breakthrough

How Garvan researchers are tackling

Also in this issue Genome Power and the power of philanthropy

way and

Karla's story



Garvan Institute of Medical Research

Welcome from our Executive Director



Dear Garvan family,

As we journey through the second half of 2020, I think you'll agree with me when I say that this year has indeed been challenging. Yet, however unprecedented the times, it has been heart-warming to see our community rally together and invigorating to be part of the most impactful and collaborative global research effort to date.

In our second *Breakthrough* for this year, we're thrilled to share with you how our researchers are fighting COVID-19 through a number of research projects (page 6). You'll read about how cancer develops resistance to treatment, affecting hundreds of thousands of cancer patients every year. You'll also meet Karla, a young girl with a devastating immune condition, whose life was saved by the genomics research of the CIRCA program (page 10).

On page 8, you'll discover the outcomes of the Lions Kids Cancer Genome Project. The program has supported the Zero Childhood Cancer program, led by Children's Cancer Institute and the Kids Cancer Centre at Sydney Children's Hospital, Randwick, to offer personalised treatment approaches to all Australian children living with high-risk or relapsed cancer.

Finally, I'd like to extend my most sincere thanks and appreciation to you. Your support, and the support of people just like you means our researchers are able to continue their critical investigations into disease through this most challenging time. Thank you for your continued belief in our research.

Yours sincerely,

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

NEW RESEARCH

How cancer develops drug resistance

Garvan researchers have uncovered a fundamental survival strategy that cancer cells use to develop drug resistance – one of the leading causes of cancer-related deaths that affects hundreds of thousands of patients every year.

Published in the prestigious scientific journal *Science*, researchers led by Professor David Thomas revealed how cancer cells undergo a process called 'stress-induced mutagenesis' when exposed to targeted therapies, a common treatment for many forms of cancer.

In a broad range of cancers, including melanoma, pancreatic cancer, sarcomas and breast cancer, the team discovered that cancer cells shuffled their genome when exposed to targeted therapy, generating a high number of errors that lead to drug resistance. Bacteria use a similar process to develop antibiotic resistance.

Combining conventional targeted cancer therapy with drugs that target DNA repair mechanisms, the researchers say, may lead to more effective therapeutic strategies.

In an experimental model, the researchers combined a cancer treatment with a drug that selectively targets cells with impaired DNA repair. They were able to reduce cancer growth by almost 60%, compared to the cancer drug alone. The researchers are now designing clinical trials for the potential approach, in the hope of improving clinical outcomes for those affected by cancer drug resistance.

Visit: garvan.org.au/resistance

Prof John Shine AC honoured by Royal Society

Garvan's Professor John Shine AC, also known as the 'father of gene cloning', was this year elected as a Fellow of the Royal Society for his scientific leadership and pioneering research in molecular genetics. The Royal Society is a Fellowship of the most eminent scientists, engineers and technologists from the UK and the Commonwealth, and Professor Shine was elected from more than 700 distinguished nominees across the globe.

Professor Shine laid the groundwork for genetic engineering techniques that helped launch a therapeutics industry which now benefits millions of people across the globe, and was Executive Director of the Garvan Institute of Medical Research for 21 years.

His discoveries made it possible to use bacteria as factories for producing human proteins on demand. Today, all who receive therapies such as insulin, growth hormone, erythropoietin or immunotherapy, have benefitted from his transformative genome research, which spans a career of 50 extraordinary years.

Professor Shine joins a distinguished list of Fellows to the Royal Society, including Garvan's Professor Chris Goodnow and Professor Johnathan Sprent.

Visit: garvan.org.au/fellow

THROUGH THE MICROSCOPE



As Garvan researchers peered down the microscope, they uncovered an ancient process.

In this image, researchers visualised DNA damage (green) in human breast cancer cells (blue) that had been treated with a targeted anticancer treatment.

Targeted therapies block the growth of cancer by interfering with molecules that are needed for tumour growth, and are a common treatment for many forms of cancer – but they do not directly damage DNA.

As you would have read on page 2, Garvan researchers revealed that cancer cells exposed to targeted therapies undergo a process called stress-induced mutagenesis – they generate random genetic variation at a much higher rate than cancer cells not exposed to anti-cancer drugs. This allows them to become resistant to the cancer treatment. "This process is ancient – single-celled organisms, such as bacteria, use the same process to evolve when they encounter stress in their environment," says Dr Arcadi Cipponi, first author of the study.

This crucial discovery has revealed a fundamental strategy cancers use to become drug resistant – a leading cause of cancer deaths. The researchers hope their discovery will lead to more effective therapeutic strategies for advanced cancers.

This work was supported by the Australian National Health and Medical Research Council and donations from the Girgensohn Foundation.

Local community, international impact

A career cross-roads and love of community led Jacqui Rodgers to join the Garvan family in more ways than one.



The big-city lure of Sydney was irresistible to Jacqui Rodgers, who settled in Sydney 21 years ago from Perth, after travelling overseas and working in London. She was drawn to the vibrant community of Darlinghurst, also home to the Garvan Institute of Medical Research, for the "real sense of community from the people who live here." Her warmth and generosity is felt by her

community of family and friends, who she loves to entertain and spend time with.

"Living in the local area, I would walk past the Garvan building and think to myself, 'I wonder what they do in there?' The sign outside said medical research, so I figured they must be doing something good," explains Jacqui. "Two years ago, I came to a career crossroads, wanting to explore opportunities in the not-for-profit sector after many years in the corporate world. I applied for an opportunity as the Senior Corporate Partnerships Officer at Garvan, and the rest is history!"

Medical research is close to Jacqui's heart, so much so, she has become a Partner for the Future by including a gift in her Will to the Garvan Institute. "My mother passed away from abdominal cancer 26 years ago. By the time they found it, the cancer had progressed aggressively and she lived only 6 months after being diagnosed. I wonder every day, what her chances might have been if we knew then, what we know now. I want my future bequest to go towards helping others so they don't have to wonder like me."

Jacqui's role at Garvan gives her a unique insight into how difficult it can be to get critical research off the ground. "Working at Garvan, I get to see the reality of medical research, so for me, leaving a bequest to Garvan was a simple decision," she explains. "I see our researchers' passion and determination, and the truly extraordinary work they are doing. It is often difficult with long hours, trialling multiple experiments, in an extremely competitive funding environment."

"I now understand how vital community support and funding is – from being able to run our high-tech equipment, purchasing new equipment and technology, employing the best in their field and to supporting our young up-andcoming researchers enabling them to undertake groundbreaking research. None of this would be possible without community support."

"Now, more than ever, medical research needs to be the top priority in the prevention and treatment of the myriad of diseases we all face in our community," she says. "COVID-19 is a very real example of how we can benefit from medical research, and what could happen if we do not keep investigating."

"Leaving a bequest to Garvan is investing in the future health and wellbeing for everyone. I want my legacy to enable research that continues to ask tough medical questions and does whatever it can to find the answers. It just makes sense, and it's the right thing to do, for all of us."

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

A LOVE OF ART AND SCIENCE

Garvan extends its sincere congratulations to Cav. Simon Mordant A0 for the recognition of his dedication to the arts and philanthropy with an **Order of Australia and a knighthood** in the order of Cavaliere dell'Ordine della Stella d'Italia.



Simon is well known throughout the Australian art world for his longstanding support of contemporary art. In 2010, with his wife Catriona, Simon led the redevelopment of the Museum of Contemporary Art (MCA) in Sydney and drove both State and Federal Governments to each contribute \$13 million to the project. Today, the MCA is the most visited contemporary art museum in the world.

Less well known is Simon and Catriona's passion for medical research – Simon has been a director of the Garvan Research Foundation board since 2009. "Garvan is at the apex of being able to analyse our propensity for disease and how to target treatment most effectively," says Simon. "This area of research is so fascinating, genomics is a global research area and Garvan is a key part of that global community."

While art and science may seem worlds apart, there is a common thread that connects the two for both Simon and Catriona. "Amazing creative talent. For Catriona and I that is what we thrive being surrounded by - extraordinary creative talent," explains Simon. "Research talent sets Garvan apart from other medical research institutes globally. The collective talent and teamwork is world class."

Of his recent accolades, Simon says: "As someone who was born in the UK and migrated to Australia alone in my early 20s, and has adopted both Italy and Australia, to be honoured by both countries in this way, for doing things we love, is very humbling."

RESEARCH NEWS

Precision approach for lung adenocarcinoma

In a proof-of-principal laboratory study, Garvan researchers uncovered a new precision approach for treating lung adenocarcinoma – the most common type of lung cancer, which is the leading cause of cancer-related deaths worldwide.

Led by Dr David Croucher, researchers discovered that blocking the enzyme P70S6K in some lung adenocarcinoma cells could improve the efficacy of platinum-based chemotherapy, which has been used in the clinic for over four decades but is effective in less than a third of patients.

In the lab, the Garvan-led researchers investigated how different lung adenocarcinoma cells responded to cisplatin treatment, and discovered that P70S6K was found in higher levels than in cells which were effectively targeted by the drug. In experimental models, the researchers found when they inhibited P70S6K with a drug, or genetically reduced the enzyme's levels, they could sensitise resistant lung adenocarcinoma cells to cisplatin.

While more research is needed, the researchers are hopeful the findings will inform the design of future precision therapy for lung adenocarcinoma, and light the way to better clinical outcomes.

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Visit: garvan.org.au/precision

Baxter Scholarships awarded to Garvan PhD students

Garvan PhD students, Cecilia Chambers and Yolande O'Donnell, have each been awarded a prestigious Baxter Family Postgraduate Scholarship with UNSW Sydney. The scholarship will support the development of their research in both pancreatic cancer and breast cancer.

Cecilia's research will use a multidisciplinary approach that combines standard-of-care treatment for pancreatic cancer with the inhibition of the molecule NPY in an experimental model, with the aim of extending patient survival. Her team have identified NPY playing a role in promoting tumour growth and spread in pancreatic cancer, and hope that by blocking NPY, they might provide novel therapeutic options to those suffering from the devastating disease.

Yolande's project will utilise a novel experimental model of mammary gland formation in collaboration with the Garvan-Weizmann Centre for Cellular Genomics to understand the functional role of JNK proteins in breast cancer development. It is essential to understand this function as part of the teams ongoing drug development, ensuring that tumour suppression is maintained in the presence of clinically viable breast cancer treatments.

The Baxter Scholarships will allow these young women to continue their research and develop their skills in finding therapeutic treatments for cancer.



Garvan's researchers are **tackling COVID-19**

Our COVID-19 research is focused on understanding the disease at a biological and genomic level, and, critically, improving outcomes for patients.

Medical research is the only solution to COVID-19, which has to date affected millions of people worldwide, and claimed hundreds of thousands of lives.

Researchers at the Garvan Institute of Medical Research responded immediately to the pandemic, joining a global effort to find solutions to the central issue in the COVID-19 crisis as quickly as possible. Primarily, reducing the number of people infected with the coronavirus, curing people who do get infected, and reducing deaths.

Garvan's excellence in antibody research, immunology, cellular genomics and whole genome sequencing perfectly positions us to contribute to the global research effort to fight COVID-19. Yet, at the same time, our scientists are maintaining their ongoing research endeavours in cancer, diabetes and metabolism, diseases of the immune system, diseases of bone and neurodegeneration, as well as genomics and epigenetics.

Engineering antibodies for COVID-19 protection and therapy

A research team led by **Professor Daniel Christ** is developing genetically engineered antibodies designed to target surface proteins of SARS-CoV-2, the novel coronavirus that causes COVID-19, which the virus uses to infect human cells. These highly specific antibodies are standardised and can be produced in unlimited quantities in the laboratory, bypassing the genetic variability of antibodies produced by people's own immune responses. They could provide immediate immunity, both for the treatment of COVID-19 and prevention for at-risk, to at-risk individuals, including the elderly, chronically ill patients, and health workers on the frontline.

Image: A 3D rendering of a coronavirus particle showing the classic molecular morphology of the spike proteins coloured blue here. In this image, antibodies are coloured yellow and are shown binding to spike proteins, marking this virus particle for destruction by immune cells. Image by Dr Kate Patterson, Garvan Visual Science Communicator

The researchers have rapidly developed a research pipeline to test more than 100 million different antibody variants for SARS-CoV-2. Antibodies are now undergoing neutralisation testing at UNSW Sydney's Kirby Institute, on live virus samples isolated from Sydney COVID-19 patients.

Early results are promising, with the engineered antibodies able to effectively stop virus replication in the laboratory. The researchers are now optimising and narrowing down the pipeline to identify the final and most powerful antibody candidate, which will progress to clinical trials.

Tracing coronavirus evolution



Garvan researchers, led by **Dr Ira Deveson**, are analysing the genetic material of virus samples isolated from COVID-19 patients at hospitals in NSW, to detect genetic variation that may provide critical data to inform Australia's COVID-19 response in real-time. The team's work has potential to shed light on how the coronavirus evolves, identify virus sub-strains that may be more or less infectious and crucially, guide better treatments. To date, the team has analysed more than 250 SARS-CoV-2 genome samples and is contributing to a collaborative research study charting the transmission of the coronavirus in NSW throughout the pandemic.











Professor Stuart Tangye

Associate Professor Joseph Powell

Investigating genes linked to severe COVID-19

A Garvan research team led by **Professor Stuart Tangye** is working to identify genetic variants that could predispose healthy individuals to developing severe COVID-19 rather than a mild form or being asymptomatic. The researchers are analysing the DNA of individuals in Australia who were diagnosed with SARS-CoV-2 infection and developed severe symptoms, despite not having any pre-existing health conditions. Through this, the researchers hope to uncover genes and immune pathways critical for protection against COVID-19.

The team is currently recruiting patients for the research study, which aims to point to new therapeutic targets for COVID-19 as part of the global research effort.

Another Garvan team, led by **Associate Professor Joseph Powell**, is leading a global effort to uncover how the genetics of different immune cells determines susceptibility, severity and outcomes of COVID-19. The researchers are using sophisticated statistical methods at the Garvan-Weizmann Centre for Cellular Genomics to analyse the genetic variation associated with severe COVID-19 symptoms, through data made available by the COVID-19 Host Genetics Initiative.

Associate Professor Powell is also using cellular genomics and machine learning techniques to investigate the differences in the immune response between patients with mild and severe symptoms. His team aims to develop a test that provides a 'snapshot' of the immune cells in a patient's blood that could predict how severe their respiratory symptoms will be over time.

To find out more about Garvan and our work on COVID-19 please visit garvan.org.au/covid19-research

Professor Daniel Christ

Dr Ira Deveson



Antibodies could provide

and for prevention.

immediate immunity, both

for the treatment of COVID-19

Genome Power and the Power of Philanthropy

The Lions Kids Cancer Genome Project, *Genome Power*, has completed the genome sequencing for 400 Australian children with cancer to bring them personalised treatment plans.

The desire to make a difference in the lives of children with cancer brought together three industry-leading organisations at the right moment.

In 2016, Garvan was ready to utilise the whole genome sequencing capability of the Kinghorn Centre for Clinical Genomics (KCCG), enabled through generous philanthropic support from the Kinghorn Foundation, to assist in the personalised treatment of children with cancer by sequencing the entire genome of their tumours. At that time, the Australian Lions Childhood Cancer Research Foundation was looking for new approaches to improve the lives of children diagnosed with cancer, while researchers at the Children's Cancer Institute, together with paediatric oncologists at the Kids Cancer Centre at Sydney Children's Hospital, were establishing the Zero Childhood Cancer program. Through a partnership between Lions, Garvan and the Children's Cancer Institute and its hospital partners, the Lions Kids Cancer Genome Project, or 'Genome Power', was formed.

Genome Power's mission was to sequence the tumour and normal DNA of 400 children with high risk cancers, those most difficult to treat, that were enrolled into the Zero Childhood Cancer program, to see whether the power of genomic sequencing could contribute to improving their chance of survival and quality of life. The project was made possible by funding from the Lions Club International Foundation, a global charitable organisation, as well as through community fundraising by the Australian Lions Childhood Cancer Research Foundation along with Lions Clubs across Australia. In mid-2016, the first children in Sydney were enrolled into the pilot program for Zero Childhood Cancer, before the program was expanded nationwide the following September, bringing cutting-edge precision medicine to children with high risk cancers across the country. The whole genome sequencing made possible through the Lions Kids Cancer Genome Program and the extensive analysis undertaken by the Children's Cancer Institute and research partners through the Zero Childhood Cancer program has allowed researchers to analyse each child's cancer in incredible detail, enabling clinicians to identify the best targeted treatment for each child. Over 70% of children in the program have received personalised treatment recommendations as a result of the genome sequencing and analysis of their individual tumours. This has been life-changing for many children and their families.

One remarkable example is Ellie, a little girl who developed a rare cancer in her chest at only 11 months of age. After the genome of her tumour was analysed, the Zero Childhood Cancer team discovered that a drug recently developed by a US pharmaceutical company could target the specific genetic change of her tumour. Ellie received the drug on compassionate grounds and her tumour went into remission. The ability to pinpoint the genetic change in Ellie's tumour through whole genome sequencing is now helping other children in the program who have different types of cancer, but due to the same genetic change, are now also receiving the drug that enabled Ellie to go into remission.



Ellie and her parents

In other children, the genome sequencing was used to identify genetic changes in the DNA from their normal cells that indicated they had a genetic predisposition to cancer. In the future, this vital information could help predict a child and their family's susceptibility to developing cancer.

In June 2020, a tumour sample from the 400th child in the program was sequenced. With this milestone, the Lions Kids Cancer Genome Project has now been completed. The anonymised genomic, biological and clinical data from the 400 children in the program will provide a valuable resource for childhood cancer clinicians and researchers across the world, as they continue working to find cures and improve the outcomes for children with cancer. "Genome Power, powered by philanthropy, has enabled Garvan's capability in genome sequencing to contribute to the success of the Zero Childhood Cancer Program." – Professor Marie Dziadek, Garvan's Chief Scientific Officer

While the Lions Kids Cancer Genome Project has concluded, its contribution to the success of the Zero Childhood Cancer program has resulted in a gamechanger for all children with cancer. The Australian Government recently announced a major grant of \$54.8 million from the Medical Research Future Fund that, together with additional support from the Minderoo Foundation, will ensure every child in Australia diagnosed with cancer will have access to genomically guided, precision treatments through the Zero Childhood Cancer precision medicine program.

Professor Marie Dziadek, Garvan's Chief Scientific Officer, who coordinated the Lions Kids Cancer Genome Project, says: "Genome Power, powered by philanthropy, has enabled Garvan's capability in genome sequencing to contribute to the success of the Zero Childhood Cancer Program. This has not only changed the lives of children with cancer today, it will inform future research needed to defeat these cancers tomorrow. Even more importantly, this success has led to ongoing funding of the Zero Childhood Cancer program by the Australian Government. In the coming years, as the program rolls out, all children who are unfortunate to have a cancer diagnosis will have increased hope of a bright future. That is the legacy of the Lions Kids Cancer Genome Project, and Garvan is so proud to have been a partner in this remarkable program."



To find out more about Genome Power please visit garvan.org.au/genome-power



Karla's story

Whole genome sequencing at Garvan guided life-changing targeted therapy for a severely painful, rare immune disorder.

Karla, now seven years old, has a rare gene variant that affects an immune 'checkpoint' protein, resulting in an imbalance in her immune system. Through fortnightly injections of a functioning replacement protein, Karla's condition has since vastly improved.

Karla was one year old when she started walking, but a few months later she couldn't hold herself upright. At only 20 months, she was diagnosed with childhood onset autoimmune hepatitis, which severely affected her liver. Less than two years later, Karla was diagnosed with painful inflammatory arthritis affecting multiple joints.

Karla was initially treated with a series of immunosuppressant drugs including the steroid prednisolone, however these had significant side effects, were often traumatic, and did not relieve her severe joint pain.

"For two to three years, we went through continuous blood tests to try and optimise her medication, but the trial and error was very hard – when Karla's liver got better, her arthritis would get worse. Often treatments were traumatic, and she didn't want to go to the doctor," says Barbara, Karla's mother. Karla was referred to the Clinical Immunogenomics Research Consortium Australasia (CIRCA), a multidisciplinary team of researchers and clinicians investigating the causes of rare immune diseases. In 2017, Karla's genome was sequenced at the Garvan Institute.

"Through whole genome sequencing, we discovered a gene variant in Karla's CTLA4 gene, which provided a genetic diagnosis to the immune symptoms she was experiencing," says Garvan's Executive Director Professor Chris Goodnow.

CTLA4 is an immune 'checkpoint' protein, located on the surface of some immune cells, which controls the extent of the body's immune responses. The research team discovered the gene variant (Y139C) prevented Karla's CTLA4 protein from 'docking' to its target, causing her immune system to go unchecked and attack her joints and liver. This discovery pointed directly to a treatment.







Life changing arthritis treatment



Based on her genetic diagnosis, Karla's treatment was altered by adding abatacept – a synthetic form of the CTLA4 protein that is already used clinically for the treatment of adult rheumatoid arthritis.

"Without the genetic analysis, Karla might not have received this life-changing treatment," says Professor Goodnow. "The challenge we are now pursuing is to use genomics to identify all children or adults who will respond exceptionally well, like Karla, to this targeted treatment."

Two years after her diagnosis, Karla is doing well and her arthritis has been in remission for over 12 months.

"I see a huge difference," says Barbara. "Before, Karla used to limp a lot because her joints were sore – that's what she was used to, the pain, and it was constant. Now she doesn't have the pain, so when it's about time for her next dosage, or if she hits her arm by accident, she tells me because she knows what the difference is."

This project was funded by the National Health and Medical Research Council, and with philanthropic support of the John Brown Cook Foundation. Professor Goodnow holds The Bill and Patricia Ritchie Foundation Chair.

To find out more about CIRCA please visit garvan.org.au/life-changing





Clinical Trial **Spotlight**

An innovative research and clinical trial program aims to identify drugs that can help slow, stop and ultimately, cure Parkinson's disease.



Over 100,000 Australians are living with Parkinson's today, with 38 people being diagnosed every day. There is currently no way to detect and diagnose the disease early, with current treatment only helping to control the symptoms that have presented in a patient. Without a medical breakthrough the number of Australians with Parkinson's will double approximately every 15 years.

The Australian Parkinson's Mission, an innovative 5-year Garvanled research program, combines clinical trials and biomarker technologies with breakthrough genomics for people living with Parkinson's. The first clinical trial will test 3 repurposed drugs (drugs that have been approved for other conditions) that have demonstrated neuroprotective effects in preclinical experiments. By using drugs that have already passed rigorous safety and toxicology trials, the APM aims to cut the time for a potential treatment to move from the laboratory to clinical trials and Parkinsons's patients.

The clinical trial is now active, with 8 confirmed sites across Australia (in NSW, VIC, SA, WA and QLD). The APM is recruiting patients in accordance with eligibility criteria, and will continue to do so for 12 months from the initial intake stage.

To be screened for participation in the clinical trial, please contact the closest location in your state. Clinical trial site details and more information about the program can be found on the Australian Parkinson's Mission website, theapm.org.au.

Thank you to our generous donors and the Federal Government for supporting the Australian Parkinson's Mission to slow, stop and reverse Parkinson's disease.



Garvan Institute





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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

PREDICT prediabetes clinical trial

We are seeking men and women aged 20-70 years who have pre-diabetes or who have been recently diagnosed with types 2 diabetes and have not yet been treated with a sugar-lowering medication. This study investigates blood sugar response to personalised diet and diabetes medication. HREC Approval: SVH 17/080.

For further information, please contact Dr Dorit Samocha-Bonet (02) 9295 8309 predict@garvan.org.au



Jewellery with Purpose

Paspaley have launched a new addition to their Kimberley range - the Dark Kimberley Bracelet, which features darkened sandalwood with either a single or double pearl.

Even more beautiful than the bracelet, is the sentiment behind it. Paspaley have been long-time supporters of Garvan, and help create a healthier future for everyone by donating 20% from the sale of each of these stunning pieces, to people living with rare and less common cancer.

To give a gift that means more, please visit garvan.org.au/paspaley today.