Issue 50

breakthrough

A new approach to improve treatment for childhood cancer

50 Celebrating the 50th edition of *Breakthrough*

Also in this edition

Osteoporosis medication boosts immune response in lungs

Garvan Institute of Medical Research

Welcome from our Executive Director

Dear Garvan family,

It is a pleasure for me to share with you not only our first edition of *Breakthrough* for 2022, but the 50th edition of this magazine!

Looking back over 50 issues, it's incredible to see how much Garvan has evolved as an Institute. It has been a pleasure to have been able to share our discoveries and news with you as we have grown and changed over the years, and it's been truly wonderful to have had so many members of our Garvan family supporting *Breakthrough* since the beginning.

I hope you and your loved ones have been managing well through the Omicron wave of COVID-19. While it may have felt like a step back after having reached initial vaccination milestones, researchers at Garvan are working on developing a strategy to generate a future-proof COVID-19 vaccination, which you can read more about on page 11.

As we enter 2022, researchers across the Institute are travelling at full-steam as they continue their innovative research across a range of disease areas. I'm delighted to be able to share just a handful of research updates and news coming out of Garvan.

On page 6 you'll read about the discovery of a potential therapy that may improve how effectively chemotherapy targets neuroblastomas, a rare but aggressive cancer that is usually diagnosed in children under five. On page 8 you'll find out about the link discovered by Garvan researchers between a commonly prescribed drug for osteoporosis and respiratory illness.

Finally, on page 4 you'll hear from one of our new Partners for the Future, Claire, on why she is supporting Garvan by leaving a gift in her Will. I hope you enjoy reading about all the exciting research and work we have underway.

Thank you for your unwavering support and passion for research, without you these discoveries simply wouldn't be possible.

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

Front cover image:
Neuroblastoma cells

50 Celebrating the 50th edition of *Breakthrough*

This April's *Breakthrough* marks a major milestone – it's the 50th edition! 50 magazines sharing our latest research breakthroughs, major news updates and stories from you, our wonderful Garvan family.

Our very first issue was released in March 2006, over 16 years ago – and while the magazine has changed remarkably over the years, the support of our donors has remained steadfast. We would like to extend a heartfelt thanks to each and every one of you for your continued support and kind words that have been sent through about *Breakthrough*. We truly appreciate your support, engagement and enthusiasm.

We hope that *Breakthrough* has inspired you to find out more about the research undertaken at Garvan and the lives it has changed. We look forward to the prospect of the next 50 issues!

RESEARCH NEWS

Advanced imaging reveals breast cancer's weakness.

A new treatment approach being investigated by a team at Garvan may help stop breast cancer cells right as they begin to spread. There is currently an urgent need for treatments targeting breast cancer metastasis; while 99% of patients survive five years or longer if the tumour is only located at the site of origin, this rate drops to 27% if the breast cancer has spread to other locations in the body.

"Using live imaging techniques, we were able to pinpoint a narrow window of vulnerability for metastasising breast cancers," says Professor Paul Timpson, Invasion and Metastasis Lab Head at the Garvan Institute and co-senior author of the findings published in *Cell Reports*.

"For the first time, we visualised Rac1 – a signalling molecule that makes breast cancer cells more resilient as they begin to travel around the body. We showed that targeting this molecule could significantly reduce breast cancer spread."

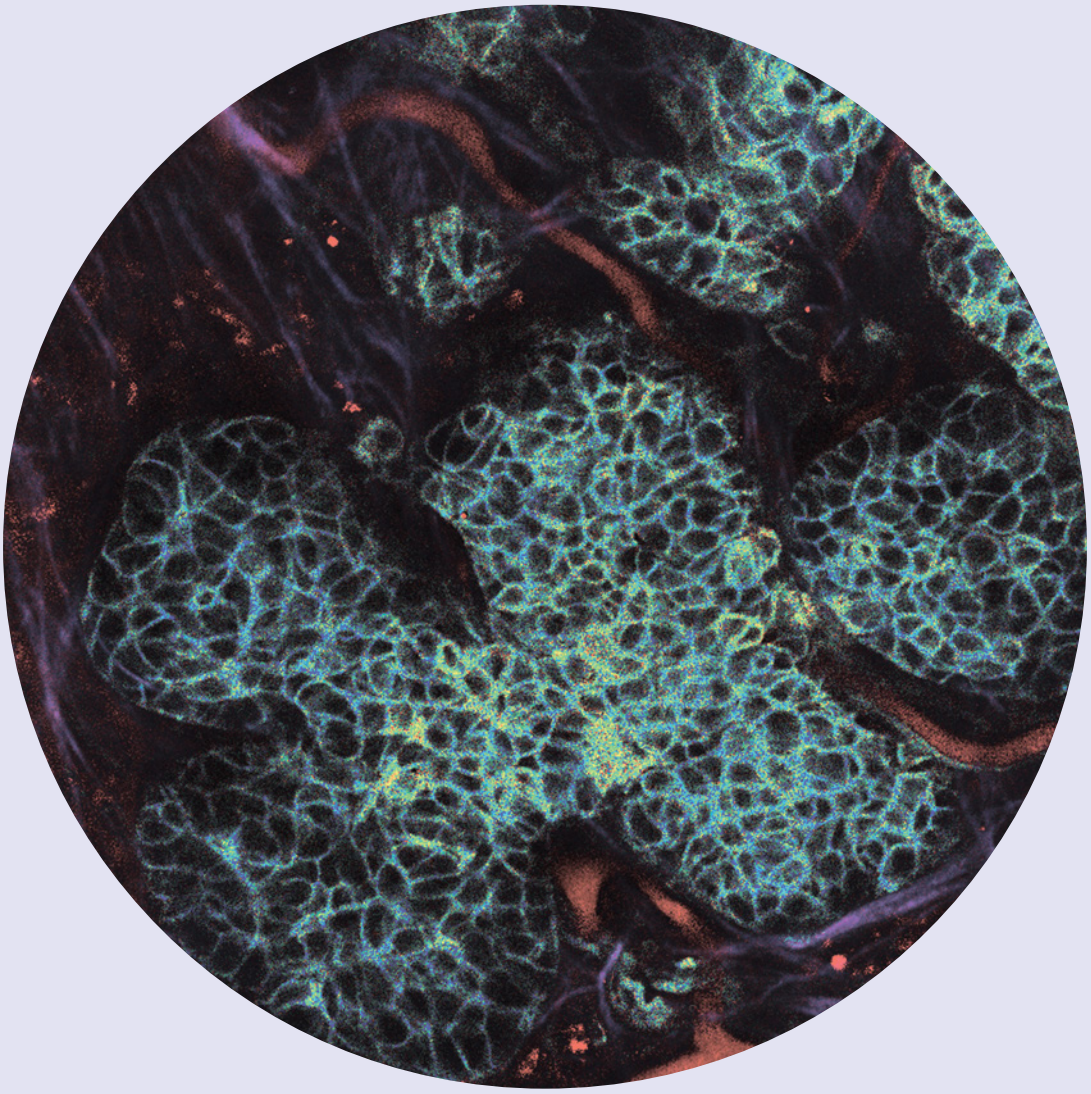
When the researchers targeted Rac1 with an experimental treatment, they found that they could reduce cancer spread in their models by 73%.

"The insights obtained in our study suggest existing treatments could be repurposed to reduce breast cancer metastasis. This could potentially fast-track the new approach to patients," says Professor Timpson.

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

THROUGH THE MICROSCOPE

Breast cancer's Achilles' heel revealed.



Using advanced intravital imaging techniques developed in-house at Garvan, Professor Paul Timpson and his team were able to pinpoint a narrow window of vulnerability for metastasising breast cancers.

This image shows the activity of the metastasis-driving Rac1 protein deep within live tumours, tracking it as breast cancer cells metastasise. Time-resolved mapping of the activity of Rac1 was performed live using a biosensor (shown in rainbow colour scale) in the context of the local tumour extra cellular matrix collagen I (in magenta) and the tumour vasculature (in red).

Thanks to our imaging techniques, we were able to track the time at which inhibiting Rac1 was most effective at stopping cancer spread. Based on this data, we speculate that targeting Rac1 in combination with chemotherapy may be an effective approach to reduce the likelihood of cancer metastasis and recurrence.

Read more at: **garvan.org.au/achilles**

Image by Dr Max Nobis

Heart & Soul

Claire, Garvan's new *Partner for the Future*,
is living life to the fullest, thanks to medical research.

One thing is for sure, I love life and challenging myself in all kinds of ways. Among the many things I put my heart and soul into is my passion for music and fitness. I have my own wedding singing business and enjoy composing my own music. Growing up, I competed in gymnastics at State level across Australia. Now, I use any excuse to stay active, like rolling in the mud at Tough Mudder or swinging upside down in my Lyra hoop!

I 'live life to the fullest' and the person I have become is in part, thanks to medical research. When I was 8, I suffered a severe silent asthma attack. I couldn't breathe or speak and eventually turned blue. If it had not been for the urgent medical treatment received, I wouldn't be here today.

I believe everyone should have the same opportunity to live their life to the full, like I do every day. That's why I am so passionate about supporting medical research, to improve health outcomes for everyone.

Claire Tregidgo
Garvan Partner for the Future

I first discovered Garvan when looking for the next step in my career. I saw the amazing research at Garvan and thought… *"I want to be a part of this, how do I sign up?!"* I now have a dream job working in the Garvan Research Foundation and I am proud to be supporting our wonderful and talented researchers.

I am excited to be getting married later this year, but it has made me think about the next chapter of my life, the importance of planning for the future and the legacy I want to leave behind. I chose to make my Will using an online service and included a future bequest to Garvan's important medical research. This was an easy and cost-effective way to make my first Will.

"I know I'm young but it's never too early to plan your legacy and make a Will, both for your loved ones and the causes you care about." – Claire Tregidgo

I love giving back to others and creating music - and just like music, a gift in your Will is something to share to make the world a better place and I think there is no better feeling.

Of all the things I've achieved in my life so far, becoming a *Partner for the Future* by including Garvan in my Will is one I am incredibly proud of!

Would you consider this special way of giving to the future of medical research?

To request our Bequest Giving brochure or for a no obligation conversation, please contact our Bequest Manager, Donna Mason on **(02) 9295 8559** or **bequests@garvan.org.au** or visit **garvan.org.au/bequest**

PEDAL FOR POSSIBILITIES

On March 15, a group of cyclists undertook the Pedal for Possibilities Tour in Western Australia.

This unique bike tour commenced in picturesque Albany, some 700km south of Perth and finished in the beautiful city of Fremantle 5 days later. The ride proved to be one of the best experiences of friendship, camaraderie and fun for all involved, all while raising vital funds for Garvan.

"A number of weeks ago, a feature on *A Current Affair* caught my attention. It highlighted the work done by the Garvan Institute through their Disease Dilemmas campaign. Brian's story really touched me," said Reon Botha, the organiser of the fundraiser.

Reon lost his mother to Chronic Obstructive Pulmonary Disease (COPD) a few years ago and particularly values that genomic research can be applied across a wide range of diseases.

Many of the riders and support team work in the financial services industry and have first-hand experience of seeing clients, friends and family struck down by various diseases. This special group of individuals decided that the Pedal for Possibilities Tour was one way they could make a difference.

Starting in October, the team woke up at 4am several times a week to train for the event. "We wanted to make sure we were able to complete this tough journey, despite it being not nearly as tough as the journey some folks have to endure with various sickness – we're doing this for them."

Reon and the team completed the **700km** trip over the **5 days** and **raised over $48K for Garvan** - helping our researchers to find answers sooner, creating a healthier future for all.

To support Reon and the team, visit www.bit.ly/garvanpedal

Reon and the Pedal for Possibilities teammates

RESEARCH NEWS

Garvan-led CIRCA program uncovers the cause of a young family's rare illness.

Garvan researchers have discovered an 'elusive' genetic variant causing a rare immune disorder in two young children from the same family.

The Clinical Immunogenomic Research Consortium of Australasia (CIRCA) program led by Associate Professor Cindy Ma and Professor Stuart Tangye found the disease-causing variant impacted the DOCK8 gene that plays an important role in healthy immune function and can led to a rare but often fatal condition known as DOCK8 deficiency. The variant was, surprisingly, found in a section of the childrens' DNA that does not code for protein production.

"Because this genetic variation was located outside of the 'protein-coding' region of the DOCK8 gene, it took a long time to pin down the root cause of the children's poor health," says Professor Tangye.

When the team was initially unable to identify the genetic cause of disease, they adopted a multidisciplinary approach using a variety of advanced diagnostic tools to eventually make a genetic diagnosis, which enabled bone marrow transplantation to be used to successfully treat the two children.

Visit: **garvan.org.au/elusive-gene**

Epigenetic change found in cancers linked to DNA's 3D instability.

A team of Garvan researchers led by Professor Sue Clark has discovered new insights into DNA demethylation – a change to our epigenome where loss of DNA methylation occurs in our cancer cells.

The discovery contributes to an entirely new understanding of how cancers may initially develop. Over recent years, we have learnt that cancer is associated with more than just changes in the letters of our genome. Demethylation – whereby DNA loses methyl tags usually attached to it – also commonly occurs in most cancer types.

Using a single cell analysis technique, they developed at Garvan, her team investigated the effects of DNA demethylation on the cotrol of DNA replication.

"This study provides evidence that DNA methylation controls more than how DNA is read – but plays a key role in how the DNA is organised in our cells in 3D and how DNA replicates when the cell divides," says Professor Clark.

These findings provide new insights on cancer formation and how loss of DNA methylation can modulate the control of cell division and potentially influence DNA damage.

Visit: **garvan.org.au/dna-instability**

New approach to improve treatment for childhood cancer

Garvan researchers have found a potential new way to effectively target neuroblastomas.

Research led by the Garvan Institute has uncovered a potential approach to improve outcomes for a rare but often aggressive cancer known as neuroblastoma.

Neuroblastoma is usually diagnosed in young children under the age of five. Associate Professor Alex Swarbrick, senior author of the research published in Molecular Therapy and Garvan Lab Head, says it can be difficult to treat the aggressive disease without adding additional risks to the young patients.

"High-dose chemotherapy is part of the standard treatment for high-risk neuroblastoma, but there is a narrow window between efficacy and toxicity to the patient."

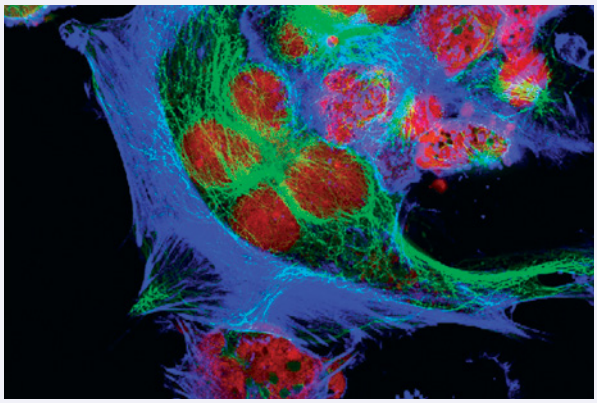
"High-dose chemotherapy can have significant side effects, especially in children. Our research has focused on finding a way to more effectively target a tumour with chemotherapy but that doesn't impact normal cell types, so that the dosage given to patients can be reduced."

Switching on sensitivity

The team identified three microRNAs – short molecules of genetic material that turn off genes – which made the cancer cells more sensitive to chemotherapy while leaving normal cell types unharmed.

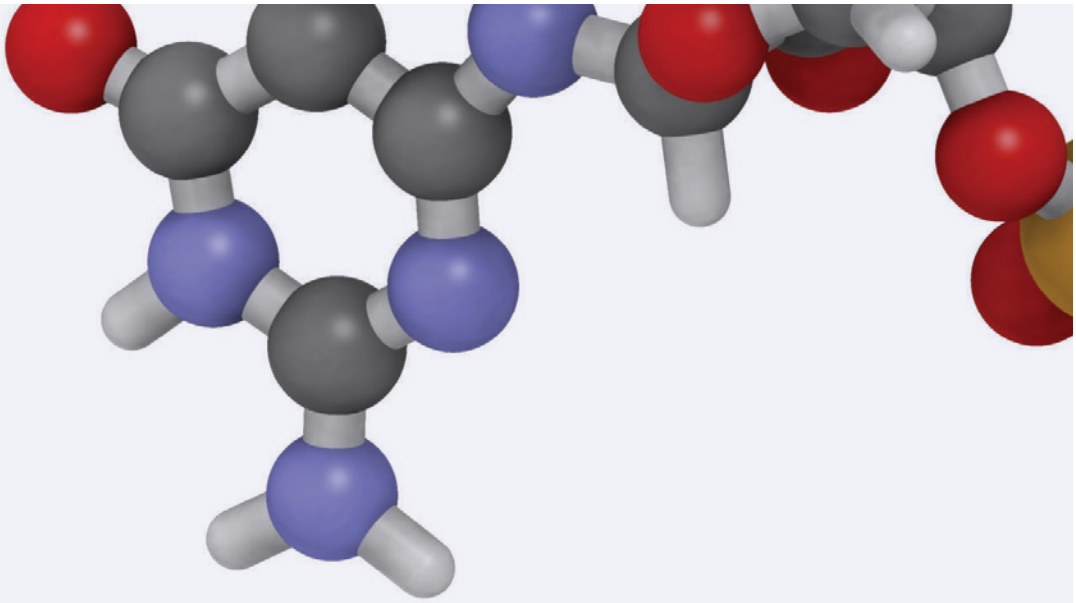
"MicroRNAs are key regulators of development – they target different locations across the genome to 'tune' genetic systems. We tested 1,200 microRNAs for their effect on neuroblastoma cells," explains first author Dr Holly Holliday.

"We identified three microRNAs that were potent chemosensitisers, meaning they enhanced the effects of chemotherapy on neuroblastoma cells without being toxic to other cell types. These microRNAs targeted a number of genes that are essential to neuroblastoma survival, which we verified in mouse models. By looking at prior studies, we also found they were often absent in patients that had a particularly poor prognosis," Dr Holliday says.



Neuroblastoma cells

Associate Professor Alex Swarbrick



The search for better treatments

Improved treatment options for neuroblastoma are urgently needed. One in two children with an aggressive form of the disease sadly pass away, with survivors often affected by chronic side effects following therapy.

If successful in further preclinical studies and clinical trials, these microRNAs may help make chemotherapy more effective for neuroblastoma patients.

"Our findings lead us to believe that restoring the function of these microRNAs by administering them to patients may be a valuable therapeutic strategy for neuroblastoma," adds Associate Professor Swarbrick.

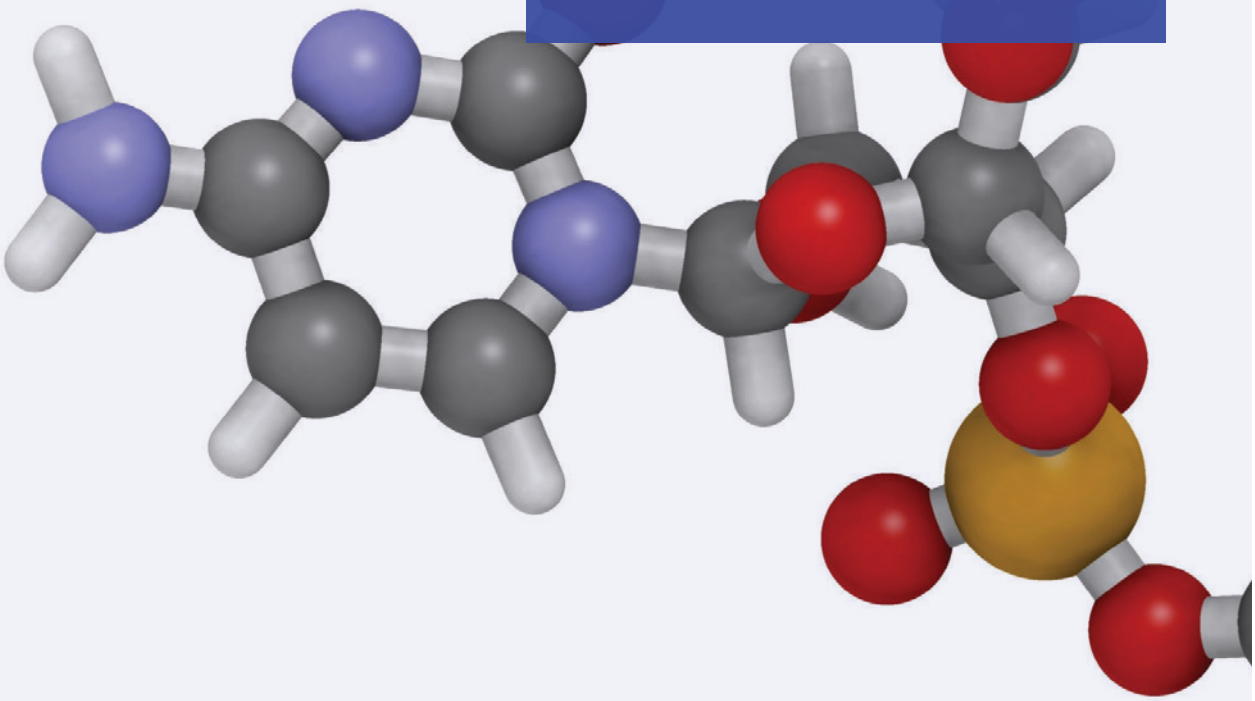
The next steps in this research will be to move to comprehensive preclinical studies, followed by clinical trials.

"We hope that this feasibility study will ultimately help improve treatments – getting a better hit on the cancer while dialling back the toxicity to the patient," he says.

The impact

This new strategy for treating neuroblastoma could be a vital new tool to make chemotherapy more effective in young children without harmful side-effects.

To find out more visit garvan.org.au/childhood-cancer-therapy



Osteoporosis medication boosts immune response in lungs

Garvan researchers reveal a link between osteoporosis and respiratory immunity.

Researchers at the Garvan Institute have revealed that a common osteoporosis treatment boosts immune cells in the lung that form one of the first lines of defence against pathogens.

In experimental models, bisphosphonate treatment stimulated lung macrophages to mount a stronger response against an immune challenge. The findings follow observations made in previous clinical trials that individuals who took bisphosphonates had a reduced risk of pneumonia.

"Bisphosphonates are a safe and effective class of osteoporosis medication that have been the standard-of-care since the 1990s to prevent loss of bone and reduce the risk of fractures," says senior author Professor Mike Rogers, who heads the Bone Therapeutics Lab at the Garvan Institute.

"We have found an added potential benefit for this treatment – it can boost the immune function of lung cells, which may protect against respiratory infection and pneumonia. Our evidence warrants further investigation that we hope will lead to improved health outcomes in the older population, who are at higher risk of pneumonia and osteoporosis."

Immunity boost

Respiratory infections, such as acute pneumonia, are a major cause of death from infection worldwide. They increasingly affect the older population, as our ability to generate protective immune responses against infectious diseases declines with age.

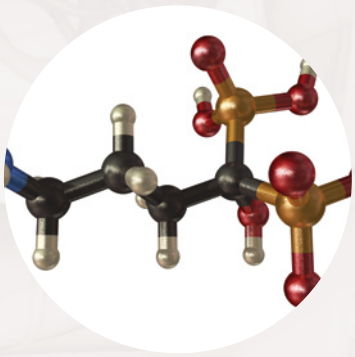
The researchers administered a bisphosphonate called zoledronic acid to mouse models and tracked how the medication moved into different cells.

"It was previously thought that bisphosphonates act only in the bones, but we found that they are taken up by macrophages in the lung, which are 'first responder' cells that can recognise, engulf and destroy a pathogen during an immune response," says Dr Marcia Munoz, first author of the paper.

The team then tested their model's immune response by exposing them to LPS, a molecule found on the surface of bacteria, which is commonly used to assess response to infection. They found that even after just one bisphosphonate dose, the activity of macrophages in the lung had increased compared to mice that had not received the treatment.

Professor Mike Rogers

Dr Marcia Munoz



Bisphosphonates

The potential to impact millions

"Macrophages are one of the first lines of defence against infection," says Professor Rogers. "If bisphosphonates are ramping up the ability of these cells to respond when they encounter a viral or bacterial infection, a stronger initial immune response may help clear the infection and lead to a better outcome. This is what we will be investigating next."

In Australia alone, 3.7 million individuals aged over 50 have a high fracture risk and are eligible for bisphosphonate treatment. However, less than 30% of individuals who should be receiving the medication under existing clinical guidelines are currently treated.

"This leaves a large population of individuals who may receive additional benefits," Professor Rogers adds. "Clinical trials are warranted to determine whether bisphosphonates, aside from preventing bone loss, can provide protection against pneumonia infection in vulnerable individuals, for instance, patients in aged care homes."

"Clinical trials are warranted to determine whether bisphosphonates, aside from preventing bone loss, can provide protection against pneumonia infection in vulnerable individuals, for instance, patients in aged care homes." – Professor Mike Rogers

The impact

This discovery could help protect against dangerous lung infections and incentivise more people to start using this treatment to protect bone health.

To find out more visit garvan.org.au/response

This research was supported by Australia's National Health and Medical Research Council, Mrs Janice Gibson and the Ernest Heine Family Foundation, and a Perpetual IMPACT grant.

New DNA test screens
50 genetic diseases at once

A single test for over 50 genetic diseases could cut the time for diagnosis from decades down to days.

Dr Ira Deveson

Dr Kishore Kumar

A single test for over 50 genetic diseases could cut the time for diagnosis from decades down to days thanks to research led by Garvan's Dr Ira Deveson.

The new test has been shown to identify a range of hard-to-diagnose neurological and neuromuscular diseases including Huntington's disease, Fragile X syndrome and motor neurone disease faster and more accurately than existing tests.

These diseases belong to a class of over 50 diseases caused by unusually long repetitive DNA sequences known as Short Tandem Repeat (STR) expansion disorders. They can be passed on through families and generally involve muscle and nerve damage as well as other complications throughout the body that can be life-threatening.

"They are often difficult to diagnose due to the complex symptoms that patients present with, the challenging nature of these repetitive sequences, and limitations of existing genetic testing methods," says Dr Deveson, co-senior author of the paper published in *Science Advances.*

Visit: **garvan.org.au/single-test**

Using new Nanopore sequencing devices, which are only the size of a stapler, the team was able to successfully diagnose all patients with conditions that were already known.

Current testing for STR expansion disorders usually involves a diagnostic odyssey which can go on for years before the genes causing the disease are successfully found. Nanopore sequencing can test for all of these diseases at once and is significantly cheaper than other DNA sequencing technologies.

"This new test will completely revolutionise how we diagnose these diseases, since we can now test for all the disorders at once with a single DNA test and give a clear genetic diagnosis, helping patients avoid years of unnecessary muscle or nerve biopsies for diseases they don't have, or risky treatments that suppress the immune system," says Dr Kishore Kumar, co-senior author of the paper.

A strategy for next-generation COVID-19 vaccines

Garvan-led researchers outline a strategy to generate future-proofed COVID-19 vaccines that can resist emergent new viral strains.

A study led by Garvan researchers Dr Deborah Burnett, Professor Chris Goodnow and Professor Daniel Christ has revealed a guide to developing COVID-19 vaccines that both prevent the coronavirus from infecting human cells and that are more resistant to evolving viral strains.

The team's key criteria for antibodies generated by future vaccines are to target regions of the SARS-CoV-2 viral surface that are unlikely to mutate and share key features that the researchers found could block the virus from infecting human cells.

Remarkably, the researchers found in experimental models that immunising with surface proteins from related viruses, such as SARS-CoV-1, the virus responsible for the original 2003 SARS epidemic, generated antibodies that met these criteria. The findings, published in the journal *Immunity,* provide a new direction for vaccine development.

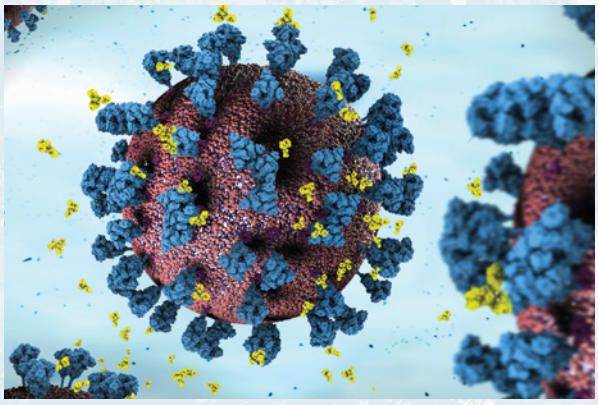
"Our research aimed to identify a vaccination strategy that would target a key site of vulnerability on the virus surface that is unlikely to change over time. This site is unchanged in different coronavirus strains, meaning that the virus may be less likely to mutate to escape from an antibody immune response targeting this site," says Dr Burnett, first author of the paper.

Relying on developing variant-dependant vaccines would always leave Australia vulnerable to disruptive waves of infection, even under idealised production and distribution systems that do not yet exist in Australia. "Waves of new variants would engulf the population faster than variant-specific vaccines could ever be deployed."

"To progress our proposed vaccine approach, we are now aiming to test next-generation vaccines in our preclinical models, to determine if they can generate these antibodies, which can protect against different strains of the virus," says Professor Goodnow, Executive Director of the Garvan Institute and Head of the Immunogenomics Laboratory.

"We now know what to look for in an antibody response. Our goal for this research is to help develop a vaccine that would need no updating and that could ultimately lead to better control of COVID-19."

Dr Deborah Burnett



3D Visualisation of COVID-19 virus by Garvan's Dr Kate Patterson

The study was conducted with collaborators at UNSW Sydney, the Kirby Institute, the Centenary Institute, Australian National University and the University of Erlangen (Germany).

This research was supported by Australia's National Health and Medical Research Council, Australian Research Council Discovery, Garvan COVID-19 Catalytic Funding, the Bill and Patricia Ritchie Family Foundation, University of Technology Sydney, Rainbow Foundation, the Snow Medical Research Foundation, the Bundesmininisterium für Bildung und Forschung, DFG, the Bayrische Forschungsstiftung, the Bavarian State Ministry for Science and the BMBF-funded COVIM project.

Visit: **garvan.org.au/next-generation-vaccines**

Clinical Trial **Spotlight**

MetMemory study to explore common diabetes drug's role in slowing age-related cognitive decline.

Do you live in the greater Sydney region and are you interested in participating in a placebo-controlled study aiming to slow cognitive decline, using a safe medication used to treat diabetes and metabolic conditions?

The study, led by the Garvan Institute of Medical Research and UNSW Sydney's Centre for Healthy Brain Ageing (CHeBA), builds on the team's earlier breakthrough research which found that older people with type 2 diabetes who were being treated with metformin experienced slower cognitive decline with lower dementia rates than those who did not use the medication.

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 people using it to optimise their blood glucose levels. Metformin is also used to treat other metabolic and hormonal conditions.

Our new MetMemory study will examine the effects of metformin on cognition and explore whether metformin affects other aspects of metabolism, inflammation and the ageing process. This study will take place over 3 years.

We are looking for volunteers living in the greater Sydney region, over 60 years old, who do not have diabetes have recently experienced changes in memory or had trouble thinking. Participants should not currently be taking metformin.

For further information on how to participate please email **MetMemory@garvan.org.au,** call **(02) 9295-8585** or visit **garvan.org.au/metmemory.**

CLINICAL TRIALS

We offer a range of clinical trials at The Kinghorn Cancer Centre for the treatment of patients with breast cancer. Find the full list at garvan.org.au/breast-cancer-clinical-trials.

Personalised therapy for rare and uncommon cancers

We offer the Molecular Screening and Therapeutics (MoST) clinical trials which personalise experimental treatment for patients with rare cancers based on an individual's unique personal and cancer genetic profile.

Find more information at
garvan.org.au/genomic-cancer-medicine-program

PREDICT prediabetes clinical trial

We are seeking men and women aged 20-70 years who have pre-diabetes or who have been recently diagnosed with type 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

Become a *Partner for Discovery* today

By becoming a Partner for Discovery and donating monthly, you can help ensure Garvan's cutting edge research can continue long into the future. Garvan's breakthrough discoveries are often years in the making, so long-term, dependable support from our generous community is vital. Monthly giving is a flexible and convenient way to support our innovative research.

If you'd like to become a *Partner for Discovery,* please call 1300 73 66 77, visit garvan.org.au/regular-giving or fill in and return the slip attached to this *Breakthrough*.

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