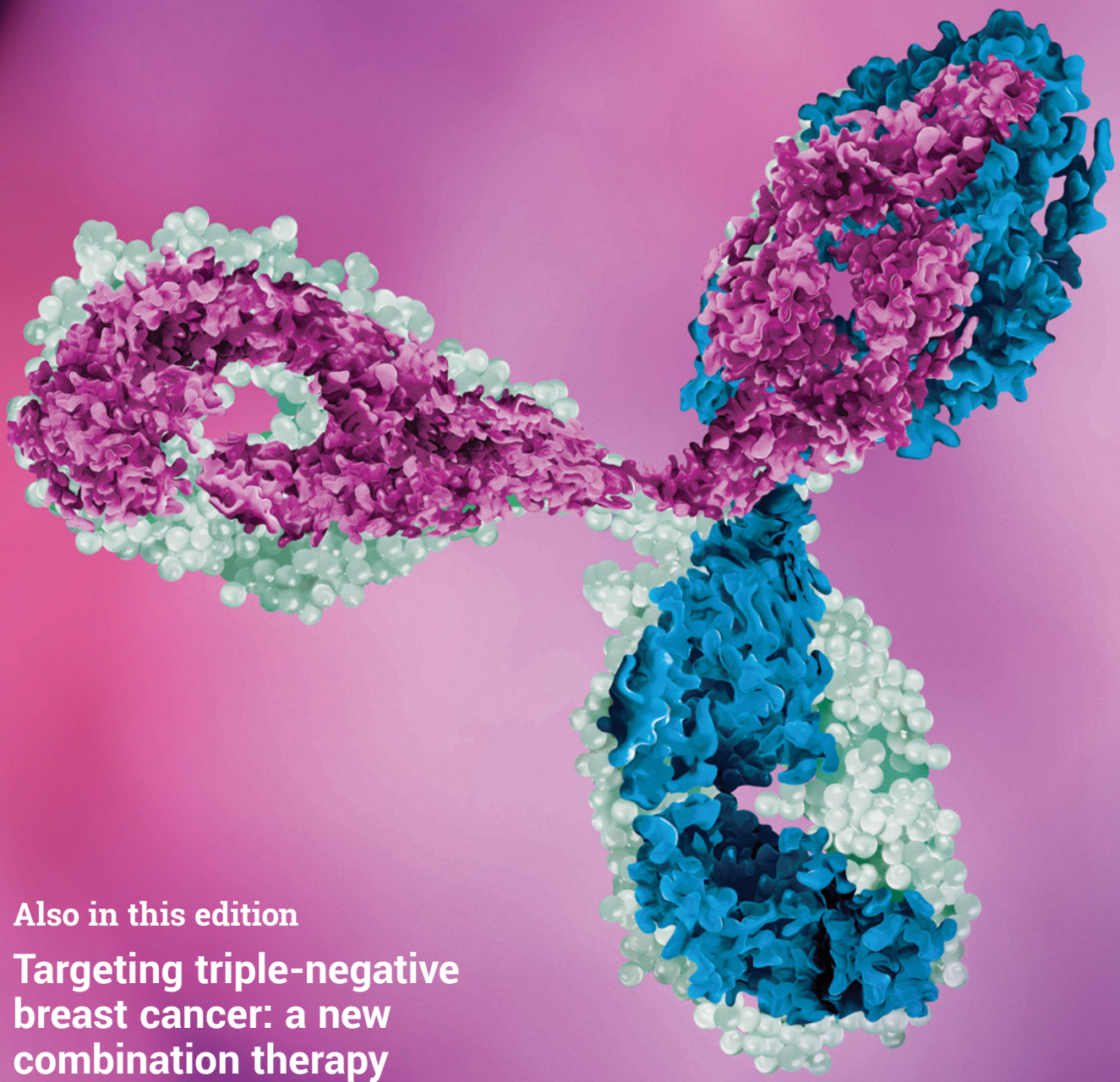
Issue 51

breakthrough

Immune ‘fingerprint’

reveals path for better treatment of autoimmune diseases



Also in this edition

Targeting triple-negative breast cancer: a new combination therapy

Professor Chris Goodnow receives AAI-BioLegend Herzenberg Award

Garvan Institute of Medical Research

Welcome from the Executive Director (interim)

Dear Garvan family,

The last two years of the pandemic have brought so many challenges, but it has also been a time of reflecting on the importance of family, human connection and work-life balance.

This has been keenly felt here at Garvan, with the regrettable news that Professor Chris Goodnow has stepped down from the Executive Directorship due to health complications of COVID-19. While we will miss his inspiring leadership, we fully support his decision to focus on his health and wish him well in his recovery. We look forward to seeing him back at Garvan to play an important role as a senior member of Faculty and mentor to the next generation of scientists soon.

We exist to help people: To diagnose the previously undiagnosable, to treat the underlying genetic causes of disease, to predict and prevent disease before it starts.

I'm pleased to share with you in this issue, some of our latest research news of how we are working towards that purpose.

On page 6 we detail an exciting new clinical trial for triple-negative breast cancer, led by Associate Professor Christine Chaffer, which will test a new treatment method to make chemotherapy more effective.

On page 8, you'll find out about an international study led by Professor Joseph Powell, which identified a genetic 'fingerprint' that links specific genetic markers to a wide range of autoimmune diseases.

This month, we also celebrate the 10-year anniversary of The Kinghorn Cancer Centre. This ambitious collaboration brought together researchers from Garvan and clinicians from St Vincent's Hospital to provide bench to beside care for patients, a magnificent leading-edge and innovative initiative. In the last decade, the Centre has treated more than 20,000 patients and produced more than 770 research papers.

Thank you for your unwavering support of our research. We could not do what we do without our Garvan family.

Professor Peter Croucher
Executive Director (interim)

TKCC 10TH ANNIVERSARY

This month heralds the 10th anniversary of the opening of The Kinghorn Cancer Centre. The Centre was established to bring together the cutting-edge research of the Garvan Institute of Medical Research and the clinical expertise of St Vincent's Hospital, Sydney to create a new model of personalised cancer treatment for patients — from bench to bedside and back again.

Over the last decade, the Centre has supported more than 20,000 patients, including over 25% from rural areas, and published more than 770 research discoveries in prestigious scientific journals.

Key impacts include the establishment of the Australian Genomics Cancer Medicine Centre (AGCMC), a nationwide network of research and treatment centres that facilitates, supports and promotes clinical trials in genomic cancer medicine, and the New South Wales Early Phase Clinical Trials Alliance (NECTAR),

"In realising its vision to bring innovative personalised medicine to people affected by cancer, The Kinghorn Cancer Centre has had enormous impact over the last 10 years. We have improved access to new drugs for patients across the country, curated areas of sub-speciality expertise for rare cancers, helped poor and vulnerable populations access cancer care and worked closely with our laboratory colleagues to discover the next generation of cancer treatments across the spectrum of drugs, theranostics and radiation therapy," says Professor Anthony Joshua, Head of the Department of Medical Oncology St Vincent's Hospital, Sydney and Head of the Oncology Translational Research lab at Garvan.

"Over the last decade it's been wonderful to see clinicians and researchers coming together to realise the vision of personalised cancer treatment. There have been breakthrough clinical trials that made a real difference in patients' lives. We are proud to be supporting this important work", says Nelune Rajapakse AM, co-founder of the NELUNE Foundation, which supports the Centre.

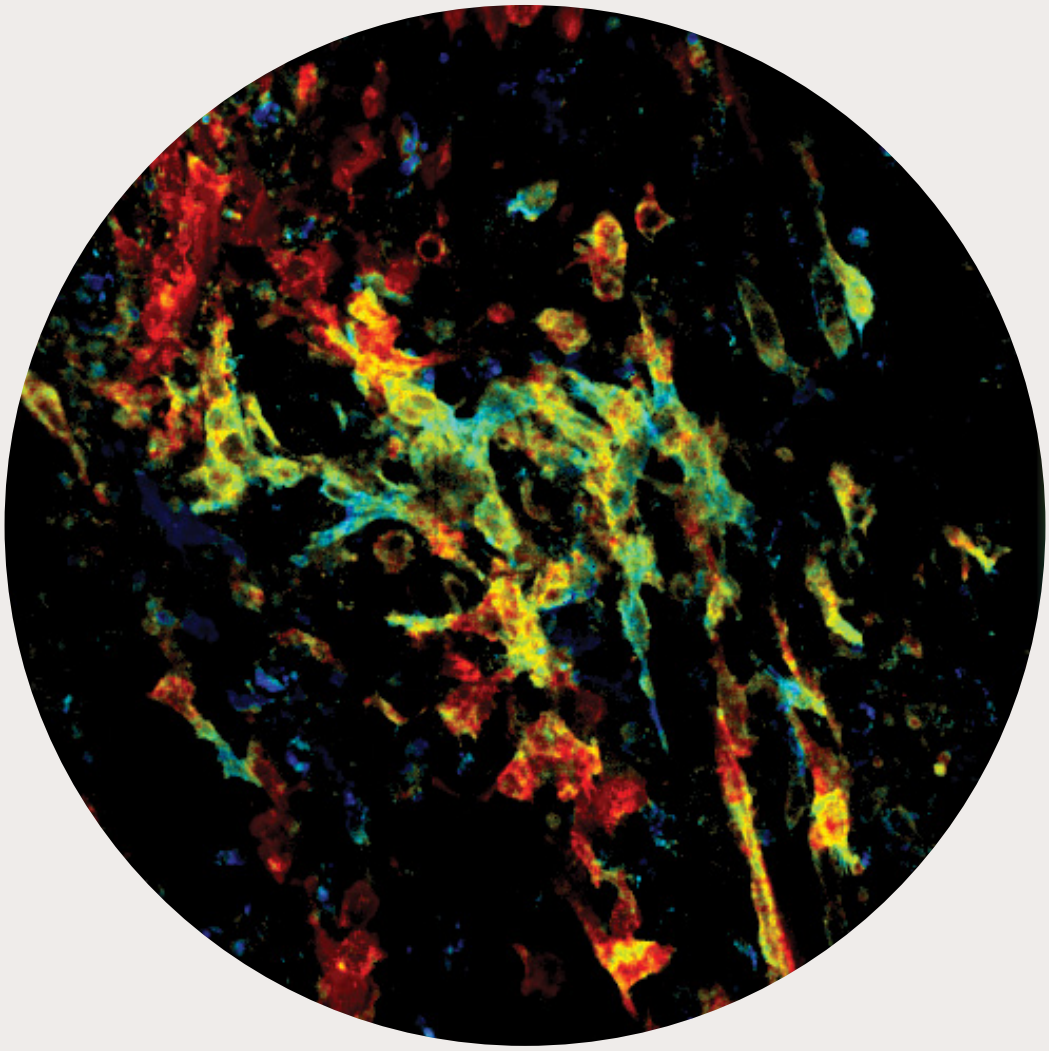
We humbly thank and acknowledge The Kinghorn Foundation, the NELUNE Foundation and the foundational visionary donors who made the establishment of The Kinghorn Cancer Centre possible.

The Kinghorn Cancer Centre

A joint initiative of Garvan Institute of Medical Research | St Vincent's Hospital Sydney

Front cover image: *Antibody*

THROUGH THE **MICROSCOPE**



Located at the Garvan Institute, the Australian Cancer Research Foundation Centre for Intravital Imaging of Niches for Cancer Immune Therapy (ACRF INCITe Centre) officially launched in June.

The Centre, which houses two Australian-designed microscopes, will address a major challenge in the treatment of cancer: why some patients respond to immunotherapies, designed to arm the immune system against cancer, while others do not.

One of the diseases in focus will be pancreatic cancer - a highly aggressive, metastatic and treatment resistant malignancy. At the time of clinical diagnosis, most patients only have a 10% chance of surviving pancreatic cancer within five years. Using the cutting-edge imaging technology housed in the Centre, we can visualise tumour cells before they escape the primary tumour, allowing us to optimise drug timing schedules and stop disease spread in its tracks.

This image of our FAK biosensor shows the activity of the FAK protein deep within pancreatic tumours in real-time. Here, we can visualise (in red) highly aggressive and invasive cancer cells around the border of the tumour, whilst less aggressive cells are in the central region (blue).

Thanks to our imaging technology, we are able to pin-point the specific window-of-opportunity when we can target FAK activity in these aggressive cells and effectively stop cancer spreading. From here we speculate that targeting FAK activity prior to chemotherapy will render pancreatic cancer cells exquisitely sensitive to subsequent treatment and potentially reduce the likelihood of cancer metastasis.

Visit: **garvan.org.au/acrf**

Vale Bill Walker

18 May 1916 – 21 April 2022

"Service to others is the rent you pay for your room here on Earth."
– Muhammad Ali

In April we mourned the passing and celebrated the life of our wonderful *Partner for the Future,* Mr Bill Walker. Bill was a dear friend and one of Garvan's most passionate advocates and generous supporters. He was a regular visitor and attended many of our seminars, morning teas and tours, always curious and excited by the research being undertaken and in awe of the amazing scientists he met.

Bill was born in 1916 and at just two weeks of age he developed acute gastritis and wasn't expected to live. However, with care from a doctor and his mother he survived to live a full and interesting life. He passed away just 26 days shy of his 106th birthday.

As an apprentice in the 1930s, Bill helped to build the original Sydney Luna Park face and met his first wife on the slippery dip on the opening day! Bill lived and worked in New Zealand for many years as a carpenter building public housing, repairing planes during WWII and later training as an industrial arts teacher. He eventually returned to teach in Australia until his retirement.

Later in life, Bill discovered he was born with a congenital heart condition and required a pacemaker. Bill told us, "It is because of medical research that I am still here today, and I'm very grateful for the science that has gone to make it happen."

It is from Bill's gratitude and wish to give back to medical research and to help others living with disease, that he generously included a bequest in his Will to Garvan. When we asked Bill why he included Garvan in his Will, he had lots to say:

***"I have a dream that if I support Garvan they may be able to come up with treatments that could eliminate cancer. I made a Will and I have left most of my estate to Garvan for that reason, I want to support it as much as I can."* – Bill Walker**

"I have visited the cancer researchers at Garvan and I have seen first-hand where my money goes; I'm happy to give as much as I can.

It's a big job but I feel if the research work can continue as it is, I know the answer will come. I might not see it, but I know it will come. And I urge everyone else who can help, to do so for the cause."

Thank you Bill for your friendship to Garvan and farsighted generosity to the community. It has been a pleasure knowing you and you will be greatly missed. As per your wishes, your bequest will go on in perpetuity to help improve the lives of future generations.

Would you consider this special way of giving to the future of medical research?

To request our Bequest Giving brochure or for a no obligation conversation, please contact our Bequest Manager, Donna Mason on **(02) 9295 8559** or **bequests@garvan.org.au** or visit **garvan.org.au/bequest**

Pearls
with a purpose

This August we celebrate a significant milestone with iconic Australian pearl company. **Paspaley: raising $1.6 million in donations to support Garvan's cancer research.**

Over six years ago, Paspaley and Garvan formed a partnership supporting our Molecular Screening and Therapeutics (MoST) clinical trials program, which focuses on accelerating Garvan's pioneering research into rare and less common cancers.

MoST currently has 20 clinical trial sites open nationally. It is open in every state and territory in Australia and has recently expanded to New Zealand. The partnership with Paspaley has been fundamental in the continued success of this program.

Today, more than 4,400 people have been recruited into the MoST program, which provides a novel approach to treating patients with rare and uncommon cancers who have exhausted all other treatment options. In that time, 3,905 tumour molecular profiling reports have been issued and 2,463 patients have had additional treatment recommendations identified.

A total of 486 individuals with bowel cancers have been recruited and of these patients 70% have had new treatment options identified. Additionally, 199 individuals with ovarian cancer have been recruited, of which 47% have had new treatment options identified.

Paspaley is a world-leading luxury brand and continues to be a family owned and run business. Garvan is very grateful and fortunate to have the generous support of Paspaley, and the Paspaley family, who are innovative and forward thinking, and understand the benefits of long-term investment in medical research.

We also thank the Paspaley customers who purchased the stunning custom-designed Kimberley bracelet, with proceeds donated to cancer research at Garvan.

RESEARCH NEWS

Award for an Outstanding Outcome in Cancer Research

The Cancer Council NSW and Cancer Voices NSW have presented Professor Elgene Lim with the Sally Crossing AM Award for an Outstanding Outcome in Cancer Research. The award was given in recognition of his contributions to breast cancer research and the impact of his research on patient outcomes.

Professor Lim is Head of Garvan's Connie Johnson Breast Cancer Research Lab, a translational research lab that was established in 2015 in close collaboration with patients through St Vincent's Hospital Sydney and The Kinghorn Cancer Centre to perform clinically focused research.

One of the major outputs from Professor Lim's research program has been to successfully repurpose two medications to treat hormone-receptor-positive breast cancer.

The award is dedicated to the memory of the late Sally Crossing AM, who was a pioneer and advocate for consumer involvement in cancer research.

Visit: **garvan.org.au/elgene**

More chance of genetic diagnosis with follow-up testing

A Garvan-led study shows that people can increase their chances of diagnosis by 10% if they have a follow-up analysis of their genetic test.

Half of all people who undertake genetic testing don't receive a diagnosis, but a new study by Professor Tri Phan and Dr Pei Dai reveals that a follow-up analysis around two years later increases their likelihood of a diagnosis by 10%.

In the intervening period, identification of new genes or variants, and advances in technology improves the likelihood of diagnosis.

"Getting one test is not the end of the line. Just because you've had a negative test, it doesn't mean something isn't wrong — just that science hasn't caught up yet," says Dr Dai. "We should think of the genetic test as a living, breathing test that we need to keep going back to until we can find out what's wrong."

Once there is a diagnosis, patients can explore personalised treatment that targets the gene, as well as access genetic counselling and assistance.

Visit: **garvan.org.au/diagnosis**

Clinical trial to test potential new combination therapy for aggressive breast cancer

Repurposing an existing medication could be a new way to target breast cancer's ability to evade chemotherapy and spread around the body.

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer that currently lacks any targeted treatments. A new combination therapy currently being trialled could change that, helping thousands of Australian women each year.

The trial will test whether seviteronel, an experimental new medication, can be used in conjunction with traditional chemotherapies to better target TNBC, which makes up around 10-15% of breast cancer cases.

"Triple-negative breast cancer is an aggressive disease with a greater likelihood of spreading around the body and recurring within five years than other breast cancers," says Associate Professor Christine Chaffer, Rebecca Wilson Fellow and leader of the trial at the Garvan Institute.

"In preclinical studies, we found that an experimental drug, seviteronel, combined with chemotherapy, could be twice as effective in reducing the size of tumours than chemotherapy alone."

Flipping the switch on chemotherapy resistance

Associate Professor Chaffer and her team have found that one of the reasons why TNBC has poorer outcomes than other forms of breast cancer is due to its ability to 'switch' to a more aggressive form that can evade treatment when exposed to chemotherapy.

"We found that chemotherapy triggers a change in cancer cells that enables them to build a defence against the chemotherapy. This means that a different type of cancer cell emerges after treatment, which has become resistant to the chemotherapy and is a major cause of cancer relapse," Associate Professor Chaffer says.

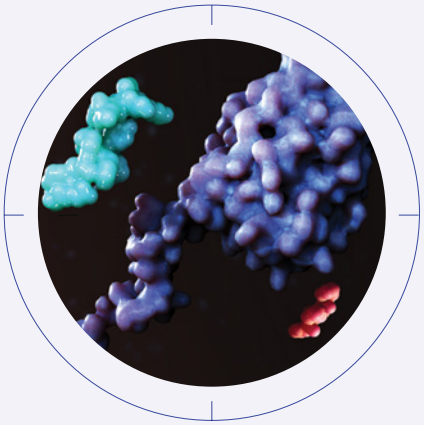
"We aim to put a stop to this cancer resistance strategy to improve the effectiveness of chemotherapy for triple-negative breast tumours."
– Associate Professor Chaffer

Dr Beatriz Perez San Juan, the post-doctoral researcher in Associate Professor Chaffer's lab who led the preclinical study, discovered that activation of androgen receptors in breast cancer cells triggers the cell-state switching. Androgens are commonly thought of as male sex hormones but are also found at lower levels in women.

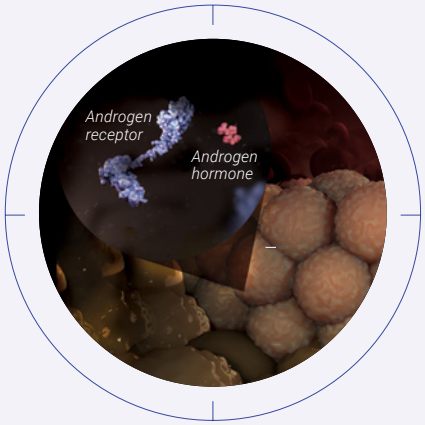
In preclinical models of triple-negative breast cancer, the researchers administered chemotherapy together with seviteronel, an experimental treatment that blocks androgen production. The combination approach caused a 70-100% greater reduction in tumour size, compared to chemotherapy alone. This strategy prevented the emergence of chemotherapy-resistant cells and reduced the spread of the cancer around the body.

A/Prof Christine Chaffer, Nelune Rajapakse AM and Anna Guillan AM

Associate Professor Christine Chaffer



Androgen receptor, seviteronel, androgen



Epithelial cells and androgen receptor and androgen hormone

This research was made possible with the generous support of The NELUNE Foundation which established the Rebecca Wilson Fellowship in honour of the late Rebecca Wilson, who sadly passed from triple-negative breast cancer.

"It is a tremendous honour to have been able to support this work from its very beginnings through to this exciting stage. We were very lucky to bring Associate Professor Chaffer back to Australia from the US with the Rebecca Wilson Fellowship. To see this project now progress to patient trials is testament to Rebecca's legacy, the power of philanthropic support, and the dedication and expertise of the team at The Kinghorn Cancer Centre."
– Nelune Rajapakse AM and Anna Guillan AM, Co-Founders The NELUNE Foundation

The clinical trial

The Garvan team, working with colleagues at St Vincent's Hospital Sydney, are currently seeking volunteers to further this discovery. Based at The Kinghorn Cancer Centre in Darlinghurst and open to patients with TNBC from anywhere in NSW, this trial follows Phase II trials that show seviteronel to be a safe therapy on its own.

"We hope that this new combination treatment approach will drastically reduce drug resistance to improve the effectiveness of standard-of-care chemotherapy and, ultimately, improve outcomes for patients."
– Dr Perez San Juan

The impact

This trial could lead to a much-needed targeted treatment for TNBC to improve patient outcomes and reduce incidences of breast cancer relapse.

To find out more visit garvan.org.au/tnbc

For further information about this clinical trial (NCT04947189) please see the eligibility criteria. [MJ1] To register interest for the trial please contact the St Vincent's Hospital Sydney Research Office, SVHS.Research@svha.org.au, 02 8382 4960.

Declaration: *The clinical trial is sponsored by St Vincent's Hospital Sydney and supported by Kembi Therapeutics Pty Ltd. The trial was made possible by research supported by The NELUNE Foundation, The Paramor Family, the Girgensohn Foundation, Tour de Cure, Australia's National Health & Medical Research Council, Cancer Institute NSW, the National Breast Cancer Foundation and the St Vincent's Hospital Research Foundation.*

The research has ethics approval from St Vincent's Hospital Human Research Ethics Committee (HREC 2020/ETH03307).

Immune 'fingerprint' reveals path for better treatment of autoimmune diseases

Most autoimmune diseases are easy to diagnose but hard to treat. New research shows a unique immune cell fingerprint could be used to rapidly identify which treatments will work for an autoimmune disease.

The Garvan Institute, with partners across Australia and in the United States, reported major findings from an analysis of the genomic profiles of more than 1 million individual cells from 1,000 people.

The analysis clearly identified a genetic 'fingerprint', the unmistakeable signature that links specific genetic markers to a wide range of autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, lupus and more.

"Because of our immune system's complexity, and how vastly it varies between individuals, we don't currently have a good understanding of why a treatment works well in some people but not in others," says Professor Joseph Powell, joint lead author and director of the Garvan-Weizmann Centre for Cellular Genomics.

This is the largest study to date to link disease-causing genes to specific types of immune cells. It paves the way for precision medicines — therapies that specifically target and tame genetic markers to turn off the overactive immune response without causing the unwanted side effects of so many current treatments.

Professor Joseph Powell

Immune fingerprint a path to personalised treatment

The body's immune system is designed to fight external threats but autoimmune diseases occur when the immune system takes aim at its own healthy cells. They affect about one in 12 Australians, are incurable and require lifelong treatments to minimise the damage.

Often, patients will trial many different treatments before finding one that works for them.

"Pharmaceutical companies may have hundreds of targets and have to make decisions about which they will take forward to Phase I clinical trials, knowing that 90% of potential drug candidates fail during clinical development," says Dr José Alquicira-Hernández, co-first author and researcher at the Garvan Institute.

***"Understanding which cell types are relevant for a particular disease is key for developing new drugs."* – Joseph Powell**

(L-R) Dr José Alquicira-Hernández, Dr Seyhan Yazar and Professor Joseph Powell

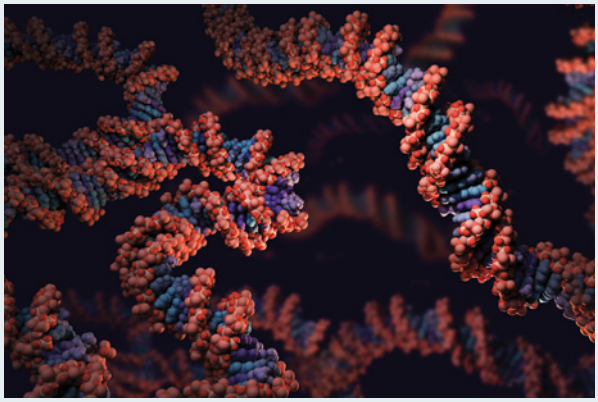


Image: Garvans: Kate Patterson

Pathway to clinical trials

The findings of this study have led to clinical trials, with the aim of establishing additional trials in a range of autoimmune diseases.

"We are working on a study of Crohn's disease in collaboration with St George Hospital that will determine how a patient's immune genotype affects their response to different treatments," says Professor Powell.

"This is a significant milestone of Garvan's pioneering OneK1K study, aimed at showing how genetics contribute to the risk of immune disease at a cellular level."

OneK1K is a study demonstrating how genetics contribute to the risk of immune disease at a cellular level. Using the ground-breaking technology of the Garvan-Weizmann Centre for Cellular Genomics, the study aims to identify and prioritise new drug targets for specific cell types in individual patients and will have an impact on three main areas: autoimmunity, immuno-oncology and haematology disease.

The impact

The discovery could help individuals find tailored treatments that work for them and guide the development of new drugs.

To find out more visit garvan.org.au/immune-fingerprint

Professor Chris Goodnow receives AAI-BioLegend Herzenberg Award

Professor Chris Goodnow is recognised for pre-eminent contributions to immunology.

The American Association of Immunologists (AAI) has bestowed Garvan's Professor Goodnow with the prestigious AAI-BioLegend Herzenberg Award in recognition of his outstanding contributions to the field of immunology.

Professor Goodnow has been a pioneer in the use of emerging DNA technologies and genome sequencing to understand how the immune system uses checkpoints to recognise 'self' and 'non-self'.

In particular, his research has focused on how these processes go awry in autoimmune diseases, which occur when the body attacks its own cells.

His work has led to the discovery of the vital and previously unknown role of 14 essential genes controlling the immune system, as well as four previously unrecognised genes that impact neurodegeneration and infertility.

Professor Goodnow accepted the award at the AAI's annual conference in Portland, Oregon in May. This is the first time the award has been given to a researcher outside the United States since its inception in 2015.

Professor Chris Goodnow (center)

Investing in immune system research pays dividends

Professor Chris Goodnow walks us through how we discovered life-changing immune treatments and how we can take them to the next level.

The long haul of the last two years has revealed many lessons about the need for more research into viruses and other pathogens and given a vivid demonstration of how incredibly quickly we can mobilise as a sector to produce vital vaccines – given the funding.

But while the past offers insight into how we can better prepare for the future, it is also measure of how far we have come.

Never has there been a better time for us to appreciate the benefit of investing in immune system research over past decades. But this return was far less clear not so long ago.

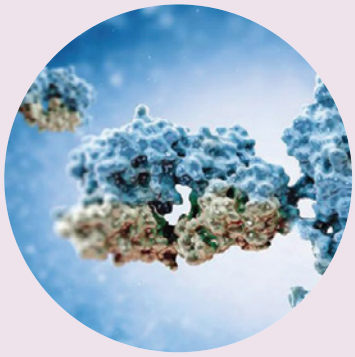
Back in the 1990s I walked medical students through the complexity of our immune system, showing how immune checkpoints hold the antibodies and T-cells of our immune system in check to prevent 'friendly fire' against parts of our own body. But outside of steroids and poisons, few treatments existed for the complex conditions that occur when then these checkpoints stop working.

The students would often complain about having to learn all the fine, complicated details of immunology when all we could work with were old, blunt tools.

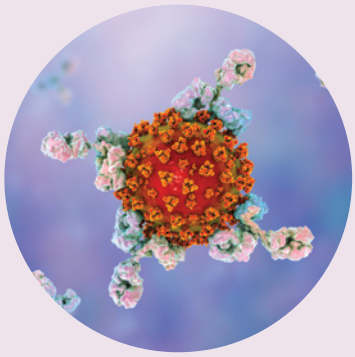
In early May, at a meeting of the American Association of Immunologists, I had the privilege of seeing outstanding presentations explaining how, three decades later, those checkpoints now form the basis for a suite of targeted immune therapies for cancer. They work by giving patients antibodies engineered in a lab, instead of our own bodies, that block the checkpoints and take the brakes off the immune system's attack on cancer cells.This same family of targeted treatments also help reduce the inflammation that causes arthritis, and has also proved incredibly effective at staving off severe COVID-19 for people in the ICU.

This foundational understanding of how the immune system works led to the blisteringly fast development of mRNA vaccines against COVID-19. In fact, I'd just had my booster to ensure a healthy and safe trip to that meeting.

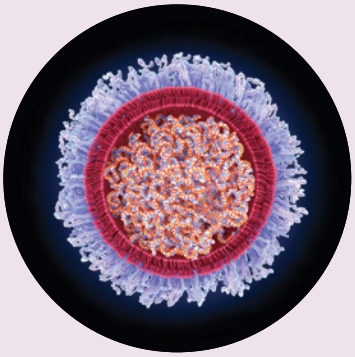
However, we are yet to engineer a vaccine that gives durable and wide-ranging immunity better than natural infection with a coronavirus. And there remain so many more diseases requiring targeted treatment, including cancers and autoimmune diseases. If there was ever a time to invest in such an ambitious goal, surely it is now.



Targeted immune therapies for cancer



Antibodies attacking SARS-CoV-2 virus



mRNA vaccines

DONATIONS

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Donations made in memory of loved ones

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CLINICAL TRIALS

We offer a range of clinical trials at The Kinghorn Cancer Centre for the treatment of patients with breast cancer. Find the full list at garvan.org.au/breast-cancer-clinical-trials.

Personalised therapy for rare and uncommon cancers

We offer the Molecular Screening and Therapeutics (MoST) clinical trials that personalise experimental treatment for patients with rare cancers based on an individual's unique personal and cancer genetic profile.

Find more information at
garvan.org.au/genomic-cancer-medicine-program

PREDICT prediabetes clinical trial

We are seeking men and women aged 20-70 years who have prediabetes or who have been recently diagnosed with type 2 diabetes and have not yet been treated with a sugar-lowering medication. This study investigates blood sugar response to personalised diet and diabetes medication. HREC Approval: SVH 17/080.

For further information, please contact
Dr Dorit Samocha-Bonet
Phone: (02) 9295 8309
Email: predict@garvan.org.au

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