bastion in gaining an understanding of the molecular basis of lipid mediated immunity was that of knowing how TCRs recognised CD1c plus lipid antigen. Understanding this is a key question as the 3D architecture of CD1c is distinct from other CD1 family members; it possesses a distinct tissue distribution from the other CD1 family members; and CD1c-restricted T cell immunity has been implicated in autoimmunity, tumour immunity, as well as immune responses to Mycobacterium tuberculosis. Yet, the particular role of T cell reactivity to CD1c in health and disease remained unknown and understanding how TCRs recognise this antigen-presenting molecule is central to filling this knowledge gap.

In the paper to the right, this is precisely what Imaging CoE scientists achieved. It had long been understood that many T cells exhibited autoreactivity towards CD1c, but the basic mechanism underpinning this was unknown. In collaboration with the Moody lab (Harvard), it was shown that TCRs could recognise CD1c directly, in a manner that did not involve co-recognition of the associated self-lipid antien.

This finding is in stark contrast to the co-recognition paradigm centric to peptide mediated immunity for which Zinkernagel and Doherty received the Nobel Prize (1996). Instead, small self-lipids were sequestered deep inside the CD1c molecule, stabilising this molecule while enabling the TCR to closely approach the CD1c molecule itself, whereas other lipid antigens essentially obstruct this recognition. This provided a model by which CD1c-restricted T cell responses are governed by lipid-mediated inhibition of CD1c recognition. As such, Centre scientists defined a new mechanism of TCR recognition.

PAPER:
Wun, K.S., Reijneveld, J.F., Cheng, T.Y., Ladell, K., Uldrich, A.P., Le Nours, J., Miners, K.L., McLaren, J.E., Grant, E.J., Haigh, O.L., Watkins, T.S., Suliman, S., Iwany, S., Jimenez, J., Calderon, R., Tamara, K.L., Leon, S.R., Murray, M.B., Mayfield, J.A., Altman, J.D., Purcell, A.W., Miles, J.J., Godfrey, D.I., Gras, S., Price, D.A., Van Rhijn, I., Moody*, D.B. & Rossjohn*, J. T cell autoreactivity directed toward CD1c itself rather than toward carried self lipids. Nature Immunol. 19, 397-406 (2018).



Cotton et al. COI 2018

ACHIEVEMENT

PROFESSOR JAMIE ROSSJOHN AWARDED ROYAL SOCIETY OF VICTORIA MEDAL FOR EXCELLENCE

Imaging CoE Chief Investigator Professor Jamie Rossjohn, Head of the Monash Biomedicine Discovery Institute's (BDI) Infection and Immunity Program, was awarded the distinguished Royal Society of Victoria's (RSV) Medal for Excellence in Scientific Research in Category II: Biomedical and Health Sciences.

The Research Medal recognises peak research career achievements and outstanding leadership in research by scientists working in the State of Victoria.

He is currently an ARC Australian Laureate Fellow (2017-2021) and was previously a NHMRC Australia Fellow (2011-2016) and ARC Federation Fellow (2007-11).

RSV President David Zerman emphasised that the Medal is not just about discovery and innovation, but also about fostering and supporting a thriving research community and workforce to achieve collective impact.

"Some of this is demonstrated through a scholar's personal output of journal articles and the related citations, or through patents and commercialisation, but it is also the research ecosystem that a leader supports through mentorship, collaboration and public engagement," Mr Zerman said.

"We look very favourably on research leaders who bring effective teams together, and who actively promote younger scientists in particular, either through direct supervision, co-authorship of major papers, or simply creating opportunities for meaningful, purposeful work in an intensely competitive job market," he said.

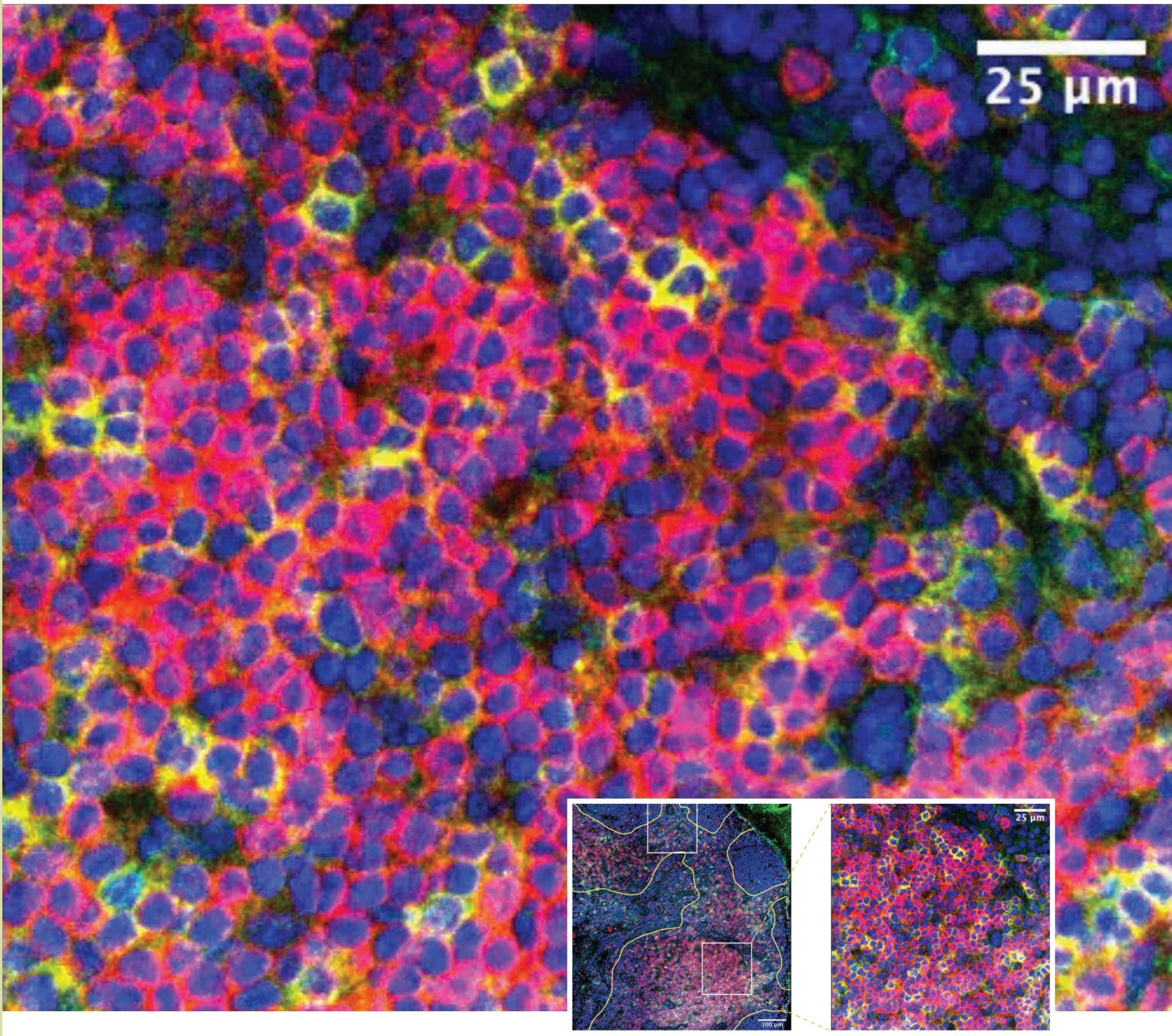
This year, the Medal was jointly awarded to both Professor Rossjohn and Professor Anthony Burkitt from Bionic Vision Australia and the Melbourne School of Engineering.

ARTICLE SOURCE:
https://www.monash.edu/discovery-institute/news-and-events/news/professor-jamie-rossjohn-awarded-royal-society-of-victoria-medal-for-excellence

L-R Professor Anthony Burkitt, Her Excellency, the Honourable Linda Dessau AC, Governor of Victoria and Professor Jamie Rossjohn.

Adrienne Bizzarri Photography.

IMAGING METABOLITE-MEDIATED IMMUNITY



"Imaging CoE scientists developed novel biochemical reagents (MR1 tetramers) that have enabled the phenotypic characterisation of MAIT cells."

MAIT cells (yellow) identified by MR1-5-OP-RU tetramer (green) and CD3 (red) costaining, predominantly reside in T cell zones of lymph nodes. Blue depicts cell nuclei (DAPI) and yellow lines separate T cell zones from B cell zones. Tissue derived from Va19Ja33 T cell receptor transgenic mice.

In 2012, Imaging CoE Centre scientists made the startling find that an abundant T cell population, termed Mucosal-associated invariant T (MAIT) cells were activated by metabolites of vitamin B (namely riboflavin) (Nature 2012).

Using a combination of chemistry, cellular immunology and structural biology, they subsequently showed that the most potent MAIT cell antigen arose from the convergence of two distinct metabolic pathways, namely riboflavin metabolism and metabolites from glycolysis (Nature 2014).

Armed with this information, the field is now empowered to understand MAIT cells in homeostasis, health and disease. To further enable this, Imaging CoE scientists developed novel biochemical reagents (MR1 tetramers) that have enabled the phenotypic characterisation of MAIT cells.

PROF. JAMIE ROSSJOHN
PROF. DALE GODFREY
PROF. DAVID FAIRLIE

AT A GLANCE

Work in this area has helped establish:

1. A greater understanding of the complexity of MAIT cell phenotypes in humans and problems with pre-MR1 tetramer based identification of these cells (ICB).
2. The role of MAIT cells in transplantation (JCI).
3. The role of MAIT cells in infection (JI and Nature Comms).
4. The involvement of MAIT cells in multiple myeloma (Scientific Reports).

ACTIVITY PLAN

1. Continue investigations into MAIT cell antigen recognition and activation.
2. Exploring what other ligands bind MR1.
3. Investigate role of MAIT cells and other MR1-restricted T cells in immune regulation.

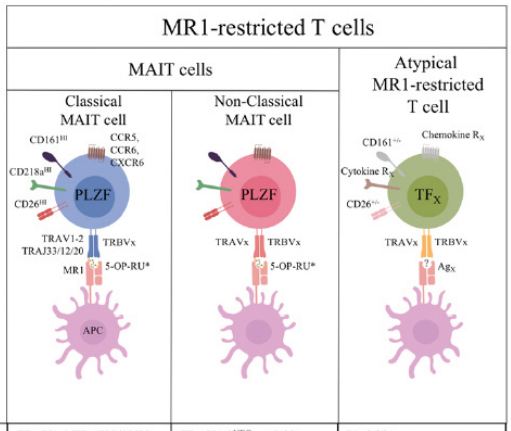
HIGHLIGHT

HUMAN BLOOD MAIT CELL SUBSETS DEFINED USING MR1 TETRAMERS

For many years, MAIT cells have been identified based on the expression of a combination of cell surface markers (CD3, CD8, CD161 and TRAV1-2). This is the basis for literally hundreds of studies of these cells. Based on our studies identifying the antigen specificity of MAIT cells for riboflavin derivatives (especially 5-OP-RU), and the use of this information to develop MR1-5-OP-RU tetramers to specifically identify MAIT cells, we have identified and characterised 5 distinct subsets of human MAIT cells, based on CD4, CD8α and CD8β coexpression: CD4+CD8-, CD4+CD8+, CD4-CD8-, CD4-CD8α+CD8β-, CD4-CD8α+CD8β+.

Further subdivision of MAIT cells was also apparent using other cell surface markers, such as CD56, NKG2D and other cell surface receptors. This highlights the fact that MAIT cells are a heterogeneous mix of cells and it is important to understand the developmental and functional relationship between these cell populations. We also demonstrated an unexpected correlation between the frequency of MAIT cells, NKT cells and γδT cells in human peripheral blood and show that the CD4+CD8- MAIT cell subset differs from the others with regard to cytokine production, and population kinetics with age.

This study also compared the populations defined by MR1 tetramer to the earlier techniques for identifying MAIT cells by surrogate cell surface markers CD3, CD8, CD161, TRAV1-2. While these previous techniques for identifying MAIT cells are reasonably accurate for studying CD8+ MAIT cells, in most but not all, healthy human samples; they were less effective for isolating CD8- MAIT cells and poor at isolating CD4+ MAIT cells. This highlights the need for caution in interpreting earlier studies of MAIT cells where surrogate markers were used.



TCR-a	TRAV1-2/TRAJ33/12/20	TRAV1-2^{NEG}, variable	Variable
TCR-b	Enriched for TRBV6, 20	Variable	Variable
Ag(s)	All 5-OP-RU *Subset-specific recognition of other Ags	All 5-OP-RU *Subset-specific recognition of other Ags	Variable
PLZF	Yes	Yes	Variable?
Selection	MR1^{+} DP thymocytes	MR1^{+} DP thymocytes	Unknown
Resting Blood Phenotype	Mostly: CD161^{HI}, CD218^{HI}, CD26^{HI}, Tissue Homing, Effector Memory	Resting blood, mostly: CD161^{HI}, CD218^{HI}, CD26^{HI}, Tissue Homing, Effector Memory	Unknown/variable

MR1-restricted T cells, defined using MR1 tetramers, are more diverse than generally appreciated. These include at least three distinct cell types based on TCR usage, cell surface phenotype, and transcription factor expression.

Gherardin, N. A., J. McCluskey, J. Rossjohn, and D. I. Godfrey. 2018. The Diverse Family of MR1-Restricted T Cells. J Immunol 201: 2862-2871.

PAPER:

Human blood MAIT cell subsets defined using MR1 tetramers. Gherardin NA, Souter MN, Koay HF, Mangas KM, Seemann T, Stinear TP, Eckle SB, Berzins SP, d'Udekem Y, Konstantinov IE, Fairlie DP, Ritchie DS, Neeson PJ, Pellicci DG, Uldrich AP, McCluskey J, Godfrey DI. Immunol Cell Biol. 2018 May;96(5):507-525. doi: 10.1111/imcb.12021. Epub 2018 Mar 25

ACHIEVEMENT

DR DANIEL PELLICCI WINS TOP AWARD FOR RESEARCH INTO IMMUNE SYSTEM 'FIRST RESPONDERS'

Dr Daniel Pellicci, who has dedicated his career to solving the mysteries of the immune system, won the Commonwealth Health Minister's Award for Excellence in Health and Medical Research for 2018.

University of Melbourne's Dr Daniel Pellicci, Senior Research Fellow from the Imaging CoE and The Peter Doherty Institute for Infection and Immunity, focuses on the 'first responders' of the immune system, particularly the roles of cells known as unconventional T cells.

These cells kick-start an immune response and can recruit other aspects of the immune system within minutes to mount a comprehensive fight against infection.

"With a better understanding of these T cells, we could potentially exploit them to treat human disease. In fact, some of them are already being trialled as immunotherapeutic targets to fight cancer and infections," Dr Pellicci said.

"I'm tremendously excited to receive the Commonwealth Health Minister's Award and to have my work as a cellular immunologist recognised in this way."

Imaging CoE Chief Investigator Professor Dale Godfrey, who heads a laboratory at the Doherty Institute, said Dr Pellicci is emerging as a key international player in this field of immunology research.

"Daniel's enthusiasm and dedication to his work is exemplary. He has always taken great pride in his work and it's been a great pleasure to see him moving his way up the ladder with many great achievements and high-impact papers along the way," Professor Godfrey said.

"This honour is well-deserved and I look forward to ongoing collaborations with Daniel as he establishes his own laboratory in the near future."

Dr Pellicci is very passionate about turning his focus to understanding how these T cells work in the context of Mycobacterium Tuberculosis (TB).

"It's not acceptable that over a million people continue to die from TB every year. I would like to find a way to exploit unconventional T cells to potentially boost the current BCG vaccine, and reduce the number of people dying from this devastating disease," he said.

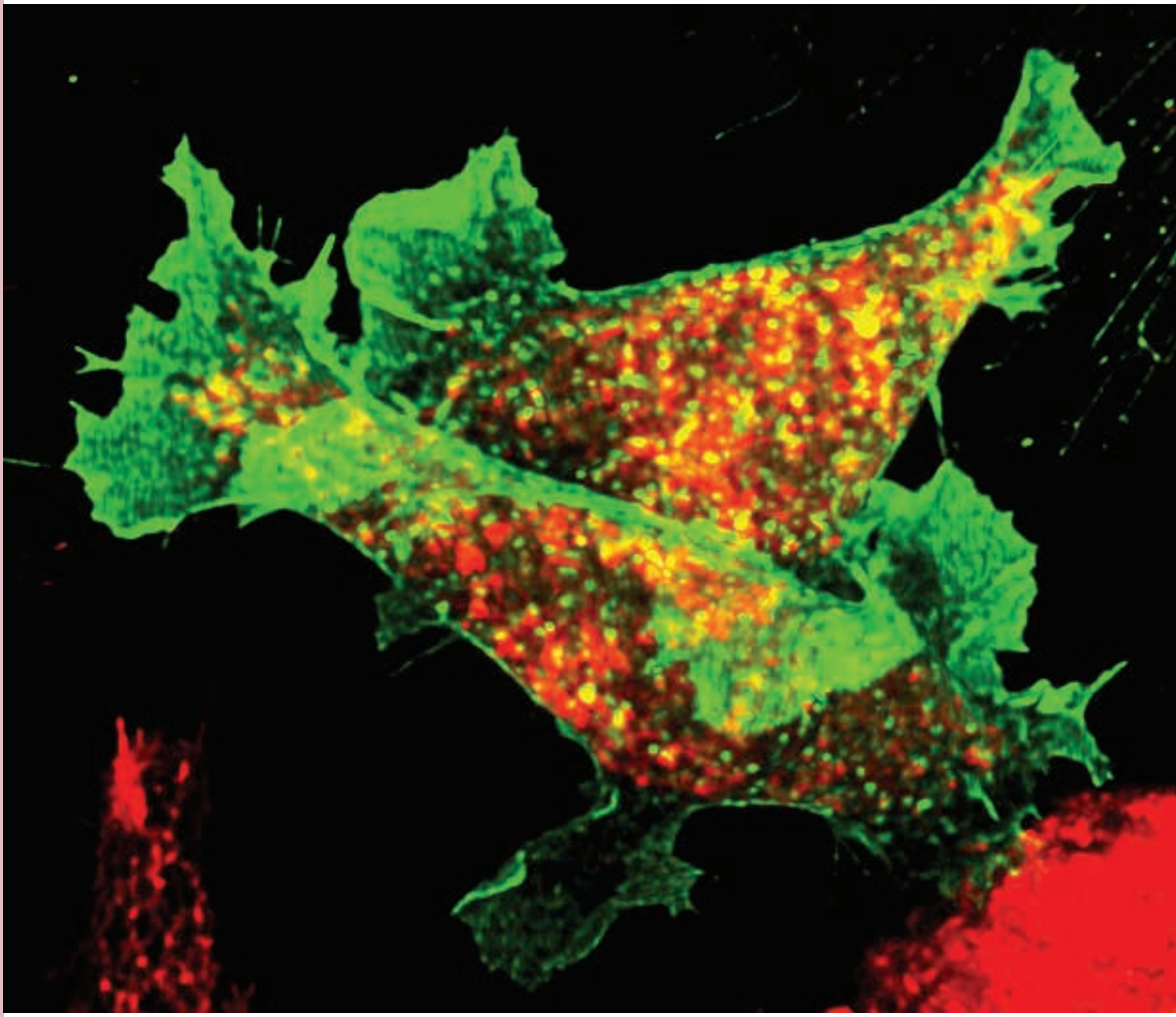
The Commonwealth Health Minister's Award for Excellence in Health and Medical Research recognises outstanding individual achievement by a mid-career Australian researcher. Dr Pellicci received the medal and $50,000 to help further his research at the Australian Society for Medical Research (ASMR) Victorian Gala Dinner.

ARTICLE SOURCE:
https://www.doherty.edu.au/news-events/news/dr-daniel-pellicci-wins-top-award-for-research-into-immune-system-first-res

Dr Daniel Pellicci

THEME 8

IMAGING INNATE IMMUNE RESPONSES

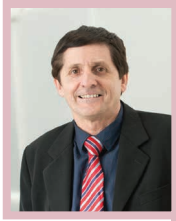


"The CoE is identifying important membrane proteins on innate immune cells that respond to infection by activating key signalling proteins inside."

Inflammatory protein C5aR (green) expressed on the surface of an epithelial cell signals via endosomal signaling protein Rab5 (red) inside cells. This live cell image was taken using high spatial and temporal resolution microscopy - Lattice Light Sheet Microscope (LLSM). Credit: Kai-Chen Wu.

Innate immune cells provide the first line of defence against infection and injury. Some innate immune cells are resident in our tissues and exposed to the environment, others are recruited to tissues in response to infection or injury.

Their role is to monitor tissues and maintain them in a healthy state, quickly identifying and removing threats and eliminating microorganisms and damaged cells.



PROF. DAVID FAIRLIE

AT A GLANCE

We are developing and deploying chemical probes and imaging approaches to study innate and innate-like immune cells and their properties. These studies are helping us to understand the molecular basis of innate immune cell mediated defence, how tissues function and repair, and how threats can be combatted with new kinds of drugs that target proteins on innate immune cells and related cancer cells.

Innate immune cells include many diverse types including mast cells, neutrophils, macrophages, dendritic cells and natural killer cells. Their maturation, temporal engagement, activation and interplay are still not well understood. Even the way they recognise pathogens and cancer cells through protein-protein interactions is still poorly understood. We now know that they also respond to chemical imbalances that disrupt cellular and tissue homeostasis.

The Imaging CoE is studying the different responses of innate immune cells to infectious and non-infectious stimuli, as well as their roles in cancer, metabolic and inflammatory disease.

New information can better inform on how, when and where innate immune cells work in different settings to protect our tissues and maintain good health. This information can also help us design more effective drugs for treating disease.

Scientists in our Centre are developing new approaches and technologies to observe and track key ligands and proteins that activate innate immunity to learn more molecular details about how mammals defend themselves against infection, tumours and injury.

ACTIVITY PLAN

1. Develop fluorescent ligands for imaging the activation or inhibition of inflammation-related proteins (GPCRs) involved in innate immune responses to microbes, tumours or chemicals.
2. Image the motility and migration of innate immune cells and cancer cells in vitro and in vivo.
3. Discover, map and selectively block signalling pathways that mediate innate immunity.
4. Discover links between surveillance, metabolism and inflammation in innate immunity.
5. Develop fluorescent proteins, peptides and drugs to target protein-protein interactions in innate immune cells and their interactions with cancer cells.
6. Target specific proteins on specific innate immune cells that mediate immune responses.
7. Image dendritic cells and receptors to study structure and function.
8. Image NK cells and receptors in innate immunity.

HIGHLIGHT

LINKING INFLAMMATION AND CANCER

University of Queensland researchers in the CoE for Advanced Molecular Imaging discovered an important clue connecting inflammation to cancer. They found that a key inflammatory protein (protease activated receptor 2) substantially overexpressed on the surface of innate immune cells (e.g. mast cells, macrophages) is also present on cancer cells and similarly promotes their movement along chemical gradients.

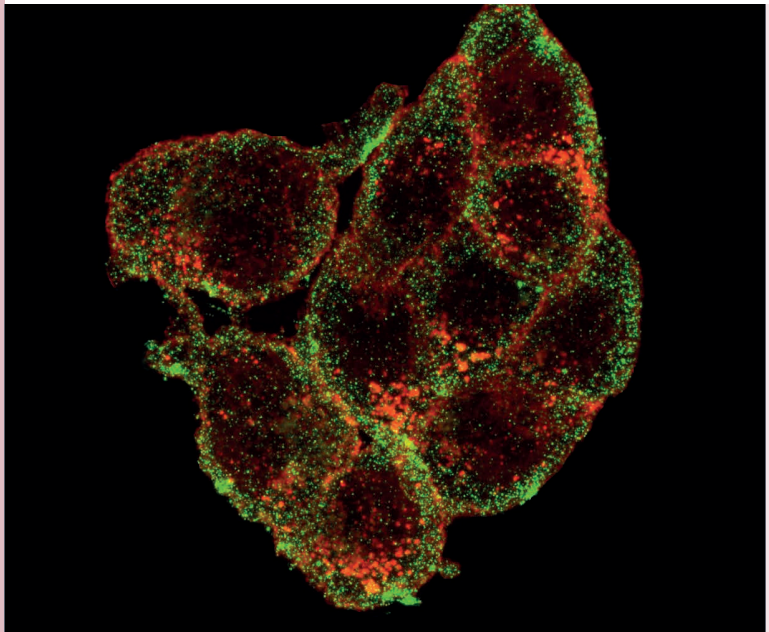
The team led by Imaging CoE Chief Investigator, Professor David Fairlie will use this information and new molecular tools to better understand the molecular basis of signalling responses that control detection and eradication of cancer cells and immune cells damaged by infectious and chemical stimuli that can cause diseases. These studies could lay the groundwork for developing new therapeutic agents.

The researchers, including cell biologists PhD student Yuhong Jiang, Dr James Lim, Dr Jacky Suen and Ms Kai-Chen Wu, have learned that activation of PAR2 leads to similar signalling in cancer cells as in macrophages. They have now mapped the intermediate PAR2-dependent signalling pathways in cells that lead to recruitment of beta arrestins 1/2, calcium release, ERK 1/2 phosphorylation, RhoA activation, and inhibition of forskolin-induced cAMP accumulation.

Functional consequences of this signalling include secretion of inflammatory cytokines, apoptosis and cell migration.

Of potential therapeutic interest, these researchers have also identified a potent inhibitor of PAR2 that blocked all of these signalling pathways in cancer cells and in innate immune cells. This new chemical can also block production of inflammatory cytokines and PAR2-induced motility of human macrophages and migration of breast and colon cancer cells. Cancer cell migration and invasion is relevant to metastasis, the spread of cancer cells to different sites.

The research has led to a better understanding of intracellular signalling in macrophages versus cancer cells, the role of PAR2 in the cell membrane, and how activating compounds outside cells can trigger molecular signalling inside cells and produce functional responses associated with protection, cell migration, dysfunction and cell death.



Surface expressed protein PAR2 (green) and plasma membrane stain (red) co-staining. PAR2 induces migration of innate immune and cancer cells.

ACHIEVEMENT

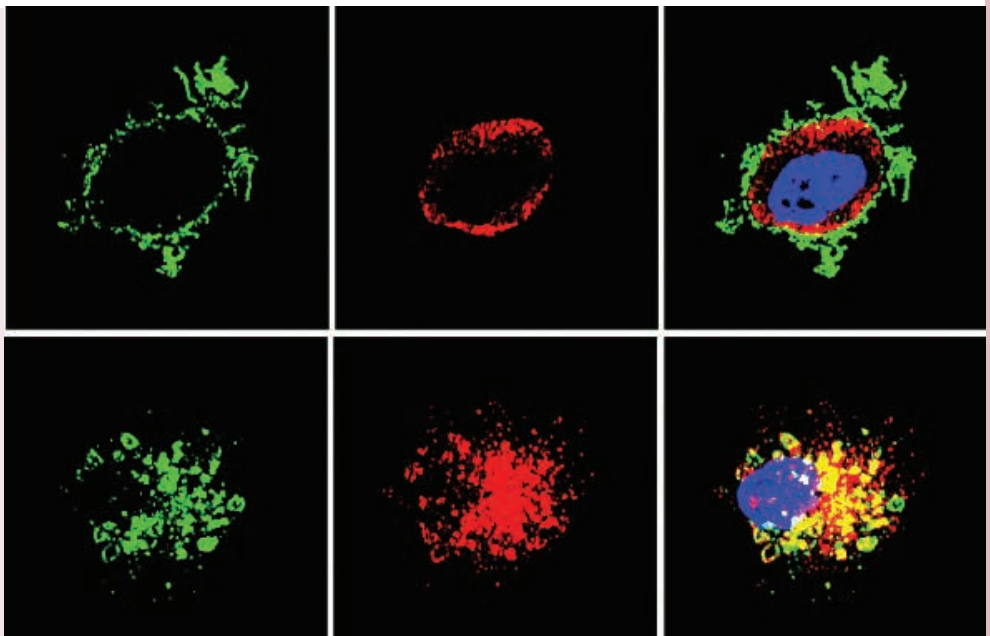
INNATE IMMUNE SIGNALLING IN MACROPHAGES

Rab proteins are key signalling molecules in innate immune cells. Impairment of Rab signalling pathways can result in immunodeficiencies, inflammatory diseases and cancers. Imaging CoE researchers have discovered intracellular trafficking of the C5a receptor via Rab GTPase.

Activation of C5aR leads to its internalisation, recycling and degradation and these events have been found to be associated with Rab5a in early endosomes. Rab5 is highly expressed in macrophages and is required for these events. Rab5 dysfunction prevents C5aR internalisation. This research has linked C5aR with Rab5a signalling to inflammatory responses in macrophages. The C5a receptor was tracked initially in HEK293 cells expressed C5aR conjugated to green fluorescent protein. Rab5a S34N was monitored using the td-Tomato orange fluorescent protein. The C5aR-Rab5a association was then found to regulate proinflammatory chemokine/cytokine mediators in primary human macrophages and the signaling pathway was mapped.

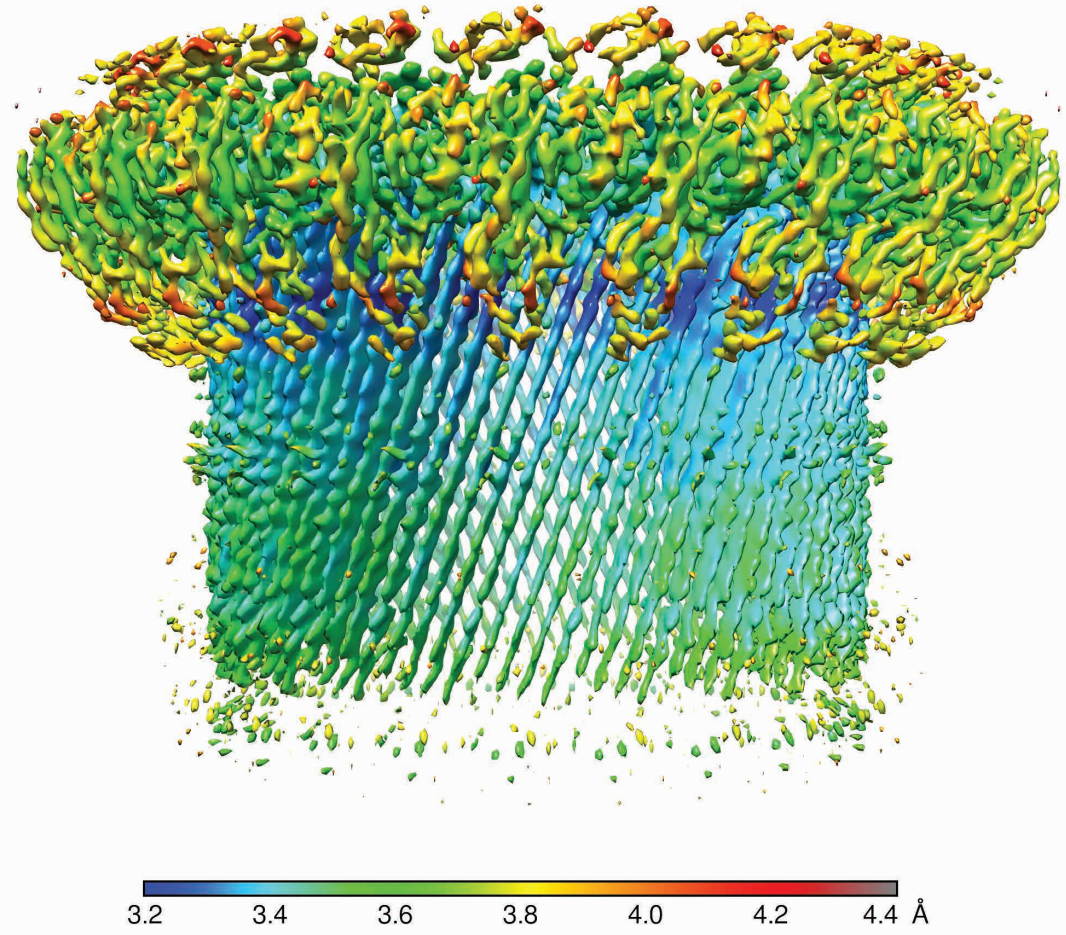
This work has allowed us to track the fate of C5aR from the cell surface and Rab5a from endosomes to unravel molecular and signalling mechanisms that lead to inflammation, disruptions to cell homeostasis, and restoration of normality.

Scientists at Imaging CoE are deploying novel compounds to modulate different innate cell functions mediated by these same proteins on and near the cell surface.



Human macrophages (top row) stained to monitor membrane-bound protein C5aR (green), endosomal signalling protein Rab5 (red) and nucleus (blue). Activation with unstained proinflammatory protein C5a induces internalisation of C5aR into the cytoplasm and co-localisation with Rab5 (bottom row).

IMAGING IMMUNE EFFECTORS



"These data will be crucial for the development of new molecules to regulate complement in a wide range of different immunity-related disorders."

Resolution map of the poly C9 pore.

Brad Spicer (Spicer et al., 2018)

Our work aims to understand how immune effectors are triggered to destroy targets. In particular we are interested in three pore forming proteins - Complement component-9 (C9), Macrophage Expressed Gene-1 (MPEG-1) and Perforin. These three molecules play key roles in the destruction of pathogenic microbes, virally infected cells and malignant cells. In working on these protein complexes, we have also recognised the importance of developing new and better approaches for sample preparation for EM and for structure determination.

PROF. JAMES WHISSTOCK

AT A GLANCE

In 2018, we reported the structure of the terminal pore-forming portion (C9) of the complement Membrane Attack Complex (MAC; Spicer et al., Nature Communications 2018). Our work gave long-sought-after insight into how this crucial part of the immune system assembles into a pore. We also identified the regions of C9 that must move and interact during complex formation. These data will be crucial for the development of new molecules to regulate complement in a wide range of different immunity-related disorders.

The immune complexes our team works on are typically very hard to produce in large quantities and often are challenging to prepare for EM experiments. Accordingly, our team has been working to develop new and improved techniques to prepare a sample in the first place, and furthermore to improve our ability to rapidly analyse data from the images we collect.

In regards to developing new and improved techniques to prepare a sample, we are using nanofluidic approaches to deposit very small amounts of material onto EM grids, such that blotting away excess sample is no longer needed. With respect to data analysis, together with the MASSIVE team at Monash, we are developing software workflows that permit "on-the-fly" analysis of EM data as it is produced by the microscope. Such approaches will greatly speed up EM experiments and will further permit a greater number of samples to be processed through the microscope.

ACTIVITY PLAN

1. Determine the high-resolution structures of the perforin-1 and perforin-2 pore form.
2. Develop new workflows to visualise and characterise large protein complexes *in situ*.
3. Build and further refine new sample preparation devices for single particle cryo EM.
4. Develop new computational workflows for determining the structure of protein complexes using single particle cryo EM.

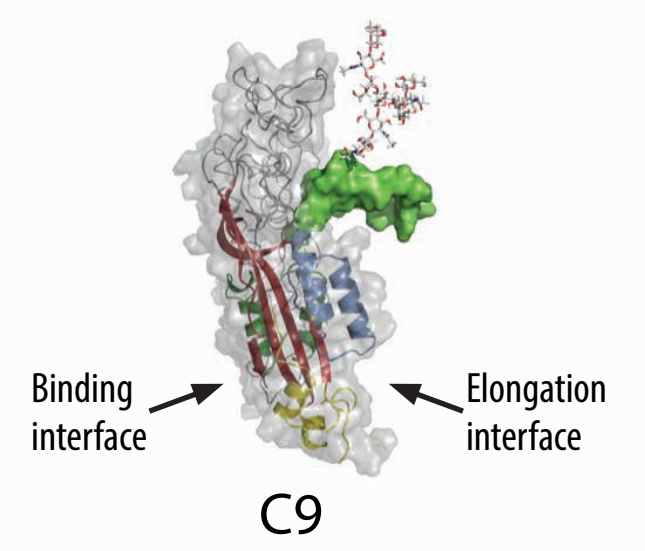
HIGHLIGHT

THE ATOMIC RESOLUTION STRUCTURE OF THE IMMUNE EFFECTOR COMPLEMENT COMPONENT-9 (C9)

In 2018, Centre scientists determined the long sought-after structure of the immune effector C9, in both the soluble, monomeric state, and in the pore form. The team used X-ray crystallography to determine the structure of the C9 monomer (see figure below) and single particle cryo Electron Microscopy to determine the structure of the complete pore (see figure, right).

The structure revealed how the complement system assembles to form a pore in a stepwise fashion, with the first membrane spanning region functioning as a crucial control point to regulate the addition of new C9 monomers into the growing pore. This work demonstrates the power of combining two distinct methodologies for structure determination – both X-ray crystallography and cryo-electron microscopy - in order to yield new insights that could not be gleaned from each individual structure alone. The team anticipate that the new discoveries could lead to better approaches to control C9 in a range of different inflammatory conditions.

Structure of the C9 polymer.



Structure of monomeric C9.

ACHIEVEMENT

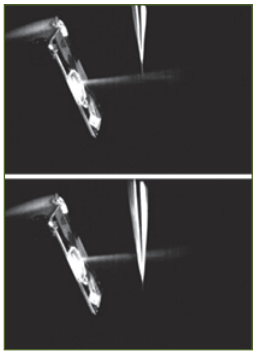
A NEW APPROACH FOR SAMPLE PREPARATION FOR CRYO-TRANSMISSION ELECTRON MICROSCOPY

Historically, the most commonly used method for cryo-EM sample preparation comprises depositing an excess of sample solution on a holey-carbon EM grid, which is reduced to a thin film (~100 nm) via mechanical blotting prior to plunge-freezing in liquid ethane. This approach is sub-optimal because more than 98% of the sample is wasted as part of the process, and can also be problematic in terms of the protein distribution on the grid. In 2018, Imaging CoE scientists developed two proof of principle approaches capable of resolving these limitations.

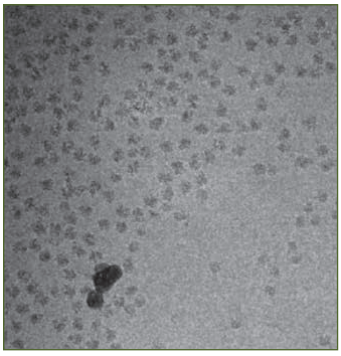
In order to limit the sample waste and improve grid quality, we developed an approach to atomising the sample solution iton droplets with a diameter of ~6 µm and then spraying this material onto a cryo-EM grid while it is being plunged into liquid ethane. The new system only requires 50 nL of sample per grid. Further, the time that the sample spends on the grid prior to cryo-fixation is less than 50 ms, reducing issues with preferential orientation occurring when a grid is prepared through conventional blotting. The time that the sample spends on the grid prior to cryo-fixation is less than 50 ms, reducing issues with preferential orientation occurring when a grid is prepared through conventional blotting.

A second approach we developed involved a nanofluidic chamber, which can be used for cryo-EM imaging of samples that are sensitive to the atmosphere or that need to be kept at a specific pressure while in liquid phase such as when studying nanoparticles. A thin channel sandwiched between two silicon-nitride membranes is plunge-frozen in liquid ethane and imaged under cryoTEM. This method, again only uses a tiny amount of sample that can be imaged with no losses. In parallel it completely resolves the known problem of the segregation of molecules at the air-water interface because it takes place in a sealed compartment.

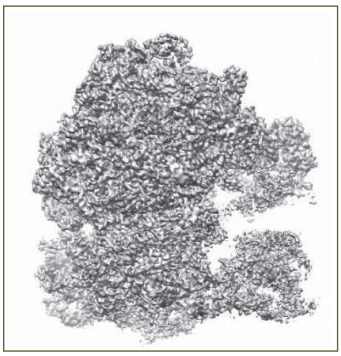
Together we anticipate that these novel methods for sample preparation will lead to future advancements in the cryo-electron microscopy such as the development of time-resolved imaging and the analyses of processes extremely sensitive to the environment such as oxidation states.



Atomised protein solution being sprayed onto an EM grid.[1-3]



Ribosomes in thin ice preserved for TEM experiments.[1-3]



High resolution structure of a ribosome obtained from the new methodology.[1-3]

1. Ashtiani D., Venugopal H., Belousoff M., Spicer B., Mak J., Neild A.*, de Marco A.* (2018) "Delivery of femtolitre droplets using surface acoustic wave based atomisation for cryo-EM grid preparation" Journal of structural biology 203(2), p.94-101.
2. Ashtiani, D; de Marco A.*; Neild, A.* (2019) "Tailoring Surface Acoustic Wave Atomisation for Cryo-Electron Microscopy Sample Preparation" (in press).
3. Gorelick S.; Alan T., Sadek A., Tjeung R., de Marco A. (2018) "Nanofluidic and monolithic environmental cells for cryogenic microscopy" Nanotechnology 30(8), 085301.

STUDENT AND GRADUATE SUCCESS

The Imaging CoE strives to not just attract the best research talent nationally and internationally, but is actively building a pipeline of next generation researchers who are globally engaged and focussed on excellence and impact. As 2018 marked four full years into Imaging CoE's operating term, the Centre saw it's second cohort of PhD students graduate, along with an impressive group of Masters and Honours students.

A hugely successful year, Imaging CoE congratulates every one of our students.

HONOURS STUDENT

Dominique Livingstone	Monash Univeristy
Rachel Zhang	University of Melbourne
Elena Batleska	University of Melbourne
Calvin Xu	University of Melbourne
Katherine Gourley	University of Melbourne
Samuel Redmond	University of Melbourne
Maud Ginestet	University of New South Wales
Caroline Kopecz-Muller	University of New South Wales
Christopher Witzany	University of New South Wales
Justin Juang	University of New South Wales
Aditya Arora	University of New South Wales
Camelia Wang	University of New South Wales
Xena Yap	University of New South Wales

MASTER STUDENT

Wedad Almutairi	La Trobe University
Aeshah Alotaibi	La Trobe University
Aaron Bell	La Trobe University
Christopher Witzany	University of New South Wales
Justin Juang	University of New South Wales

PHD STUDENT

Christina Lucato	Monash University
Yuhong Jiang	University of Queensland
Salman Maqbool	La Trobe University
Nicholas Phillips	La Trobe University
Sophia Alfonso	University of New South Wales
Geva Hilzenrat	University of New South Wales
Jason Tran	University of New South Wales

STUDENT HIGHLIGHTS

veski @ THE IMAGING CoE SUMMIT

On Monday, 19 November 2018 the Centre for Advanced Molecular Imaging partnered with veski, to deliver a veski kickstart to 25 students in attendance at the 2018 Imaging CoE Summit (Undergrad, Masters, PhD).

The veski kickstart, under veski's skills, training and education banner, is a key program designed to inspire students to engage and network with experienced leaders and discover career opportunities that go beyond a lab.

The students had the opportunity to hear from industry representatives - Dr Erol Harvey, Ms Sophie Krantz, Dr Bill Hill, Dr Neda Mirzadeh and Ms Marilyn Jones – who reflected on their experiences, and shared insights into their career pathways, moving from academia to industry.

Ms Marilyn Jones, from Marilyn Careers, then delivered a workshop providing students with practical tools and knowledge to help students navigate the recruitment process to assist in attaining jobs in either academia or industry.

The event concluded with facilitated networking sessions with the industry partners in attendance.

"Adding the veski kickstart program to our Centre of Excellence annual summit was invaluable. The variety of topics covered and real life advice provided to our students was something they not only needed and wanted, but deserve," said Professor James Whisstock, Imaging CoE Director.

ARTICLE CREDIT: veski - www.veski.org.au

Delegates at the veski kickstart program.

COMMUNICATING OUR SCIENCE

IMAGING CoE BRINGS BIOMEDICAL RESEARCH TO THE LOW VISION COMMUNITY

In an innovative Monash University led outreach initiative, the *Infection and Immunity Program* at the Monash Biomedicine Discovery Institute launched a sensory exhibition specifically aimed at the blind and low vision community.

The *Sensory Science Discovery Day* was held in May 2018, attracting almost one hundred members of the blind and low vision community, including school age children and older adults, who were interested in science, but had hitherto not had an opportunity to access such an event.

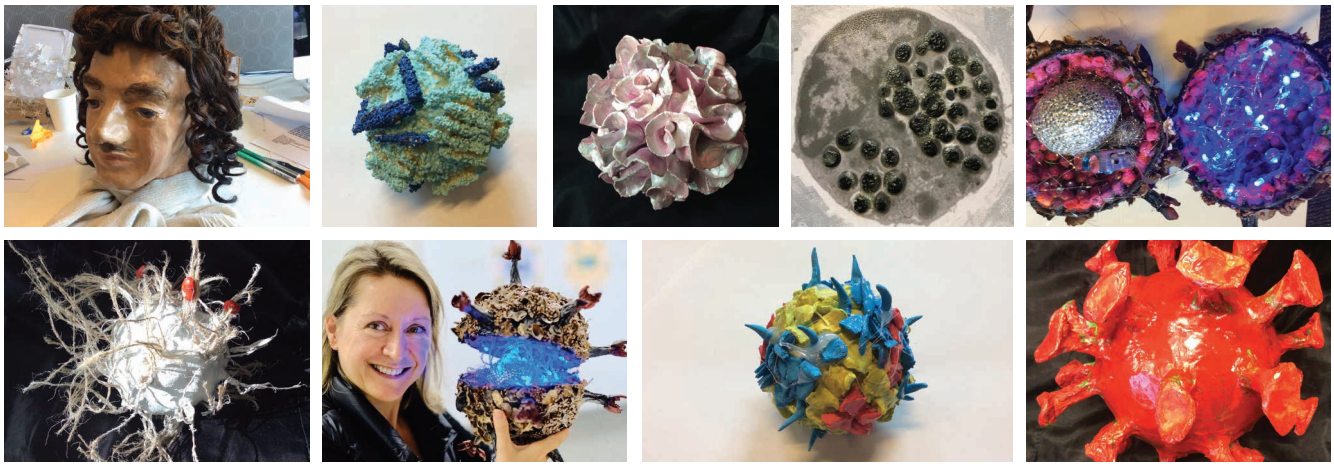
The exhibition was initiated by Professor Jamie Rossjohn, Head of the Infection and Immunity Program at the Monash Biomedicine Discovery Institute and ARC Australian Laureate Fellow and Chief Investigator within the ARC Centre of Excellence for Advanced Molecular Imaging, who considers that discoveries in the life sciences should be inclusive of those with blindness, low vision and other disabilities.

Community engagement, cultural exchange and dialogue between scientists, researchers, universities and members of the public with low vision are very scarce, and this event went to significant lengths to bridge the gaps between these groups.

In conjunction with a legally blind artist, Dr Erica Tandori, researchers created tactile 3D models, 2D graphic and olfactory displays, large print and braille format posters, sculptures and conceptual works that effectively communicate and convey key concepts in infection, immunity, and biomedicine, to a lay and low vision audience.

Members of this community welcomed the invitation to learn about science in a way that was accessible to them and accommodative to their needs, and while many attendees were older, school age children also found the event engaging and informative. Several students showed interest in pursuing work experience with Monash University and BDI, and the university, with a view to exploring science and STEM subjects in tertiary education and beyond. This was a significant step forward in breaking down barriers between the disabled community, scientists and the university, challenging and shifting the perceptions of all key stakeholders in this important event.

After the success of this program, it was then extended to the University of NSW, where Imaging Chief Investigator Professor Kat Guas and her team participated. See page 28 (Theme 3, Highlight) for more.



Top L-R Antonie - father of biomedicine, Couscous Zika virus christmas bauble, Dendritic cell, Infected mouse cell painting with tactile surfaces, Inside a HIV model with capsid.

Bottom L-R Macrophage catching bacteria, Dr Erica Tandori, legally blind artist with her model of HIV, Rhinovirus christmas bauble, Rotavirus.

Stephen Blake (Dr Erica Tandori, legally blind artist with her model of HIV.)

OUTSTANDING CONTRIBUTIONS TO INCLUSIVITY RECOGNISED

The team behind the Sensory Scientific Exhibit were recognised at the recent 2018 Vice Chancellor's Diversity and Inclusion Awards.

The Vice-Chancellor's Diversity and Inclusion Awards recognise students and staff who have made an outstanding contribution to supporting diversity and fostering inclusion at Monash. Recipients of these awards have gone above and beyond to further inclusion, connection and belonging for people from disadvantaged or marginalised groups.

The team was also recognised for their work experience program, aimed at providing members of the blind and low vision community with an opportunity to get hands-on experience in a biomedical research laboratory. This program began when Professor Rossjohn put out the call for anyone interested in completing work experience in his lab at the inaugural Sensory Scientific Exhibition and Discovery Day earlier in the year. They have had one student complete the program, with more interested in doing so in 2019.

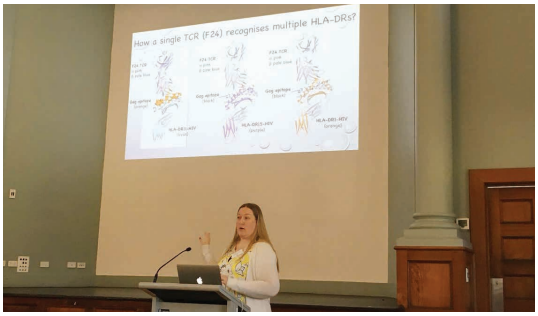
The Vice-Chancellor's Diversity and Inclusion Awards. L-R: Sabrina Constantin, Dr Gabrielle Watson and Dr Erica Tandori.

Monash Biomedicine Discovery Institute

STEPHANIE GRAS PRESENTS LATEST HIV RESEARCH

As part of a series of seminars at the Hudson Institute of Medical Research, Imaging CoE AI's Stephanie Gras presented the Rossjohn Lab's latest research on newly identified HIV-specific cytotoxic CD4 T cells in HIV controller individuals.

The researchers discovered CD4 T cells that can control HIV in 1% of people. They have T cell receptors that cross-react between individuals (with different HLA) by specifically targeting an HIV peptide and gaining killing capacity.



Stephanie Gras presenting at the Hudson Institute

COMMUNICATING OUR SCIENCE CONT.

IN THE NEWS: IMAGING CoE AI A/PROFESSOR KATE SCHRODER

A discovery by Queensland scientists could be the key to stopping damage caused by uncontrolled inflammation in a range of common diseases including liver disease, Alzheimer's and gout.

University of Queensland researchers have uncovered how an inflammation process automatically switches off in healthy cells, and are now investigating ways to stop it manually when it goes awry.

UQ's Institute for Molecular Bioscience (IMB), and Imaging CoE AI Associate Professor Kate Schroder said this inflammation pathway drove many different diseases.

"Now that we understand how this pathway naturally turns off in health, we can investigate why it doesn't turn off in disease — so it's very exciting," Dr Schroder said.

Her work at IMB's Centre for Inflammation and Disease Research focuses on inflammasomes, which are machine-like protein complexes at the heart of inflammation and disease.

"These complexes form when an infection, injury or other disturbance is detected by the immune system, and they send messages to immune cells to tell them to respond," Dr Schroder said.

"If the disturbance can't be cleared, such as in the case of amyloid plaques in Alzheimer's, these molecular machines continue to fire, resulting in neurodegenerative damage from the sustained inflammation."

Dr Schroder's team, led by Dr Dave Boucher, discovered that inflammasomes normally work with an in-built timer switch, to ensure they only fire for a specific length of time once triggered.

"The inflammasome initiates the inflammation process by activating a protein that functions like a pair of scissors, and cuts itself and other proteins," Dr Schroder said.

"What we've found is that after a period of time this protein cuts itself a second time to turn off the pathway, so if we can tweak this system we may be able to turn it off manually in disease."

Dr Schroder's laboratory has begun studying the inflammasome in fatty liver disease, a rapidly growing health issue due to the increasing global incidence of obesity and diabetes.

"In some patients with this condition the liver becomes increasingly fatty and inflamed, and this can lead to cirrhosis – which can require liver transplantation – or even liver cancer."

Compounds to block inflammasome have been developed by IMB researchers including Dr Schroder, and are being commercialised by start-up drug development company Inflazome Ltd.

The research, published in the Journal of Experimental Medicine (DOI: 10.1084/jem.20172222), was supported by the Australian Research Council, and involved laboratories at IMB and the UQ School of Chemistry and Molecular Biosciences.

Imaging for the project was performed in the IMB Cancer Biology Imaging Facility, funded by the Australian Cancer Research Foundation.

ARTICLE SOURCE:
https://www.uq.edu.au/news/article/2018/02/scientists-discover-switch-molecular-machine%E2%80%99-active-many-diseases

Imaging CoE AI Associate Professor Kate Schroder discovered that inflammasomes normally work with an in-built timer switch when they activate the inflammation process.

Institute for Molecular Bioscience

HOW BACTERIA PLAY PASS THE PARCEL - AND HELP EACH OTHER EVADE ANTIBIOTICS

Scientists at Imaging CoE and Monash University's Biomedicine Discovery Institute, working with the Australian Synchrotron, have answered a key question about how a dangerous bacterium, Clostridium perfringens, shares its genetic information.

Bacteria are very sneaky in their efforts to develop resistance to antibiotics. Some strains of bacteria package up the genetic instructions for how they defend themselves and cause disease, and pass this information on to neighbouring, naïve, bacteria – essentially gifting their colleagues with the defences they need to survive against our medical armoury of antibiotics.

If that isn't bad enough, the information transferred also allows the receiving bacteria to pass on the same information to others, meaning that the ability to resist antibiotics and produce toxins rapidly spreads from one bacterium to another.

C. perfringens causes more than one million cases of food poisoning every year in the United States and causes the rapidly spreading, fatal condition 'gas gangrene'. It is also an economically important cause of disease in chickens, sheep and cattle.

The team, including Dr Daouda Traore, Dr Jess Wisniewski, Dr Vicki Adams, Professor Julian Rood and Professor James Whisstock discovered information about how a previously unknown gene - called tcpK - functions to help pass the genetic instructions (DNA) for antibiotic-resistance from one C. perfringens bacterium to another.

These findings were published in Nature Communications in September 2018.

When they initially identified the new gene the team searched international databases for information about how it might work.

"We couldn't find any clues as to TcpK function anywhere," said Imaging CoE researcher Dr Traore said.

"It's only found in C. perfringens and related disease causing bacteria, but is critical for the bacteria to spread antibiotic resistance," Dr Adams said.

Firing high energy X-rays generated by the Australian Synchrotron at a TcpK protein crystal, the researchers were able to determine the 3D molecular structure of the protein.

"Our structural analysis revealed that the molecule resembles a universal DNA binding module called a winged-Helix-turn-Helix. This was the key breakthrough that allowed us to discover that TcpK works by marking the DNA for transfer to another bacterium," Dr Traore said.

Dr Traore and his colleagues anticipate that this discovery will facilitate future research aimed at controlling the spread of antibiotic resistance and toxin genes.

The full paper in Nature Communications is titled Crystal structure of TcpK in complex with oriT DNA of the antibiotic resistance plasmid pCW3.

ARTICLE SOURCE:
https://www.monash.edu/discovery-institute/news-and-events/news/how-bacteria-play-pass-the-parcel-and-help-each-other-evade-antibiotics

L-R Professor James Whisstock, Dr Daouda Traore, Professor Julian Rood and Dr Vicki Adams.

Monash Biomedicine Discovery Institute

COMMUNICATING OUR SCIENCE CONT.

SUPER-RESOLUTION MICROSCOPY ALLOWS RESEARCHERS TO SEE TELOMERE BREAKTHROUGH

A team of Sydney scientists – including Imaging CoE Kat Gaus – have made a groundbreaking discovery in telomere biology thanks to advent of super-resolution microscopy.

Telomeres are DNA segments at the ends of every human chromosome. As we age, telomere length naturally decreases. Over the course of a lifetime, telomere shortening instructs ageing cells to stop dividing. This normally functions as a critical barrier to stop cancer. However, some people are born with abnormally short telomeres and suffer from bone marrow failure, pulmonary fibrosis and high rates of cancer. It has remained a mystery why telomeres change from healthy to unhealthy with age. This research has identified the underlying cause.

The research project was led by Dr Tony Cesare, Head of the Genome Integrity Unit at Children's Medical Research Institute (CMRI) at Westmead, in collaboration with scientists from CMRI as well as UNSW Sydney's Kat Gaus.

The new new data explains the trigger that makes telomeres unhealthy. Telomeres normally form a loop structure, where the chromosome end is hidden. The researchers found that when the telomere-loop unfolds, the chromosome end is exposed and the cell perceives this as broken DNA.

Therefore it is not telomere length that matters, but telomere structure. The telomere-loop becomes harder to form as telomeres get short.

The results of this study have also proven how important technological advances are in the field of research. Dr Cesare first developed his theories about telomere-loops in 2002 when studying for his PhD. However, the technology was not available at the time to easily visualise telomere-loops using microscopy.

The advent of super-resolution microscopy, which was awarded the 2014 Nobel Prize in Chemistry, made it possible to see telomere-loops with a microscope. To complete this research, the team used super-resolution microscopes at four Sydney research institutions, and purchased the first "Airyscan" super-resolution microscope in Australia.

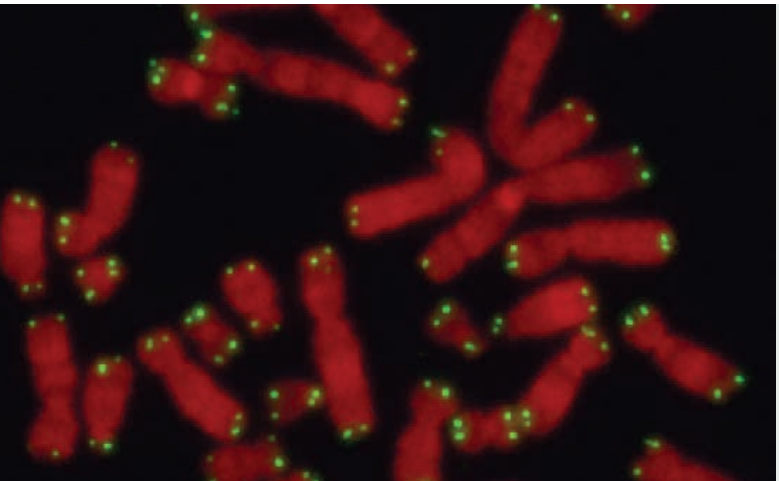
This technology allowed the researchers to see 10 times more detail than we had in the past. They could pass the physical limits of light and see the telomere-loop structure. To complete the project, the team combined this breakthrough technology with powerful genetic models that mimic cellular aging.

This is only the second group in the world to see telomere-loops with super-resolution microscopes and the first to determine their function. It took them four and a half years to complete the project.

The group showed that it's not just telomere length, but telomere structure and telomere health that they need to understand. The researchers said the next step is to ask, can we correlate human health with telomere health? Their work suggests there is more to the story than just measuring telomere length.

The paper describing these studies, 'Telomere-loop Dynamics in Chromosome End Protection', was published online by Molecular Cell in July 2018. Other authors on this paper include David Van Ly, Ronnie Ren Jie Low, Sonja Frolich, Tara Bartolec, Georgia Kafer and Hilda Pickett of CMRI, and Katharina Gaus of UNSW.

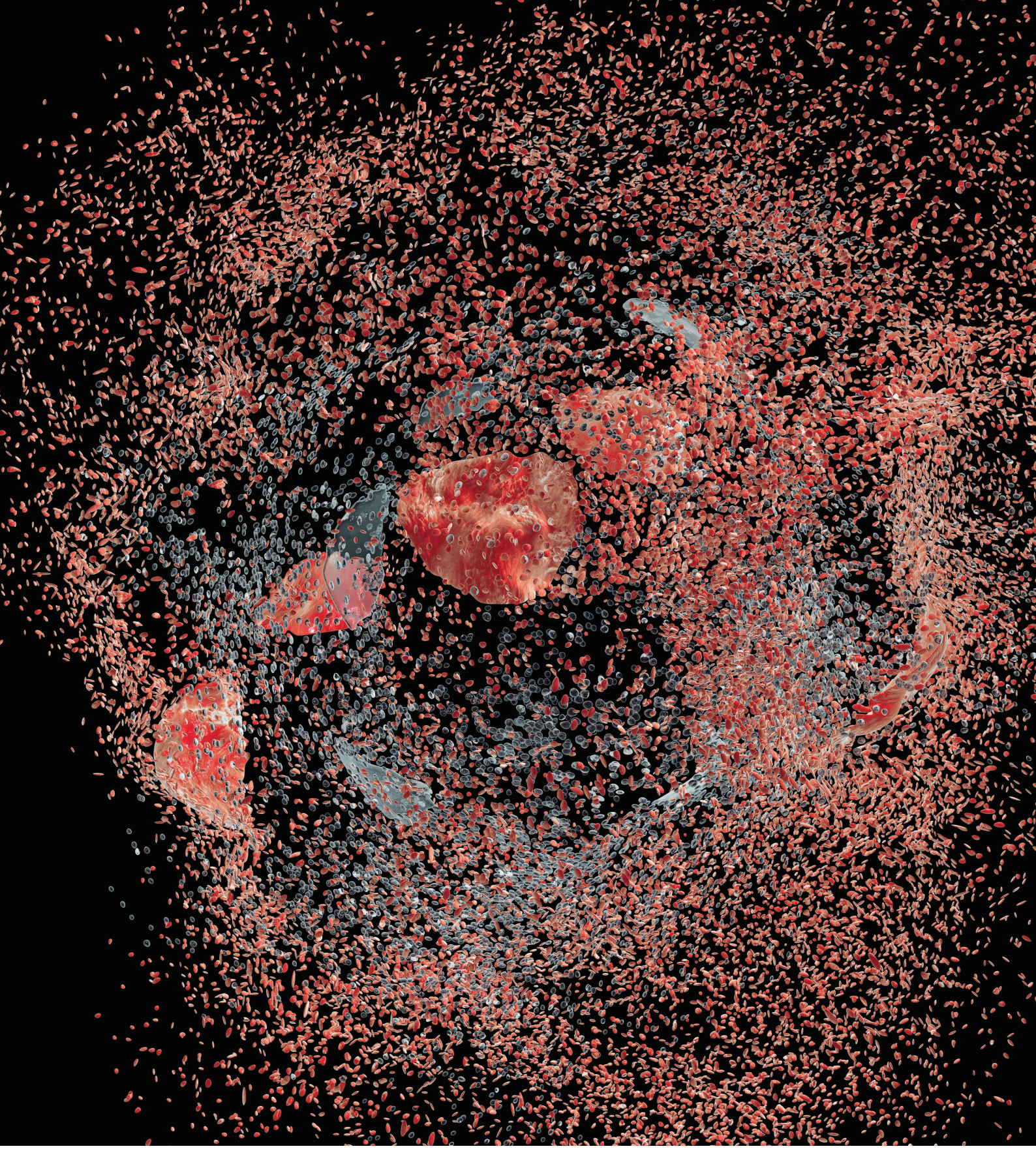
ARTICLE SOURCE:
Children's Medical Research Institute, appearing at https://newsroom.unsw.edu.au/news/science-tech/breakthrough-could-impact-cancer-ageing-and-heart-disease

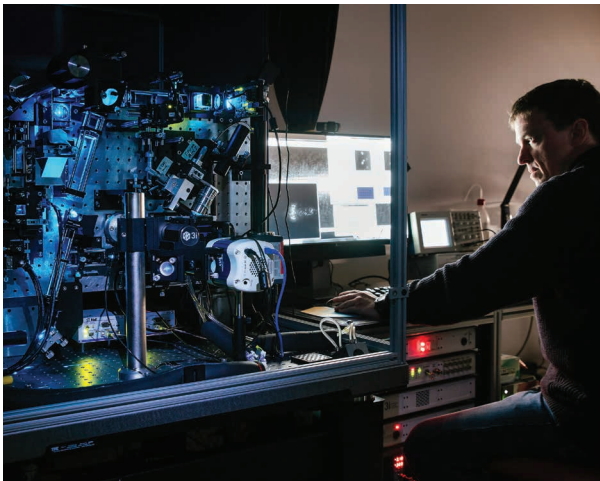


Top right: Pair correlation microscopy reveals the role of nanoparticle shape in intracellular transport and site of drug release.

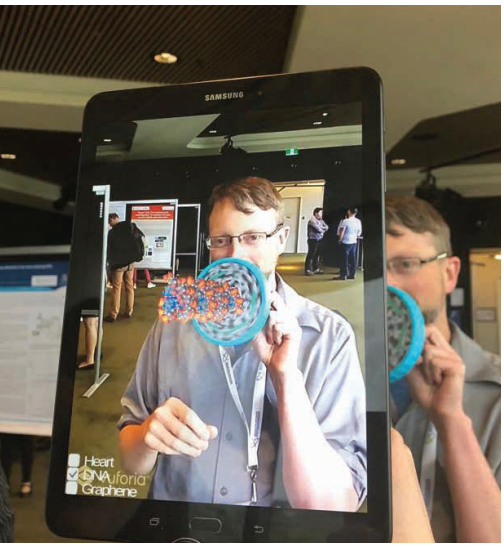
(Nature Nanotechnology, Vol 12, pg 81–89)

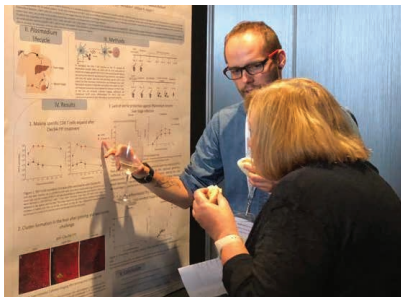
Children's Medical Research Institute





HIGHLIGHT EVENTS





Imaging CoE proudly hosted 130 delegates at the 2018 Summit in the stunning Cape Schanck, Victoria. Over two and a half days, Centre members came together to discuss, discover and deep dive into the science that makes our Centre so crucial to understanding molecular interactions that underpin immunity.

This year held some new initiatives including the highly successful inaugural Student Professional Development session hosted by veski. (See page 55, Student and Graduate Success for more). Fostering student development is essential for the Imaging CoE and we look forward to building on this program.

For the first time we also incorporated a children's room, working towards a family friendly working environment that can ensure that no one misses out on this vital collaborative event.

Invited talks included ISAC members Professor Ilme Schlichting and Professor Jeff Errington. We also heard from Dr Adrian Mancuso from European XFEL and Eva Pereiro from ALBA Synchrotron.

Our CI's delivered theme talks, followed by a variety of our members presenting their work in a theme relevant abstract.

Afternoons on both days saw a program of dynamic Short Poster Talks, where submitted abstracts were presented in four minute slots, testing our centre members to quickly and easily communicate their research to a large audience.

The final night's conference dinner and awards provided the Centre members an opportunity to relax and mingle, and Centre Director Professor James Whisstock addressed the room with pride on the years achievements and the talent that was in the room. He congratulated the poster prize winners Marie-Sophie Philipp, Eugeniu Balaur and Blake Mazzitelli. Professor Whisstock encouraged everyone to act upon their newly acquired connections, friendship and knowledge to ensure the Centre keeps providing progressive research.

Left: First prize poster winner Marie-Sophie Philipp (poster winner) with Professor Dale Godfrey.

Middle: Joint second place poster winner Eugeniu Balaur.

Right: Joint second place poster winner Blake Mazzitelli.

2018 INFLAMMATION SYMPOSIUM

This year the Imaging CoE sponsored the Centre of Inflammation and Disease Research's Annual Symposium. This allowed the program to incorporate several outstanding interstate speakers, which made for a dynamic and exciting Symposium. Co-organised by Imaging CoE Chief Investigator Professor David Fairlie, the annual symposium is an opportunity for research students, postdoctoral staff and group leaders to get together to exchange ideas and techniques, and discuss the basis and role of inflammation in multiple human diseases.

IMAGING CoE CONTINUE TO SUPPORT DAY OF IMMUNOLOGY

The Day of Immunology is celebrated world-wide annually on the 29th April and aims to strengthen public awareness of the importance of the immune system to each person's health and wellbeing, especially highlighting the relevance and benefits of medical research. The Australasian Society for Immunology (ASI) celebrates the day by running events in multiple locations around Australia and New Zealand.

As a gold sponsor, Imaging CoE is committed to ensuring the growth of national activities on this day, which aims to strengthen public awareness of the importance of the immune system to each person's health and wellbeing.

The tour offered 70 Year 11 students the chance to don white lab coats as they visited real biomedical research laboratories, and immerse themselves in the fascinating world of immunology for a few hours.

The labs of Professor Jamie Rossjohn, Associate Professor Stephanie Gras and Dr Natalie Borg gave the students a glimpse into the science of protein crystallography (used to discover the structure of molecules in our immune system) and gave them a turn at looking down the microscope to try to 'fish' out some of the tiny crystals.

"The day was really well received," said Imaging CoE's Professor La Gruta.

"I had students come to my own lab and my postdoc, Dr Pirooz Zareie said they were really impressed by the fact that we could grow cells in vitro and were excited to be able to see the cells and participate in feeding and splitting cells."

ARTICLE SOURCE: https://www.monash.edu/medicine/news/latest/2018-articles/monash-bdis-day-of-immunology-tours,-talks-and-trivia

Part of the Day of Immunology events at Monash BDI.

Monash Biomedicine Discovery Institute

AWARDS AND ACCOLADES

Our Centre Investigators are amongst the very best in the world in what they do. We are very proud to have such an eminent list of scientists amongst our Centre, and in 2018 a number of them were given richly deserved recognition for their groundbreaking impact and dedication to their fields of specialty.

2018 VICE-CHANCELLOR'S EDUCATION AND RESEARCH AWARDS

This year Imaging CoE Director Professor James Whisstock was honoured at the Vice-Chancellor's Education and Research Awards.

Celebrating Monash's leaders in both education and research, nominees' achievements epitomise the talent and potential of the university, demonstrating innovation and excellence.

Showcasing the world-leading research undertaken by our scientists, the Vice-Chancellor's Award for Research Enterprise was presented to a dedicated team of collaborators for 'Advancing Immunotherapeutic Innovation from Promise to Product'.

The team includes Monash BDI researchers ARC Laureate Professor James Whisstock and Dr Andrew Ellisdon, along with their Hudson Institute of Medical Research colleagues, Professor Marcel Nold and Associate Professor Claudia Nold.

The team has made ground-breaking discoveries on signalling mechanisms of anti-inflammatory mediators, with immense potential benefit for millions of patients worldwide across a broad spectrum of diseases.

NANOMSLIDE A WINNER IN 2018

This year A/Professor Brian Abbey's group celebrated two successes with their NanoMSlide - a new technology that enables any optical microscope to be used for instant, label-free, stain free, tissue imaging, an invention which can then help fast track the pathology blood testing process.

In September they were honoured with the Bendigo Inventor Award (health category) - an invention program which connects industry, government and community.

A/Professor Brian Abbey, Dr Belinda Parker, Dr Eugeniu Balaur and Dr Caroline Bathje also battled it out with Australia's brightest MedTech entrepreneurs at the National MedTech's Got Talent National Finals in Melbourne, winning the Medtronic award and $10,000 non-dilutive, stage-gated funding to kickstart their MedTech start-up towards product-market fit and investor readiness.

At the Bendigo Inventor Awards: Dr Eugeniu Balaur, A/Professor Brian Abbey and Dr Caroline Bathje.

Photograph Courtesy of the Bendigo Advertiser, 4 September 2018

Associate Professor Claudia Nold, Dr Andrew Ellisdon, Professor Marcel Nold and Professor James Whisstock.

ARC AUSTRALIAN LAUREATE FELLOWSHIP

Professor James Whisstock was awarded an ARC Australian Laureate Fellowship in 2018, joining a distinguished group of researchers. The Australian Laureate Fellowship scheme reflects the Commonwealth's commitment to support excellence in research by attracting world-class researchers and research leaders to key positions, and creating new rewards and incentives for the application of their talents in Australia.

Professor Sue Thomas, CEO of the Australian Research Council, Professor James Whisstock and Mr Andrew Laming MP.

FOUR IMAGING CoE CHIEF INVESTIGATOR'S NAMED IN THE PRESTIGIOUS 2018 HIGHLY CITED RESEARCHERS LIST

The Imaging CoE were proud to see Professor Jamie RossJohn, Professor David Fairlie, Professor Dale Godfrey and Professor Bill Heath all recognised for their exceptional research performance this year.

Now in its fifth year, the Clarivate Analytics analysis identifies influential researchers as determined by their global peers – those who have consistently won recognition in the form of high citation counts over a decade.

Clarivate Analytics Scientific and Academic Research group CEO Annette Thomas said making the list was a significant achievement.

"The Highly Cited Researchers 2018 list helps to identify the researchers who are having the greatest impact on the research community as measured by the rate at which their work is being cited by others," she said

SPOTLIGHT ON IMAGING CoE ASSOCIATE INVESTIGATORS

2018 proved a highly successful year for the Imaging CoE's Associate Investigators (AI). They alone brought in $16.6 million in a combination of ARC, NHMRC and other awards and grants. In total AIs were awarded 12 ARC grants, 13 NHMRC grants, and a range of other accolades including a Collaborative Grant, a UQ-NHMRC Research Excellence Award, an Innovation and Science award, Joint Medicine Pharmacy Grant, a Platform Access Grant, a Monash Research Impact Fund award, a Basic Science Researcher Award, an Early Career Researcher Grant 2019, an Early Career Investigator award, a CSL Centenary Fellowship and a 2018 Commonwealth Health Ministers Medal for Excellence in Health and Medical Research.

The Imaging CoE prides itself in supporting mid-career researchers and are excited to see where their careers will take them.

NEW GRANT FOR UQ TEAM LOOKS TO NATURE TO LEAD FIGHT AGAINST TUBERCULOSIS

A team of Queensland researchers, including Imaging CoE Chief Investigator Professor Fairlie, who are developing new antibiotics to treat tuberculosis have been awarded $1.45 million by the US Department of Defense in August of 2018.

The three-year multidisciplinary project is a collaboration between The University of Queensland's Associate Professor Antje Blumenthal, Professor Rob Capon and Professor David Fairlie.

The new antimicrobials are planned to originate from naturally occurring compounds.

Approximately 10 million cases of tuberculosis are diagnosed annually, with the disease causing 1.7 million deaths every year. There is a current need for new antibiotics, with the ones currently used used for treating tuberculosis having serious, toxic side effects.

The funding will allow the team to progress towards the most promising compound identified in an earlier study in 2014.

The project follows research previously co-funded in 2016 by an Australian Tropical Medicine Commercialisation grant from the Australian government, the UQ Diamantina Institute and UQ's Institute of Molecular Bioscience.

GRANTS AND FELLOWSHIPS

2018 has been a very successful year for Imaging CoE. Our investigators has secured over **$14M** in ARC grants and over **$19M** in other Australian and international competitive grants.

ARC GRANTS

Centre Investigators	Projects
James Whisstock	An in situ structural study of Drosophila embryonic patterning.
David Fairlie	Compressing small peptides for cell absorption.
Jing Fu	Engineering approaches towards atomic imaging of bacterial cells.
Bayden Wood; Philip Heraud	Probing antimicrobial drug resistance by multimodal molecular analysis.
Maté Biro	Search strategy optimisation by theory, functional analysis and simulation.
Spencer Williams	Using chemistry to illuminate sulfoglycolysis, a major organosulfur pathway.
Jennifer Stow	Machine learning for organelle selection & feature detection in live cells.
Paul Young	Koala retrovirus epidemic: genetic diversity, genome invasion and disease.
Jamie Rossjohn	Gas chromatography: separating inseparables, identifiying unidentifiables.
Katharina Gaus; James Whisstock; Dale Godfrey; Woei Ming Lee	Confocal and single molecule microscopes for systems microscopy.
Jing Fu	Xe-plasma dual beam for advanced future materials.
Till Boecking; Antoine van Oijen	Pushing the limits of fluorescence microscopy with adaptive optics.
Kathryn Poole	Electrophysiology facility for cell phenotyping and drug discovery.
Chen Davidovich	Regulation of histone methylation by polycomb-like proteins
Scott Mueller, William Heath	A cellular hub for the organisation of T cell priming
Brian Abbey	Multi-functional 3D imaging system for micro and nanoscale devices
Connie Darmanin; Peter Berntsen	Probing nanoscale disorder in 3D with x-ray free-electron lasers
Woei Ming Steve Lee	A multiplex microscope platform to define molecular events in fluid systems
Bostjan Kobe	Molecular mechanisms of signalling by plant immune receptors
Stephanie Gras	Lifespan-dependent molecular shaping of the T cell receptor repertoire.

NHMRC GRANTS

Centre Investigators	Projects
Edwin Hawkins	In situ visualisation of cell fate commitment in haematopoiesis, immune cells and tissue remodelling.
Stephanie Gras	T cell-mediated responses to influenza and Human Immunodeficiency virus (HIV) infection
Paul Young	Clamp stabilized vaccines to provide broad spectrum protection against influenza
Bostjan Kobe	Molecular basis and inhibition of TIR-domain function in Toll-like receptor and neuronal cell-death pathways
Chen Davidovich	RNA-mediated regulation of the histone methyltransferase PRC2: a new link to disease-associated and causing mutations.
Edwin Hawkins	Cell fate regulation by microenvironments
James Whisstock	Controlling the function of pore forming perforin-like proteins in immune mediated disease
Katharina Gaus	T cell receptor (TCR) singalling efficiency
Stephanie Gras	T cell-mediated responses to influenza and Human Immunodeficiency virus (HIV) infection
William Heath	Immunity to intracellular infections
Kathryn Poole, Maté Biro	The role of force-sensing ion channels in melanoma migration
Scott Mueller	The neuro-immune interface in lymphoid tissues
Hugh Reid	Defining key determinants of HLA mediated T cell tolerance and autoimmunity
Katharina Gaus, Jesse Goyette	Signal iteration of chimeric antigen receptors and the inhibitory PD-1 receptor
Katharina Gaus, Justin Gooding	Building better ex vivo 3D cancer models with 3D printing
Katharina Gaus	Regulation of the signalling efficiency of the T cell antigen receptor
Adam Uldrich, Julian Vivian	Functional and molecular studies of an interaction between the antigen-presenting molecule MR1 and LILR immune regulatory receptors
Nicholas Gherardin	Investigating diversity within the MR1-restricted T cell repertoire in humans
Hui-Fern Koay	Characterisation and Development of MAIT cells
David Jaques, Till Boecking	Control of HIV Capsid Uncoating

KPI'S

2018 PERFORMANCE MEASURES AND KEY PERFORMANCE INDICATORS FOR IMAGING CoE

	Target 2018	Actual 2018
Research Findings		
Number of journal articles	80	145
Number of patents	3	9
Number of publications in top 5 journals relating to Centre disciplines	8	11
Number of citations (Accummulated 2014-2018)	3,000	6,717
Number of invited conference talks	30	75
Number of Awards, Prizes & Fellowships	5	57

	Target 2018	Actual 2018
Reseach Training and Professional Education		
Number of training skills-based / technical courses held/offered by the Centre	3	4
Number of training courses: Diversity and Inclusion held/offered by the Centre	1	4
Number of workshops/conferences held/offered by the Centre	6	30
(Scientific Summit, professional and sponsor conferences/workshops)		
Number of new postdoctoral researchers recruited	4	6
Number of new PhD students	8	9
Number of new Honours students[1]	10	21
Number of new Associate Investigators	2	2
Number of postgraduate completions[2]	15	25
Number of mentoring programs offered by the Centre	2	4

	Target 2018	Actual 2018
International, national and regional links and networks		
Number of international visitors and visiting fellows	20	20
Number of visits to overseas labs, facilities, workshops and partners	40	45
Examples of relevant interdisciplinary research supported by the Centre	5	19

	Target 2018	Actual 2018
End-user links		
Number of presentations/briefings to the public	5	78
Number of presentations/briefings to government[3]	2	2
Number of presentations/briefings to industry/business/end-users[4]	20	25
Number of website hits	20,000	11,229
Number of media articles	100	169
Number of media releases	4	5

	Target 2018	Actual 2018
Organisational Support		
Annual cash contributions from Administering and Collaborating Organisations	1,333,333	1,366,666
Annual in-kind contributions from Collaborating Organisations	2,684,041	3,888,153
Annual cash contributions from Partner Organisations	160,000	534,181
Annual in-kind contributions from Partner Organisations	1,518,572	1,645,772
Number of new organisations collaborating with, or involved in, the Centre	2	5

1. Includes pre-PhD interns and Master students under the Melbourne model.
2. Includes 5 Honours, 5 Masters and 7 PhD students.
3. Parliamentarians and departments/agencies at both State and Federal level.
4. Including briefings to Partner Organisations.

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Prof. Jeff Errington

(Chair, International Scientific Advisory Committee)
Director, Centre for Bacterial Cell Biology
University of Newcastle

Jeff is current Chair of the ISAC and an eminent cell and molecular biologist who was one of the founders of the field of bacterial cell biology. His research interests focus on fundamental biological problems including the cell cycle and cell morphogenesis using bacteria as model organisms. 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. Jeff is a Fellow of the Royal Society, a Fellow of the UK Academy of Medical Sciences, and an elected member of EMBO.

Prof. Ilme Schlichting

Director
Department of Biomolecular Mechanisms
Max Planck Institute for Medical Research, Germany

Ilme has been a director at the Max Planck Institute (MPI) since 2002. Her research aims to understand how proteins achieve their unique functional properties. She wishes to answer the important question of how proteins fine-tune the reactivity of cofactors (e.g. Flavin, haem) and intermediates occurring during reactions. To observe the latter at high spatial and temporal resolutions she uses advanced X-ray methods. Her current interests include the application of X-ray free-electron laser radiation for structural biology.

Prof. Volker Saile

Distinguished Senior Fellow
Karlsruhe Institute of Technology, Germany

Volker boasts a long and distinguished career in physics and mechanical engineering. He is a member of several German and international science and technology committees, and also served until this year as the President of the Micro, Nano and Emerging Technology Commercialization 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, optics and engineering.

Prof. Jose-Maria Carazo

Head
Biocomputing Unit National Centre 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, that since 2014 is a fully Perkin-Elmer Compay.

INTERNATIONAL SCIENTIFIC ADVISORY COMMITEE CONT.

Prof. E. Yvonne Jones

Joint Head Division of Structural Biology and Interim Director
Wellcome Centre for Human Genetics
University of Oxford

Yvonne's research is focussed on the structural biology of extracellular recognition and signalling complexes. Her group aims to integrate high resolution structural information (from protein crystallography and electron cryo microscopy) with cell-based advanced light microscopy, electron cryo tomography and functional studies, to probe molecular mechanisms at the cell surface. In 1999 Yvonne cofounded the Division of Structural Biology (STRUBI) within the Wellcome Centre for Human Genetics in the Nuffield Department of Clinical Medicine at Oxford. She is a Fellow of the Royal Society, a Fellow of the Academy of Medical Sciences, a Member of the European Molecular Biology Organization (EMBO) and a Senior Research Fellow at Jesus College.

Prof. Cait McPhee

Director
National Biofilms Innovation Centre
The University of Edinburgh, Scotland

Cait is part of the Physics of Living Matter and Soft Matter Physics groups at the University of Edinburgh where she researches biological self-assembly mechanisms. She enjoys the challenges of interdisciplinarity (originally training in the biosciences before she moved across to physics), and overcoming the barriers facing women in STEM fields. Cait is a Fellow of the Institute of Physics, the Royal Society of Chemistry and the Royal Society of Biology. In 2016 she was elected a Fellow of the Royal Society of Edinburgh, and awarded a CBE in the New Year's Honours List.

Prof. Mike Dunne

Director
Linac Coherent Light Source (LCLS)
Stanford University, USA

Mike is an international leader in the field of high power lasers, with substantial experience in the design, construction, operation and exploitation of a wide variety of photon science research facilities. His personal research focuses on the development and application of high power lasers to high energy-density science and laboratory astrophysics. Mike is also Associate Laboratory Director for the SLAC National Accelerator Laboratory and a full Professor of Photon Science at Stanford University.

Prof. Thomas Kay

Director
St Vincent's Institute of Medical Research, Australia

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.

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FINANCIAL STATEMENT

STATEMENT OF OPERATING INCOME AND EXPENDITURES FOR THE CALENDAR YEAR ENDED 31 DECEMBER 2018

Income	**2018 Budget $**	**2018 Actual $**
ARC Centre Grant	4,000,000	4,394,937
Administering Organisation Cash Support	400,000	399,999
Collaborating Organisations Cash Support	933,333	966,667
Partner Organisations Cash Support	160,000	534,181
Other Income	50,000	2,600
Total	**5,543,333**	**6,298,384**

- Total 2018 in-kind contribution is $ 5,930,616.
- Partner Organisations Cash Support includes late income payments from previous years.

Expenditure	**2018 Budget $**	**2018 Actual $**
Salaries	4,289,628	4,728,755
Research Support	843,693	1,065,048
Scholarships	77,142	167,819
Media, Comms & Outreach	142,477	210,350
Centre Administration	259,761	238,889
Total	**5,612,701**	**6,410,862**
Surplus	- 69,368	- 112,478

- Centre Administration expenditure include national and international travel and meeting expenses of $192,234.
- Media, Comms & Outreach expenditure include the 2018 Summit costs of $162,044 which have been covered by 2018 indexation.

NOTES

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