

breakthrough



Hope

**Tracing
autoimmune
disease to
its origins**

**Uncovering
the genomics
of health**

**Also in this issue
'Fingerprinting' human cells**



**Garvan Institute
of Medical Research**

Welcome from our Executive Director



Dear Garvan family,

I hope you and your loved ones are well during this new and challenging period. In times like this, we must come together in whatever way we can to support each other, and ensure that the most vulnerable in the community are protected. We are incredibly grateful for the tireless effort of our frontline workers - our healthcare workers, scientists, government officials, custodial and supermarket employees - who are working tirelessly to make sure our community stays healthy and safe.

The rapid escalation of COVID-19 underscores the importance of nimble medical research. At Garvan, our researchers have joined forces with local and global collaborators to contribute our knowledge, expertise and resources to the fight against COVID-19.

We have four active research programs into COVID-19, one of which is led by Professor Daniel Christ, who is developing antibodies that target the 'spike protein' of COVID-19, which the virus needs to infect human cells. This innovative approach could both treat and prevent COVID-19 infection, and is particularly suited to immune-compromised, at-risk individuals. We look forward to keeping you informed on this research, and more, as it progresses. While we will assist in the global efforts to combat COVID-19, Garvan is still focused on research that will improve outcomes for people across the world.

In this edition, you'll learn about a new way to 'fingerprint' cells from Associate Professor Joseph Powell and his team, as well as how cells can help us understand treatment resistance in breast cancer patients. You'll explore Garvan's lung cancer research, where Dr Venessa Chin is developing a diagnostic tool that will change the management of the disease, and a new autoimmune disease research breakthrough from my own laboratory, led by Dr Joanne Reed.

You'll also meet Marion O'Farrell. Marion has generously included a gift for Garvan in her Will, in memory of her late husband, Finbarr. It's this generosity, and that of people just like you in our Garvan family, that allows our researchers to create a future where everyone can live longer, healthier lives.

Yours sincerely,

Professor Chris Goodnow FAA FRS
Executive Director
The Bill and Patricia Ritchie Foundation Chair

NEW RESEARCH

'Fingerprinting' human cells

A new method to analyse the unique features of individual human cells - much like a fingerprint - could be a step-change for diagnosing and treating some of the most devastating diseases that impact our community. Thanks to cellular genomics technology, researchers are able to take snapshots of over 20,000 different pieces of information about which genes are active in a cell, for tens of thousands of cells at a time.

Developed by a team led by Associate Professor Joseph Powell, the new method, called '*scPred*', short for 'single cell prediction', analyses this vast information to distinguish different cell types from one another, at a much higher resolution than previously possible. The *scPred* method, which combines techniques that analyse single cells with machine learning algorithms, allowed the researchers to identify colorectal cancer cells from the data of a tissue sample with over 98% accuracy.

The new method opens cellular genomics technology to diagnostic applications for the first time and may lead to earlier detection of cancer, identifying the cells at the root of autoimmune disease, and helping personalise treatments to individual patients.

Visit: garvan.org.au/fingerprint

Drug target for autoimmune disease

New research suggests autoimmune diseases that currently have few treatment options could potentially be treated with existing cancer medication.

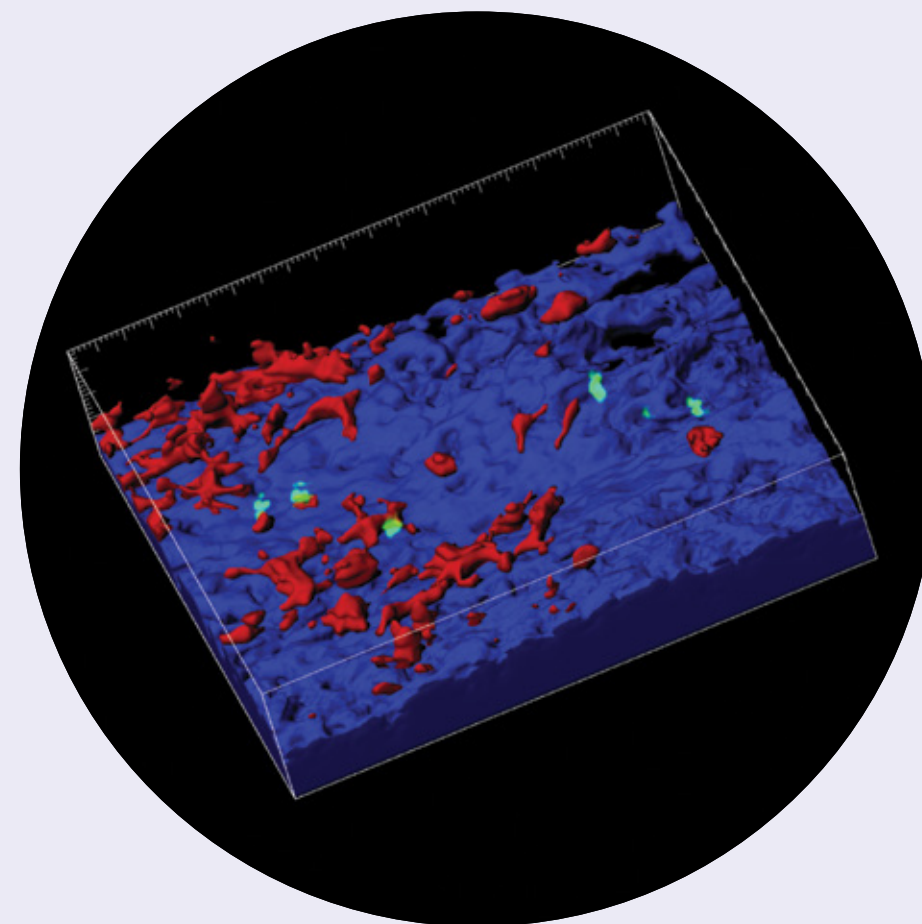
By studying the immune cells of patients with rare genetic variants in a protein called PI3K, a team led by Associate Professor Elissa Deenick and Professor Stuart Tangye uncovered a critical pathway that prevents immune cells from targeting the body's own cells, a process which goes awry in autoimmune disease.

The patients' immune cells produced high levels of 'autoantibodies' that target healthy tissues and organs, and which are associated with common autoimmune diseases, including thyroid disease and lupus. Treatments that 'switch off' the PI3K protein are already available and used to treat patients with lymphomas and leukaemia.

Targeting PI3K in individuals with autoimmune disease through this existing medication may help prevent autoimmune disease progression, the researchers say. The discovery is an example of the enormous potential that rare clinical cases can have to guide better treatment options

Visit: garvan.org.au/target

THROUGH THE MICROSCOPE



Garvan researchers are taking a closer look at the cells inside bones than ever before.

A common misconception is that our bones are rigid, lifeless tissue. In fact, bone is a dynamic environment of cells, nerves and blood vessels that are all crucial to the body's function.

But the unique environment inside bone can be a convenient hiding spot for unwanted visitors. Cancer cells, for instance, can spread to the bone during cancer treatment and lie dormant, only to return years later and cause a cancer relapse.

To understand how cancer cells can lie dormant, and how to help prevent this, Dr Michelle McDonald is using an advanced imaging technique called 2-photon microscopy to visualise the 3D cell environment of the inner lining of bone.

Captured in this image is a 3D reconstruction of the inner surface of a mouse bone (blue).

Perched on the bone surface are osteoclasts (red), cells that break down bone tissue and are involved in the normal maintenance of bone. But nestled among these osteoclasts are dormant cancer cells (green), which interact with the osteoclasts.

Dr McDonald is using these images to help uncover crucial interactions between dormant cancer cells and osteoclasts that have never before been observed, a key first step to stopping these dormant cancer cells from growing into aggressive tumours.

Excitingly, these findings may additionally offer promise for how we can improve treatment approaches for osteoporosis.

Image: A molecular illustration of the antibody proteins identified by the researchers as the 'rheumatoid factors' that are known to cause autoimmune disease. Image by Dr Ofir Shein-Lumbroso, Biomedical Animator through the Garvan-Weizmann Partnership. Ofir's secondment to Garvan has been generously funded by Mr Bob Magid OAM and Mrs Ruth Magid.

H O P E



Breakthrough cellular genomics technology has allowed researchers to reveal genetic mutations causing 'rogue' behaviour in the cells that cause autoimmune disease.

There are more than 100 different autoimmune diseases. But what unites them all is that they arise from an individual's own cells – rare and mysterious immune cells that target not external viruses and bacteria but the body's own healthy organs and tissues.

For the first time, a team led by researchers at the Garvan Institute has pinpointed individual cells that cause autoimmune disease from patient samples.

The findings, which are part of the visionary Hope Research program, could have significant implications for the diagnosis and treatment of autoimmune disease, which affects one in eight individuals in Australia.

"Current treatments for autoimmune disease address only the symptoms, but not the cause," says Professor Chris Goodnow, co-senior author of the published work, Executive Director of the Garvan Institute and Director of the UNSW Sydney Cellular Genomics Futures Institute.

"To make more targeted treatments that address disease development and progression, we first need to understand the cause. We have developed a technique that allows us to look directly at the cells that cause autoimmune disease – it's as though we're looking through a new microscope lens for the first time, learning more about autoimmune disease than was ever possible before."

"Identifying these rogue immune cells is a significant step forward for how we study autoimmune disease – and crucially the first step to finding ways to eliminate them from the body entirely," says Professor Goodnow.

Tracing autoimmune disease to its origins

Because 'rogue' immune cells are so rare in a blood sample – less than one in 400 cells – studying them has been a challenge.

The research team developed a new cellular genomics method to isolate the immune cells that produced 'rheumatoid factors' – antibody proteins that are known to target healthy tissues in the body and that are associated with the most common autoimmune diseases.

After isolating these rogue cells from blood samples of four patients with cryoglobulinemic vasculitis – a severe inflammation of the blood vessels – the researchers scanned through more than a million positions in the cells' genomes to identify DNA variants that may be at the root of disease.

Remarkably, the researchers uncovered 'lymphoma driver mutations', which allowed the rogue immune cells to evade immune tolerance checkpoints and multiply unchecked. In lymphomas (cancerous immune cells), these mutations allow cancer cells to multiply unchecked.

Professor Goodnow first hypothesised that disease-causing autoimmune cells employ this cancer tactic in 2007.

Personalised diagnosis and treatments

The ability to identify and investigate specific immune cells at such resolution has vast potential to improve diagnostics and develop future treatments to target the cause of autoimmune diseases.

The researchers are now planning follow-up studies to investigate how autoimmune cells might mutate to cause a range of other diseases, including lupus, celiac disease and type 1 diabetes.

The philanthropic support of The Bill and Patricia Ritchie Foundation has been a key driver in establishing Hope Research. Hope Research is also supported by Mr Ken Allen AM & Mrs Jill Allen, the Croall Foundation and Mergen Family, John Brown Cook Foundation, Mr John Roth & Ms Jillian Segal AO, the UNSW Triple I Sphere Consortium, the Rebecca L Cooper Medical Research Foundation, UNSW Sydney, and Australia's National Health and Medical Research Council.

 Visit: garvan.org.au/rogue-cells



Living **Finbarr's** Legacy

Marion is honouring Finbarr's memory by traveling to the places they planned to go together and leaving a gift in her Will to Garvan.

Finbarr and Marion O'Farrell were always destined to be together. Even though Finbarr was born in Surrey, in the south of London, and Marion was born on the other side of the Atlantic Ocean in Brooklyn, New York; an introduction by a mutual friend in London during the 1970s marked the beginning of a new life together – one that spanned decades and brought them to settle in Australia.

In 1977, an opportunity arose for Finbarr and Marion to move to Sydney when Finbarr was offered the chance to work in the Sydney office of his company, Lloyds Insurance Brokers. As a double-certified theatre nurse, Marion's experience and qualifications meant that they were settled and working in Sydney in only a few months. Finbarr, a passionate hobby sailor who raced over the Atlantic, in Bermuda and who crewed in the Admiral's Cup along with the British Prime Minister, Sir Edward Heath, was able to fulfil his ambition of racing in the Sydney to Hobart that year.

Over the years, Finbarr and Marion relished their life in Australia together – their shared love of music, theatre and traveling, formed together in the UK, continued here, where they also discovered the joys of camping in the Australian bush.

Sadly, in late 2004 Finbarr was diagnosed with inflammation of the heart, or pericarditis. Three months later, in February 2005, Marion noticed a yellow tinge in Finbarr's eyes. He was diagnosed with advanced pancreatic cancer which came as a shock to them both, as he had not shown any symptoms prior to his diagnosis.

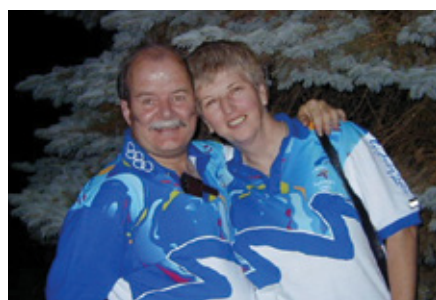
Finbarr had always been a positive person and this did not change after his diagnosis. He was determined to fight his cancer and concentrate on getting well. Marion cared for Finbarr during his journey, but knew that advanced pancreatic cancer had an especially poor prognosis. Finbarr passed away on 16 October 2005, just 8 months after his diagnosis.

In recent years, Marion has been honouring Finbarr's memory by travelling to the places they planned to go to together, including the top end of Australia as well as Russia and Egypt. She is also honouring his memory by leaving a gift in her Will to Garvan, in Finbarr's honour.

"I always knew I wanted to make a difference with mine and Finbarr's legacy. Overall, Australia needs more funding for medical research, and the government just aren't doing enough. Australia is world leading in science but we are continually losing our brilliant researchers to overseas because of poor funding. My hope is that the future support from my bequest will make an impact on this terrible disease, pancreatic cancer, which is becoming more and more common," says Marion.

"A gift in my Will in memory of Finbarr is my way to contribute to research that will really help others who are suffering with a truly horrible disease."

If you would like information about leaving a gift in your Will as a tribute to your loved ones, please contact Donna Mason, Bequest Manager on 02 9295 8559 or email bequests@garvan.org.au or visit garvan.org.au/bequest

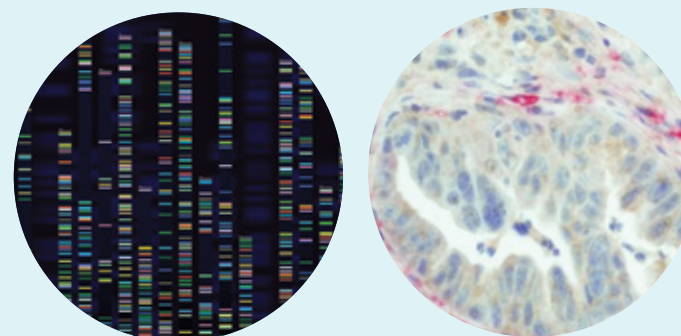


Helping build a global cancer 'map'

The Australian Pancreatic Cancer Genome Initiative (APGI) is a world-leading initiative, founded and administered by the Garvan Institute, that includes genome data and a 'biobank' of thousands of pancreatic tumour samples that have been donated by patients.

Recently, the APGI contributed genomes to the Pan-Cancer Project, a global effort to create the most comprehensive database of cancer genomes in the world. To date, the database consists of over 2600 cancer genomes of 38 different tumour types, from 37 countries.

This new resource will allow researchers from Garvan and across the globe to better access cancer genome data, which they will use to study pancreatic and other cancers.



Over recent years, researchers have discovered more and more relationships between different cancer types.

Contributing the APGI's genomic data to the Pan-Cancer Project will help the global research community to uncover the differences and similarities between different cancers, and will ultimately advance discoveries that enable better diagnostics and treatments.

Visit: garvan.org.au/map

Driving pancreatic cancer research

To mark World Pancreatic Cancer Day on 21 November last year, Suttons announced their funding for Professor Paul Timpson's innovative pancreatic cancer research.

Professor Timpson and his team are using cutting-edge imaging technology to pinpoint the molecular drivers of pancreatic cancer progression and the factors in the tumour environment that cause resistance to therapy.

The treatment for, and survival of patients with pancreatic cancer has barely changed for more than 30 years due to the complexity and molecular variation in pancreatic cancer. Pancreatic cancer is one of the most aggressive cancer types – by the time most cases are diagnosed, the cancer is advanced and spreading to other parts of the body. With a five year survival rate of only ~9%, the work undertaken by researchers such as Professor Timpson is critical.

The Sutton family both personally, and through Suttons Motors has been generously supporting Garvan's research for over 28 years. This long-term investment in medical research first began with the late Sir Frederick Sutton OAM, and continues today with Laurie and Di Sutton – Life Governors of Garvan and Visionary Donors of the Garvan-Weizmann Centre for Cellular Genomics.

"As a family, pancreatic cancer is a disease that unfortunately is very close to our hearts, and we are honoured to support this ground-breaking research. As a company, Suttons is incredibly proud of our long-standing relationship with Garvan, and their inspirational people, who are making a profound impact on the future of healthcare," says Lauren Sutton.

Professor Paul Timpson is the recipient of the Len Ainsworth AM Pancreatic Cancer Fellowship and we are grateful for his generous philanthropic investment over the last 5 years of Professor Timpson.



Professor Paul Timpson



Di Sutton, Lauren Sutton, Mara-Jean Tilley and Laurie Sutton.

UNCOVERING THE GENOMICS OF HEALTH

A DNA database of thousands of healthy older Australians is set to change how we determine which genes underpin disease.

Most diseases have a genetic component. To better understand these diseases, researchers led by the Garvan Institute are analysing genetic information to determine what keeps us healthy.

In a world first, the team has compiled a genome reference database of thousands of healthy older Australians, which has the potential to predict disease-linked gene variants more accurately than has been previously possible.

The researchers recently released the first 2,570 genomes of the Medical Genome Reference Bank (MGRB), a collaboration led by Garvan, Monash University's ASPREE study and the Sax Institute's 45 and Up Study.

"By doing a comprehensive analysis of healthy individuals, we can get a much clearer understanding of which genes are and which are not linked to disease," says Professor David Thomas, Garvan Cancer Research Theme Leader and Director of The Kinghorn Cancer Centre.

A baseline of healthy ageing

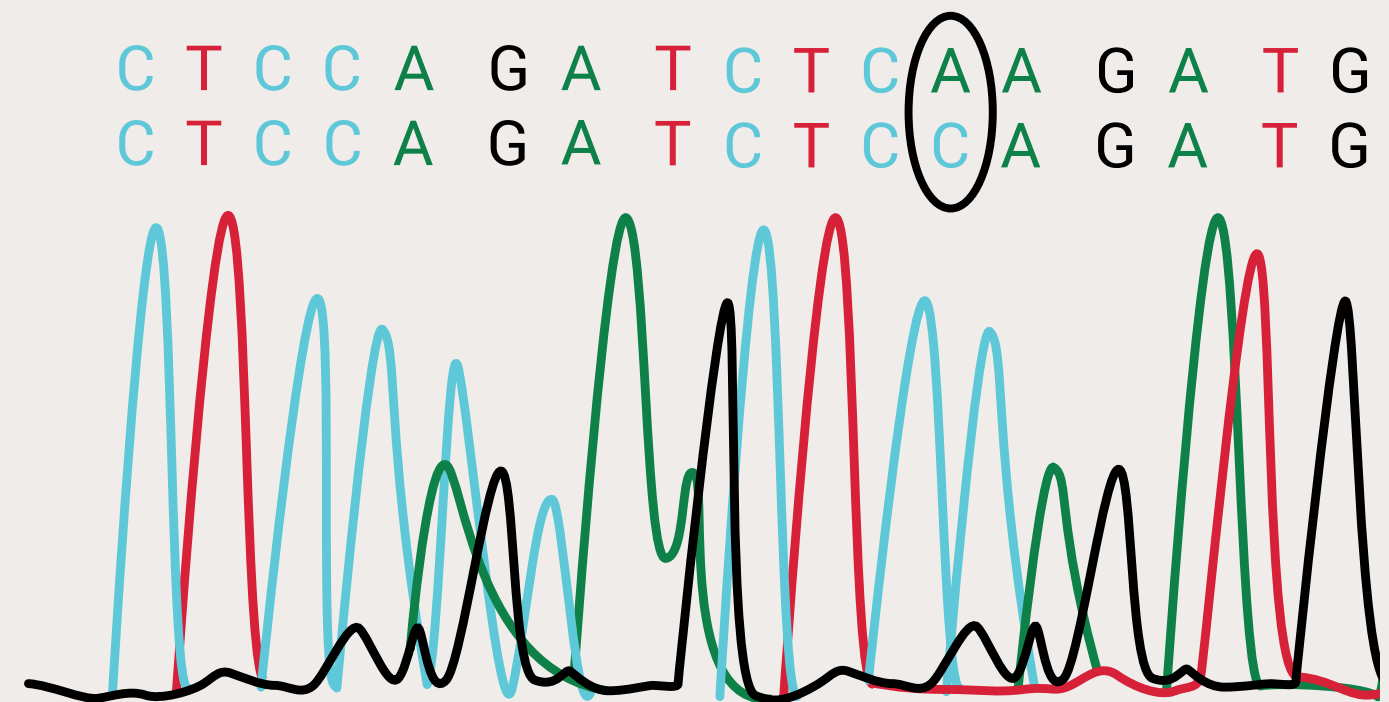
Every person has around 6 billion DNA 'letters' in their genome, which encodes all of the information needed to make and run every cell in the body. Between any two unrelated people, there are millions of single letter differences, or variations.

Variations make us different, but some of them can cause disease – the challenge for researchers is to pinpoint which these are.

The release of the MGRB consists of genomic data of 2,570 healthy older Australians (64 – 95 years old) that were free from cancer, cardiovascular disease or neurodegenerative disease until the age of at least 70. These individuals were participants of the ASPREE study and the 45 and Up Study.

"This first release of data from the Medical Genome Reference Bank gives researchers a much more statistically powerful framework to identify new disease-causing gene variants," says Professor Thomas.

"For instance, when we analysed genomes of prostate cancer patients, we found that using the MGRB as a 'control' gave us a 25% higher predictive power of disease-linked gene variants than another genome database that is commonly used by researchers to find such variants."



Determining biological age from DNA

Using whole genome sequencing, the researchers were able to detect genetic changes associated with ageing, including shorter telomeres, the 'caps' at the ends of chromosomes, and less mitochondrial DNA, which codes for the energy generators of cells. Interestingly, the researchers found that the amount of mitochondrial DNA was associated with a higher grip strength in men.

"We were able to detect changes in the genomes that could distinguish between healthy older individuals that share the same age, but have different physical function. This indicates that the DNA in an individual's blood sample may provide a better indicator of their 'biological age' than their chronological age," says Professor Thomas.

"The ability to derive a measure of biological age may better predict health outcomes for individuals. As our population ages, understanding the genetic basis for healthy ageing will become more and more important."

Visit: garvan.org.au/genomics-health



Professor David Thomas

"We were able to detect changes in the genomes that could distinguish between healthy older individuals that share the same age, but have different physical function. This indicates that the DNA in an individual's blood sample may provide a better indicator of their 'biological age' than their chronological age," says Professor Thomas.

Marking a new path for lung cancer therapy

Cutting-edge cellular genomics technologies will enable Garvan's Dr Venessa Chin to undertake research to change the management of lung cancer.

Dr Venessa Chin, Research Officer in the Single Cell and Computational Genomics Laboratory at the Garvan Institute of Medical Research and Medical Oncologist at St Vincent's Hospital Sydney, has received a prestigious Lung Foundation fellowship, to progress her pioneering lung cancer research.

Dr Chin will employ Garvan's state-of-the-art cellular genomics technology to develop a diagnostic tool that will change the management of lung cancers.

“As a clinician I see a need for tools that will give us a better indication of which patients are likely to benefit from immunotherapy,” says Dr Chin. “I hope to develop such a tool and make a significant impact on patient outcomes.”

Predicting treatment response

Lung cancer is a leading cause of cancer-related death worldwide, with many cases diagnosed when the disease has already progressed to advanced stages. In Australia alone, lung cancer resulted in over 9000 deaths last year.

Administering the most effective treatment is crucial. Immunotherapy, a cancer treatment designed to activate the immune system to better target a tumour, is gaining ground as a treatment option for lung cancer, however less than 50% of patients respond well to the therapy. There are no tests currently available to predict which patients will respond, and which will not. Such a test is urgently needed, says Dr Chin.

Using cellular genomics technology at the Garvan Institute, Dr Chin aims to identify immune and tumour cell 'biomarkers' – unique cellular signatures – to predict which lung cancer patients will respond to different immunotherapies.

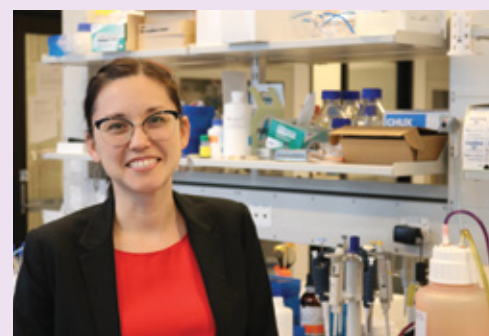
Developing diagnostics for better outcomes

In her research project, Dr Chin will analyse biopsy samples collected from patients with advanced lung cancer from St Vincent's Hospital and the Nepean Cancer Research Biobank.

She will expose cells taken from different patients to immunotherapy in tissue culture, and use single cell genomics to perform an in-depth genomic analysis of both lung cancer cells and immune cells.

Using this information, Dr Chin aims to identify biomarkers in the cells of patients that respond well to immunotherapy and which could be screened for in a patient's biopsy before a treatment is administered. The work is a crucial first step to developing a diagnostic test that can help doctors assess whether a patient is likely to respond to the treatment.

Visit: garvan.org.au/lung-fellowship



Dr Venessa Chin

“Cellular genomics has a vast potential to guide more personalised treatment strategies and improve patient outcomes,” says Associate Professor Joseph Powell, Head of the Garvan-Weizmann Centre for Cellular Genomics.

Image: 3D illustration X-ray transparent lungs

Clinical Trial Spotlight

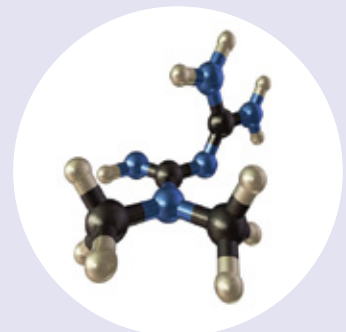
Could metformin reduce the long-term risks associated with insulin resistance in individuals with type 1 diabetes?

On average, seven new cases of type 1 diabetes are diagnosed in Australia every day – most of them in children – and many of these affected individuals will require approximately 100,000 insulin injections over their lifetime.

These regular insulin injections can come with long-term health impacts. Individuals with type 1 diabetes often develop insulin resistance, which means the body's cells respond less to insulin in the blood. This in turn results in weight gain and a three times greater risk of both heart disease and premature death.

Our new INTIMET study (Insulin Resistance in Type 1 Diabetes Managed with METformin) will investigate whether metformin, which improves the body's response to insulin and is commonly used to treat type 2 diabetes, can counter the negative effects of insulin resistance in individuals with type 1 diabetes, when combined with conventional insulin therapy.

Our new INTIMET study will investigate if metformin can counter the negative effects of insulin resistance in individuals with type 1 diabetes



The 6-month study will also determine which individuals would benefit most.

We are currently recruiting individuals with type 1 diabetes with the following criteria:

- Age 20-50 years
- Diagnosis more than 10 years ago
- HbA1c < 9.5%
- Non-smoker

We are also recruiting individuals without diabetes, aged 20-50 years who are non-smokers.

Through this study, and our other ongoing research projects, we hope to help improve the management of type 1 diabetes and improve quality of life for patients in Australia and across the world.

For further information on the trial, please contact Dr Jennifer Snaith:
Email: INTIMET@garvan.org.au

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Wendy Ell
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CLINICAL STUDIES

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 which 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 pre-diabetes or who have been recently diagnosed with types 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**
02 9295 8309
predict@garvan.org.au



Jewellery with Purpose

Paspaley have launched a new addition to their Kimberley range – the Dark Kimberley Bracelet, which features darkened sandalwood with either a single or double pearl.

Even more beautiful than the bracelet, is the sentiment behind it. Paspaley have been long-time supporters of Garvan, and help create a healthier future for everyone by donating 20% from the sale of each of these stunning pieces, to people living with rare and less common cancer.

To give a gift that means more, please visit garvan.org.au/paspaley today.