Issue 42

breakthrough

Targeting dormant cancer cells

Also in this issue

How disease affects us as we age

A genomic barcode tracker for immune cells

Garvan Institute of Medical Research

Welcome from our Executive Director

Dear Garvan family,

I have now had the privilege of being in my role as Executive Director of the Garvan Institute for 15 months.

Recently I have spent some time thinking about what it is that makes us who we are. Throughout my career, I've worked at many different institutes and universities, but none quite compare to Garvan.

What sets Garvan apart is our clinical interface – being part of the St Vincent's precinct and able to directly interact with patients in our research. Our brilliant scientists – the best and brightest people seeking to address the biggest health challenges of our time. Finally, you, our community who engage with us and generously support our research.

I am constantly impressed and inspired by the discoveries of my colleagues and am delighted to be able to share many with you in this edition of *Breakthrough*. In this issue, you'll learn the key to targeting dormant cancer cells in bone, which could help prevent the spread of cancer.

You will also have the chance to see how microscopy images are helping researchers to unpick the intricate details of the human immune system. As well as a new technology called RAGE-seq that can spot rare immune cells that are reactive against cancer cells, from within a patient's own immune system.

Without you, our family and supporters, we simply wouldn't be able to do the work we do. On page 5, you'll meet Sophie Juresic who is generously supporting our research through The White Butterfly in memory of her sister, Vanessa.

I hope that our paths will cross soon and that you will be able to attend one of our free public seminars either in person in Darlinghurst, Sydney or online at garvan.org.au. The seminars are an opportunity to hear directly from our researchers, and give you the chance to ask them questions in our interactive Q&A sessions.

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

NEW RESEARCH

Comfort food weight gain

It's no secret that overindulging on high-calorie foods can be detrimental to health, but it turns out that under stress, watching what you eat may be even more important.

A team led by Professor Herbert Herzog discovered in an animal model that a high-calorie diet when combined with stress resulted in more weight gain than the same diet caused in a stress-free environment. The researchers revealed a molecular pathway in the brain, controlled by insulin and a molecule called NPY, which drives the additional weight gain.

In mice, the scientists discovered that chronic stress and a high-calorie diet raised the blood insulin levels to 10 times higher than mice that were stress-free and received a normal diet. The study revealed a vicious cycle, where chronic, high insulin levels driven by stress and a high-calorie diet promoted more and more eating.

While insulin imbalance is at the centre of a number of diseases, this research indicates that insulin has more widespread effects in the brain than previously thought.

Read more at: **garvan.org.au/stress-eating**

A driver of inflammation

Inflammation is crucial to keeping the body healthy, for example in response to infection – but in excess, it can be devastating. A study led by researchers Professor Mike Rogers and Dr Marcia Munoz has revealed a piece of the puzzle of how a genetic variant triggers flares of inflammation in a rare childhood condition known as mevalonate kinase deficiency (MKD). The researchers investigated 'inflammasomes' – molecules which assemble together into larger structures within cells to trigger an inflammatory response.

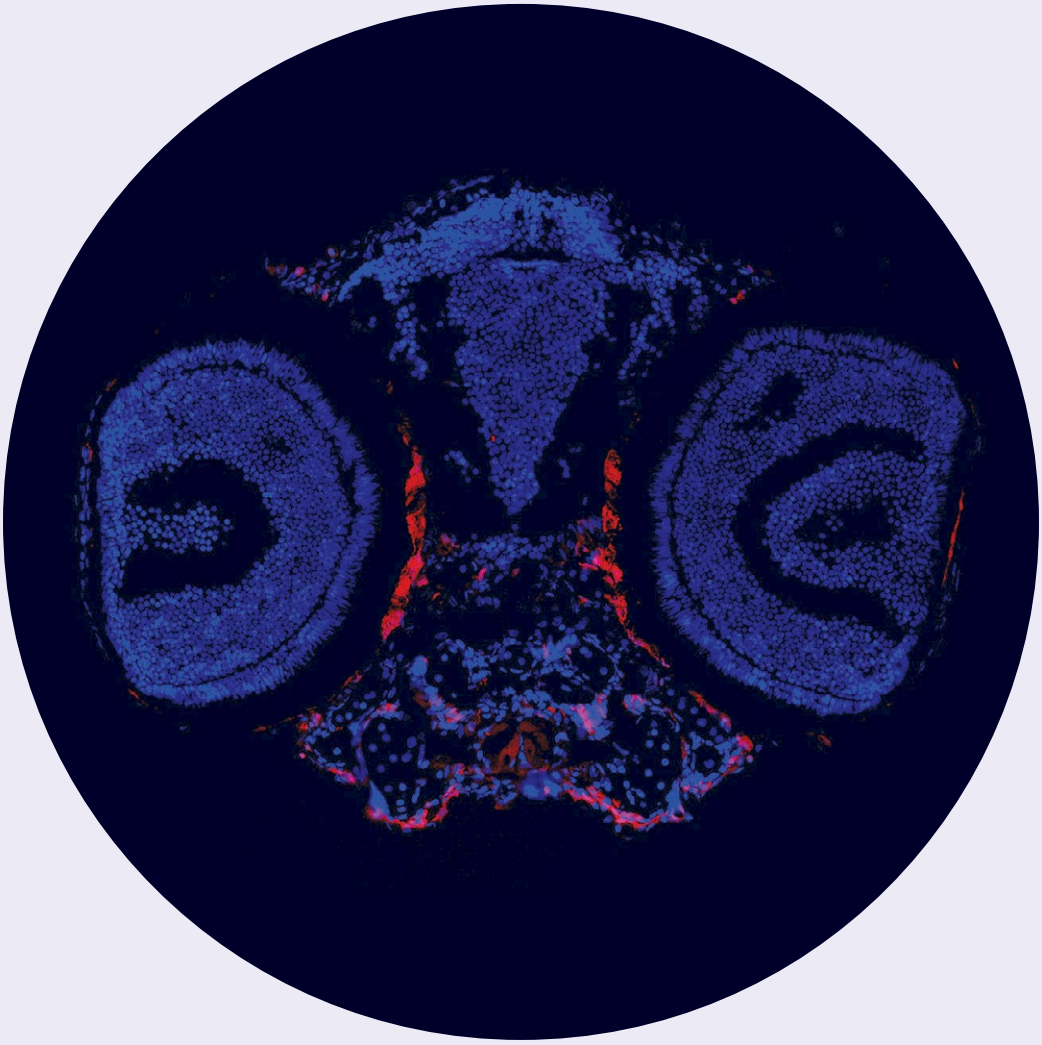
In white blood cells, the researchers simulated the MVK gene variants found in MKD patients and investigated two molecules – NLRP3 and pyrin – the building blocks of two different types of inflammasomes. The team discovered the NLRP3 inflammasome likely plays a key role in the imbalanced inflammation that occurs in MKD patients.

Currently, individuals suffering from MKD are treated with anti-inflammatory therapies, which are not effective in all patients, but blocking inflammation more specifically through the NLRP3 inflammasome may provide a better alternative. The findings bring new hope for treatment to those affected by this rare autoinflammatory disease.

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

THROUGH THE **MICROSCOPE**

Fluorescent microscopy images of zebrafish are helping Garvan researchers understand inflammatory diseases.



" The remarkable symmetry of this image shows that even in complex systems as variable and as adaptable as the immune system there is always an underlying elegance." – Dr Cultrone

You may be quick to think you are looking at a Rorschach inkblot. But such microscopy images are not used to study the mind – they are helping researchers unpick the intricate details of the immune system.

Pictured in this fluorescent microscopy image is a section of a zebrafish head, a small translucent fish commonly used as a model to study human diseases, imaged by our researcher Dr Daniele Cultrone. Visible in red are macrophages – cells of the immune system that are activated when pathogens are present in the environment.

Using zebrafish, Dr Cultrone is investigating the effects that human variants of a gene called TNFAIP3 have on the immune system and how they are linked to critical inflammatory diseases, such as rheumatoid arthritis, Crohn's disease and type 1 diabetes. By better understanding the mechanisms that drive inflammatory disease, Garvan researchers hope to help find better ways of treating them.

A five-star future

★ ★ ★ ★ ★

A first-hand encounter with a Garvan researcher was the catalyst for Graham Curtis to not only start a journey supporting the Institute which has lasted for fifteen years, but to also become one of Garvan's special *Partners for the Future.*

It was in 1997 when Graham had a conversation with Professor Ken Ho, at the time a clinician at St Vincent's Hospital and a Garvan researcher in what was then called the Pituitary Research Unit. Professor Ho was treating Graham for a rare disorder of the pituitary gland - acromegaly, which at the time affected only 81 people in Australia. Professor Ho encouraged Graham to attend one of the free Garvan Public Seminars happening at the time, which was fortuitously all about the pituitary system.

"I was blown away by the seminar, and the work the researchers were doing, it was all five-star," says Graham.

Graham began helping out at Garvan as a volunteer and within two years of seeing the excellent work of the researchers, he made the farsighted and generous decision to include a gift in his Will to Garvan. "I'm no multi-millionaire, but I thought bugger it," he says. "The scientists at Garvan helped keep me alive. I'll never be able to fully repay them for what their research has done for me, but for me it's a start."

Becoming a *Partner for the Future* was not only Graham's way to give back to the researchers and Institute that had helped change his life, but also to give back to the community. "Giving to Garvan is a way to give back to everyone. Going to the seminars or reading the stories in *Breakthrough*, you see all the amazing work that is happening. You can only imagine what new breakthroughs are around the corner," he says.

"Leaving a gift in my Will to Garvan is a way of achieving research breakthroughs sooner and if other people can do it, they absolutely should."

If you would like information about leaving a gift in your Will to transform future medicine and become a Garvan *Partner for the Future*, please contact Donna Mason, Bequest Manager on (02) 9295 8559 or visit garvan.org.au/bequest

Breast cancer's white butterfly

Breast cancer tragically claimed the life of Vanessa Juresic in 2018. Now, her sister Sophie is hosting an annual fundraising event in Vanessa's memory to fulfil her wish of supporting Garvan, The White Butterfly.

Vanessa was just 36 when she was diagnosed with triple negative breast cancer. Sadly, 15 months later, she lost her life.

Speaking about her sister at a recent breast cancer symposium at Garvan, Sophie said, "Vanessa was strong, tenacious, beautiful and my intelligent big sister. She made it her mission to be kind to anyone that walked into her life, even if it was the ones that were giving her the bad news that she had a year to live.

"She brought cupcakes for the nurses, she befriended other patients on their first day of chemo or radiology, letting them know it was going to be okay. She did all she could to become best friends with her oncologists [Associate Professor Elgene Lim, an oncologist at St Vincent's Hospital and breast cancer researcher at the Garvan Institute], and knock down the walls of those patient-doctor relationships.

"She created partnerships and friendships with anyone that crossed her path. What Vanessa has done for the Garvan Institute, for her family and for the world is selfless, and what this means for us, what this gives us the opportunity to do, is to make that love stronger than death.

"I speak to 500 people today - you tell a friend and we speak to 1000," Sophie Juresic urged the packed audience "They tell a friend and we speak to 2000, and so on. No one is protected from this disease".

"Together we can research, operate, nurse, fundraise, but most of all care, and take a stab at finding a cure for triple negative breast cancer."

The White Butterfly fundraiser, 19th October at the Woolwich Pier Hotel, will raise money for Garvan's breast cancer research.

For information please visit **www.thewhitebutterfly.org** write to **info@thewhitebutterfly.org** or contact Sophie on **0438 481 479.**

WHITE BUTTERFLY

2019 Garvan Researcher Awards

Held annually, the awards provide recognition and support of our early-mid career researchers' innovative research ideas.

The Young Pioneer Award from CHAMP Private Equity was awarded to Dr Nathan Zammit, Research Officer in the Transplant Immunology Laboratory. He will use the award to investigate why a novel immunomodulatory drug, TGN1412, surprisingly did not work as expected in a clinical trial and why adverse effects were not predicted in preclinical testing.

The Palmer Innovation Prize is funded by the Joseph Palmer Foundation. Ghamdan Al Eryani, Mandeep Singh, Shaun Carswell, and Katherine Jackson, who work right across the Institute will use the prize to leverage current technologies to obtain a comprehensive description of gene expression in a large number of cells, that will have applications in many areas of research, including cancer and autoimmune disorders. See more information on page 7.

The Ridley Ken Davies Award from Ridley Corporation is awarded in memory of Ken Davies. Dr Eva Chan, Senior Research Officer/Analyst in the Human Comparative and Prostate Cancer Genomics laboratory, is developing new ways to look in the 10% of the genome that is not able to be sequenced by current methods.

The Miriam Douglass Blue Sky Endowment Award for 'blue sky' research projects into breast or prostate cancer. The award was established in memory of Miriam Douglass, a generous and visionary *Partner for the Future*. The inaugural recipient of the award is Dr Christine Chaffer, Head of the Cancer Cell Plasticity laboratory, to develop novel therapeutic strategies to inhibit the spread of breast cancer.

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

BONE HEALTH

Osteoporosis drugs linked to reduced risk of premature death.

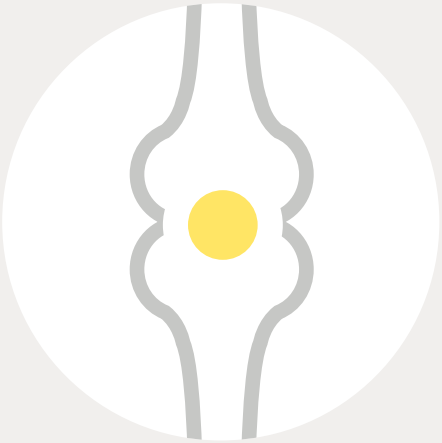
Garvan researchers have revealed that nitrogen-bisphosphonates, drugs commonly prescribed for osteoporosis, reduced the risk of premature mortality by over one-third in a study of over 6,000 individuals.

Osteoporosis affects around 200 million people worldwide, and is a progressive disease in which bones become more porous and fragile, often without symptoms until the first fracture occurs.

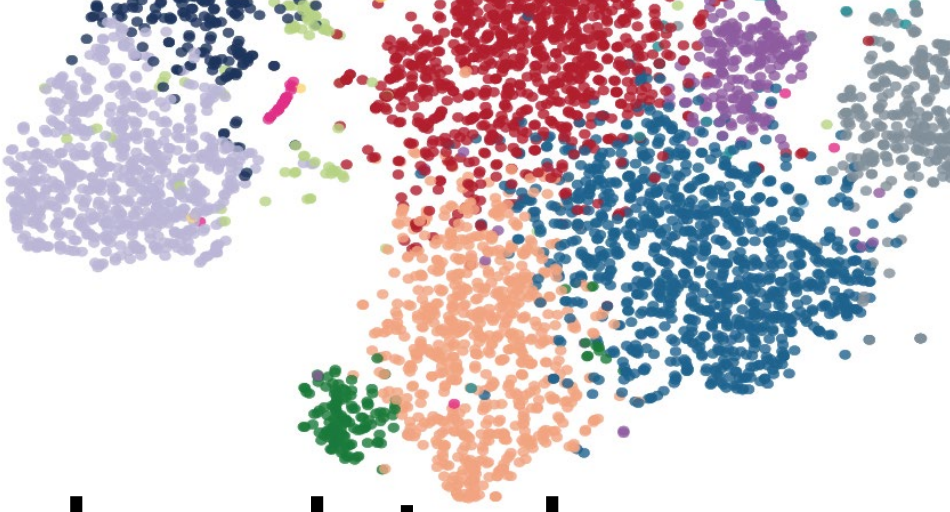
The Garvan study, led by Professor Jacqueline Center, presents new evidence of the significant benefits of taking approved osteoporosis medicine for those with, or at risk of the disease.

Our researchers analysed data from participants aged over 50, who took part in the observational Canadian Multicentre Osteoporosis Study – showing that individuals treated with nitrogen-bisphosphonates had a 34% reduction in mortality risk over the subsequent 15 years, compared to non-treated individuals.

For many individuals with osteoporosis, bone health is not front-of-mind with fewer than 30% of women and 20% of men with fragility fractures taking approved treatments. However, the studies provide additional evidence that the recommended nitrogen-bisphosphonate treatment can not only reduce the risk of further fractures in patients, but decrease mortality rates long term.



Research indicates that individuals treated with nitrogen-bisphosphonates had a 34% reduction in mortality risk over the subsequent 15 years, compared to non-treated individuals.



A genomic **barcode tracker** for immune cells

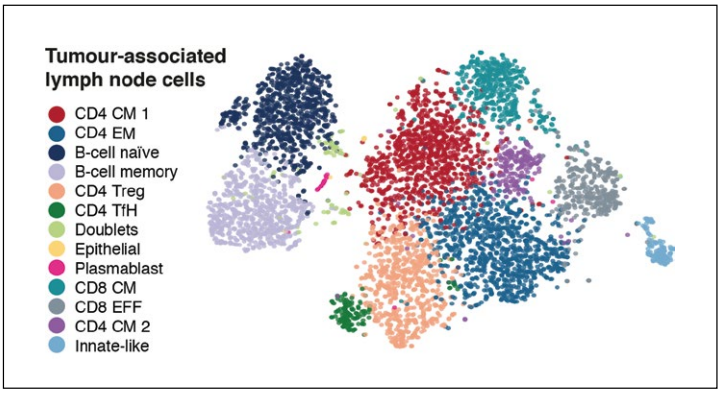
Our researchers have developed a new method to spot rare immune cells that are reactive against cancer cells, from within a patient's own immune system.

The patented 'RAGE-seq' method enables scientists to track how immune cells evolve inside tumour tissue for the first time, revealing unprecedented insight into how to better arm the immune system to target cancer. The technique can be likened to a barcode tracker, able to scan detailed information from each of thousands of of immune cells at a time.

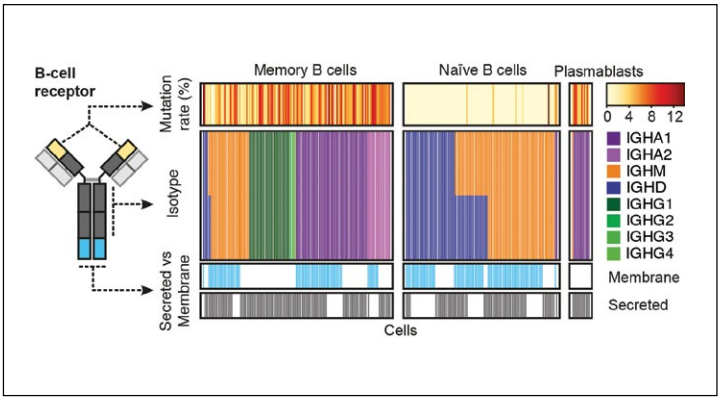
Development of the method, by Ghamdan Al Eryani, Mandeep Singh, Shaun Carswell, and Katherine Jackson, gives us the most detailed view yet of how immune cells behave in the human body. The ability to find and barcode these rare cells of the immune system will give researchers the power to guide treatment strategies.

The team is now applying the technique to biopsy samples from melanoma patients, to understand why half of patients receiving immunotherapy have a poor response. In addition, they believe the method could be used more broadly to provide a better understanding of autoimmune and inflammatory diseases.

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



RAGE-seq provides a snapshot of different immune cells found within a tumour.



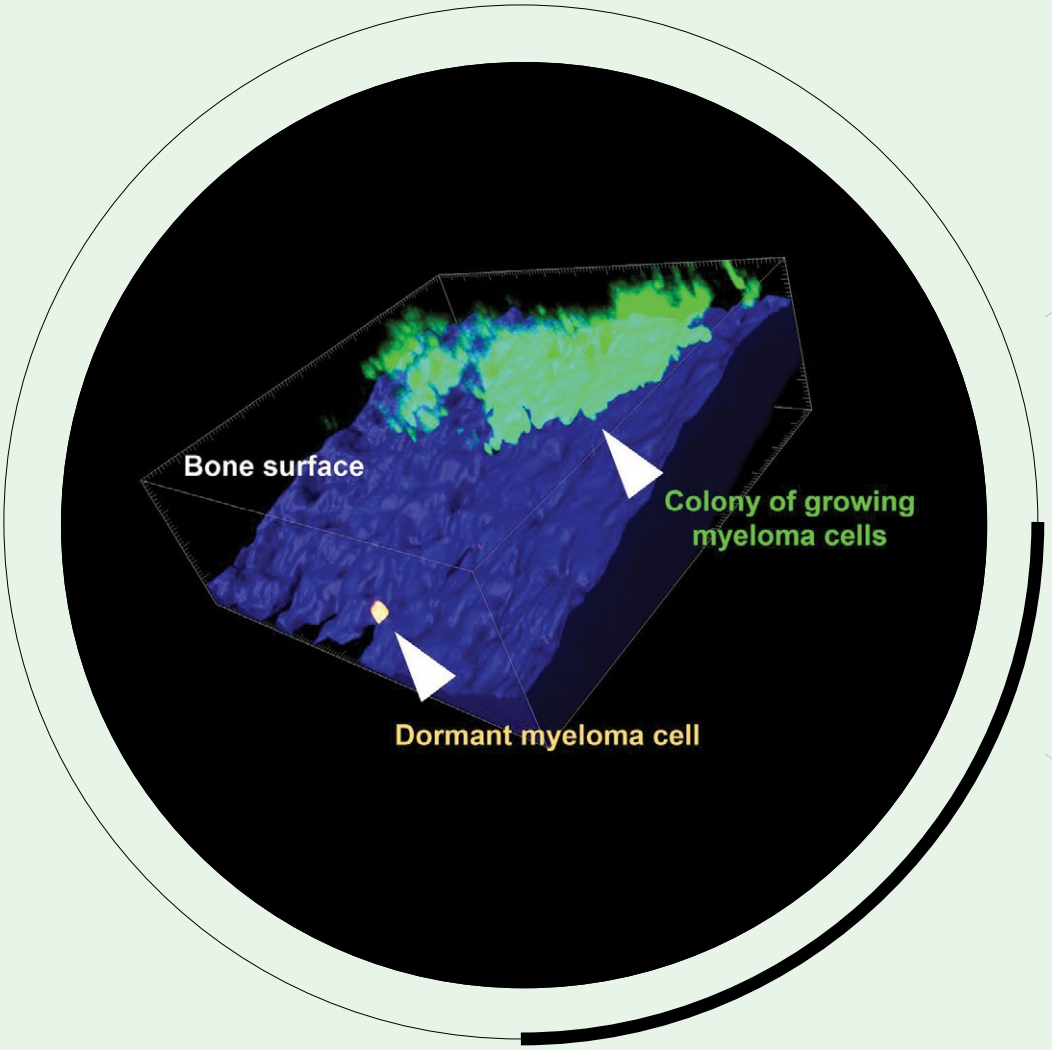
Much like a barcode, RAGE-seq can scan detailed information from thousands of immune cells at once.

THE KEY TO TARGETING
DORMANT CANCER CELLS

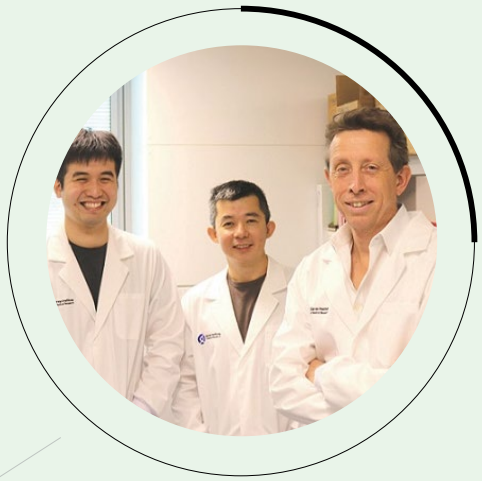
Researchers have identified what keeps some cancer cells dormant – a finding which could uncover new approaches to preventing the spread of cancer.

Most will associate cancer with fast growing cells that spread uncontrollably – but in fact, it's often the cancer cells that are dormant and inactive that pose the greatest threat. Dormant cancer cells, when 'woken up', are a major cause of cancers coming back, or relapsing, after treatment – often as metastases, which are estimated to cause 90 per cent of all cancer deaths.

In collaboration with the Weizmann Institute of Science in Israel, a Garvan team lead by Professor Peter Croucher and Associate Professor Tri Phan has uncovered the unique set of genes that keeps some cancer cells dormant. The research may reveal new therapeutic targets for multiple myeloma (a blood cancer that arises in bone) and other cancers such as breast and prostate cancer, which spread or metastasise to bone.



"The aim now is to bring data from many cancer types together to find a unifying approach to understanding how dormant cells control cancer relapse and metastasis."
– Professor Peter Croucher



Uncovering cancer's hiding place
When cancer metastasises, it spreads to different organs in the human body. Some cancer cells can stop dividing and hide in a 'dormant' state, tucked-away in niches such as the inner lining of bones. Once dormant, the immune system, our natural protector, cannot target them and conventional chemotherapy is ineffective.

To help prevent dormant cancer cells from being reactivated, Garvan researchers are investigating what makes cancer cells dormant. But isolating the cells to study them has been a challenge – they are rare, often less than one in hundreds of thousands of cells in the bone, and scientists have not known how to identify them.

"It's not just the cancer cell but the other cells in their microenvironment which determine their fate," says Associate Professor Phan. "We are trying to find what genes get switched on by the microenvironment and how those genes make the cancer cell dormant."

The Garvan researchers first developed a way to track dormant multiple myeloma cells inside the bones of living mice four years ago using a technique called intravital two-photon microscopy. They have now isolated these rare cells to analyse the dormant cells' transcriptome – a snapshot of all the genes that are switched on in the cell and could potentially control dormancy.

A new way to target cancer
The team analysed the single cell transcriptomes at the Garvan-Weizmann Centre for Cellular Genomics and confirmed their findings independently with their collaborators at the Weizmann Institute of Science. Unexpectedly, the dormant myeloma cells had a similar transcriptome signature to immune cells, but which was only 'switched on' when the cells were located next to osteoblasts, specialised cells found in bone.

"This showed us just how crucial the crosstalk between the tumour cells and the tumour microenvironment is for cancer dormancy," says Professor Ido Amit, Principal Investigator at the Weizmann Institute.

The researchers are now using their method to collect data on dormant cancer cells from other cancer types, with the hope of finding a common signature of all dormant cancer cells. The team is also working to develop potential therapies that target the unique features of dormant cells, now uncovered by this research.

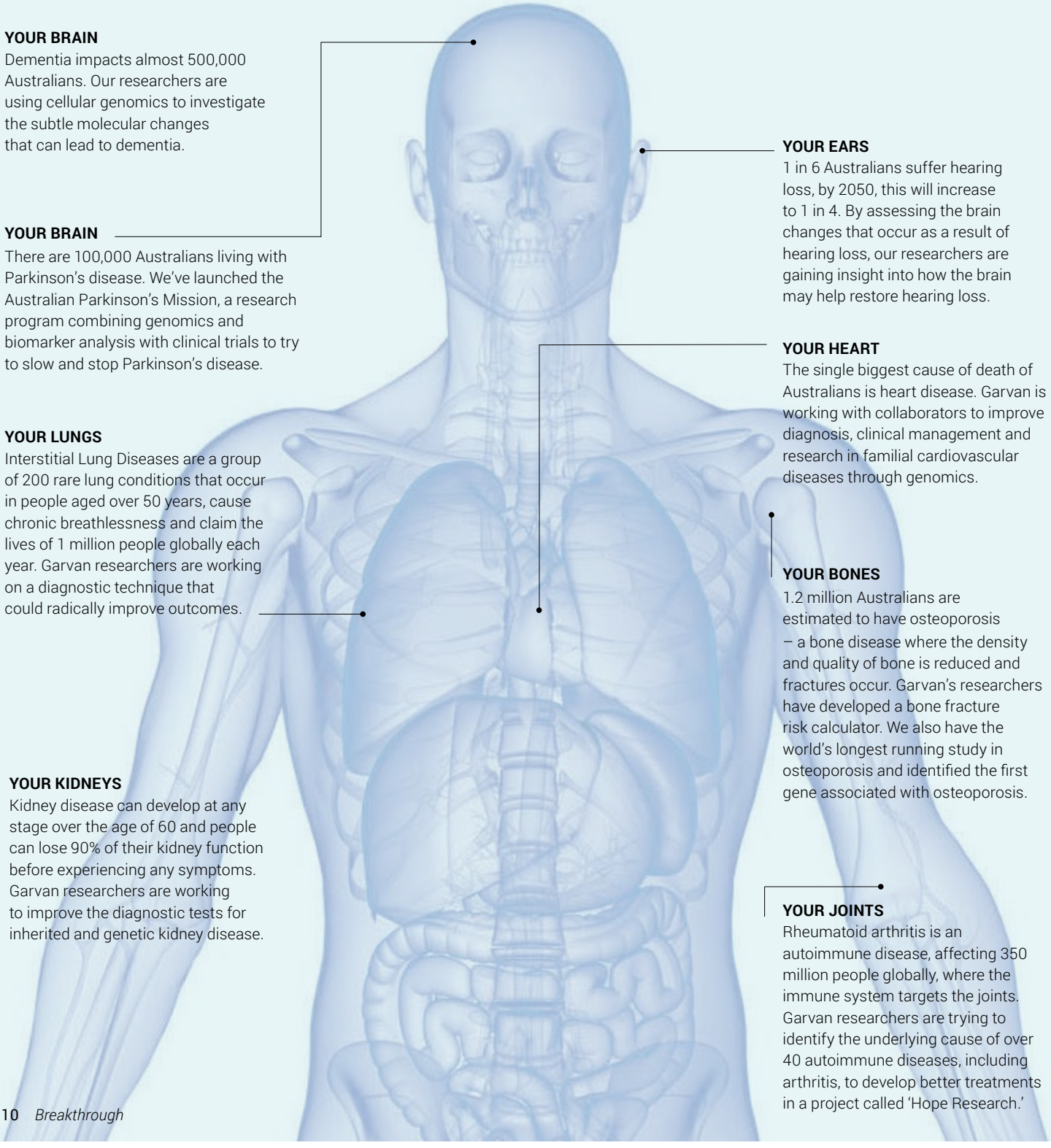
Read more at: **garvan.org.au/dormant-cancer**

The crosstalk between tumour cells and their environment is crucial to cancer dormancy.

How disease affects us

AS WE AGE

By 2050, 20% of the world's population will be aged over 60. Garvan researchers have numerous programs focused on diseases of ageing. Discover some examples below.



YOUR BRAIN
Dementia impacts almost 500,000 Australians. Our researchers are using cellular genomics to investigate the subtle molecular changes that can lead to dementia.

YOUR BRAIN
There are 100,000 Australians living with Parkinson's disease. We've launched the Australian Parkinson's Mission, a research program combining genomics and biomarker analysis with clinical trials to try to slow and stop Parkinson's disease.

YOUR LUNGS
Interstitial Lung Diseases are a group of 200 rare lung conditions that occur in people aged over 50 years, cause chronic breathlessness and claim the lives of 1 million people globally each year. Garvan researchers are working on a diagnostic technique that could radically improve outcomes.

YOUR KIDNEYS
Kidney disease can develop at any stage over the age of 60 and people can lose 90% of their kidney function before experiencing any symptoms. Garvan researchers are working to improve the diagnostic tests for inherited and genetic kidney disease.

YOUR EARS
1 in 6 Australians suffer hearing loss, by 2050, this will increase to 1 in 4. By assessing the brain changes that occur as a result of hearing loss, our researchers are gaining insight into how the brain may help restore hearing loss.

YOUR HEART
The single biggest cause of death of Australians is heart disease. Garvan is working with collaborators to improve diagnosis, clinical management and research in familial cardiovascular diseases through genomics.

YOUR BONES
1.2 million Australians are estimated to have osteoporosis – a bone disease where the density and quality of bone is reduced and fractures occur. Garvan's researchers have developed a bone fracture risk calculator. We also have the world's longest running study in osteoporosis and identified the first gene associated with osteoporosis.

YOUR JOINTS
Rheumatoid arthritis is an autoimmune disease, affecting 350 million people globally, where the immune system targets the joints. Garvan researchers are trying to identify the underlying cause of over 40 autoimmune diseases, including arthritis, to develop better treatments in a project called 'Hope Research.'

An atlas for breast cancer

An ambitious project is underway to better understand the complex molecular environment of breast cancers.

A breast tumour is not just a cluster of a single type of cell – it is a complex mixture of many different cancer cell types, connective tissues and immune cells.

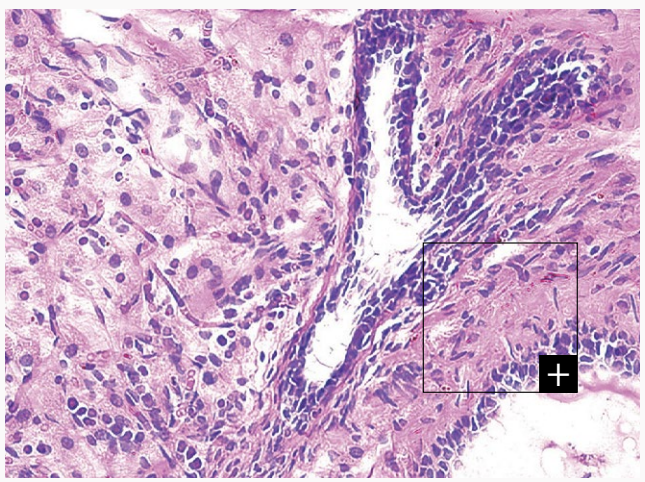
Led by Associate Professor Alex Swarbrick, Associate Professor Elgene Lim, Professor Sandra O'Toole and Associate Professor Joseph Powell, the 'Breast Cancer Cell Atlas' will catalogue data from a million individual cells from patient breast tumours, collected over the past five years.

Using cutting-edge cellular genomics technologies, researchers will measure the levels of more than 20,000 genes and more than 150 proteins from around 5,000 cells per sample. Combined with years of clinical data collected for each patient, this project will advance researchers' ability to understand the important interactions between cells and enable a completely new way to look at breast cancer, with the aim of finding new drug targets for cancers with poor clinical outcomes.

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

Combining cellular genomics information with years of clinical data collected for each patient will provide an unprecedented look into breast cancer biology.

Associate Professor Alex Swarbrick



The 'Breast Cancer Cell Atlas' will catalogue data from a million individual cells.

Clinical Trial **Spotlight**

Could a nutritional supplement help build muscle and prevent a disease that affects 30% of people over 50?

As we age, our bodies naturally lose muscle mass and strength, a condition known as sarcopenia. It's a disease that affects up to 30% of people over 50 and leads to frailty, risk of falls, loss of mobility and a diminished quality of life. Periods of inactivity, which could be due to illness or hospitalisation, can increase the onset on sarcopenia.

Sarcopenia
A disease that affects up to 30% of people over 50

Now, one of our clinical trials is testing whether a molecule called 'ursolic acid', found naturally in the skin of apples, cranberries and many herbs, can improve skeletal muscle strength and function, preventing sarcopenia. Previous research in experimental models has revealed that ursolic acid, when given as a supplement, can help build muscle and prevent it from wasting away.

Dr Andy Philp
Mitochondrial Metabolism and Ageing Group Leader

As we don't absorb much ursolic acid naturally from the food that we eat, we will first trial the best way to administer ursolic acid as a supplement. For this first phase of our study, we are currently enrolling healthy male participants aged 18 to 35. Each participant will ingest small capsules of ursolic acid at different times, and we will measure the amount absorbed, from a blood sample.

After determining the best approach to administer ursolic acid, we will examine whether the supplement can improve skeletal muscle size and function during strength training and periods of inactivity in both young and old individuals.

Through this work, we hope to make a difference to those at risk from suffering from sarcopenia. With the help of you, our supporters, we hope to find new ways to promote healthy ageing and improve quality of life.

For further information on the trial, please contact Dr Gareth Fletcher:
Email: g.fletcher@garvan.org.au

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Donations made to celebrate a special occasion

Pat Allsopp's 80th Birthday
Sue Morris' Birthday
William Walker's 103rd Birthday

CLINICAL STUDIES

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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