

breakthrough



Australian Parkinson's Mission

**Collaboration brings realistic
hope for Parkinson's.**

Also in this issue

How does cellular
genomics work

Solving mysterious
immune conditions



Garvan Institute
of Medical Research



Welcome from our Executive Director

Dear Garvan family,

It's with a great sense of pride and enthusiasm that I greet you in our first *Breakthrough* of 2019.

In this issue, you will be introduced to the Australian Parkinson's Mission, a collaborative program integrating clinical trials with genomics research for Parkinson's. You will also learn about CIRCA, a team of doctors and researchers changing the lives of people with rare immune diseases, just like Oscar featured on page 8.

Understanding the role of genomics, or our DNA, in health and disease is becoming more and more important. The expertise of the researchers here in genomics and cellular genomics – the genomics of single cells – is something I'm extremely proud of. On page 10, you'll see an infographic that gives an overview of how we analyse the genomes of cells using the cutting-edge capability in our Garvan-Weizmann Centre for Cellular Genomics.

Throughout 2019, we are hosting a series of free and informative tours and seminars to share exclusive updates about our research. I extend my warmest invitation to you, your family and friends, to join us, please register here: garvan.org.au/public-seminars.

There are many exciting research breakthroughs, clinical trials and updates on collaborative programs to share with you, as well as inspiring stories of people like you, Garvan's generous supporters, so please read on.

With very best wishes,

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

NEW RESEARCH

Targeting tuberculosis

The key to better tuberculosis prevention – and to improving the odds for millions of patients globally – could lie in boosting the body's natural levels of a small immune molecule called interferon gamma, our scientists have revealed.

Together with an international team of researchers, Professor Stuart Tangye studied patients with rare genetic variants that left them more susceptible to developing tuberculosis than the general population. The scientists investigated the intricate mechanisms of the patients' immune systems and discovered that they produced less of the immune molecule interferon gamma, which fends off bacterial and viral infections.

This work could significantly change how scientists think about developing tuberculosis therapies in the future. Current treatments target the bacteria that cause the disease, but they have side effects and many patients become drug resistant. Treatments that boost the body's natural production of interferon gamma could give those exposed to tuberculosis a better chance of avoiding the disease.

Read more at: garvan.org.au/tb-molecule

New clues from cancer DNA

Our researchers have discovered a new pattern of chemical tags on DNA which reveals new insights into how cancer develops. A team led by Professor Susan Clark and Associate Professor Clare Stirzaker took a close-up view of the two meters of DNA wrapped up inside prostate cancer cells. They investigated 28 million chemical tags that can attach to DNA and change how the DNA is read.

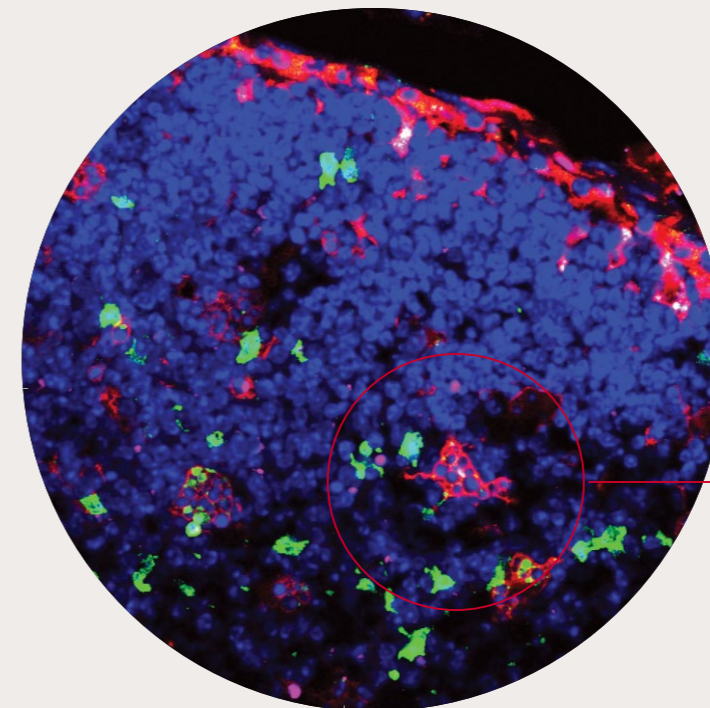
By comparing the pattern of DNA tags between prostate cancer and normal cells, the team discovered a surprising pattern which is common in different cancer cell types and which has never been seen before. This pattern revealed that specific molecules around which DNA wraps may provide a 'seed' for cancer to develop.

The discovery is an important first step towards improving cancer therapy. By understanding the precise changes that take place when normal cells become cancerous, our researchers hope to uncover new ways to treat or even prevent cancer from developing.

Read more at: garvan.org.au/new-clues

THROUGH THE MICROSCOPE

A close-up image of the immune system in action is giving Garvan researchers **new insight into autoimmune disease.**



Pictured in this image in red is an immune cell called a macrophage - a 'big eater' that cleans up dying B cells, whose nuclei are shown here in blue.

'Taking out the garbage' is not just a household chore - your immune system works hard to remove waste each and every day. To better understand the body's cleaning processes, our researcher Associate Professor Tri Phan is using advanced intravital two-photon microscopy to investigate immune cells in action.

Pictured in this image in red is an immune cell called a macrophage - a 'big eater' that cleans up dying B cells, whose nuclei are shown here in blue. These dying B cells, if not removed from lymph nodes, can trigger dangerous signals in the body that activate the onset of autoimmune conditions such as lupus. Understanding how these big eaters take out the B cell 'garbage' is a key first step to better understanding these chronic debilitating conditions - and ultimately to developing better treatments.

Read more at: garvan.org/immunology

Passing on the baton of a Better Life

You could say that leaving a **legacy for the next generation** is in the DNA of Peter Olive, one of Garvan's *Partners for the Future*.

Both Peter's parents and grandparents grew up in the bush, and their families lived through both World Wars and the Great Depression. Peter's grandmother sent his mother to a boarding school for a chance at a better life, and his grandfather encouraged his father to gain an apprenticeship in Sydney to avoid the hardship of life in the country during the Depression and the First World War. These events helped to foster a desire in Peter to help create a brighter future for the next generation.

When Peter made the important decision to leave a bequest to Garvan in his Will, becoming a *Partner for the Future*; he was carrying on a family trait of wanting to leave a better life for those that come after him.

"My parents and grandparents passed the baton of a better life to me and I feel it's my duty to continue this and give back to others. It's reassuring to think that something I've accumulated throughout my lifetime can bring benefit to humanity as a whole."

Medical research and the importance of finding cures – or at least better treatments for a range of diseases – is close to Peter's heart after both his parents lived with prolonged illnesses.

When Peter was in his 20s, his mother Dorothy developed a form of chronic haemophilia for which there was no known cause or cure. After living with the illness for almost a decade, she sadly passed away. After this devastating loss, Peter's father Carl decided he wanted to leave money to medical research, but unfortunately did not get the chance to amend his Will after suffering a stroke in 1989, before passing away five years later.

As a Garvan *Partner for the Future*, Peter is honouring his father's wishes and his parents' memory.

If you would like information about leaving a gift to Garvan in your Will as a tribute to your loved ones, please contact Donna Mason, Bequest Manager, on (02) 9295 8559, or visit garvan.org.au/bequest.



MAKING GENOMICS TEACHABLE

A Garvan-Weizmann collaboration is upskilling science teachers to educate students about genomics.

In education, a new collaborative research project has been established, bringing together extensive educational research expertise at Weizmann with Garvan's molecular visualisation and genomics education expertise.

Concepts about genomics, and processes that occur at the molecular level are challenging to teach and also to learn. Videos and animations can help, however a gap exists between their potential for science teaching and their actual use in the classroom.

Garvan science communicator, Bronwyn Terrill and molecular animator, Dr Kate Patterson, have teamed up with education researchers Professor Ron Blonder and Dr Bat-Shahar Dorfman of the Weizmann Institute of Science in Israel to find out how the gap could be bridged.

In a four-day workshop, the team collaborated with a group of year 12 science teachers on ways to incorporate scientific videos and animation into their lesson plans.

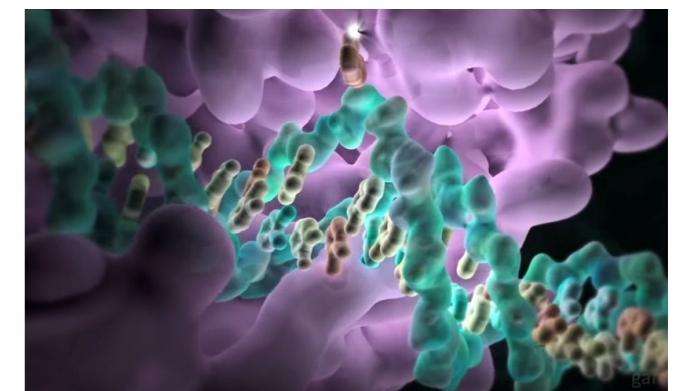
"Our aim is to investigate and deliver the most meaningful usage of 3D science animations for teachers in the classroom," said Professor Blonder.

"Garvan is a leader in genomic research and has invested in genetics education and research to improve health professionals' and community literacy. Teachers are key to that program because they are ideally placed to prepare the next generation of healthcare consumers and citizens for genomics and precision medicine," said Ms Terrill.

"This is a new content area and we have specific expertise in genetics education and molecular animation, so it was fantastic to be able to learn from each other," said Dr Patterson.

The project was funded by a seed grant from the Garvan-Weizmann Partnership, a collaborative international endeavour that harnesses the synergistic strengths of two world-class research institutes.

"Our aim is to investigate and deliver the most meaningful usage of 3D science animations for teachers in the classroom." - Professor Blonder



Close up of DNA methylation (tiny chemical tag shown as a glowing particle being added to one of the DNA bases)

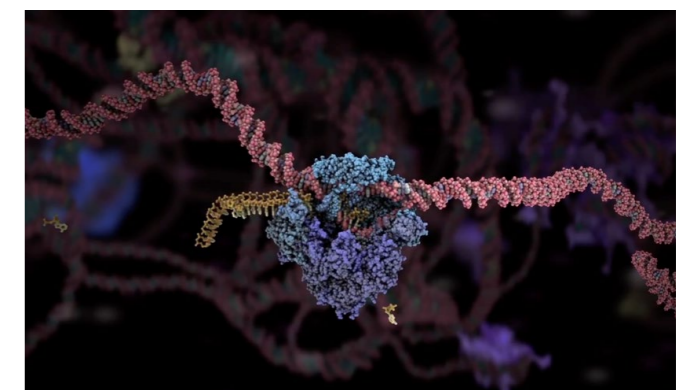


Image taken from one of the animations used in the workshop showing one RNA molecule (yellow) being transcribed from DNA.

ONE STEP CLOSER

Launched at the end of January 2019, the **Australian Parkinson's Mission is a world-first program integrating clinical trials with biomarkers and genomics that aims to slow, stop and ultimately cure Parkinson's disease**, a devastating illness that affects approximately 100,000 Australians today.

Not having control over your body may seem like an alien notion to the vast majority of us, but this is the reality for 10 million people living globally with Parkinson's disease.

Parkinson's disease is a progressive neurological disorder where the brain does not produce enough dopamine – a neurotransmitter that relays chemical messages between cells in the brain. Dopamine is used by the brain in many ways, but is particularly important in controlling movement. This lack of dopamine is what causes the most well-known symptoms of Parkinson's – body tremors, muscle rigidity and difficulty moving, which gradually progress and worsen over time. However, people with Parkinson's can also be affected by a broad range of non-motor symptoms including cognitive impairment and mood disorders.

The cause of Parkinson's is unknown, with available treatments only masking the symptoms of the disease. There is no way for clinicians to detect and diagnose the disease early, meaning that a person diagnosed with Parkinson's will already have irreversible symptoms of the illness, with current treatments unable to stop, or even slow its progression.

An international effort

Without a medical breakthrough, the number of Australians diagnosed with this devastating illness is set to double every fifteen years. To address the critical need for more effective treatments, the Garvan Institute of Medical Research in collaboration with the Shake It Up Australia Foundation, Parkinson's Australia, The Cure Parkinson's Trust (UK) and The Michael J. Fox Foundation for Parkinson's Research (USA) have launched the Australian Parkinson's Mission (APM), a world-first clinical trial design.

The unique design of the APM will not only enable faster delivery of effective treatments, but enhance our understanding of the underlying causes of Parkinson's.

The APM, an Australian-led initiative, will take a new approach to researching Parkinson's treatments by integrating clinical trials which will test four repurposed drugs, with whole genome sequencing and biomarker analysis.

The APM, an Australian-led initiative, will take a new approach to researching Parkinson's treatments by integrating clinical trials which will test four repurposed drugs, with whole genome sequencing and biomarker analysis. Each patient enrolled in the clinical trial will have their genome – their entire DNA – sequenced with the aim to reveal the different disease subtypes of Parkinson's and uncover which drug will work for each subtype. Analysis of patient biomarkers – naturally occurring measurable indicators of a disease – will further enable researchers to identify and measure the efficacy of the repurposed drugs.

Trial to patient, fast-tracked

"One of the aims of the APM is to be able to deliver effective treatments to people with Parkinson's as quickly as possible," says Associate Professor Antony Cooper, Head of the Neurodegeneration and Neurogenomics Program at Garvan who is spearheading the program.

An ongoing mission

The APM will begin enrolling people with Parkinson's onto the program in mid-2019 when clinical trials are due to begin, but the breadth of this program will see it evolve over time.

"We've identified complementary expertise from across the globe to create what can be a truly game-changing clinical program for people with Parkinson's", says Associate Professor Cooper.

Thank you to Geoff and Dawn Dixon, David and Helen Baffsky, Dr Richard Balanson and Dawn Talbot, the Shake It Up Australia Foundation and the Federal Government for supporting the APM.

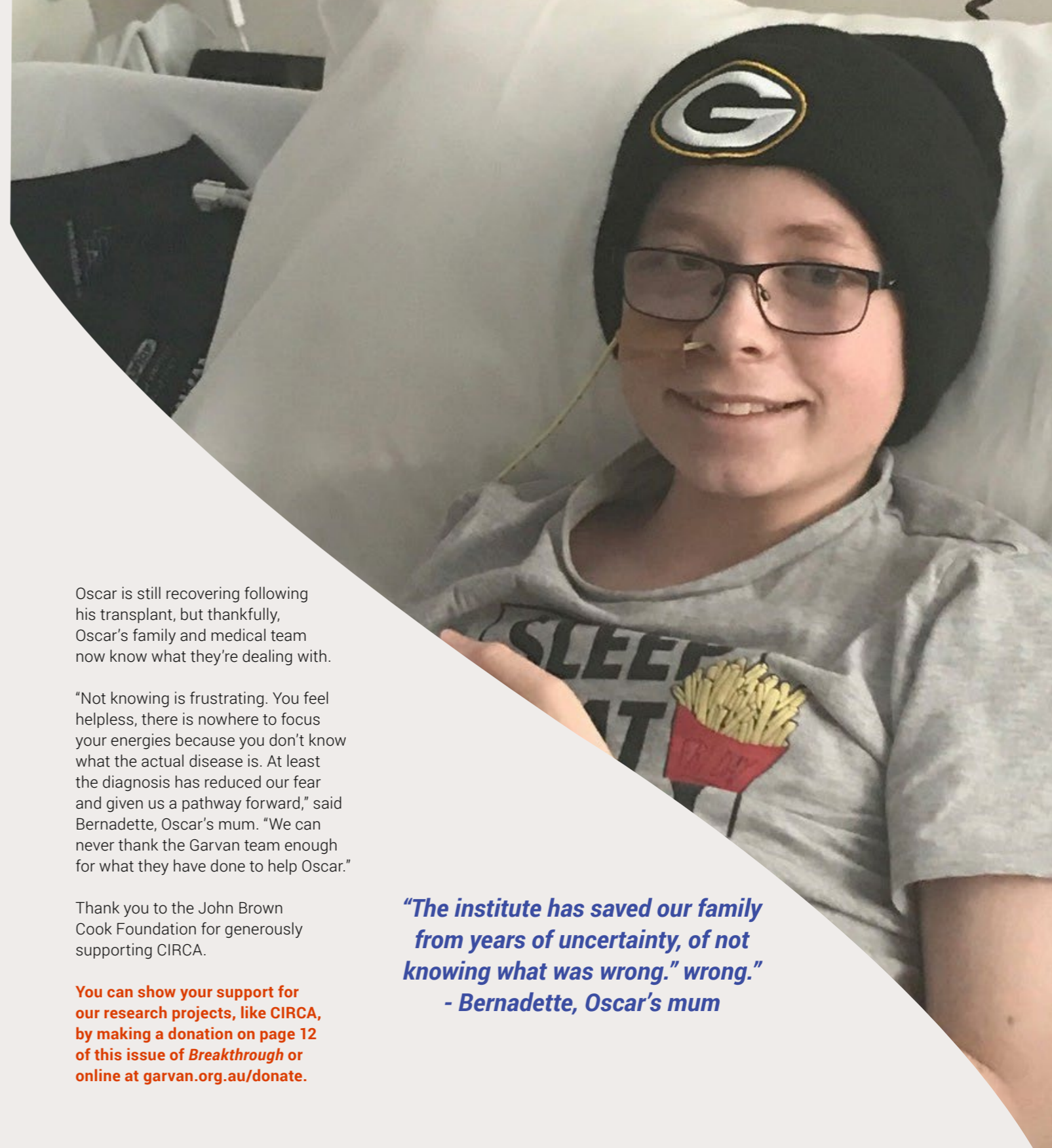
"Without the support of the community, many whose lives have been touched by Parkinson's, a project this ambitious would never have been possible," possible." - A/Prof Antony Cooper



To show your support for Garvan's collaborative work, please consider making a donation using the form on page 12 or at garvan.org.au/donate.

More information about the clinical trial and how to get involved at theapm.org.au

Discovering ~~The fear of~~ the unknown



A Garvan-led research team called CIRCA is giving new hope to patients like Oscar, who are living with critical, rare immune conditions.

Oscar was six when a constant cough led him to get a chest x-ray. What followed were five years of scans and invasive tests, with no answers as to why he was still sick.

One day before Christmas, at only 11 years old, Oscar suffered a stroke. He was placed in ICU after suffering three more strokes in the hospital emergency department. The doctors couldn't understand why an otherwise healthy looking boy was having a stroke, but what they did know was that his body was battling something serious.

A life-saving discovery

With nowhere else to turn, Oscar's doctors referred his case to the Garvan led Clinical Immunogenomics Research Consortium Australia (CIRCA) – a research network of scientists and clinicians with diverse backgrounds that come together to understand the causes of disease in patients with rare immune conditions.

Oscar's genome was sequenced at Garvan, where an underlying driver of Oscar's previously undiagnosed condition was identified.

Genome sequencing uncovered that Oscar has a variation in a gene called MAGT1 which results in a disease called X-linked Magnesium EBV neoplasia, or XMEN. This disease is a rare immunological genetic condition which only affects the immune system of males (in the X-chromosome), reducing the number of T cells or causing them not to function properly.

Even though Oscar is one of less than 15 people in the world with XMEN disease, the diagnosis guided Oscar's treatment path and he received a bone marrow transplant.

Light at the end of the tunnel

Genome sequencing is making it possible to diagnose rare, critical immune conditions when all other avenues fail.

Since its launch in 2015, CIRCA has grown from three members to an international consortium of 15 organisations. So far, over 150 patients have been recruited. With generous support, this new and emerging research is set to provide not only more answers but also precise and targeted gene-specific therapies.

"We are quickly identifying the underlying genetic causes in people with faulty immune systems, and are providing access to therapies within months, says Professor Stuart Tangye, Head of Immunology at Garvan and lead researcher with CIRCA.

Oscar is still recovering following his transplant, but thankfully, Oscar's family and medical team now know what they're dealing with.

"Not knowing is frustrating. You feel helpless, there is nowhere to focus your energies because you don't know what the actual disease is. At least the diagnosis has reduced our fear and given us a pathway forward," said Bernadette, Oscar's mum. "We can never thank the Garvan team enough for what they have done to help Oscar."

Thank you to the John Brown Cook Foundation for generously supporting CIRCA.

You can show your support for our research projects, like CIRCA, by making a donation on page 12 of this issue of Breakthrough or online at garvan.org.au/donate.

***"The institute has saved our family from years of uncertainty, of not knowing what was wrong." wrong."
- Bernadette, Oscar's mum***

Oscar's genome was sequenced at Garvan, where an underlying driver of Oscar's previously undiagnosed condition was identified.



Professor Stuart Tangye



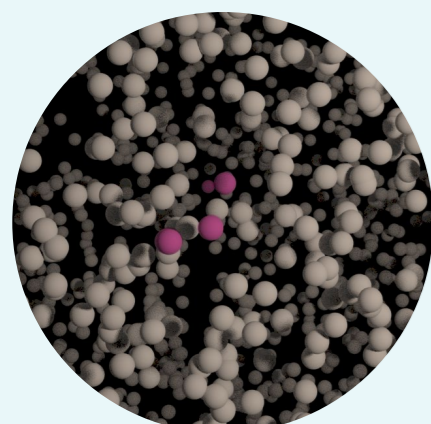
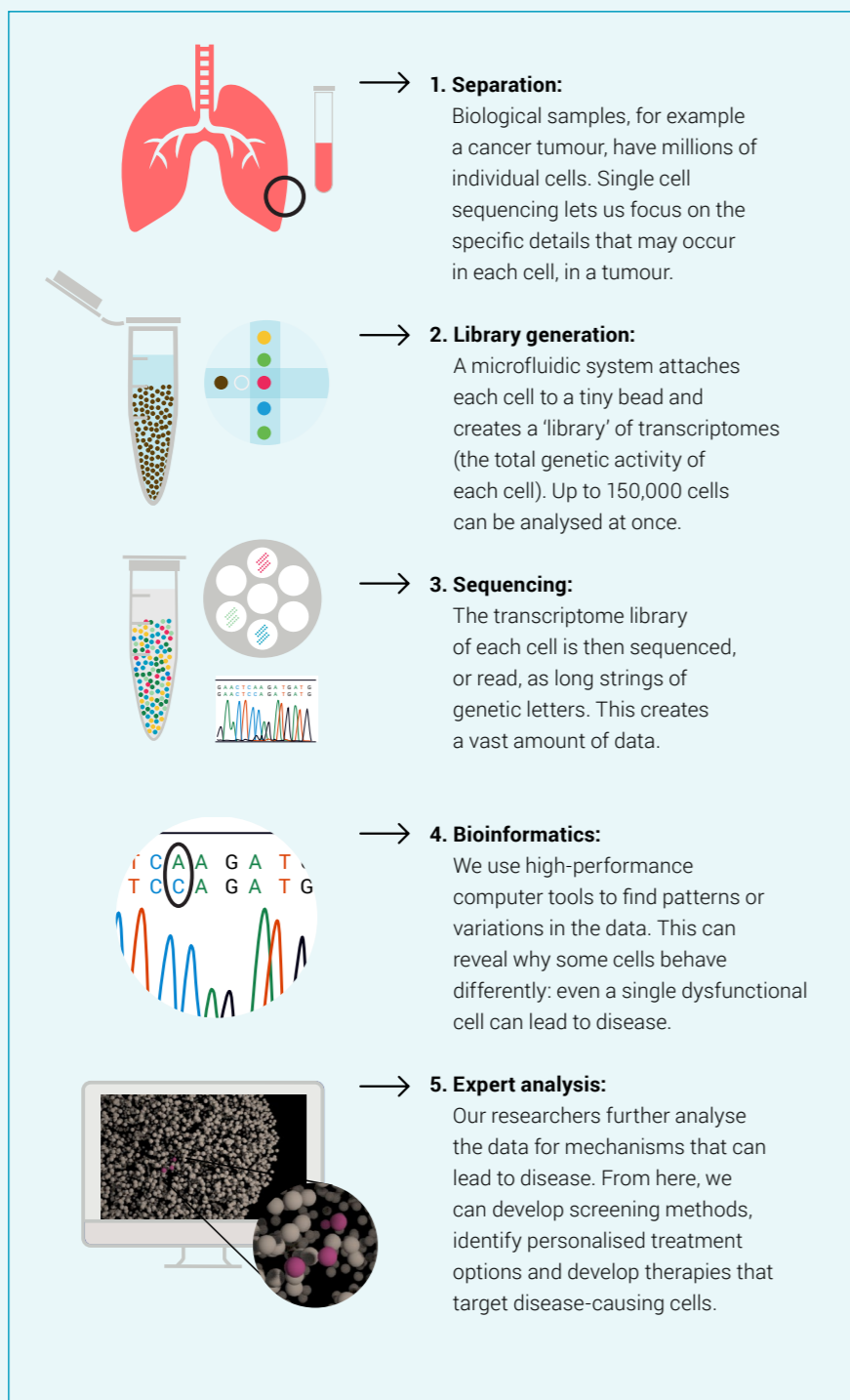
HOW DOES CELLULAR GENOMICS WORK?

We have trillions of cells in our body – a single, individual cell can impact health and disease.

Cellular genomics is a revolutionary technology that's transforming biological and medical research. Where whole genome sequencing is the study of all our DNA averaged over millions of cells, cellular genomics is the study of the genetic makeup of a single cell – from the cell's entire DNA code (its genome), to the secondary code that organises the genome (its epigenome), and the total genetic output of the cell (its transcriptome). Cutting-edge cellular genomics technologies make it possible to unlock unprecedented insights into how cells work individually, and how they function together, in ways that were impossible only a few years ago.

The Garvan-Weizmann Centre for Cellular Genomics, led by Associate Professor Joseph Powell, is one of the few global sites where state-of-the-art technologies are seamlessly integrated, including the latest platforms in flow cytometry, microfluidics, genomics, high-performance computing and bioinformatics.

Even a single cell can lead to disease.



STORM IN A D CUP

When Kari Esplin was diagnosed with breast cancer in October 2018, she was determined to make sure that something positive came out of her diagnosis. A big personality with infectious optimism, Kari decided that before she started her chemotherapy, she'd raise money for breast cancer research by shaving her head and set-up a fundraising page called 'Storm in a D-Cup'.

Kari chose to raise money for the Connie Johnson Breast Cancer Research lab at Garvan after finding out her oncologist, Associate Professor Elgene Lim was the head of the lab. "I had always been aware of what Samuel and Connie Johnson had done with the Love Your Sister Foundation, and as soon as I made the link with Elgene, I knew instantly what I was going to raise the money for," says Kari.

Setting a fundraising goal of \$2000, with the support of her family and friends, Kari reached and exceeded that amount in less than 24 hours. Donations are now five times her original goal, more than \$10,000, a testament to Kari and the people around her. "I felt so excited when I found out how much money we raised, and so uplifted," says Kari. "Even now we still have money coming in, which is absolutely amazing."

Earlier this year in January, with a champagne in hand and a smile on her face, Kari shaved her hair off in front of family and friends, using the opportunity to encourage other women to make sure that they are being breast aware.



Kari Esplin

"My tumour was found through a routine mammogram," says Kari. "Since being diagnosed I've had discussions with so many women about their breast health who have put off getting a mammogram. I can't stress how important it is to go beyond self-checks and make mammograms routine. I understand that some women feel awkward about it – but I say go do it. It saves lives."

While her diagnosis has been a life altering experience, Kari remains positive about the future. "I have an absolutely amazing support system around me – my husband and children have been incredible and this experience has overall been more positive than negative."

"I'm definitely more of a 'just do it' person now. If there's an opportunity out there – I'm going to take it." She laughs, "what could possibly go wrong?"

The generosity of the community is critical to Garvan's research. You can team up with your friends, family and colleagues to support innovative research projects like this.

RESEARCH NEWS

Blood test to track chemotherapy

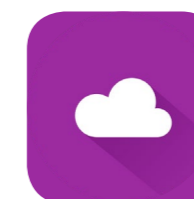
A simple blood test could improve the clinical outcomes of advanced prostate cancer patients by tracking whether chemotherapy is working – as they are undergoing treatment. Garvan researchers led by Professor Susan Clark, together with clinicians and scientists at Chris O'Brien Lifehouse, completed the world-first phase 3 clinical trial, which measured a biomarker, called mGSTP1, in patients with metastatic, castration-resistant prostate cancer who were receiving chemotherapy.

The researchers detected mGSTP1 in the blood samples of 81 percent of patients before treatment and in 53 percent of patients after two cycles of the chemotherapy drug docetaxel. The trial results showed that patients whose blood sample lacked mGSTP1 had both longer overall survival and slower disease progression.

While further clinical trials of mGSTP1 are still needed, this research may ultimately improve the treatment of advanced prostate cancers and guide clinicians to tailor an individual patients' therapy to the most effective treatment plan.

Read more at: garvan.org.au/prostate-blood-test

Fast-tracking cancer research globally



In 2015, Garvan and Vodafone launched the DreamLab App, a smartphone super computer which harnesses the idle power of your phone or device to fast-track cancer research.

Four years later, DreamLab has gone global, launching in New Zealand, the UK and Hungary, with more countries getting on board this year. Thanks to 122,000 worldwide users, we have completed three projects within DreamLab, and researchers at the Garvan Institute have published findings, revealing a new way to make sense of cancer.

Megan Retka-Tidd, Senior Manager, Partners & Programs at the Vodafone Foundation, says, "The world is getting increasingly smaller, but cancer is still a big problem. We encourage you to tell everyone you know to download DreamLab, and help us fast-track Garvan, and others, cancer research."

The Vodafone Foundation also supports Garvan's Australian Genomic Cancer Medicine Centre, a clinical trial for people with rare cancer.

Read more at: garvan.org.au/dreamlab

Clinical trial Spotlight

For those living with type 2 diabetes, we are trialing a new precision treatment – a custom-matched diet – based on an individual's gut microbiome.

Garvan diabetes and obesity researchers are leading an exciting clinical trial called PREDICT which is testing how a tailored diet can improve the body's response to the common diabetes drug metformin.



Our collaborators at the Weizmann Institute of Science created an algorithm which can predict how a person's blood sugar will respond to different foods, based on individual variables including their 'gut microbiome' – a unique set of thousands of species of microorganisms that reside in the gut. We are now trialing these tailored diets on people in Australia with prediabetes and diabetes.

During the six-month study, participants wear a glucose monitor for two weeks before and during treatment and document all their food intake in a specialised mobile phone app.

The PREDICT clinical trial is now looking to enrol men and women aged 20 to 70 years who have prediabetes or recently diagnosed type 2 diabetes, that have not yet been treated with blood sugar-lowering medication. Over the next couple of years we hope to recruit 200 new patients.

We aim to translate the findings from the PREDICT study to tools for clinicians and patients to better guide medication, diet and lifestyle choices, to stop prediabetes from progressing to type 2 diabetes, and also to assist those living with diabetes in better manage their health.

What drives us is our patients. Together with the generosity of you, our supporters, we can make a difference for those living with type 2 diabetes and other metabolic conditions.

Dr Dorit Samocha-Bonet
Clinical Insulin Resistance Group Leader

For further information on the trial, please contact:
Email: PREDICT@garvan.org.au.
Phone: + 61 2 9295 8215
HREC ref: SVH 17/080

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CLINICAL STUDIES

Breast cancer 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

Appetite study for genetic obesity

We are seeking healthy, normal or overweight male volunteers between the ages of 20 and 52. This study investigates appetite regulation and gastric emptying in a genetic form of obesity called Prader-Willi syndrome. HREC Ref: 15/SVH/437

For further information, please contact Associate Professor Alex Viardot.

Phone: (02) 8382 2622 or email: pws@garvan.org.au

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