

# breakthrough

**New cell  
subtypes found  
in triple negative  
breast cancer**

Also in this issue

**New hope for  
dementia care**

**A life changing discovery  
through CIRCA**



**Garvan Institute  
of Medical Research**



# Welcome from our Executive Director



**Dear Garvan family,**

Welcome to the final edition of *Breakthrough* for 2020. I am delighted to be able to round out this challenging and uncertain year by sharing some outstanding research breakthroughs from our dedicated scientists.

In this *Breakthrough*, you'll read about the discovery of four new cell subtypes in triple negative breast cancer (page 6). You'll meet Michael, who after decades of unexplained immune symptoms, received life changing treatment following a genetic diagnosis through the Garvan-led CIRCA program. You'll also discover the results of a six-year research study revealing a link between metformin use (a common treatment for type 2 diabetes) and slower cognitive decline and lower dementia rates.

I know we've all been spending some time reflecting on how much we as a community have had to confront this year. The globe has and is being threatened by a virus, an illness, and at its core, finding a solution to an illness or disease is something every researcher works towards. The recent evidence of COVID-19 protection from vaccines is a reason to be cheerful: the war is going our way but we've a long way to go, and Garvan researchers are at the front-line. We know now, more than ever, the vital importance of scientific research for the benefit of humanity.

Throughout the challenges of this time, your unwavering support for Garvan's research has inspired our researchers to strengthen their resolve and continue to strive for ways to solve disease. Thank you.

I look forward to welcoming you all back to Garvan just as soon as it is safe to do so.

To you, your friends and loved ones, I extend my most sincere well wishes for a happy and healthy festive season.

Regards,  
Yours sincerely,

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

## RESEARCH NEWS

### Guiding the next generation of advanced ER+ breast cancer therapy

In a proof-of-principle study, Garvan researchers have revealed a potential therapeutic approach for targeting oestrogen receptor positive (ER+) breast cancers resistant to current therapies.

By combining current gold-standard treatments with a drug that restores the activity of p53, a cancer suppressor protein, the researchers found they could sensitise breast cancer cells to therapy and slow cancer growth in laboratory models of ER+ breast cancer.

The findings are a promising step towards better treatments for breast cancer, which affects almost 20,000 individuals each year in Australia alone.

The researchers are now developing clinical trials at St Vincent's Hospital Darlinghurst to test the new approach in patients with advanced breast cancer.



Visit: [garvan.org.au/therapy](https://garvan.org.au/therapy)

### The Variant Atlas data platform

A new genomics platform, called Variant Atlas, developed by a team of Garvan researchers, will provide new insights into some of the most devastating inherited conditions through anonymised genomic and clinical summary data made available by Australian Genomics.

Variant Atlas connects the genomic and clinical data of research participants from four Australian rare disease clinical studies, including studies of mitochondrial disorders and brain malformations. It's hoped this platform will drive new insights and help identify better treatments for a range of conditions.

"Genomic data can be challenging to work with, yet accessibility of data is so critically important to resolving undiagnosed cases, fostering research collaborations and for making those all-important breakthroughs," says Dr Warren Kaplan, Chief of Informatics at the Kinghorn Centre for Clinical Genomics at Garvan. His team manages the processing and integration of genomic and clinical data into the platform.



Visit: [garvan.org.au/genomic-data](https://garvan.org.au/genomic-data)

# New hope for dementia care

A six-year study of older Australians with type 2 diabetes has uncovered a link between metformin use and slower cognitive decline and lower dementia rates.



***“This study has provided promising initial evidence that metformin may protect against cognitive decline.”***

**– Professor Katherine Samaras**

**Metformin is the first-line treatment for most cases of type 2 diabetes and one of the most commonly prescribed medications worldwide, with millions of individuals using it to optimise their blood glucose levels.**

A new research study, conducted over six years in the Sydney Memory and Ageing Study in 1,037 Australians (aged 70 to 90 years old at baseline), has revealed an additional effect: individuals with type 2 diabetes who used metformin experienced slower cognitive decline with lower dementia rates than those who did not use the medication.

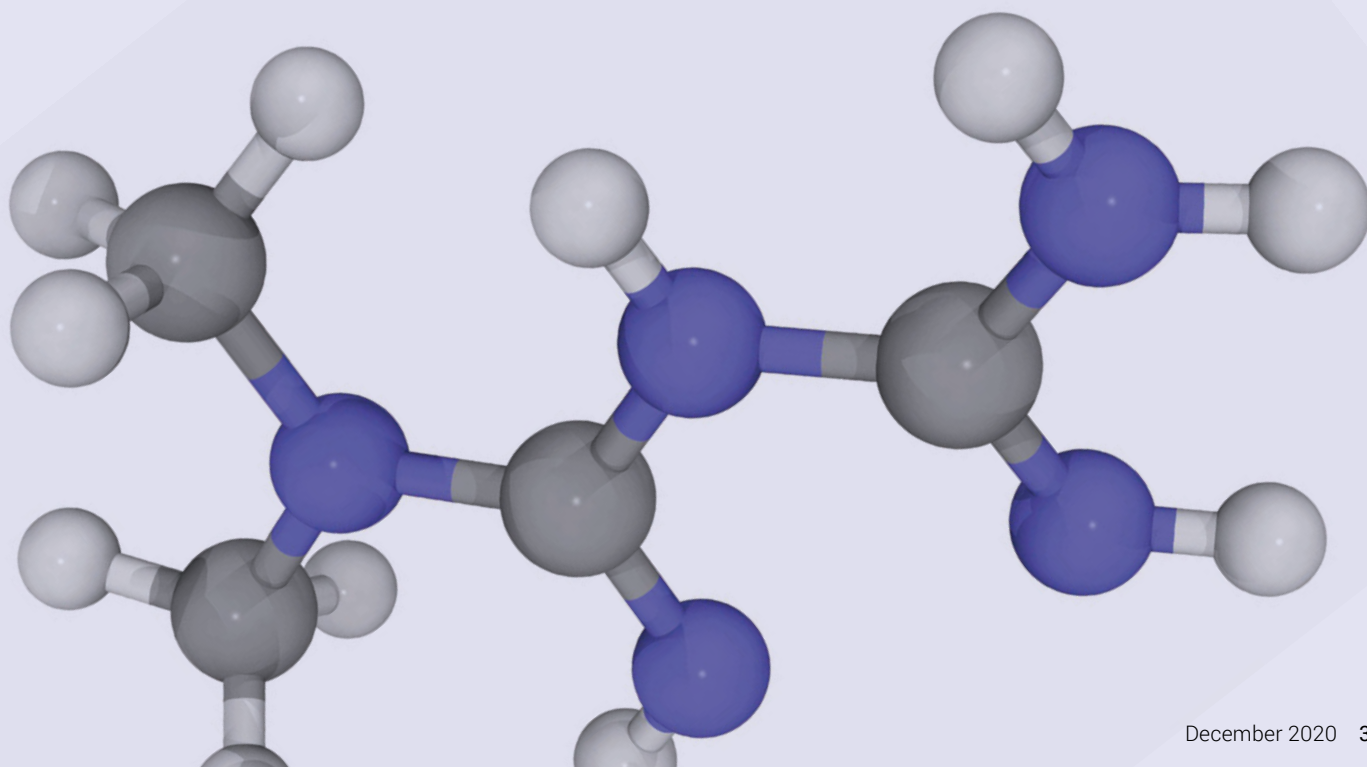
The study, led by researchers at the Garvan Institute of Medical Research and the Centre for Healthy Brain Ageing (CHeBA), UNSW Sydney, provide new hope for a means of reducing the risk of dementia, which is currently estimated to affect nearly 47 million people worldwide.

“This study has provided promising initial evidence that metformin may protect against cognitive decline,” says study author Professor Katherine Samaras, Leader of the Healthy Ageing Research Theme at the Garvan Institute and endocrinologist at St Vincent’s Hospital Sydney.

“To establish a definitive effect, we are now planning a large, randomised controlled trial of metformin in individuals at risk of dementia and assess their cognitive function over three years. This may translate to us being able to repurpose this cheap medication with a robust safety profile to assist in preventing against cognitive decline in older people.”



Visit: [garvan.org.au/cognitive](https://garvan.org.au/cognitive)





# Partner for the Future

In honour of Diana Walder OAM



Diana Walder OAM. Former President and Life Governor of the Art Gallery of New South Wales was awarded the Medal of the Order of Australia in 1992 for her service to the arts.

Samantha Walder understands how disease can tragically touch the lives of almost anyone, after her mother, Diana Walder OAM passed away from dementia, spurring Samantha to become a *Partner for the Future* by including a future bequest in her Will to Garvan.

"My mother gave me a wonderful life and after caring for her in her last few years while living with dementia, I knew I wanted to do something in tribute of her amazing life and the contributions she made to the community and Australia".

Samantha was first introduced to Garvan several years ago by her friend Ross Steele AM, and has been a devoted supporter ever since. "I was aware of the Garvan Institute's good work and excellent reputation alongside their long-term relationship with St Vincent's Hospital."

"I also knew I wanted to do all I can to help people and families living with the impacts and consequences of dementia. Following a tour of Garvan's facilities and the opportunity to speak with their leading neuroscience researchers, it was an easy decision for me to include a future gift in my Will to Garvan."

"I feel proud that my future bequest, the Endowed Diana Walder OAM Research Fellowship for dementia research, will be honouring Mum and that both our legacies will be making a positive impact on future generations".

"During the difficulties faced by the world in the last 9 months, my commitment to supporting Garvan in my Will is even stronger."

***"I believe in medical research as the starting point for understanding the chronic diseases that affect most families and in finding better treatments and cures one day." – Samantha Walder***

**To find out how easy it is to help change the future of medicine with a gift in your Will, please contact our Bequest Manager, Donna Mason on (02) 9295 8559 or [bequests@garvan.org.au](mailto:bequests@garvan.org.au) or visit [garvan.org.au/bequest](http://garvan.org.au/bequest)**

# CITY2SURF goes virtual

**Community fundraising has looked a little different this year with COVID-19 restrictions impacting the ability for many of our fundraisers to hold or join their usual events.**

This year marked the City2Surf's 50th anniversary and the launch of its first ever virtual event. Instead of joining the throngs running down William St towards Bondi, Team Garvan members proudly took to their own neighbourhood streets between the 16-18 October to complete 14kms of fun, whether that was walking, skipping or running. Garvan would like to sincerely thank all of the participants for their amazing efforts raising much needed funds for our research.

Staff from Garvan's Australian BioResources took to their local areas not only supporting Garvan's research through their wonderful fundraising efforts but also in solidarity with their local community affected by the bushfires in December 2019. Jane Kirschner, Senior Animal Technician, completed her 4th year running for Team Garvan and this year was joined by her 9-year-old son Jimmy. They chose to complete their 14kms over their local fire trails in Yanderro and Bargo, in the Southern Highlands, where some of their neighbours lost their houses to the bushfires. Thank you to Jane and Jimmy for raising over \$400 for Garvan's research.



Jane Kirschner and her son Jimmy walking their local fire trails

## Thank you to our community fundraisers

In these uncertain times we have seen the best of our community emerge. With many of our fundraising events postponed due to COVID-19 restrictions, we have been very grateful to our generous supporters innovatively fundraising in other ways. Thank you to our many supporters who have asked for donations instead of receiving gifts for birthdays or other celebrations this year.

**If you would like to donate to medical research instead of receiving or giving gifts this Christmas, please contact our Supporter Care Team on 1300 73 66 77 or [foundation@garvan.org.au](mailto:foundation@garvan.org.au); or visit [fundraise.garvan.org.au/gift](https://fundraise.garvan.org.au/gift) to download a gift card.**

## Research News

### Flexible targets help immune system make finely-tuned antibodies

Garvan researchers have discovered a key strategy used by the immune system to generate effective antibodies. The team, co-led by Garvan's Executive Director Professor Chris Goodnow, found the immune system mutates its B cells to generate more finely-tuned antibodies when the targets for those antibodies, referred to as 'antigens', were structurally flexible, rather than rigid. By taking this approach, the immune system creates antibodies that are finely-tuned to foreign molecules.

"Our findings address a central issue for developing vaccines – how the immune system generates antibodies that recognise 'foreign' from 'self'," says co-senior author Professor Daniel Christ, Head of Antibody Therapeutics and Director of the Centre of Targeted Therapy at Garvan.

"Taking a comprehensive analytical approach, we found that a flexible target allows the immune system to create antibodies more finely-tuned to foreign molecules, which we hope will play a role in informing the design of future vaccines."

Visit: [garvan.org.au/tuned](https://garvan.org.au/tuned)

### Boost for Parkinson's research

Leading researchers from the USA and Garvan will use cutting-edge technology to reveal the complex interplay of genes, molecules, cells and age-related factors that trigger Parkinson's disease, through a significant grant from the Aligning Science Across Parkinson's initiative. Parkinson's is a debilitating neurodegenerative condition that is estimated to affect more than 10 million worldwide, but for which there is no known cause.

In brain cells developed from normal and patient-derived induced pluripotent stem cells (iPS cells), the researchers will investigate how genomics and the 'second hit' risk factors – the interplay of different molecules, brain cells and ageing – shape individual disease risk.

The researchers hope this new understanding will enable early diagnosis and prediction of therapeutic targets that could halt or reverse the disease, and identify subgroups of Parkinson's that may help improve the diagnosis and treatments of individual patients.

At the Garvan Institute, the project will be led by Associate Professor Joseph Powell and carried out in association with the Australian Parkinson's Mission (APM), an Australian-led international collaborative research and clinical trials program largely funded by the Medical Research Futures Fund, that aims to slow, stop and cure Parkinson's disease.

Visit: [garvan.org.au/project](https://garvan.org.au/project)



# New cell subtypes found in triple negative breast cancer

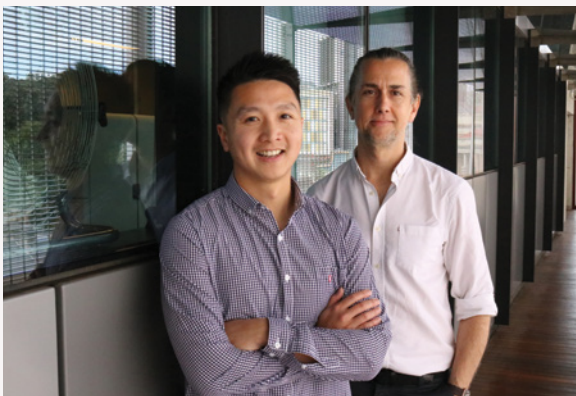
Garvan researchers have identified four new subtypes of cells in the breast cancer 'ecosystem', uncovering promising targets for therapy.

**Using cellular genomics, researchers from the Garvan Institute of Medical Research have uncovered four new subtypes of cells within triple negative breast cancers, some of which produce molecules that suppress immune cells and may help cancer cells evade the body's immune system.**

These new findings could lead to a new class of therapies for triple negative breast cancer, a devastating disease with limited treatment options.

"Patients with triple negative breast cancers have a poor prognosis, in large part because treatment approaches have advanced very slowly," says lead researcher Associate Professor Alex Swarbrick, Head of the Tumour Progression Laboratory at Garvan.

"We searched for new potential targets for therapy by analysing the individual cells inside triple negative breast tumours. This includes not only the cancer cells themselves, but also the surrounding host cells, such as immune and connective tissue cells, which can be thought of as the cancer 'ecosystem' that supports a tumour to grow and spread," explains Sunny Wu, first author of the study.



Sunny Wu and Associate Professor Alex Swarbrick

## **Cancer's 'ecosystem' suppresses the immune system**

The researchers used next-generation sequencing to create a snapshot of gene activity in 24,271 individual cells extracted from the biopsy samples of five triple negative breast cancer patients. By analysing the profiles of active genes, the researchers revealed four cell subtypes of stromal cells, which form the connective tissues in the body. Previous studies in triple negative breast cancers had generally considered there to be only one type of stromal cell.

***The researchers revealed surprising interactions between the signalling molecules produced by these stromal cell subtypes and immune cells.***

"Our findings suggest that there is significant crosstalk between the immune system and stromal cells, which were generally thought to have only a structural role in cancers," says Associate Professor Swarbrick. "This is significant because immunotherapy – which is designed to activate the patient's immune system against a tumour – has limited response in many patients with triple negative breast cancer."

### New directions for cancer treatment

The researchers say that combining immunotherapy with a treatment that stops the interaction between stromal cells and immune cells holds promise for improving the treatment of triple negative breast cancer.

The team will now analyse further breast cancer samples, to obtain an even better understanding of the cells that comprise triple negative breast cancers, their interactions and how these can be manipulated to stop disease progression.

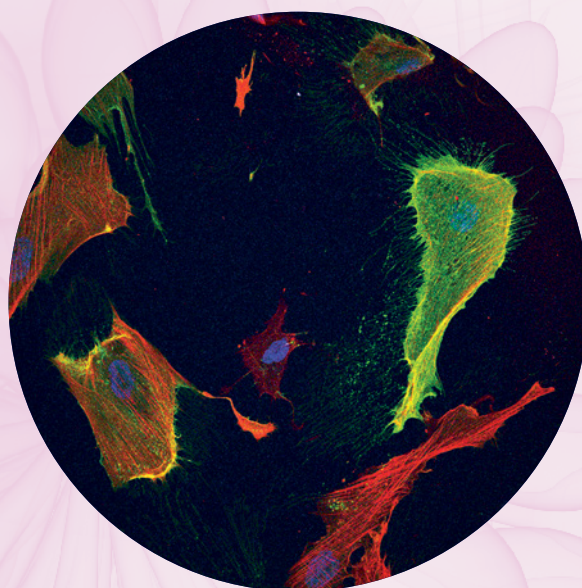
"Pathologists have been describing cancers under the microscope for more than 150 years, but we still only have a shallow understanding of the cells that are there," says Associate Professor Swarbrick.

Cellular genomics is showing us that what we once thought of as one cell type is in reality a diversity of cell types, which will have a significant impact on how we tailor treatments in future."

This research was supported by funding from the National Breast Cancer Foundation (NBCF) of Australia, Mr John McMurtrie AM and Mrs Deborah McMurtrie, G P Harris Foundation, Skipper-Jacobs Charitable Trust and the Sydney Breast Cancer Foundation.

A/Prof Swarbrick is the Petre Foundation Chair for Breast Cancer Research and Senior Research Fellow of the NHMRC.

To find out more visit  
[garvan.org.au/ecosystem](https://garvan.org.au/ecosystem)



***"Cellular genomics is showing us that what we once thought of as one cell type is in reality a diversity of cell types, which will have a significant impact on how we tailor treatments in future."  
– Associate Professor Alex Swarbrick***

# A LIFE-CHANGING DISCOVERY

Michael had suffered from mysterious medical symptoms his entire life. He received a life-changing treatment following a genetic diagnosis through the Garvan-led CIRCA program.

**Michael had severe childhood asthma and a long-standing history of cognitive dysfunction, gastrointestinal symptoms, joint pain and chronic fatigue, which began in his mid-teens and progressively worsened over four decades.**

In his 40s, he developed classic Kaposi's sarcoma, a rare cancer of the lymphatic cells, which had initially been treated successfully with chemotherapy, but had since relapsed and was not responding to treatment.

In 2015, Michael was referred to Professor Tri Phan's clinic by his immunologist through the Clinical Immunogenomics Research Consortium Australasia (CIRCA) program.

"We suspected his broad spectrum of symptoms might be due to abnormalities in his immune system," says Professor Phan, who heads the Intravital Microscopy and Gene Expression Lab at Garvan. "His blood tests revealed an unusual immune cell profile I'd only ever seen once before in a patient with a rare genetic immunodeficiency."

Professor Phan's research team analysed Michael's genome from a blood sample.

One gene variant stood out as a possible cause – a variant in the CTLA4 gene, which had not been reported as significant before. CTLA4 is an immune checkpoint protein that 'puts the brakes' on the immune system.

"In Michael's case, the CTLA4 'brake' wasn't working – the immune system was overshooting and overworking, resulting in 'exhaustion' of immune cells and an immunodeficiency," says Dr Jin Yan Yap, the first author of the study published in *Journal of Clinical Immunology*.

One gene variant stood out as a possible cause – a variant in the CTLA4 gene, which had not been reported as significant before.

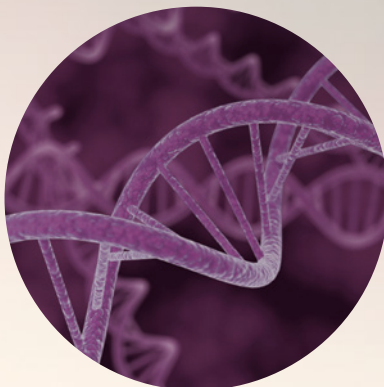
The diagnosis revealed an existing medication to be an effective treatment and provided relief after a lifetime of unexplained immune symptoms.







Michael Bucciarelli



Professor Tri Phan

## The guide to targeted therapy

This diagnosis revealed an existing medication to be an effective treatment and provided relief after a lifetime of unexplained immune symptoms.

"We administered a drug called everolimus, an immunosuppressant drug that also boosts immune cells called regulatory T cells. These cells suppress unrestrained activation of conventional T cells and restore the normal function of immune cells. For Michael, we think they restored a normal immune response and recalibrated his anti-cancer immunity," says Professor Phan.

Within a few months, Michael started feeling better and he reported higher levels of energy, a longer attention span and reduction in gastrointestinal symptoms. His cancer is now in remission.

"I have been sick since infancy but as my illness was never validated, I've suffered in silence for years. I suspected early on that my symptoms were somehow interlinked. The diagnosis and treatment has given me hope in my life," says Michael.

"Patients like Michael often suffer from long diagnostic odysseys as their conditions are very rare and difficult to diagnose without access to a multidisciplinary team of dedicated doctors and scientists. We were fortunate we were able to solve his case," says Professor Phan.

***"There is significant potential for genomic studies of patients with primary immunodeficiency diseases like Michael to teach us more about how we can harness the immune system to fight cancer."***  
– Professor Tri Phan

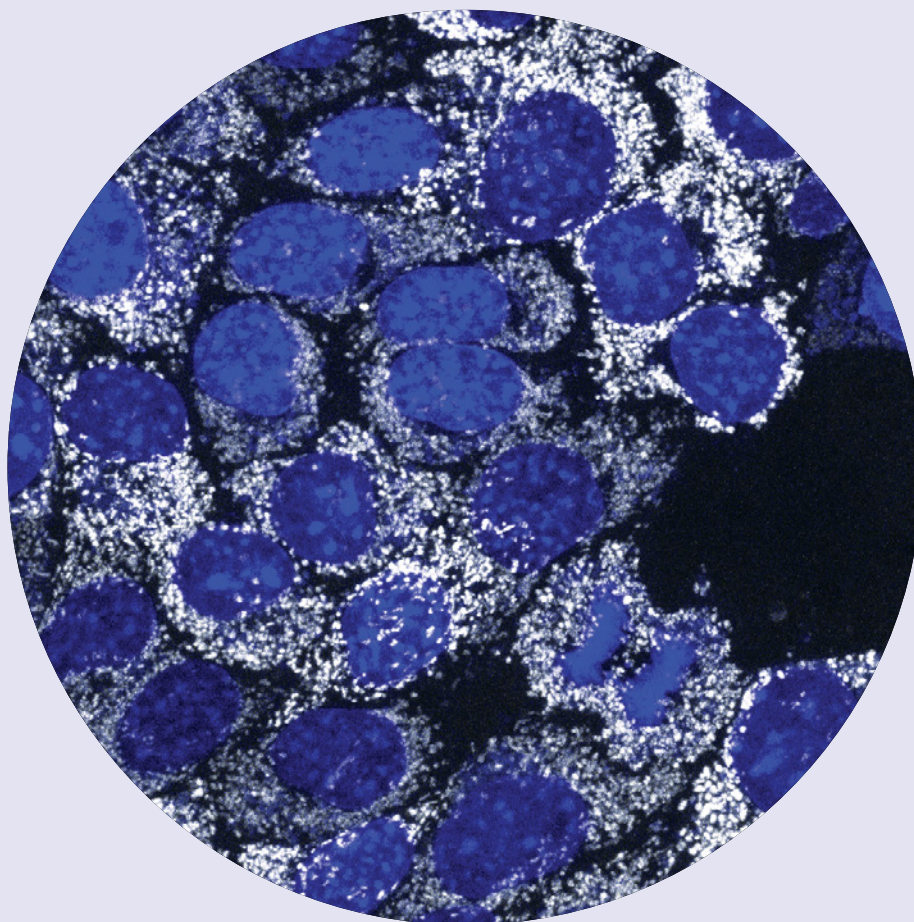
*This research was supported by the John Brown Cook Foundation, Jeffrey Modell Foundation, UNSW Triple I SPHERE Clinically Accredited Group, NSW Office of Health and Medical Research, St Vincent's Clinic Foundation, Allergy and Immunodeficiency*

*Foundation of Australia (AIFA), Garvan-Weizmann Partnership, the David Cooper Memorial Fund, NHMRC and federal funds from the Frederick National Laboratory for Cancer Research.*

To find out more visit  
[garvan.org.au/target-treatment](https://garvan.org.au/target-treatment)

# THROUGH THE MICROSCOPE

Our researchers are investigating how the firmness of tumour tissue impacts cancer behaviour.



**Even the most aggressive cancer cells need a nurturing environment to thrive. That's no different for the triple negative breast cancer cells captured in this image by Garvan researcher Dr Elysse Filipe.**

She is developing new tools that mimic the 3D properties of healthy and tumour tissue to investigate how cancer cells adapt to, and thrive in these altered environments. Dr Filipe's ultimate aim is to find new vulnerabilities that could be used to target the cancer cells.

This image shows cancer cells suspended in a physiologically relevant matrix, which mimics a tumour tissue, with cell nuclei shown in blue and mitochondria – the powerhouses of the cell – shown in white.

Dr Filipe investigates how the 3D tumour tissue can change the activity, adaptability and aggressiveness of cancer cells, including the mitochondria shown here, which can determine how and when cancer cells spread (metastasise) around the body.

Metastasis remains one of the biggest challenges in the treatment of cancer. Through a better understanding of how cancer cells behave in different environments, Garvan researchers hope to help develop new and better approaches that allow tailored treatments for individual patients.



# Philanthropy

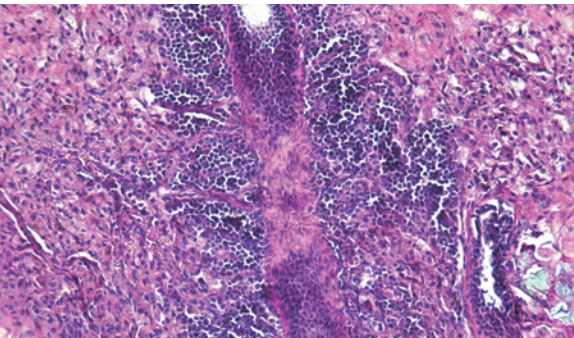
## advances science faster

Our researchers are changing the future of health through paradigm shifting research. The visionary support of our Garvan family makes it possible.

**As head of the Tumour Progression Lab, Associate Professor Alex Swarbrick and his team are dedicated to developing earlier detection and treatment strategies for breast cancer, in addition to prostate cancer, melanoma and childhood cancer neuroblastoma, through a range of novel research programs.**

Philanthropy plays a pivotal role in the developmental phases and progression of research such as A/Professor Swarbrick's programs. Through the generosity of donors such as Garvan Life Governors Mr John McMurtrie AM & Mrs Deborah McMurtrie, and Garvan Governors the Skipper-Jacobs Charitable Trust and the GP Harris Foundation, these programs have been able to flourish significantly. This long-term support has not only provided foundational funding for novel research but it also enabled the development of programs with international reach and impact.

The 'Breast Cancer Cell Atlas', an ambitious project led by A/Professor Swarbrick is one such project that will catalogue data from a million individual cells from patient breast tumours, collected over the past five years, and will be the most comprehensive view of breast cancer yet. The project will complement the Human Cell Atlas project, a global initiative aiming to map every single cell in the healthy human body, which could have a significant impact on our understanding of disease.



Microscopic image of breast cancer cells



Garvan Life Governors Mr John McMurtrie AM and Mrs Deborah McMurtrie

Enduring philanthropic funding has also enabled the development of the Metastasis Access Research (MonARCh) Collaboration, where the team collect metastatic tumours from patients with end-stage metastatic breast cancer to study how the immune system of cancer patients changes as the disease progresses.

The generous support of Garvan donors truly makes a world of difference to not only the researchers and the Institute, but to those who ultimately suffer from disease and to those that will benefit from the breakthroughs that emerge.

***"Collaboration is critical in getting research breakthroughs from the lab to clinical use, and without long-term philanthropic support from donors like Mr and Mrs. McMurtrie, the Skipper-Jacobs Charitable Trust and the GP Harris Foundation, we couldn't do what we do."***

***– Associate Professor Alex Swarbrick***

# From the Breast Cancer Lab to You

Garvan is home to one of the largest breast cancer research groups in Australia.

**Our scientists investigate how breast cancer develops, spreads throughout the body and how it is best treated. We are uniquely positioned to increase the understanding of breast cancer and create more effective personalised therapies through our deep understanding of DNA sequencing and analysis.**

'From the Breast Cancer Lab to You' is Garvan's annual community update on breast cancer. Due to COVID-19, this year we launched our first virtual version of the symposium. The event serves as a platform for Garvan researchers to provide an update on advances in new treatments, drug resistance and metastasis, as well as new clinical trials.

Dr Sarat Chandarlapaty, oncologist and Laboratory Head at the Memorial Sloan Kettering Cancer Centre, New York was awarded the Connie Johnson Award for Breast Cancer and gave a keynote talk about his research.



Dr Sarat Chandarlapaty



We have been fortunate to receive long-term support from Estée Lauder Companies from their Breast Cancer Campaign. Estée Lauder Companies provide an annual award to fund a young breast cancer researcher to undertake an innovative project which tests a novel early stage idea. This year PhD student Sarah Alexandrou was awarded the annual Breast Cancer Award to investigate the mechanisms of resistance in combination therapy in advanced/metastatic oestrogen receptor positive (ER+) breast cancer to help discover why resistance develops, and to guide the development of effective patient treatment when resistance emerges.



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## CLINICAL STUDIES

### Breast cancer clinical trials

We offer a range of clinical trials for patients with either early or advanced-stage breast cancer, and patients that are undergoing breast cancer surgery. All trials are held at The Kinghorn Cancer Centre, Darlinghurst NSW.

Find more information and the full list of trials at [garvan.org.au/breast-cancer-trials](http://garvan.org.au/breast-cancer-trials)

### 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](mailto:predict@garvan.org.au)



## Jewellery with Purpose

Paspaley, long-time supporters of the Garvan Institute of Medical Research, reached \$1 million in donations to the Molecular Screening and Therapeutics program (MoST) in September this year. Since November 2016, Paspaley have been donating a portion of each Kimberley Bracelet sold to MoST – an innovative program matching the genetic profile of patient tumours with personalised treatment plans for patients with rare and less common cancers.

The Paspaley Kimberley Bracelet and Dark Kimberley Bracelet reflect the raw beauty of Australia's North-West coast, through a striking combination of pearls, sandalwood and onyx. With the help of Paspaley's generous support, the MoST program has recruited over 2,200 patients who have exhausted all other treatment options, with 10 major centres now involved in the program across the country. We want to sincerely thank Paspaley for their continued generosity and visionary commitment to breakthrough medical research.

**To give a gift that means more this holiday, please visit [garvan.org.au/paspaley](http://garvan.org.au/paspaley) today.**



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Ruth Bell's 70th Birthday

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