December 2023 | Issue 55

breakthrough

Transforming lives

How the discovery of a rare genetic variant finally led to a diagnosis for a maths superstar

Also in this issue

Garvan Institute of Medical Research

Welcome from the Executive Director

Professor Benjamin Kile

Dear Garvan family,

It is my pleasure to share this issue of *Breakthrough* with you.

Since taking the helm at Garvan in April, I have felt inspired by the institute's talent and commitment to prevent, diagnose and treat disease. Thanks to your generosity, our medical research is advancing at pace, with discoveries happening around every corner.

In this December issue of *Breakthrough*, I am delighted to share our recent research findings with you and introduce you to the brilliant minds who are making it happen.

Opposite, you'll see the intricate world of cells within prostate cancer, a common yet complex disease. Through advanced microscopy, our researchers map the tumour's 'cityscape', exposing its diverse molecular structures. This groundwork is vital in shaping the future of personalised treatments targeting tumours' unique profiles.

On page 4, you'll read about how the discovery of a rare genetic variant led to an effective therapy.

On page 8, you'll read about a new research initiative for sudden cardiac arrest – a devastating event that is too often deadly. Through genomics and a clinical registry at Garvan, our researchers aim to identify early warning signs that improve guidelines for sudden cardiac arrest management.

On page 9, you'll read about a breakthrough finding for pancreatic cancer, which reveals an Australian drug that is already in clinical trials may be an effective combination therapy for pancreatic cancer patients.

On behalf of us all at Garvan, I sincerely thank you for your support in making this work possible and wish you a restful holiday season.

With warm regards,

Professor Benjamin Kile
Executive Director

A DAY IN THE LIFE

Associate Professor Cindy Ma

Associate Professor Cindy Ma

As an immunologist, no two days are ever the same for me. My work revolves around understanding the genetic causes and potential treatments of immune disorders. From immune deficiencies, where we are not properly protected against pathogens, to allergies, where the immune system overreacts, to autoimmunity, where it attacks the body's own tissues – these conditions present a complex yet fascinating area of study.

A typical day might start with a meeting with my research team, going over their latest experimental results – using techniques like flow cytometry to examine immune cells from patient blood samples. As we work on rare disease, we need to collaborate with other research groups with similar interests, so we often meet to discuss our results and work out ways we can help one another. A lot of my time is spent writing grants to get funding for the work we do. A more exciting aspect is writing scientific manuscripts on our research findings.

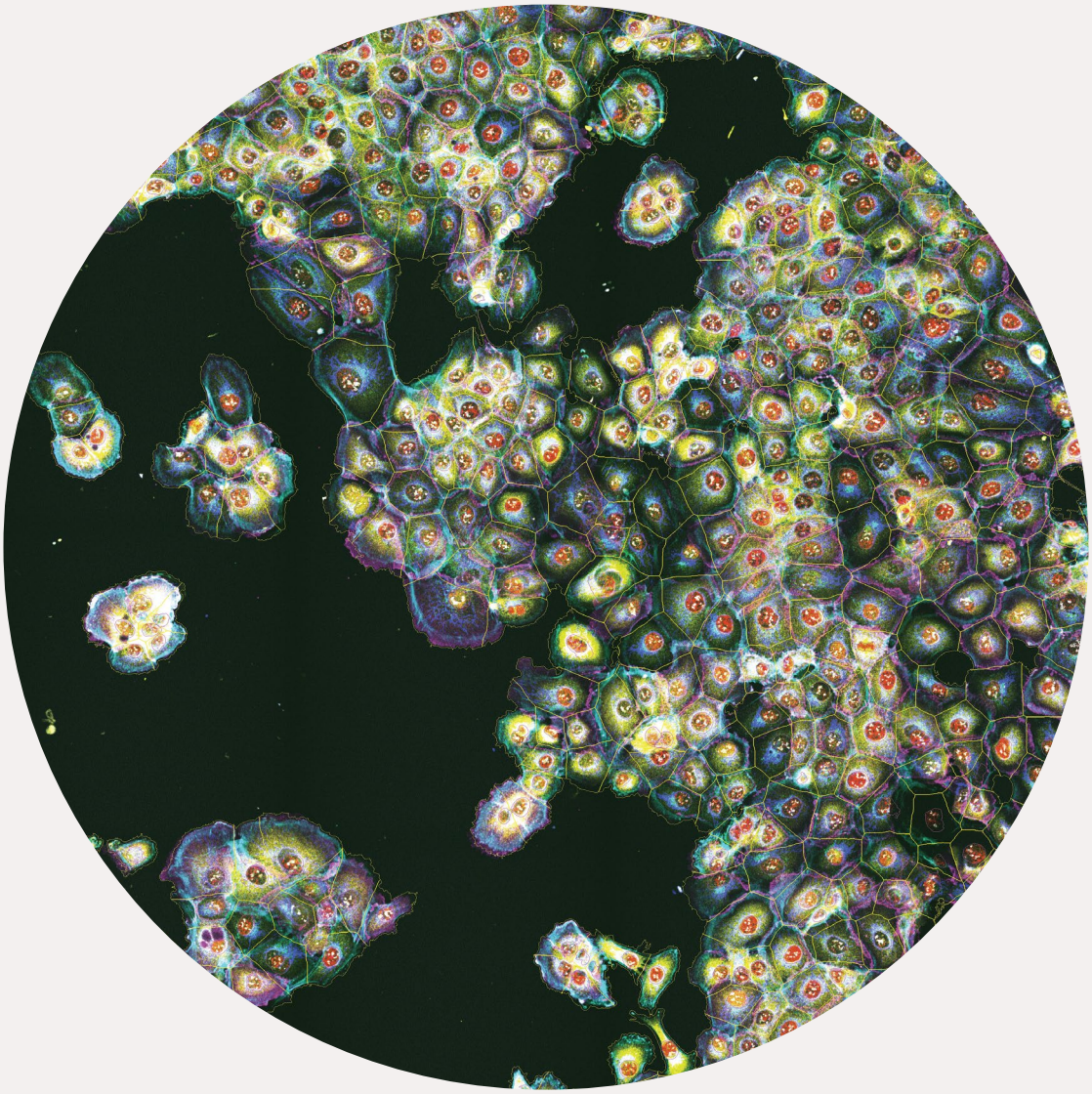
A new direction for my team is tracing the links between immunodeficiencies and allergies. We have been studying patients with inborn errors of immunity – conditions caused by variations in the genes required for a functioning immune system. I have noticed that while these individuals have problems fighting bacterial, fungal and/or viral infections, some of them also have severe allergies such as atopic dermatitis and food anaphylaxis. I'm hoping these genetic variations may shed light on new allergy pathways and improved treatments to address the cause, not just the symptoms.

While the job is challenging, it's incredibly rewarding too. The thrill of making a new research breakthrough, of finding answers for families, and of mentoring junior scientists keeps me going. After over 20 years in the field, I remain as fascinated by the immune system as ever. Who knows what new secrets we'll uncover tomorrow?

Cover image: A molecular illustration of TNFα, a key cytokine protein in our immune response, with a pivotal role in inflammation and cell death

THROUGH THE **MICROSCOPE**

A cityscape of cells



Cancer is often imagined as a homogenous mass of mutated cells. However, microscopy tells a different tale, revealing a world of remarkable molecular and structural diversity within a tumour.

This vivid image was created by PhD student Felix Kohane using 4i single-cell multiplexed imaging. The colours identify eight different proteins within prostate cancer cells, each one contributing to the cancer's survival and proliferation. Felix likens this to observing a bustling city from above, where each colour denotes a different type of building, each serving its own function.

Through a collaborative project between Associate Professor Christine Chaffer's Cancer Cell Plasticity Lab and Dr John Lock's Cancer Systems Microscopy Lab at UNSW, Felix and his team aim to decode this internal city's functioning, to understand how cancer cells adapt to and resist treatment. By mapping these cells' distinct molecular characteristics, they're laying the groundwork for personalised treatments that align with an individual's unique cancer profile.

Transforming lives

A bout of strep throat was the start of a diagnostic odyssey for Edmund. The discovery of a rare genetic variant led to an effective therapy.

As a 19-year-old uni student living in Canberra, Edmund knew something was wrong. He was suddenly always tired, constantly out of breath and started getting severe body aches.

A first visit to the GP diagnosed strep throat, but when antibiotics didn't help, more tests were done. They showed an abnormally large spleen, severe liver cirrhosis and low blood count. Doctors suspected a form of cancer, but no diagnostic tests could confirm this, or point to a treatment.

"I was 19 years old, and doctors told me I had the liver of a 40-year-old alcoholic," says Edmund. "As time went on, the 'unknown' factor, and the symptoms, were just getting worse and worse." Doctors were doing what they could to find the cause, but they came no closer and a liver transplant was fast becoming the only option for Edmund.

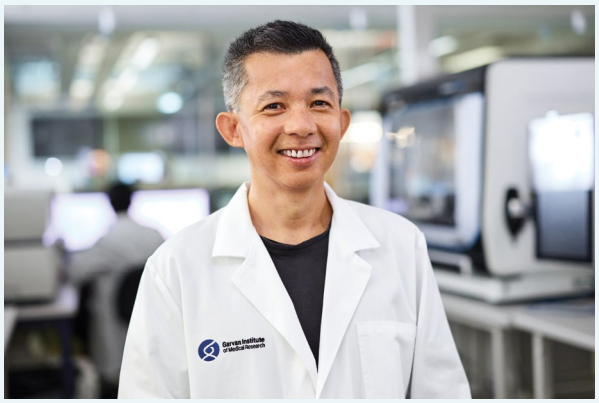
Edmund's case was eventually referred to Professor Tri Phan, co-director of the Precision Immunology Program at Garvan and immunologist at St Vincent's Hospital Sydney.

Professor Phan had read a research paper that reported a variant in the *TNFAIP3* gene, which produced overly active immune molecules that cause recurring infections and damage to organs. At the time, there were just nine patients worldwide found to be carrying this gene variant.

"The penny dropped when Edmund's mother Rebekah told me she had been diagnosed with Behçet's disease – an autoimmune condition with unknown cause. From there, a genetic test revealed that several members of the family had inherited this *TNFAIP3* variant," says Professor Phan.

On compassionate grounds, Edmund received a monoclonal antibody therapy called adalimumab. This treatment, usually used for rheumatoid arthritis, blocks the molecule that was overly active in Edmund. While his therapy is not a cure, today Edmund lives a normal, active life and next year he will head to Oxford University to embark on a PhD in mathematics.

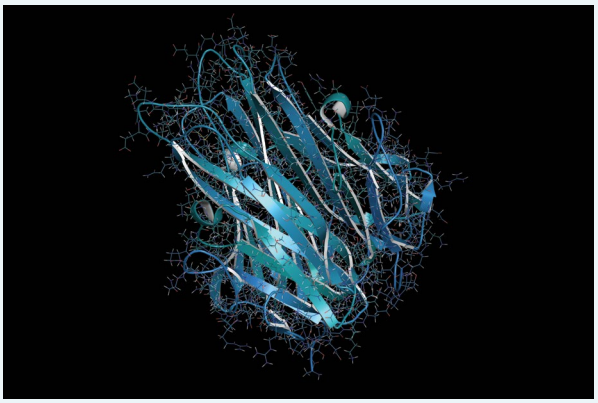
Rebekah and Edmund



Professor Tri Phan

"Having the genetic diagnosis brings the peace of mind that any additional symptoms I start experiencing would be monitored closely and taken seriously."
– Edmund

Edmund's mother Rebekah was prescribed adalimumab and is managing her rheumatoid arthritis symptoms better than previously. Meanwhile, although Edmund's siblings have no symptoms, this early genetic diagnosis provides them with immediate options should symptoms start occurring.



The TNFα immune molecule produced by the TNFAIP3 gene

Leave no one behind

Primary immunodeficiencies are rare individually, but together they are quite common – over 6 million people globally are affected by more than 430 conditions.

Associate Professor Elissa Deenick

"The more we look, the more we find," says Professor Phan. "We are trying to move to a more personalised model of care for patients, rather than trying a one-size-fits-all approach."

It took a considerable amount of time to find an effective treatment for Edmund, but this process can be even more drawn out for others with primary immunodeficiencies. To address this, Associate Professor Elissa Deenick, who co-leads the Precision Immunology Program with Professor Phan, is spearheading the TheraPID study. As co-lead, she is working closely with researchers from Garvan and St Vincent's to develop new immune function tests. By measuring treatment responses more accurately, the team aims to tailor therapies precisely to individual patients' needs.

"Patients with primary immunodeficiencies often have few places to turn," says Associate Professor Deenick. "We are finding that personalised care has better outcomes for individuals, and we want to implement this widely so that more patients can benefit."

Peace of mind –
the gift of medical research

Like all gifts in Wills, Michael's bequest is a gift of confidence to the future of medical research.

Michael

My relationship with Garvan traces back to approximately 20 years ago. During my tenure as an Information and Communications Management Consultant at St Vincent's Hospital, I had the opportunity to interact with a course participant from Garvan. This encounter piqued my interest, which was further kindled when I learned about Garvan's multi-faceted research, particularly with various forms of cancer and genomics.

More recently, I found Garvan's research into COVID-19 very encouraging, adding another layer to my enthusiasm for their work.

My wife passed away from stage 4 colorectal cancer in 2015 at the relatively young age of 62. I learned a fair bit about chemotherapy over the prior 18 months and then experienced it myself four years later when I had a skirmish with the same cancer. Fortunately, mine was caught in time at stage 3, and all now appears clear.

Having personally experienced the impact of medical research, I really value the continual progress being made in this field. I saw firsthand some of the improvements to my chemo treatment, compared to what my wife had experienced four years earlier. I'm genuinely excited by new supplements to surgery and chemotherapy offered by autoimmune and genomic research.

I felt fairly calm throughout my cancer diagnosis and treatment, largely because of developments in keyhole surgery and oncological treatment. I'm a firm believer that further research will enable us to reach a point where cancer and other serious conditions will become both more preventable, and less devastating when a person receives a diagnosis. I remain confidently optimistic about this outcome.

"I would encourage everyone to consider leaving a legacy to research institutes like Garvan in their Will, as I have." **– Michael**

Like Michael, would you consider this special way of giving to the future of medical research with a gift in your Will?

To request our Bequest Giving brochure or for a no obligation conversation, please contact Claire Swinn on **(02) 9295 8527** or **bequests@garvan.org.au** or visit **garvan.org.au/bequest**

Genomics approach to transform Crohn's disease treatment

Pioneering work by Professor Joseph Powell, Director of Cellular Science at Garvan, is unlocking the promise of personalised medicine for Crohn's disease.

His team uses single-cell sequencing to create detailed genetic maps of the individual cells driving diseases such as cancer and autoimmune disorders. Now, this approach is being tested in clinical trials for Crohn's disease across hospitals in New South Wales. By profiling the genomes of immune cells attacking the gut in Crohn's patients, Professor Powell discovered links between genetic signatures and drug responses.

As costs for genetic testing fall, such tests could become routine for complex diseases. Professor Powell also believes cellular genomics insights will allow the development of therapies that precisely target disrupted cellular pathways.

***"Patients responded differently based on their genes. Our goal is a simple, inexpensive test guiding doctors to the best treatment."* – Professor Joseph Powell.**

Professor Joseph Powell

The Autoimmune Project: Chemo to Camino

Sara Little

Sara and Emily Little, a mother-daughter duo from the Southern Highlands, NSW, co-founded the Autoimmune Project with a mission to solve the autoimmune puzzle. The project aims to raise awareness and funds for education, research and resources to better understand, diagnose, manage and treat autoimmunity. Sara is no stranger to the many significant challenges faced by those with autoimmune diseases, having experienced her own decade-long battle with a rare and life-threatening autoimmune disease. Sara chose to walk the Camino de Santiago in Spain in 2023 to symbolise how far she has come – from being bedridden for a year with weekly chemotherapy treatment, to now – being able to live a full life in service to others.

The Autoimmune Project raised an incredible $5,000 during the 930km hike. Their inspiring fundraising will benefit Garvan's HOPE Research, bringing us one step closer to identifying causes and treatments for autoimmune disease.

Read more about Sara's story:
theautoimmuneproject.org.au

Read more about Garvan's HOPE Research:
garvan.org.au/research/collaboration/hope-research

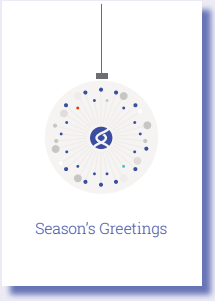
Season's Greetings

This festive season, you can choose to give something with a little extra meaning.

You can give the gift of a longer, healthier life for everyone by supporting life-changing medical research. Donate to Garvan's research on behalf of a friend or loved one and you'll help support scientists in discovering better treatments for some of the most devastating diseases affecting society today.

We have a range of personalised cards available for the festive season, birthdays, special occasions, and in sympathy including both print at home and virtual cards.

Give the gift that keeps on giving.
Visit: fundraise.garvan.org.au/shop



Identifying the early warning signs of sudden cardiac arrest

A sudden cardiac arrest can have devastating consequences, but often has no warning signs. Researchers at Garvan are working to better identify and support those at risk.

Sudden cardiac arrest is a global public health issue that affects approximately 3,000 young Australians (aged below 50) per year. It occurs when a person develops a dangerous heart rhythm that prevents the heart from effectively pumping blood through the body. Those who suffer a sudden cardiac arrest generally have no prior health conditions. There are often no warning signs and only one in 10 will survive the trip to hospital.

With the launch of a new registry, Associate Professor Jodie Ingles' team at Garvan is hoping to change the staggering death rate.

The researchers are recruiting all individuals affected by sudden cardiac arrest in NSW between the ages of one and 50, and their families, to the NSW Sudden Cardiac Arrest Registry, to help improve screening and treatment of the condition.

Through the registry, the team aims to identify early warning signs for sudden cardiac arrest that will lead to improved guidelines for healthcare professionals and identify underlying genetic causes that may ultimately guide the development of new treatments.

Associate Professor Ingles is a genetic counsellor, and head of the Clinical Genomics Laboratory at Garvan. She was an invited commissioner of the recently published Lancet Commission on Sudden Cardiac Death, which recommends improved access to genetic testing for better identification and monitoring of people at risk of sudden cardiac arrest.

Associate Professor Jodie Ingles

"The unimaginably sudden and unexpected cardiac death of a young person is something that a family will always live with. We need to identify the risk factors, so that we can better find, monitor and treat those at risk."
– Associate Professor Ingles, Head of the Clinical Genomics Laboratory at Garvan

Participation in the NSW Sudden Cardiac Arrest Registry involves informed consent for medical records, yearly health surveys and a blood sample for DNA analysis.

For more information, visit: **garvan.org.au/sca**

New hope
for pancreatic cancer

Exciting research at Garvan has revealed that a new Australian drug shows promise for treating pancreatic ductal adenocarcinoma, one of the most aggressive forms of pancreatic cancer.

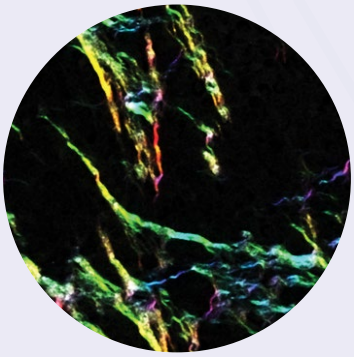
The drug, called PXS-5505, targets the scar tissue that builds up around tumours, which makes chemotherapy less effective.

Tests in animal models showed the treatment increased survival time by more than 35% when paired with chemotherapy. "PXS-5505 shows real potential to improve chemotherapy for patients," says lead researcher Associate Professor Thomas Cox, head of the Matrix and Metastasis Lab at Garvan. The combination therapy also substantially reduced the spread of the cancer to other organs, such as the liver, by 45%.

The drug was developed by Australian company Pharmaxis and has already shown promising early results in phase 2 clinical trials for bone marrow cancer.

Pancreatic cancer is often diagnosed late, with very low survival rates. This drug provides new hope of increasing chemotherapy effectiveness and patient life expectancy.

Associate Professor Thomas Cox and Dr Jessica Chitty



Collagen fibres form scar tissue around tumours

Jewellery
with purpose

Since 2016, with each sale of the Kimberley bracelet, the brand has generously donated 20% to support Garvan's Molecular Screening and Therapeutics (MoST) program.

The collection combines hand-selected Australian South Sea Pearls with regional, renewable, aromatic sandalwood for a wearable, timeless style.

We thank Paspaley for their continued generosity and visionary commitment to breakthrough medical research.

PASPALEY

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

Honour for
Professor Stuart Tangye

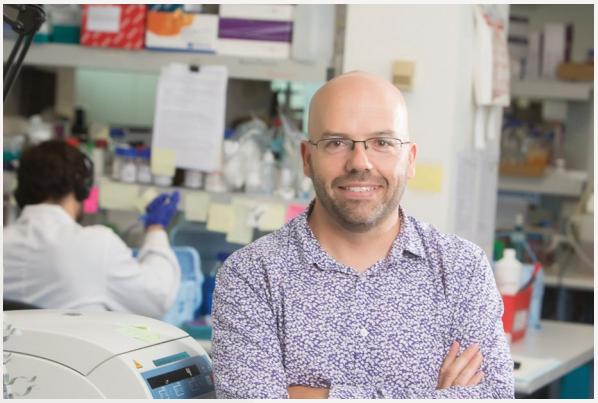
Elected a Fellow of the Australian Academy of Health and Medical Sciences.

For his leading contributions to the field of immunology, and the genetic diagnoses of inborn errors of immunity, Garvan's Professor Stuart Tangye has been elected Fellow of the Australian Academy of Health and Medical Sciences. The announcement was made at a ceremony at the Queensland University of Technology in Brisbane on 12 October.

Professor Tangye's research focus is human immunology and how immune deficiencies due to a genetic cause, otherwise known as inborn errors of immunity, can lead to disease. He has published more than 250 peer-reviewed research articles and invited reviews on these topics.

His input has been fundamental to identifying genetic variants in patients with rare immune conditions and has led to the discovery of 22 new inborn errors of immunity, reported in prestigious scientific journals.

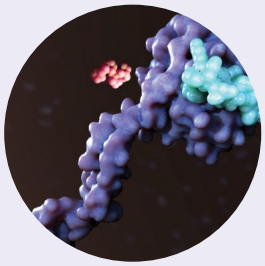
Among his outstanding achievements is the establishment of the Clinical Immunogenomics Research Consortium Australasia (CIRCA) in 2015. This multi-disciplinary collaborative network aims to expedite genomic diagnosis and treatments for individuals with inborn errors of immunity and enable new research projects to reveal how these genetic variants cause disease in individuals with these conditions.



Professor Stuart Tangye

"I'm delighted that my team's work has received this recognition. Patients with inborn errors of immunity often get left behind. Through work that was initiated in my lab many years ago, and is now embedded in the CIRCA network, we have been able to help genetically diagnose immune diseases, guide treatment and change the lives of patients affected by these conditions. I am grateful to the Academy for acknowledging this important work," says Professor Tangye.

Triple-negative breast cancer clinical trial



Androgen receptor and hormone

Associate Professor Christine Chaffer

We are recruiting volunteers for the 4CAST clinical trial, aiming to improve survival rates for patients with triple-negative breast cancer. This cancer type, known for its rapid adaptation and aggressive behaviour, currently lacks effective targeted therapies.

The trial, now underway, tests a new strategy: disabling a 'defence switch' in the cancer cells, which alerts them to the threat of treatment. It is led by Associate Professor Christine Chaffer, Head of the Cancer Cell Plasticity Lab at Garvan, along with Dr Beatriz San Juan and Senior Staff Specialist in medical oncology Dr Rachel Dear of St Vincent's Hospital Sydney.

"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 Chaffer.

In preclinical studies, the team found that combining an experimental drug, seviteronel, with chemotherapy could be twice as effective as chemotherapy alone in reducing the size of tumours. Seviteronel works by blocking androgen hormones, which usually enable the cancer cells to resist treatment.

About 10-15% of breast cancer cases are diagnosed as triple-negative, and due to the lack of effective targeted therapies, these cases often have a poorer prognosis compared to other forms of breast cancer.

Research from Associate Professor Chaffer's team revealed that triple-negative breast cancer cells 'switch' their state in response to chemotherapy, making them more aggressive and capable of evading further treatment.

The aim of the 4CAST trial is to disrupt this cancer resistance mechanism to improve the effectiveness of chemotherapy.

The trial is being conducted at The Kinghorn Cancer Centre in Darlinghurst. If you are living with triple-negative breast cancer, we encourage you to discuss this trial with your treating team.

For further information about the trial (NCT04947189), please email the St Vincent's Hospital Sydney Research Office: **svhs.cancerresearch@svha.org.au**

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

Donations made in memory of loved ones

Trevor W Annetts
James A Atputharajah
Rodney Beaver
Beverley Bolton
Lynn Bright
Jane Bryant
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Steve Cominakis
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Garvan Institute of Medical Research

Breakthrough research starts with you

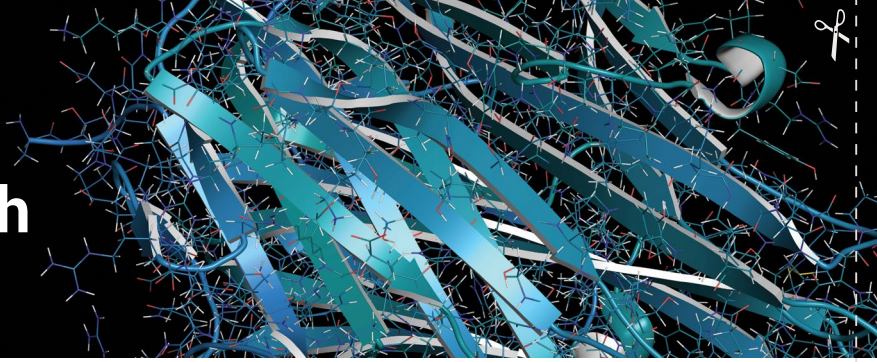

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Image: Claire Greaves, Garvan Partner for the Future