Personalised immunology: Case Study

In Australia, approximately 1.2 million people are affected by an immune-system disease. For a majority of these diseases, women are three times more likely to be afflicted than are men. As a group, immune-system diseases are the third leading cause of morbidity and mortality in the industrialised world, surpassed only by cancer and heart diseases. The NHMRC-funded Centre for Personalised Immunology (CPI) – based at the John Curtin School of Medical Research (JCSMR) at The Australian National University (ANU) – was established to help people living with immune dysregulation by providing a 'personalised' diagnosis and finding more effective treatments for their conditions.

Origin

Dysregulation (disturbed control) of the human immune system leads to: autoimmune diseases such as lupus and rheumatoid arthritis; inflammatory diseases such as sarcoidosis and vasculitis; and a variety of immune deficiency diseases ranging from exceedingly rare single gene disorders to more common diseases.

Collectively, immune dysregulation affects 4-5% of the population and, because there is currently no cure for such disorders, existing treatments focus on alleviating the signs and symptoms without addressing the underlying causes and can have severe negative side effects.

Progress in the analysis (sequencing) and understanding of the human genetic code has now enabled treatments for the immune dysregulation of individual patients, using drugs that target a single molecule in the body. This new approach – called precision medicine – requires a precise understanding of the molecular mechanisms that lead to disease.

To gain these understandings, researchers at CPI have developed a world-first approach:

1. The patient's genetic code is sequenced
2. Genetic variants within their code that may be linked to the disease are identified
3. These variants are modelled in mice to determine how they lead to disease (their 'disease pathway')
4. Pathway-specific therapies (existing or newly designed drugs) are developed and tested
5. The resultant therapy is used to treat the patient and – where a common disease pathway is discovered – the therapy may go on to be used to treat patients with similar conditions across the world.

Grants and Investment

NHMRC
NHMRC has supported CPI through a Centres of Research Excellence (CRE) grant (2014) and a Targeted Call for Research (TCR) grant (2015). NHMRC has also supported individual CPI researchers:

- **Dr Thomas Andrews**: Project Grants (PG), 2016, 2017
- **Professor Stephen Alexander**: PG, 2007, 2008, 2009 (x2), 2010 (x2), 2012 (x3), 2015, 2016, 2018, 2019; Development Grant, 2016; Ideas Grant, 2020
- **Dr Vicki Athanasopoulos**: PG, 2015; Ideas Grant, 2020
- **Professor Matthew Cook**: PG, 2016
- **A/Prof Anselm Enders**: PG, 2011, 2014, 2015, 2017, 2018; Career Development Fellowship, 2012
- **A/Prof Matthew Field**: Early Career Fellowship, 2018; Ideas Grant, 2020
- **A/Prof David Fulcher**: PG, 2007
- **Professor Arthur Kitching**: PG, 2009, 2010 (x3), 2011 (x2), 2012, 2013 (x3), 2014 (x2), 2015, 2016, 2017 (x2), 2018 (x2), 2019; Program Grant, 2005; International Collaboration Grant, 2016.
- **Professor Carola Vinuesa**: PG, 2011, 2014; Research Fellowships, 2012, 2017; TCR, 2012.
- **Cook & Fulcher**: PG, 2010 (x2), 2013
- **Vinuesa & Cook**: Program Grants, 2007, 2012, 2017; PG, 2008
- **Vinuesa, Enders & Jiang**: PG, 2017

Other funding: Australian Research Council (ARC); Australian Research Data Commons (ARDC); Belgian Science Policy Office (BSPO); EU Horizon 2020; Human Frontier Science Program (HFSP); Perpetual Fund (2013); Vasculitis Foundation; Viertel Charitable Foundation; Wellcome Trust.

Philanthropic support includes**:** Bruce and Jenny Pryor Bequest; Elizabeth Greene Industry Development Award; Harvey CVID Research Endowment; Sarcoidosis Endowment.

Discoveries

Researchers at CPI have made some major discoveries relevant to understanding and treating immune dysregulation. These include:

Lupus
A chronic autoimmune condition that can cause inflammation throughout the body, lupus occurs when the immune system struggles to distinguish viruses and bacteria from body cells. CPI researchers discovered that rare gene variants – occurring in less than 1% of the population – are found in most lupus patients and are a major cause of this disease. CPI research has characterised the functional consequences of these variants and enabled pre-clinical trials to identify effective treatments for each pathway.

Organ-specific autoimmunity
Some types of autoimmune disease affect specific organs of the body, such as the small intestine (coeliac disease) or adrenal glands (Addison's disease). CPI researchers have identified a new mechanism that regulates the function of the thymus gland to prevent these diseases.

New inborn errors of immunity
There are a large number of rare, single gene disorders that are confounding for both patients and their doctors because so few people experience them. By identifying the genetic origins of these diseases, CPI researchers have provided explanations and hope for patients, as well as a pathway to treatment.

A potential new drug: Neuritin
CPI researchers have discovered that neuritin – a protein produced by the immune system – helps to prevent the formation of rogue antibodies that can cause autoimmunity and allergy. This discovery has been patented.

Leverage

China-Australia CPI (CACPI)
The China-Australia CPI (CACPI) was established as a sister centre to the CPI in 2015. CACPI is co-directed by Professor Vinuesa and Professor Nan Shen and is located at Shanghai Renji Hospital (within Shanghai Jiao Tong University).

Industry
CPI has generated biological models of human disease that can be used to: investigate the causes of disease and reveal the way that it develops; discover biomarkers (measurable indicators of health, disease or response to treatment); and trial precision therapies so they can be administered as personalised treatments to patients. This has resulted in industry collaborations for existing and emerging precision therapies, including with Noxopharm, to understand the mechanisms by which they may inhibit autoimmunity.

Australian Genomics
The NHMRC-funded Australian Genomics (AG) implemented 'rare disease flagships'. CPI provided the hub for AG's Genetic Immunology rare disease flagship. This national effort translated genomics discovery to the clinic, providing genome sequencing to more than 200 people with rare immune disorders, and diagnosed >20% of patients.

Phenomics Translation Initiative (PTI)
CPI has established an initiative to generate mouse models carrying human disease-causing gene variants. PTI, which is funded through the Medical Research Future Fund, assists researchers from around Australia to:

- generate and/or determine the observable traits of mouse models of human disease
- undertake in-depth phenotyping (i.e. determining the observable characteristics of a disease) to identify disease biomarkers
- trial therapies.

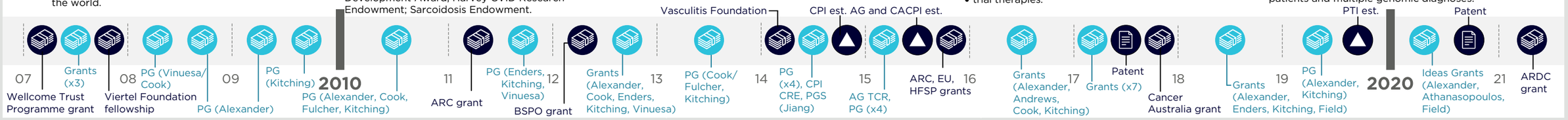
Health Outcomes and Impact

The techniques and infrastructure developed at CPI have been used to develop and implement a diagnostic genetic sequencing service: Canberra Clinical Genomics (CCG). This publicly funded service is now accredited by the National Association of Testing Authorities, Australia (NATA) and complements the discovery effort at CPI.

CANBERRA Clinical Genomics

CCG has sequenced the genomes of more than 800 individuals, resulting in life-transforming diagnoses, including for a 16 year old Canberra resident who rapidly lost the ability to talk, eat and move her hands. Her condition could not be diagnosed, deteriorated over time and was non-responsive to conventional treatments. In 2016, researchers at CPI sequenced her genome and diagnosed her as having Yao syndrome, a rare autoinflammatory disease. This led to their pinpointing the gene causing this condition and tailoring the most effective treatment, which significantly improved her condition and was described by the patient as 'life changing'.

CPI has provided national training in precision medicine and genomics through co-organisation of two CPI Schools of Personalised Immunology. It has also led the establishment of a CPI international network of clinical collaborators and a referral base extending to 13 countries on four continents (Europe, China (CACPI), the Middle East and Africa), resulting in the recruitment of >1500 patients and multiple genomic diagnoses.



Professor Carola Vinuesa

Professor Carola G Vinuesa received medical training at the University Autonoma, Madrid, and undertook specialist clinical training in the UK. She is Professor of Immunology at ANU and Co-Director of CPI and China Australia CPI (CACPI). She has expertise in the investigation of the cellular and genetic mechanisms that underpin autoimmunity.

Professor Vinuesa has received: a 2001 Wellcome Trust International Prize Travelling Fellowship; the 2008 Science Minister s Prize for Life Scientist of the Year; and the 2009 Gottschalk Medal of the Australian Academy of Science (AAS). She is Fellow of the AAS and of the Australian Academy of Health and Medical Sciences.

Professor Matthew Cook

Professor Matthew Cook is Professor of Medicine at ANU, Director of Immunology at Canberra Hospital and Co-Director of the CPI. He is a clinician scientist with more than 20 years experience in investigating immune deficiency and autoimmunity pathogenesis.

Dr Peter Yates AM

Dr Peter Yates is Chair of CPI's Advisory Board. He also chairs the Royal Institution of Australia, the Australian Science Media Centre and the Australian Research Council Centre of Excellence for Quantum Computation and Communication Technology at The University of New South Wales.

Prof A Richard Kitching

Professor Arthur Richard Kitching is a nephrologist physician scientist in the Centre for Inflammatory Diseases within the Department of Medicine at Monash University.

Prof Stephen Alexander

Professor Stephen Alexander is Professor of Paediatrics and Child Health at The University of Sydney and heads the Centre for Kidney Research at The Children's Hospital, Westmead.

Professor David Fulcher

Professor David Fulcher is a Chief Investigator at CPI. He also works in private practice, providing care for patients with immunological diseases.

Dr Matthew Field

Dr Matthew Field is a Principal Senior Research Fellow in Bioinformatics at the Australian Institute of Tropical Health and Medicine at James Cook University (JCU). Dr Field is a founder and co-director of the Centre for Tropical Bioinformatics and Molecular Biology at JCU.

A/Prof Anselm Enders

Associate Professor Anselm Enders is a Senior Research Fellow at JCSMR, ANU, where his group focuses on models of human primary immunodeficiencies.

Early & mid-career researchers

Dr Simon Jiang, Dr Vicki Athanasopoulos, Dr Bahar Miraghazadeh, Dr Katrina Randall, Dr Julia Ellyard, Dr Jonathan Rocco, Dr Paula Gonzalez Figueroa, Dr Pablo Fernandez, Dr Qian Shen, Dr Lisa Miosge.

Dr Edward Bertram

Dr Edward Bertram is Managing Co-Director of CPI and Head of Strategic Research and Commercialisation Programs at JCSMR, ANU.

Dr Bertram has experience in both immunology research and business and project management, and supports the delivery of the local, national and international programs that are led by CPI.

Dr Dan Andrews

Dr Thomas Daniel (Dan) Andrews is a Bioinformatics Manager at JCSMR. Dr Andrews has developed new tools for the interrogation and cataloguing of genome variants.

Australian Government
National Health and Medical Research Council

NHMRC

References

This case study was developed in partnership with the Centre for Personalised Immunology, based within the John Curtin School of Medical Research at The Australian National University.

The information and images from which impact case studies are produced may be obtained from a number of sources including our case study partner(s), NHMRC's internal records and publicly available materials.

The following publicly available sources were used for this case study:

- Autoimmune Diseases Fast Facts. ASCIA: Australasian Society of Clinical Immunology and Allergy. 2019
- White D. Canberra Centre for Personalised Immunology has proved life-changing. Canberra Times, 19 November 2017

Partner(s)

CENTRE FOR PERSONALISED IMMUNOLOGY