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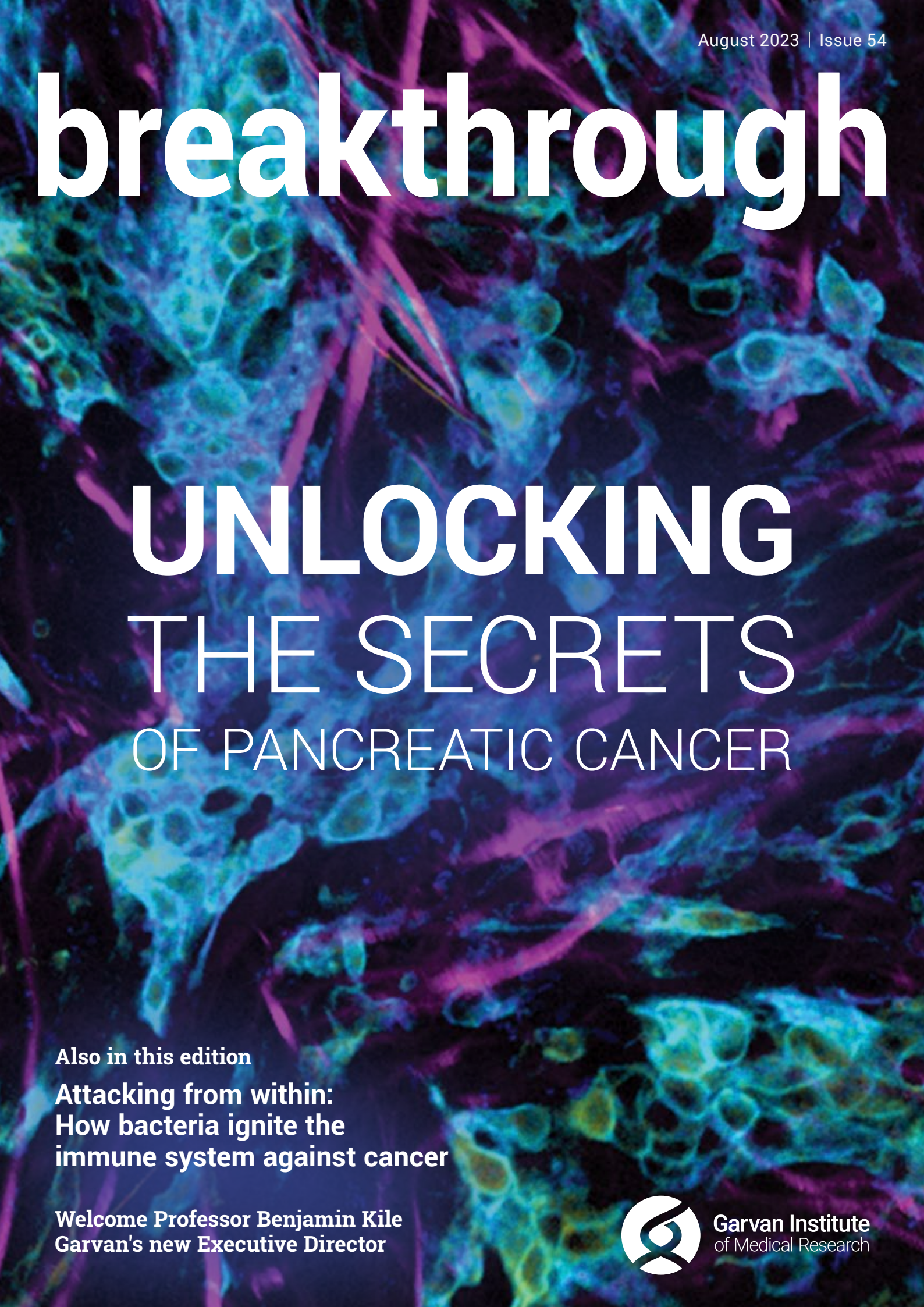
breakthrough



UNLOCKING THE SECRETS OF PANCREATIC CANCER

Also in this edition

Attacking from within: How bacteria ignite the immune system against cancer

Welcome Professor Benjamin Kile Garvan's new Executive Director

Garvan Institute of Medical Research

A warm welcome

from Garvan's new Executive Director, Benjamin Kile

Professor Benjamin Kile

It is with great pleasure (and enthusiasm) that I introduce the August edition of *Breakthrough* as the new Executive Director of the Garvan Institute of Medical Research.

First and foremost, I want to express my deep appreciation to the entire Garvan community for the warm welcome I have received, and to my predecessors, particularly Professor Chris Goodnow and Professor Peter Croucher. Their vision and unwavering commitment to advancing medical research have guided the Institute through a tumultuous period to the remarkable inflection point we now face. I am very grateful to them both.

In this August edition of *Breakthrough*, I am excited to share some of our latest news with you. On page 5, you'll read about a mysterious immune cell that acts as a 'garbage disposal' for the immune system's waste. A recent paper explores these cells' role in the development of autoimmune disorders like lupus.

Also on page 5, we highlight a study that uncovers a gene controlling the cut-off switch for kidney inflammation, which could pave the way for more precise disease diagnostics and personalised treatments.

On page 10, we shed light on the causes of rare genetic immune disorders APDS2 and APDS1. Knowing the genetic basis of a disease can enable targeted, personalised treatment plans that give patients the best chance of effective management or, hopefully over time, a cure.

I look forward to sharing with you our latest research findings, clinical trials, and progress through future editions of *Breakthrough*. My sincere gratitude goes to each and every one of you for your continued support and generosity.

With warm regards,

Professor Benjamin Kile
Executive Director

Cover image: Pancreatic cancer drug response visualised up close thanks to intravital imaging. Credit: Kendelle Murphy

A DAY IN THE LIFE

Associate Professor Jodie Ingles, Head of the Clinical Genomics Lab

Associate Professor Jodie Ingles

As a genetic counsellor and genomics researcher, I spend my days trying to solve genetic mysteries that have left families without answers for years. One of our goals is to dramatically accelerate diagnosis for patients with rare, undiagnosed diseases. Using innovative techniques, we analyse DNA to uncover the genetic secrets behind their conditions.

Today in the clinic, I met a family, three of whose members suffered cardiac arrest in their 20s. We pored over their family history, searching for clues. Obtaining a diagnosis for them could save their loved ones' lives, allowing at-risk relatives to be monitored or reassured. However, results are not always clear cut. Variants that look questionable may be red herrings, unrelated to disease. Determining what's causing a condition requires evaluating reams of data to separate signal from noise.

After the clinic, I met with my PhD students, the next generation of researchers. One is developing a psychological intervention for families who have endured the trauma of young sudden cardiac death. Having supported many such families, I know the immense grief and pain they face.

In a gene curation meeting, we debated a new variant's role in disease. Achieving consensus is arduous but guides genetic test reports worldwide. Improving diagnosis and management globally motivates me.

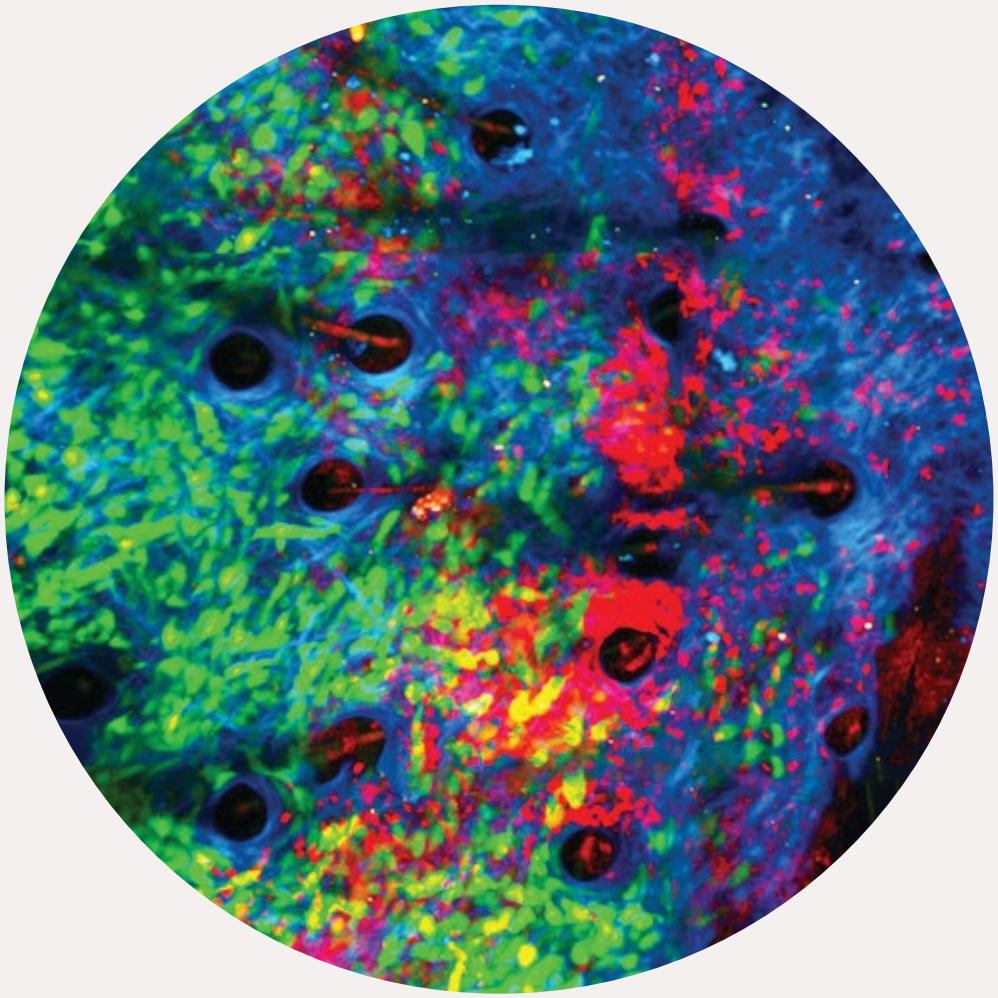
At day's end, walking my dog, I reflected on the families still suffering without answers. My vision is for equitable access to counselling and research that takes human diversity into account. In cardiac genetics, integrating genomics into care will transform lives through precise, personalised medicine.

We recently analysed 35 families, diagnosing more than half within weeks. One multigenerational family now has answers for the first time in 35 years. Better diagnosis will inform new treatments for those who need them most.

Though much remains unknown, each discovery has life-changing possibilities. I feel privileged to be a genetic detective, using DNA to rewrite stories of illness into ones of understanding and hope. The future is bright as genomics improves health care, one family at a time.

THROUGH THE MICROSCOPE

Attacking from within:
How bacteria ignite the immune system against cancer.



This striking image offers a glimpse into the battle between cancer cells (shown in green) and neutrophils (in red), which are a type of white blood cell that serve as the immune system's first line of defence.

The scene unfolds within the collagen-rich framework (in blue) of a tumour. Created by Jacqueline Bailey from Associate Professor Tatyana Chtanova's Innate and Tumour Immunology Lab, the image highlights the microbial therapy research enabled by innovative real-time microscopy at Garvan's ACRF INCITe Centre.

Associate Professor Chtanova's team discovered that introducing bacteria into the tumour's microenvironment sparks acute inflammation and activates neutrophils to target cancers, rather than shield them.

While neutrophils are typically the immune system's guardians against infections, in the context of cancer they usually promote tumour growth by suppressing the body's immune response. However, by injecting inactivated *Staphylococcus aureus* microbes into tumours, the researchers were able to reverse this effect in animal models of cancers including triple-negative breast cancer, melanoma and pancreatic cancer.

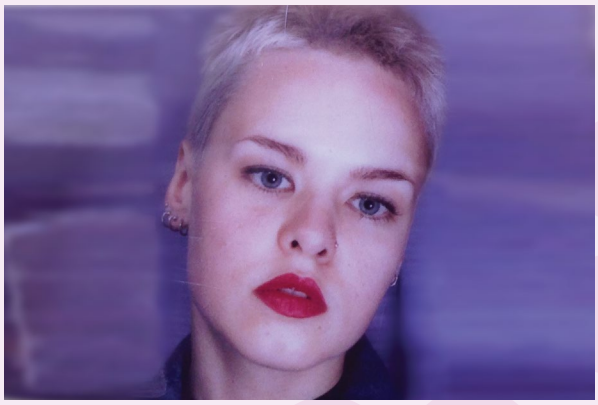
Intravital imaging shows neutrophils 'chewing up' the tumour's matrix and secreting molecules to attract fighter T cells for reinforcement.

This pioneering research highlights the promise of igniting our innate immune defences to overcome advanced or previously untreatable cancers.

Find out more

It's all about **the future**

James believes the most important gift to humanity is health and wellbeing. She is making a lasting impact by leaving a gift in her Will to Garvan's medical research.



James Belger, 1988

As a happy-go-lucky Londoner, I worked for nearly 20 years in the art studio at British Vogue. I came to Australia for a new job opportunity and to study in a less demanding field.

As an artist, your work is part of your identity. We worked and played hard, spending time with some of the most brilliant creative minds in the world.

A dream life? Perhaps. What followed showed the opposite. After never knowing a day's illness, I plunged into a world I didn't know existed after being diagnosed with a rare neurological disease called chronic inflammatory demyelinating polyneuropathy (CIDP).

When first diagnosed, I attended lectures at Garvan out of curiosity, aware some of my specialists worked there. The building itself left an impression, with its neon-lit spiral staircase leading to 'hidden' labs.

My CIDP diagnosis was followed by a flood of other autoimmune conditions, which has recently hit 13. This led to an ongoing joke between myself and Professor Tri Phan, my tenacious specialist with a lab at Garvan, about a new disease each week.

Professor Phan and the researchers at Garvan do amazing work but need funding to continue.

For me, it makes sense to leave my estate to Garvan, where researchers can put money to good use.

It's all about the future. The thought of young people dealing with similar chronic issues is chilling. The human body is disconcertingly frail. My disease collection may be incurable, so hope for others becomes paramount.

As a *Partner for the Future,* I feel a sense of pride seeing my name on the Honour Board as I walk through Garvan's doors. I've learnt that above all, the most important gift to humanity is wellbeing.

Like James, 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**

Paspaley's Jewellery with purpose

In August, we celebrate a significant milestone with Paspaley reaching $2 million in donations in support of Garvan's cancer research.

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

"Paspaley's contribution has supported treatment costs for many people with rare cancers and their funding contributes significantly to the impact and outcomes for these patients," says Professor David Thomas, Head of the Genomic Cancer Medicine Lab.

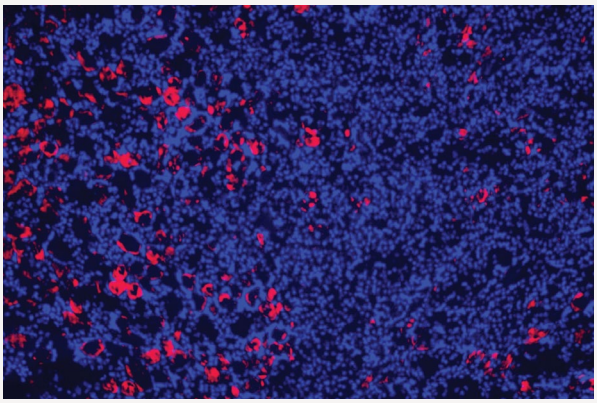
MoST currently has 20 clinical trial sites open nationally. Recently, the program also expanded to New Zealand. The partnership with Paspaley has been fundamental in the continued success of this program. MoST provides a new approach to treating patients with rare cancers who have exhausted all other treatment options. As of January 2023, more than 5,900 patients have been recruited to MoST, 80% of whom have been diagnosed with rare or less common cancer. In that time, 5,025 tumour molecular profiling reports have been issued and 3,494 patients have had additional treatment recommendations identified.

We extend our sincere thanks to the Paspaley clients who have purchased the stunning, custom-designed Kimberley bracelet, with 20% from each sale donated to Garvan. Paspaley's Kimberley Collection is available to purchase in-store and online at **paspaley.com**

PASPALEY

Predicting kidney disease risk

A Garvan-led team of researchers are investigating gene variants of an inflammation 'brake' present in some kidney disease patients.



Kidney cell nuclei (blue) and an influx of immune regulatory cells (pink) that prevent damage in an injured kidney.

Acute kidney injury – a sudden and rapid decline in kidney function that is in part caused by inflammation – is an important risk factor for progression to chronic kidney disease, a major health problem affecting approximately one in 10 Australians. Currently, there are limited treatment options for acute kidney injury and imprecise tools to predict who is most at risk of poor recovery or kidney failure.

The team, led by Professor Shane Grey, found that common variants of the inflammation 'brake' gene *TNFAIP3*, which increase inflammation in the body, can paradoxically protect the kidneys from damage in the short term by preventing cells from self-destructing.

The findings could lead to a simple genetic test that helps predict the risk of kidney disease for patients.

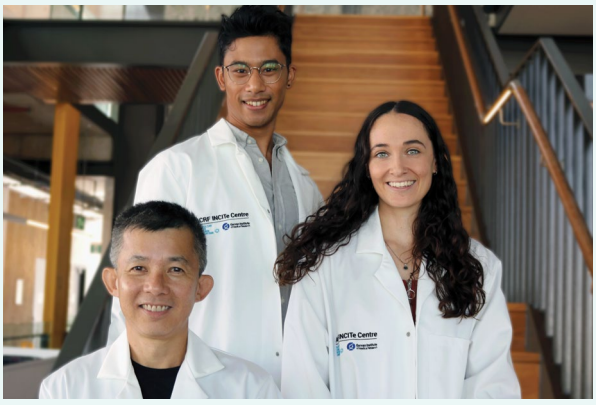
Find out more

'Garbage disposal' immune cells tracked for first time

Garvan scientists have discovered key insights into the lifecycle and function of tingible body macrophages (TBMs), a mysterious type of immune cell found in lymph nodes. This breakthrough may help us understand autoimmune disorders such as lupus.

Autoimmune diseases, affecting 10% of Australians, occur when the immune system mistakenly attacks the body. The team discovered that TBMs specialise in clearing the immune system's own waste: B cells, which proliferate during infection. Dead or dying B cells can trigger autoimmunity if not removed.

Using advanced intravital imaging techniques, the scientists observed how the macrophages form within lymph nodes and behave in real time.



Professor Tri Phan, Wunna Kyaw and Abigail Grootveld

"Understanding why somebody gets a disease like lupus in the first place, and why it keeps coming back, is an important step towards future treatments", says Wunna Kyaw, PhD student and co-first author of the study.

Find out more

Welcome

Professor Benjamin Kile

In April, Garvan welcomed Professor Benjamin Kile as the Institute's new Executive Director.

Professor Kile brings with him an extensive background in academic and research leadership, most recently serving as the Executive Dean of the Faculty of Health and Medical Sciences at the University of Adelaide, and formerly as Head of the Department of Anatomy and Developmental Biology at Monash University. He has also held leadership roles at the Walter and Eliza Hall Institute (WEHI), including Joint Head of the Chemical Biology Division, where he spearheaded a restructure of WEHI's early-stage drug discovery program, now the National Drug Discovery Centre.

Professor Kile's research career has focused on the molecular regulation of blood cell formation and function, with a particular interest in the impact of targeted cancer therapies on cellular survival. His group's work informed the development of Venetoclax, the first in a new class of anti-cancer drugs that was approved by the FDA in 2016 for the treatment of leukemia and lymphoma.

His scientific achievements have been recognised by numerous awards and fellowships throughout his career, including from the Australian Government as Life Scientist of the Year in 2010. He has served as Chief Operating Officer and Chief Scientific Officer of MuriGen Therapeutics and currently serves on the boards of the Australian Genomics Research Facility and the South Australian Health & Medical Research Institute.

In recent years, Professor Kile has played a pivotal role in the establishment of the South Australian Immunogenomics Cancer Institute (SAiGENCI) and was instrumental in developing the vision and securing significant federal funding for South Australia's first Comprehensive Cancer Centre. Professor Kile succeeds Professor Chris Goodnow, who stepped down from the role in July 2022, due to heart health complications of COVID-19.

Professor Benjamin Kile **on Garvan**

"Garvan is a great institution of global significance. Growing up as I did at WEHI, Garvan was always considered a sister institute, and the jewel in the crown of medical research in NSW. I have always followed Garvan's research and its people with great interest".

Joining this prestigious institution fills me with immense pride and excitement, as I step into a role that allows me to contribute to the remarkable legacy that Garvan has built over the years. I am humbled and incredibly excited to be given the opportunity to lead an organisation brimming with such talented, creative and passionate people, who are united in their desire to prevent, diagnose, treat and ultimately, cure disease.

I am invigorated by the potential for groundbreaking discoveries and transformative advancements that lie ahead – the field of medical research is constantly evolving, presenting us with new challenges and opportunities.

Professor Benjamin Kile

Garvan has a proud history of rigour, excellence and impact. It also has an incredible network of supporters who share the vision and help drive the Institute ever forward. Together with our foundational partners St Vincent's Hospital and UNSW, and with world-leading capabilities in molecular biology, Garvan is poised to make a profound impact in cancer, immunology and precision medicine."

– Professor Benjamin Kile

UNLOCKING THE SECRETS OF PANCREATIC CANCER

Discover how cutting-edge research is poised to transform how we treat this aggressive and often silent disease.

The pancreas, an organ nestled deep within our abdomen, plays a crucial role in digestion by producing essential hormones and enzymes. Pancreatic cancer can develop when cells within the pancreas start to grow uncontrollably, forming a tumour. This cancer, often referred to as the 'silent disease' because it hides behind the stomach, meaning it can progress to advanced stages and will begin affecting nearby organs before it is detected.

Pancreatic cancer presents a formidable challenge to treat and often has a poor prognosis. The five-year survival rate stands at a mere 12%, highlighting the urgent need for innovative treatments to combat this aggressive disease.

At Garvan, our dedicated researchers are exploring new approaches to decode the complexities of pancreatic cancer and devise new treatment strategies. By delving into the tumour biology, its evolution, and the microenvironment surrounding it, our goal is to overcome drug resistance and develop more effective, personalised treatments for those affected.

With continued progress, our efforts hold the potential to transform the outcomes for people with pancreatic cancer. By uniting clinical expertise with cutting-edge technology, we are spearheading the global fight to triple survival rates to an ambitious 30% by 2030.

This research is supported by Ainsworth 4 Foundation, Mr Len Ainsworth AM, the Girgensohn Foundation, the Philip Hemstritch Fellowship, Snow Medical Research Foundation and the Sutton family.

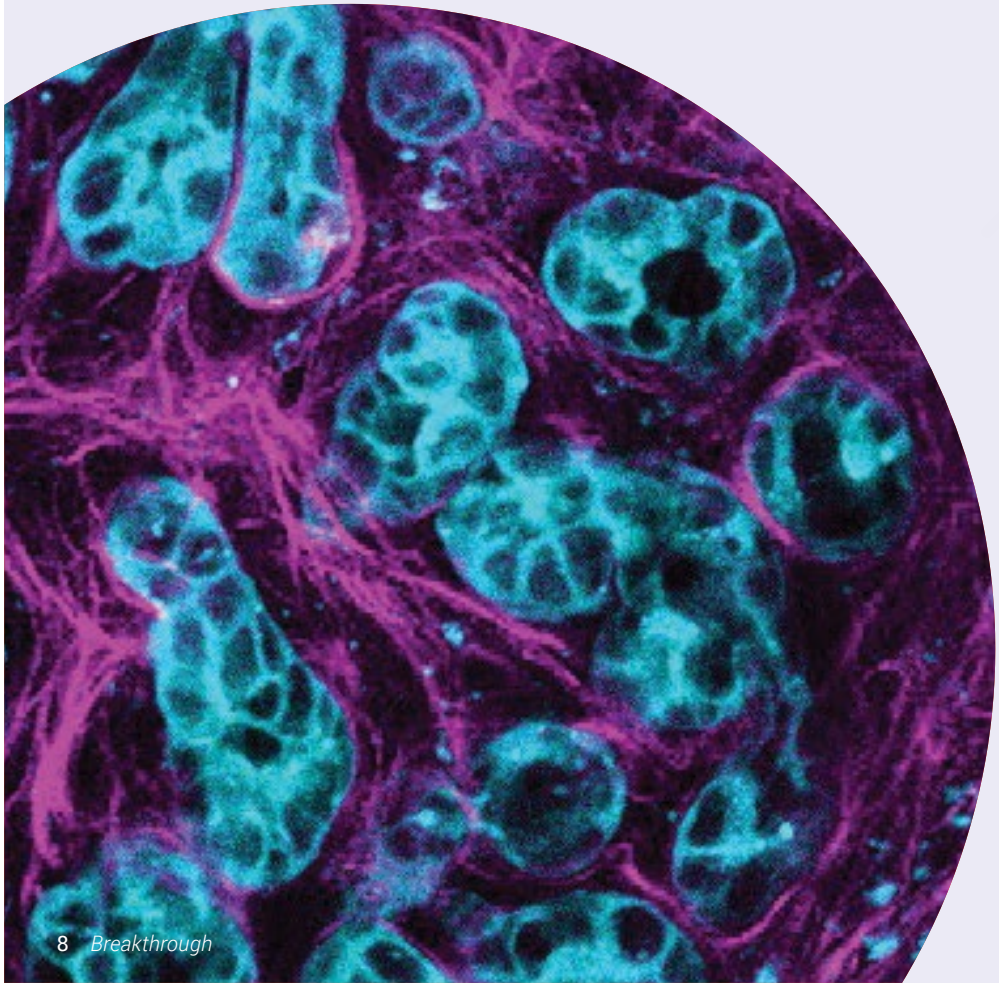


Image: Pancreatic cancer cells activate the molecule AKT (blue) to multiply and spread along connective stroma (pink) in the cancer environment. Credit: Max Nobis (VIB-KU Leuven Center for Cancer Biology)

Associate Professor Marina Pajic

Personalising therapy

Associate Professor Marina Pajic has established a precision oncology program in pancreatic cancer, which builds on our knowledge of the genomes of patient tumours and the environment that envelops and protects the cancer cells, to understand how chemoresistance develops. Her team is using this information to find new treatment targets and develop effective, personalised therapies. This includes investigation into whether short bursts of a new therapy against a cancer-promoting target (ROCK), can significantly sensitise pancreatic tumours to standard of care therapies. Building on the current clinical trials activity in her program and early promising pre-clinical data from this project, a phase 1 study based on this target is currently being planned for 2024.

Supercharging chemotherapy and immunotherapy

Dr Sean Porazinski and his team are investigating whether an existing treatment targeting a protein called PORCN (pronounced “porcupine”) that promotes tumour growth could be repurposed to treat pancreatic cancer. So far, the results are promising: this PORCN inhibitor has been shown to limit the cancer cell's ability to hide from the immune system, making targeted treatments more effective. If successful in further studies, it could be used in combination with chemo and immunotherapies that are already used in the clinic, to yield even greater results than using either treatment on its own.

Dr Sean Porazinski

Professor Paul Timpson

Imaging live drug response

Professor Paul Timpson has developed a ‘biosensor’ mouse model that produces a fluorescent version of the AKT molecule, which is often overly active in pancreatic cancer. Using live microscopy, his team found AKT remains switched on in pockets of drug resistance, especially in low oxygen areas or at the edge of tumours. The researchers will now investigate combination treatments to overcome this resistance to chemotherapy.

Insights into rare genetic immune disorders

Garvan researchers have identified the cellular glitches underlying a rare genetic disorder called activated PI3K Delta Syndrome 2 (APDS2).

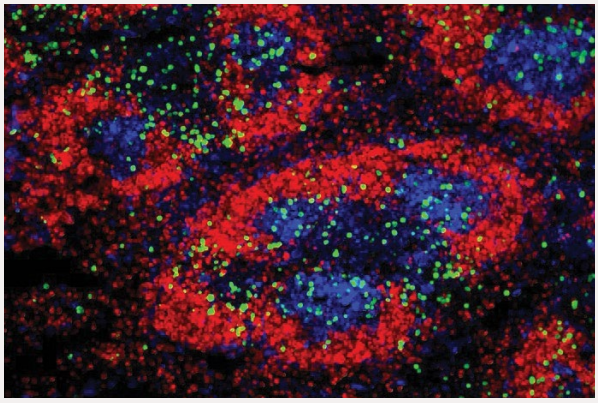
The disorder is caused by genetic variations that disrupt immune cell signalling through a protein called PI3K.

PI3K plays a crucial role in activating immune cells for growth, proliferation, survival, migration and function. The Garvan researchers, led by Associate Professor Elissa Deenick, found that the genetic variations in APDS2 and a similar disorder, APDS1, alter PI3K signalling in different ways, leading to distinct effects on the immune system.

In APDS2, fewer responding B cells are generated in response to vaccination, whereas in APDS1, the number of T cells is reduced. In both cases, the disorders result in poor antibody responses and in APDS2, variations appear to affect non-immune cells, resulting in growth delays.

The findings reveal how finely tuned immune cell signalling must be and how even minor disruptions can lead to immune deficiency or dysfunction. This is a significant step towards understanding the molecular processes involved in these disorders and developing more targeted and effective treatments.

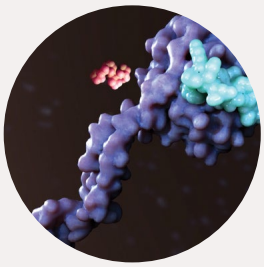
Find out more



The immune system's T cells (green) helping B cells (in the red zone) to make antibody responses inside the spleen.

Triple-negative breast cancer clinical trial

Associate Professor Christine Chaffer



Androgen receptor hormone

We are calling for volunteers for a clinical trial that aims to improve survival rates for patients with triple-negative breast cancer, a treatment-resistant form of cancer that can quickly adapt against chemotherapy.

Led by Associate Professor Christine Chaffer, the 4CAST clinical trial is testing a new combination therapy to target a 'defence switch' on cancer cells that alerts cancer to the threat of chemotherapy. The trial is being conducted at The Kinghorn Cancer Centre in Darlinghurst.

For further information about the trial (NCT04947189) or to register your interest, please email 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).

Have you recently been diagnosed with type 2 diabetes?

We are seeking volunteers to participate in the Reverse Engineering Insulin Secretion in Health and Disease (iSEC) study, focused on understanding how the pancreas regulates insulin release to manage blood sugar levels after a meal.

If you are 18 to 60 years old and have not yet received treatment with a sugar-lowering medication, or are currently treated solely with metformin, we would be interested in hearing from you. The study involves up to two visits to the Garvan Institute, you will have the opportunity to consult with a dietitian and will be compensated for your time and inconvenience.

To contact the iSEC team, email: **isec@garvan.org.au** or call: **(02) 9295 8253**

The study has been approved by the St Vincent's Hospital Human Research Ethics Committee (HREC 2020/ETH02405).

Donations made in memory of loved ones

Barbara Adamson
Gordon Adamson
Trevor W Annetts
Noel R Armstrong
James A Atputharajah
Heather Baillie
Caroline Batchelder
Vasumati Bhagwandas
Julia Blackwood
Beverley Bolton
Lynn Bright
Jane Bryant
Alannah L Buddery
Allan R Budinsky
Rex L Burchell
Gail Burgin
Frank E Burtt
Ann Callen's dear friend Annette
Franc Carter
Patricia Cheah
Peter Clarke
Margaret Collins
Craig Henry Colman
Alan and Greg Connell
John Thomas Conway
Norma & Robert Cook
Katina Costas
Suann Croker
Rosemary Crossley AM
G R Curnow
Jill Curnow
Sheila Curnow
Eva Curran
Graham W Curtis
Marie's Dad
Joan and Ross Daniels
Barbara Das
Karen Davidson
Janelle K Davis
Joseph Delia
Judith Dewick
Laurel Dixon
Helen Dowd
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Phillis Driver
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Julie Anne Fakes
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Michael Finnane
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Adrian Notley
Peter O' Neill
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Hazel Paton
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Anna Pelosi
Maryanne Pickup
Senthil Prabaharan
Henryk Pragniacy
Justin David Price
Stephen Rawlins
Katrina Roberts
Pat Robinson
Paul James Rogers
Roger Rose
Peter Rouse
Jose Maureen Ryan
S C Clacy's son
Martin Samociuk
Anthony Samons
Judy Sargeant
Amanda Scott
Eleanor Seager
Maysin Seeto
John Sewell
John Richard Shepherd
Raymond Sly
Rita Sly
Derek Smith
Joan Smith
Katie Jane Smith
Robert Smith
William Smith
William Horatio Patrick Smith (OAM)
Richard Somaratne
Sandra Spears
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June Tayler
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Geoffrey R Vinall
Kenneth D Watson
Peter White
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Allan Wolftasker
Helen Wong
Richard Yap
Yow Ming Yee
Simone Young
Chu Choi Yuk
Enrico Zanotto
Stan Zekanovic
Danuta Zmitrowicz

Donations made in celebration

Elizabeth Efinger's 90th Birthday