December 2022 | Issue 52

breakthrough

Inclusive genomics

We've launched a new centre to improve health care for all Australians

Also in this issue

A new study aims to 'prime' pancreatic cancer for more effective treatment

The latest insights into macular degeneration and glaucoma revealed

Garvan Institute of Medical Research

Welcome from the Executive Director (interim)

Dear Garvan family,

Welcome to the final edition of *Breakthrough* for 2022. We've had a successful and productive year at the Garvan Institute. Driven in large part by your generosity, our researchers continue to discover the unknown in health and disease through high impact research findings.

I am thrilled to finish the year by sharing some of our latest research and news with you. On pages 6-9, you will read about the Centre for Population Genomics (CPG) which is an exciting new partnership between Garvan and the Murdoch Children's Research Institute (MCRI) in Melbourne. CPG is an Australian-first centre that will house a genomic database of culturally and linguistically diverse populations, making it easier to tailor health care to all Australians and eventually to all people around the world.

On page 10, you will read about the single-cell genomic techniques that have revealed insights into macular degeneration and glaucoma. The research undertaken by a team of scientists at Garvan, co-led by Professor Joseph Powell, uncovered these new genetic signatures which will pave the way for better diagnosis and treatment for these two eye diseases.

Finally, on page 11, you will learn about our new Phase 2 clinical trial, which aims to provide patients with a more effective treatment for pancreatic ductal adenocarcinoma, an aggressive form of pancreatic cancer. The new study aims to 'prime' the pancreas, making it more sensitive to chemotherapy.

As the year ends and reflecting on what's been achieved with your help, I want to extend my heartfelt gratitude from everyone here at Garvan for your unwavering support. The research completed, ongoing and planned would not be possible without you. In February 2023 we will celebrate Garvan's 60th anniversary – we're looking forward to recognising this momentous milestone and the many breakthroughs we have achieved over the last six decades.

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

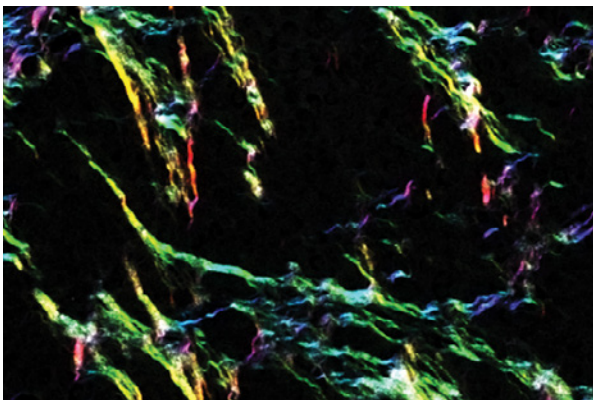
Regards,

Professor Peter Croucher
Executive Director (interim)

Front cover image:
Leading Hand Design
Garvan's Kate Patterson

RESEARCH NEWS

Collagen is a key player in breast cancer metastasis



Collagen fibres running through a cancer tumour, created using a multiphoton microscope.

The level of collagen type XII in breast tumours plays an important role in triggering the spread of cancer cells around the body – a process known as metastasis – according to a recent study by **Associate Professor Thomas Cox,** Head of Garvan's Matrix and Metastasis lab.

Associate Professor Cox's team found that collagen type XII plays a key role in regulating the organisation of the tumour matrix. The tumour microenvironment is the ecosystem that surrounds a tumour, one component of which is the extracellular matrix, which provides structural and functional support to cells and tissues.

Cancer cells constantly interact with the tumour microenvironment, affecting how a tumour grows. Collagen is an important part of this tumour microenvironment, but how it influences tumours has not been understood.

"There's still a lot we don't know about the role of the extracellular matrix in cancer metastasis. Our study shows that collagen XII plays an important role in breast cancer progression and metastasis," says senior author, Associate Professor Cox. "Imagine cancer cells as seeds, and the tumour microenvironment as the soil. By studying the soil – the extracellular matrix – we can begin to understand what makes some tumours more aggressive than others, and by extension, begin to develop new ways to treat cancer," he explains.

The team found that as levels of collagen XII increased, so did metastasis, suggesting that measuring the level of collagen XII in a patient's tumour biopsy could potentially be used as an additional screening tool to identify aggressive breast cancers with higher rates of metastasis, such as triple-negative breast cancer.

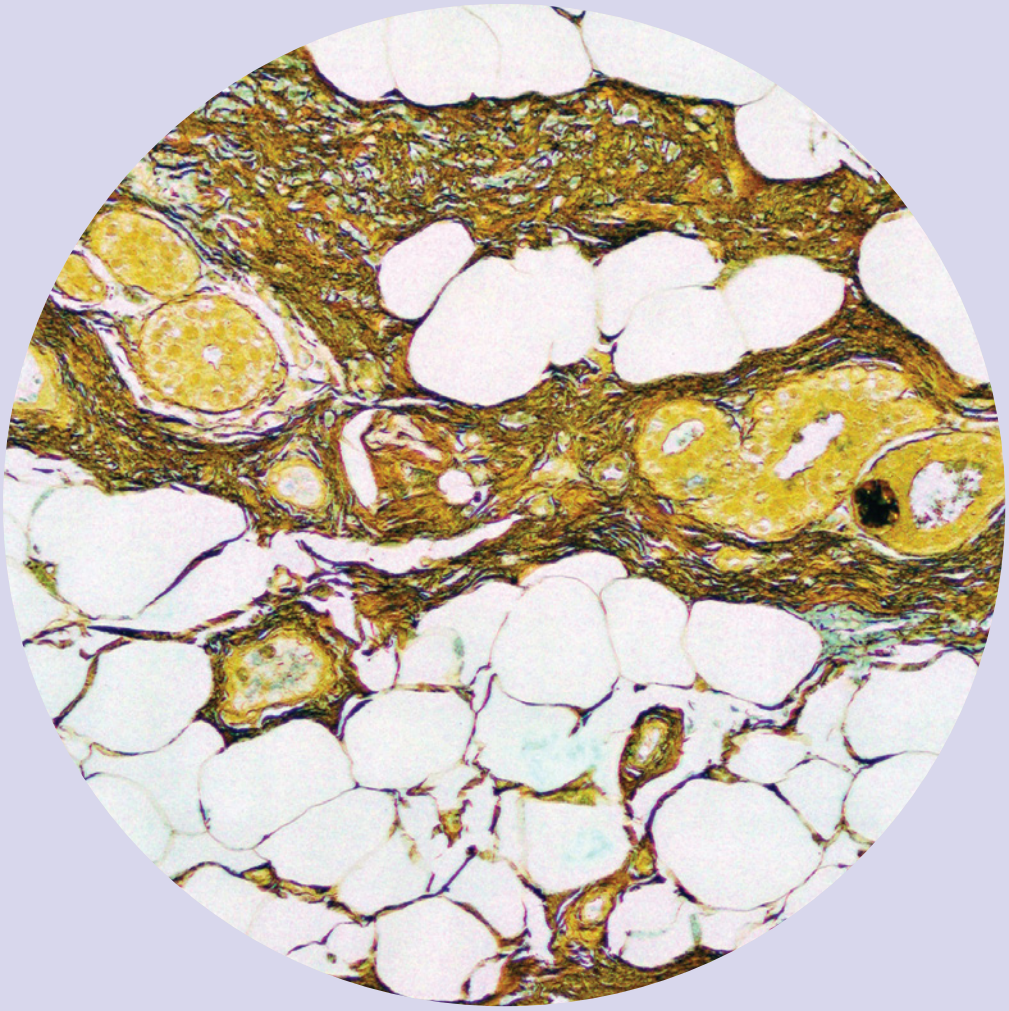
"Collagen XII seems to be altering the properties of the tumour and makes it more aggressive," says first author Michael Papanicolaou.

Further research will focus on studying more human samples and investigating possible treatment options.

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

THROUGH THE MICROSCOPE

A new type of microscope slide that makes it easier to distinguish cancer cells from healthy cells wins 2022 ANSTO Eureka Prize for Innovative Use of Technology.



The image above shows: Human invasive tissue

Kate Harvey and Professor Sandra O'Toole

Professor Sandra O'Toole and team

The whole team who won the Eureka Prize for Innovative Use of Technology

Garvan's Professor Sandra O'Toole and Kate Harvey are part of a team who have developed a new type of microscope slide that makes it easier to distinguish cancer cells from healthy cells.

In a study led by La Trobe University and published in *Nature,* Professor O'Toole and Miss Harvey demonstrated that the special coating on their new 'NanoMslide' causes light to interact differently with cancer tissue compared to healthy tissue, resulting in a striking colour contrast that makes it easier for pathologists to detect abnormal cells.

The difference between the new slide technology and previous cell staining techniques is 'like night and day' in terms of how cancer cells stand out from their background. This could lead to faster, more accurate diagnosis of disease.

Visit: **garvan.org.au/eureka-prize**

Introducing Garvan's Interim Executive Director, **Professor Peter Croucher**

"I am proud to steer the organisation over the coming months as the Institute remains steadfast in its commitment to improving human health."

Professor Peter Croucher is a bone biologist and cancer researcher with a longstanding interest in disorders of the skeleton, particularly osteoporosis and cancer-associated bone disease. His research focuses on the molecular mechanisms of bone disease, how cancers spread to bone, and what controls dormancy (sleeping) and reactivation of cancer cells within bone.

In 2011, Professor Croucher joined Garvan to lead our Bone Biology research lab and to take up the inaugural Mrs Janice Gibson and the Ernest Heine Family Foundation Chair in Osteoporosis. In 2019, he took on the role of Deputy Director, extending his responsibilities across Garvan's scientific activities. He commenced his position as Executive Director (interim) in July 2022 after Professor Chris Goodnow stepped down from the Executive Directorship due to health complications of COVID-19.

Professor Croucher undertook his postdoctoral training at the University of Cambridge and the University of Sheffield. After two years as a Senior Research Fellow at the University of Oxford's Institute of Musculoskeletal Sciences, he returned to the School of Medicine and Biomedical Sciences at the University of Sheffield as Professor of Bone Biology. In 2009, he formed and led the new Department of Human Metabolism and became the inaugural Co-Director of the Mellanby Centre for Bone Research.

Professor Croucher's research focuses on debilitating diseases of the bone, which significantly impact a patient's quality of life. In particular, Professor Croucher and his team are interested in the genetic causes and molecular mechanisms underlying the onset and progression of osteoporosis; cancer-associated bone disease in which tumour cells increase bone resorption and inhibit bone formation; and cancer cell dormancy in bone, especially relating to breast and prostate cancer.

Professor Peter Croucher

Professor Croucher and his team use state-of-the-art imaging technology and disease models to identify therapeutic targets, working towards translating their research findings and discoveries into treatments for patients.

Of taking on the role of Interim Executive Director, Professor Croucher says "I am proud to steer the organisation over the coming months as the Institute remains steadfast in its commitment to improving human health."

Running into our hearts

After a challenging couple of years for community fundraising, we are thrilled to have participated in City2Surf 2022.

This year, 253 people signed up and ran for Garvan raising over $20,000 for life-changing medical research.

Each year we rally together runners who are passionate and enthusiastic – and this year we are highlighting a group who have year after year shown enormous generosity in supporting Garvan and our researchers.

Belmadar are a Sydney-based commercial construction company and are an exceptional example of 'teamwork making the dream work'. After blood cancer insidiously struck the Managing Director's family, Alf Marrocco, alongside his Belmadar Bandits, jogged, ran and walked their way into our hearts.

Since 2015, Belmadar have participated in the City2Surf for Garvan and have raised over $100,000 for blood cancer research. This year their exceptional efforts raised $14,545.50 which will directly support Dr Jim Blackburn and his research.

Dr Jim Blackburn is the Group Leader for the DNA and RNA Methodologies team within the Genomic Cancer Medicine Laboratory. His team works on developing and deploying unique sequencing assays for comprehensive fusion gene detection in blood cancers and solid tumours.

Alfredo Marrocco, Lidia Marrocco, Cinzia Marrocco, Connor Hickman

Lidia Marrocco

Without incredible community fundraisers like Belmadar, we would not be able to fast-track our medical research. Belmadar truly embody family spirit and we are thankful to have them as Garvan Family. We look forward to next year's City2Surf.

You can make a big difference to medical research by fundraising for Garvan. If you're interested in participating in a community fundraiser or to set up your own – we would love to help you.

Visit: **garvan.org.au/support-us/fundraise-for-us**

RESEARCH NEWS

Dr Anna Cuomo

The European Molecular Biology Organization (EMBO) has awarded Dr Anna Cuomo with a prestigious and highly competitive post-doctoral fellowship to support her research into the genetic basis of human diseases.

Dr Cuomo joined Garvan as a post-doctoral researcher at the end of 2021. She is a talented computational biologist with a PhD in Statistical Genetics from the University of Cambridge and the European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI).

Her research focuses on the development of statistical models that link variants in our DNA to the unique profile of single cells. This work helps uncover the molecular mechanisms by which genetic and environmental changes drive human disease risk.

Her ultimate goal is to use these insights to better diagnose, treat and prevent disease.

"It's an honour to receive this fellowship to further my work at the Garvan Institute over the next two years," says Dr Cuomo. "I'd like to thank the EMBO for their support."

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

Insights into dangerous tick bite-related meat allergy revealed

Garvan scientists have revealed the structure and genetics of key molecules linked to the sometimes life-threatening mammalian-meat allergy brought on by tick bites.

The study, led by Professor Daniel Christ, details how our antibodies interact with the sugar molecule known as α-gal (alpha-gal), which is produced by all mammals, except humans and higher primates. After humans are exposed to α-gal through bites of certain tick species – such as the paralysis tick *Ixodes holocyclus* endemic to Eastern Australia – the immune system can flag it as a harmful allergen and instigate an allergic response, sometimes with near-fatal consequences.

About one-third of people who have developed a sensitivity to α-gal will exhibit symptoms of an allergy to mammalian meat. A second bite has been observed to more than double the allergic response.

Why some people develop anaphylaxis and others don't is unknown – it could be related to the number of tick bites, how much saliva is injected or genetic sensitivity. The study paves the way for potential therapeutic candidates to treat this rare allergic response.

Visit: **garvan.org.au/tick-bite**

An incredible opportunity to lead the world in genomic medicine

"Australia's diversity, scientific talent and healthcare system represent an incredible opportunity for us to lead the world in genomic medicine. Building that future will require us to be brave and to ensure no Australian is left behind." – Professor Daniel MacArthur

The Centre for Population Genomics (CPG) is an exciting new partnership between Garvan and the Murdoch Children's Research Institute (MCRI) in Melbourne. CPG, which has significant support from the Australian Government, generous donors and industry partners, is a national centre that will house a genomic database of culturally and linguistically diverse populations, making it easier to tailor health care to all Australians and eventually to all people around the world.

We are currently in the earliest stages of a profound transformation of the practice of medicine, in which genomic technologies - which allow the study of all of a person's genes and their interactions - allow health care to be increasingly tailored to individual patients.

Researchers can now analyse a patient's entire genome to identify commonly known disease-causing genetic variants and provide diagnoses of current diseases, predict the risk of future diseases and offer possible personalised treatment. To identify precisely which genetic changes or variants are responsible for disease, a patient's genome needs to be compared to a reference set of thousands of genomes from the wider population.

To ensure that future advances in genomic medicine are useful for all Australians, we need a much larger genomic database that represents our highly diverse population, as well as more research to identify and catalogue the genes and variants involved in disease. These are the primary aims of this new centre.

The CPG is led by Professor Daniel MacArthur, who returned to Australia in 2020 from the US where he was Co-Director of the Medical and Population Genetics Program at the Broad Institute of MIT and Harvard, to apply his experience in building the world's largest genomic databases to improve outcomes for Australian communities.

Professor Daniel MacArthur
Director, Centre for Population Genomics

Professor Daniel MacArthur is an internationally recognised genomics researcher who returned from the US to set up the CPG. He was previously Co-Director of the Medical and Population Genetics Program at the Broad Institute of MIT and Harvard and co-directed its Center for Mendelian Genomics, which analysed genomic data from more than 10,000 rare disease families and contributed to the discovery of more than 300 new disease genes. He also led the creation of the largest and most widely used set of human DNA data, gnomAD, which spanned more than 200,000 individuals.

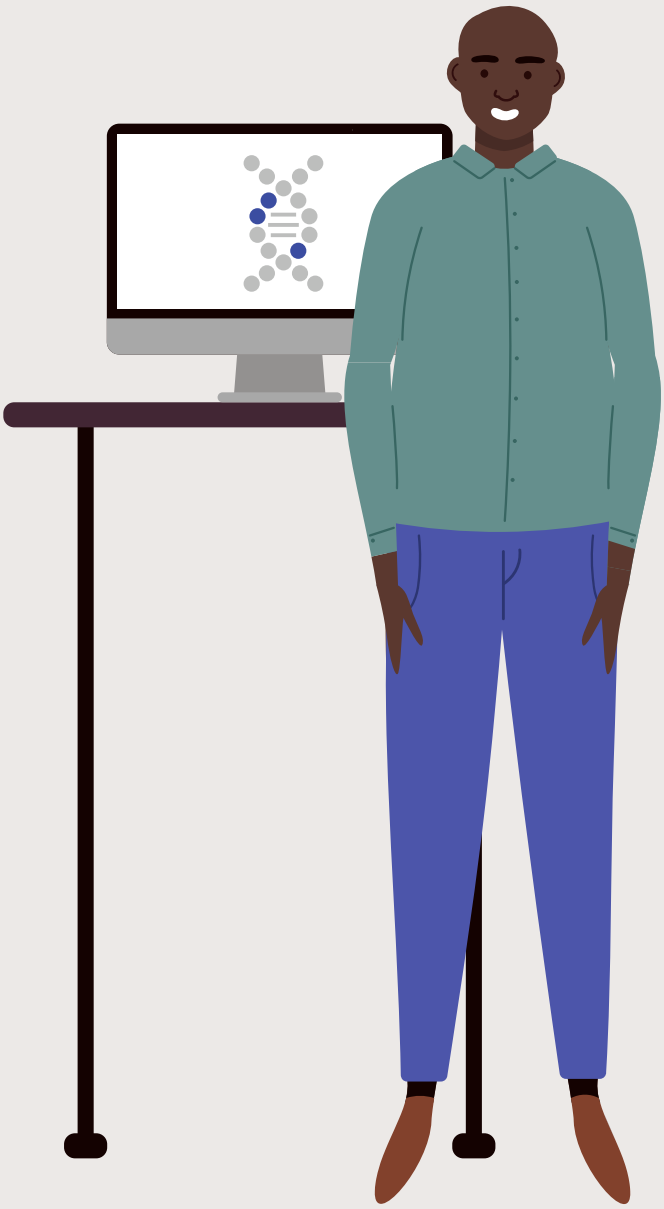
"The gnomAD project has had a massive global impact on rare disease diagnosis, helping more than two million patients worldwide, but it's missing representation from many of the communities living here in Australia."

He says the foundational aspects of the CPG are set up and it's now time to talk to the communities. "The next phase is really exciting – it's about engaging with communities and doing that at scale, to ensure we end up having a real impact on outcomes that matter to them."

Importantly, the anonymous data generated from the CPG will be made available to the research community, while strictly protecting the privacy of individual participants. "We have a responsibility to ensure that these datasets are available to drive both research and clinical outcomes," says Professor MacArthur. "It's so important that people are not sitting around and waiting – we want to improve diagnoses of patients immediately." A special thank you to the John Brown Cook Foundation for their philanthropic support of CPG.

"This will have enormous impact, through the act of making data available to the world so people can use it."

"It's so important that people are not sitting around and waiting – we want to improve diagnoses of patients immediately."



Flagship Projects for
The Centre for Population Genomics

The vision of CPG is a world in which genomic information enables comprehensive disease risk prediction, accurate diagnosis and effective therapeutics for all people.

Our DNA

People are at the heart of CPG, which is why the flagship project is the creation of a more inclusive resource of genetic variation from culturally and linguistically diverse Australian communities, called OurDNA.

Current global resources of genetic variation include data from more than 200,000 people, but have an over-representation of individuals of European heritage, and many of Australia's diverse communities are under-represented or missing. "The need for inclusive representation in genomics is urgent. Many of Australia's diverse communities already experience poorer health outcomes than other Australians, and these disparities will continue to increase over the next decade unless we ensure that all communities can benefit equitably from advances in genomic medicine," says Professor MacArthur.

Professor MacArthur and colleagues will work very closely with communities, including those of Oceanian, South-East Asian, South and East Asian, Middle Eastern, and African ancestry, to co-design the process of engaging and recruiting participants. Ultimately, the team hopes to recruit more than 7,000 individuals from under-represented Australian communities and combine the data from those individuals with other cohorts to create an accessible resource of genetic variation spanning over 20,000 Australians, directly benefiting the diagnosis of rare disease families from these communities.

The team is also collaborating with a national network led by Indigenous researchers, focused on empowering Aboriginal and Torres Strait Islander communities in genomic research, with the goal of providing better access to genomic medicine and better health outcomes for Indigenous Australians.

Rare Diseases

The second key project for CPG is to improve diagnosis rates and treatment options for patients affected by genetic diseases, such as muscular dystrophy or cystic fibrosis. While severe genetic diseases are individually rare – less than five in 10,000 people – collectively, they account for 10% of paediatric hospital admissions and up to 20% of infant deaths.

"For many decades, we have known people suffered from rare diseases, but not what was causing them. Now, diagnosis rates are approaching 60-70%, but effective treatments are only available for less than 5% of rare disease patients," says Professor MacArthur. "Our long-term goal is to dramatically change this for the better."

The focus will be on patients who have not received a diagnosis, says Dr Cas Simons, who leads the rare diseases program at CPG. The team has already analysed more than 1,000 genomes, and from a joint project of 35 families, more than half were given diagnoses within weeks. One of these was a multigenerational family who had been studied since the 1980s without successful diagnosis until now. A diagnosis opens doors to access possible treatments, support and ownership of health decisions and family planning.

The team has already analysed more than 1,000 genomes, and from a joint project of 35 families, more than half were given diagnoses within weeks.

Sue Elbazi

In 2017, the shock of performing CPR on her 19-year-old daughter who had just suffered a cardiac arrest was the introduction Sue Elbazi had to a possible rare genetic cardiac disease in her family. Sue's cousin Joseph had undergone a heart transplant in 2005 and sadly passed away 10 years later; her daughter's serious heart condition seemed a coincidence at the time, but when Joseph's daughter needed a heart transplant at the age of 15 the coincidences were just too many to ignore. "It's the fear that another person will have it," says Sue. "I don't want any mother to go through what I went through."

Sue's daughter has undergone genetic testing, but since Middle Eastern genomes are under-represented in current genetic variation resources, it wasn't possible to determine if any genes stand out from what's typical for someone of her Lebanese heritage," says Associate Professor Jodie Ingles, head of the Clinical Genomics lab at the CPG and a qualified genomic counsellor. "That's why it's so important we grow these databases to represent more Australians and give more people diagnoses and more certainty in their lives."

Partnering for greater impact

The Centre for Population Genomics is an integral partnership between Garvan and the Murdoch Children's Research Institute (MCRI) in Melbourne.

This affords the advantage of their complementary strengths: Garvan's leadership in genomics and the handling of large-scale datasets, alongside MCRI's deep expertise in working with large cohorts of children, rare paediatric diseases, and the translation of research findings into clinical outcomes.

The partnership and resources enable the deep collaboration needed to advance Australia's genomics capability, ultimately improving health outcomes for all Australians.

centre for population genomics

murdoch children's research institute

Garvan Institute of Medical Research

Spying new clues for
eye disease in our genes

Single-cell genomic techniques reveal new insights into macular degeneration and glaucoma.

A team of scientists jointly led by Garvan have uncovered new genetic signatures behind two different eye diseases, paving the way for better diagnosis and treatment.

Professor Joseph Powell, Director of Cellular Science at Garvan, co-led the project which focused on identifying genomic markers and age-related macular degeneration using promising new techniques.

"In most cases you can't directly take biopsies from eye disease – that would be a hugely invasive procedure that would have a negative impact on patients' overall eye health," says Professor Powell.

Instead, the team took skin cell samples from patients with eye disease and reverted them into a type of stem cell called induced pluripotent stem cells. They then guided the cells into becoming models of eye cells that have the exact same genetic makeup as cells that originate in the eye.

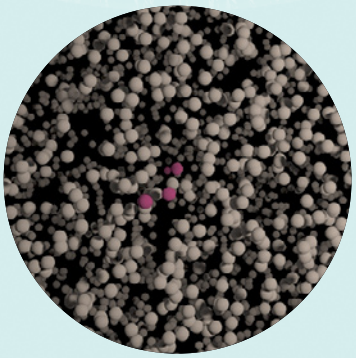
"We saw how the genetic causes of glaucoma and macular degeneration act in single cells and how they vary in different people. Current treatments can only slow the loss of vision from glaucoma, but this understanding is the first step towards therapies that target individual cell types," says Professor Joseph Powell.

Around one in seven Australians over the age of 50 is affected by age-related macular degeneration and about 15% of those aged over 80 have vision loss or blindness.

Glaucoma is the leading cause of blindness worldwide and is predicted to affect about 80 million people by 2040. Treatments options are currently extremely limited.

"This is the basis of precision medicine, where we can then look at what therapeutics might be most effective for a person's genetic profile of disease."

To find out more please visit
www.garvan.org.au/macular



Single-cell genomics

Professor Joseph Powell

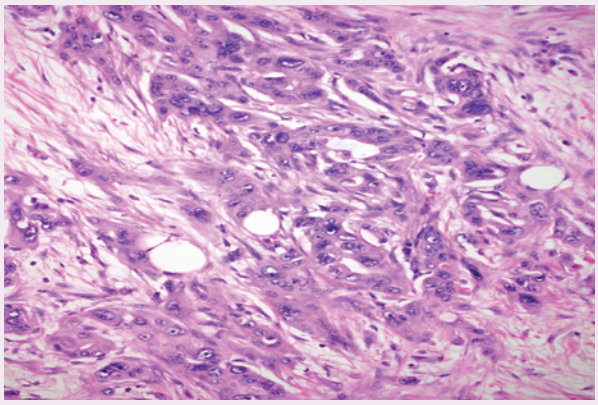
'Priming' pancreatic cancer for more effective treatment

New study aims to make cancer cells more sensitive to chemotherapy.

Pancreatic ductal adenocarcinoma is an aggressive form of pancreatic cancer and one of the most lethal cancers worldwide. Despite advances in combination chemotherapy approaches, the five-year survival rate is less than one in ten, and below 3% if the cancer has already metastasised.

Garvan researchers have been developing a new approach to 'prime' tumours to make them more sensitive to chemotherapy by targeting the tough, fibrous stroma that surrounds the cancer cells. Professor Paul Timpson and his team investigated FAK – a molecule produced by pancreatic cancer that increases the stiffness of the stroma and helps cancer cells to grow, mobilise and metastasise.

The team found that a new treatment called AMP945, developed by Melbourne-based Amplia Therapeutics, was able to block FAK. This reduced the stiffness of tumours as well as the amount and the deposition of stromal tissue surrounding the cancer cells in pre-clinical models. On this softer surface, cancer cell activity stalled, rendering them more sensitive to chemotherapy. This new approach was most effective when the treatment was administered just before chemotherapy.



Pancreatic cancer under the microscope

To find out more about the study, including the eligibility criteria and how to apply, please visit **www.ampliatx.com/accent**

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.
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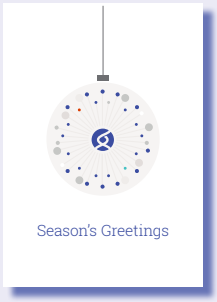

Clinical Trial Spotlight

Testing a drug treatment for dementia

A commonly used treatment for diabetes may hold the key to slowing cognitive decline to prevent dementia.

A Garvan-led study is seeking participants for a Phase 2 clinical trial to test a drug that could slow the process of cognitive decline, a hallmark of the processes that may lead to dementia.

The three-year intervention study will examine the effects of metformin – a drug used to safely and cheaply treat diabetes and other metabolic disorders – on cognition, brain anatomy, vascular health and early signs of dementia.

"We are building on promising research on the positive effects of metformin that could have real impact on reducing or stopping the progress of cognitive decline, something for which there is no effective treatment," says lead researcher Professor Katherine Samaras, Head of the Clinical Obesity, Nutrition and Adipose Biology lab at Garvan and endocrinologist at St Vincent's Hospital Sydney.

Success of the randomised-controlled trial, known as MetMemory, would mean that treatment for slowing cognitive decline could be immediately available.

The clinical trial is already underway and requires more volunteers. Participants need to be aged over 60, live in the Greater Sydney region and be experiencing symptoms of mild cognitive impairment like challenges with memory loss and thinking.

Professor Katherine Samaras

For more information,
contact by telephone or email:
Email: MetMemory@garvan.org.au
Call: (02) 9295-8585
Visit: garvan.org.au/metmemory

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Helen Wong
Desmond Yee

“I’ve been very fortunate and I would like to give back”

Diane Ferrier, Garvan *Partner for the Future*

Diane has always considered herself a fortunate person, with a happy upbringing, rewarding career, opportunities to travel and the company of good friends and family. But there is also sadness.

Both Diane’s parents passed away after significant medical ordeals – her father from dementia and her mother from leukaemia. She also had a friend who succumbed to ovarian cancer.

Witnessing the suffering of loved ones crystallised for Diane the value of medical research, and how it offers hope. Diane’s experiences combined with her gratitude for her blessings, have underpinned her decision to become a Garvan *Partner for the Future* by nominating Garvan as a beneficiary of her Will.

She says: “You can’t do medical research without financial support and that’s where I can help. I want to know that when my life ends, Garvan can progress and continue to make medical breakthroughs.”

Would you consider this special way of giving better health to future generations?

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