



Dr Andrew Stone and Dr Elena Zotenko

Making News

How breast cancer becomes resistant to hormone therapy

New findings have identified how 'oestrogen receptor positive' breast cancers become resistant to hormone therapy. Garvan's Dr Andrew Stone, Dr Elena Zotenko and Professor Susan Clark have demonstrated that highly targeted 'epigenetic' changes, or biochemical modifications, take place in specific regions of the genome as an oestrogen-dependent cancer loses its dependence on the hormone. The team believe there is now the potential to screen oestrogen receptor positive breast cancer patients and predict how they will respond to endocrine therapy.

A piece in the puzzle of primary immunodeficiency

Researchers have shed light on why some children are unusually susceptible to infectious disease. Together with international collaborators, Garvan's Associate Professor Stuart Tangye and Dr Elissa Deenick identified a new series of disease-associated mutations in a group of children with a very rare form of primary immunodeficiency. Primary immunodeficiencies are disorders in which a small part of the immune system is unable to do its job. The result is a 'hole' in the immune defence of otherwise healthy individuals, making them susceptible to particular infections. This research is an exciting step forward in our understanding of the immune system's complexity.

Making sense of "missense" mutations

Garvan's Professor Chris Goodnow has assessed how accurately we can predict the health consequences of mutations that change single letters in our genetic code – so-called "missense mutations". Within the three billion DNA base pairs of each of our genomes lurk thousands of missense mutations – single-letter "mis-spellings" in our DNA sequence that can affect the structure and function of proteins. The study demonstrates an important disjunction between the predicted and actual impacts of such mutations. Some missense mutations cause disease, yet other changes have no apparent effect.

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From the CEO

I was recently proud to launch the Garvan Research Foundation's 'Medical Research and Rural Health Report 2015'. This report examined the main health issues facing rural and regional communities, as well as examining who is impacted, why the challenges exist and finding a way to begin rectifying some of these major health issues.

Importantly, the report considers the role that medical research and, in particular, genomics can play in the health of all Australians. In an era of precision, or personalised medicine, clinical genomics is a rapidly evolving field focused on the use of genomic sequencing information in patient diagnosis and treatment.

The report highlighted some alarming statistics relating to health outcomes for rural and remote Australians. Just some of these include:

- A 40% higher death rate in remote areas than in major cities
- Life expectancy is 2.5 years lower for males, and 1.3 years lower for females in outer regional, remote and very remote areas, compared with major cities and inner regional areas
- Five-year relative survival for cancer decreases with increasing remoteness
- Diabetes ranks higher as a cause of death among people living in remote areas, compared with regional and major cities
- The rate of suicide is 66% higher in the country than in major cities.

Medical research has the potential to help change the future health of remote and rural Australians, and it is developing at a dizzying rate. For example, researchers are producing genome-wide data sets on ever-expanding study populations. Broad access to this data, stored samples, and electronic medical records are accelerating our understanding of the role of genes, the environment, and human behaviour in health and disease. Translational research is converting new scientific knowledge into improved diagnostics, targets for drug development, and new insights into how to prevent and treat disease.

It is only with your ongoing support that we can continue to make these advances that will ultimately improve the health outcomes of all Australians.

For more information about the 'Medical Research and Rural Health Report 2015', visit www.garvan.org.au

Finally, may I extend my very best wishes for a happy Christmas and 2016.



Andrew Giles, Chief Executive Officer
Garvan Research Foundation



Associate Professor Shane Grey

Major Type 1 diabetes research grant made possible thanks to philanthropic "seed funding"

Garvan's Associate Professor Shane Grey, together with collaborators from the Westmead Millennium Institute for Medical Research and the Children's Hospital at Westmead, were recently awarded \$3.3 million to extend their innovative islet transplantation research towards a cure for Type 1 diabetes. The grant was awarded by the Type 1 Diabetes Clinical Research Network (T1DCRN), an innovative clinical research program led by the Juvenile Diabetes Research Foundation (JDRF Australia) and supported by the Australian Research Council.

This promising project is an outstanding example of the importance of philanthropic support for medical research. Without seed funding from the Ross Trust, the years of preliminary research that brought the project to this crucial point, where it was eligible for this vital injection of funds from T1DCRN, would not have been possible.

This project has the potential to save many lives. Islet transplantation therapy – in which insulin-producing structures called islets, derived from donor pancreas, are transplanted into the recipient's liver – can cure individuals of Type 1 diabetes by restoring glucose-responsive insulin production. However, recipients must take powerful immunosuppressive drugs for the rest of their lives to avoid the introduced islets coming under attack from their own immune system. This prevents islet transplantation therapy being given to more people with Type 1 diabetes, including children.

Associate Professor Shane Grey says, "This is a fantastic opportunity to make a real difference to people with Type 1 diabetes and completely do away with the need for immunosuppression. If we are successful, one could imagine this new approach could be extended to other types of transplants and possibly used for the treatment of autoimmune conditions.

"We could not have reached this crucial point without the philanthropic support from organisations like the Ross Trust, who recognise the importance of finding a cure for Type 1 diabetes. On behalf of my team, I thank them for their generosity and foresight."

A legacy that will address the greatest research need

Mrs and Mr Helen and Terry Jones can't recall how or when they first heard about the Garvan Institute of Medical Research. However, it was something they'd known about for a long time. So, when they began conducting research into which organisations they would support through a bequest in their wills, the Garvan Institute made the list.

Mrs Helen Jones said, "We had actively thought about making donations, and sought information from several places, and Garvan was one. We made contact to get some information, as we did with the other organisations and we visited the Garvan Institute. Over time, we became more familiar with Garvan and how it operates."

Mr Terry Jones explained, "When we decided to include Garvan in our will, there were some key things that impressed us. We wanted to be certain that our money would be used for something significant – research that would have practical applications, helping people in the long-term. Garvan was able to assure us that the funds would be put toward the research area that we nominated. We were also really impressed by the quality of Garvan's research. Garvan has the critical mass, and the reputation to attract the best researchers from Australia and the world, and this was evident in the quality of the research being carried out. Finally, we were confident that the funds would be managed properly, and be used for things that had potential to make a real difference in the long-term."

The Jones' bequest will be put toward research into autoimmune diseases. However, demonstrating real foresight, Helen and Terry have indicated that they are willing to re-assess this every few years.

Mrs Jones said, "We realise that research needs change over time, or a new research area might open up and need support. We have to be flexible because we hope that Garvan won't benefit from our bequest for quite some time. In this case, research needs are sure to change, so we don't want our bequest to be so concrete that it can't meet the greatest research need at the time."

When reflecting on what she would hope could be achieved, with the support of her bequest, Helen says that she would love to see really good diagnostic tools and treatments for people with autoimmune diseases.

"Autoimmune diseases are hard to diagnose because the symptoms are so vague, and they can affect so many different parts of the body. People can go for years knowing they aren't well, but without a diagnosis, and this can be frustrating and limiting to the way they live life. You never know – Garvan's researchers might even be able to prevent autoimmune diseases from developing in the first place."

Helen added, "If you are considering leaving a gift to Garvan in your will, I would highly recommend visiting, seeing the building, learning more about the research, the quality of the researchers and the professionalism of the staff. All these factors added to my confidence that we were making the right decision."



Mrs and Mr Helen and Terry Jones



Associate Professor Antony Cooper

MLC Community Foundation – helping Garvan identify genetic factors in bipolar disorder

With the support of the MLC Community Foundation, Garvan researchers, along with colleagues from Neuroscience Research Australia and UNSW Australia, have embarked on a collaborative project to sequence the genomes of individuals in families living with bipolar disorder. In doing so, they anticipate identifying some of the complex genetic factors that underlie the disease.

Bipolar disorder is characterised by episodes of mania and depression. It is a debilitating disease that requires lifelong treatment. Bipolar disorder runs in families, so researchers know that genetics must contribute to the disease – but it has been very challenging to identify the specific genetic signatures involved.

Now, Associate Professor Antony Cooper (who heads Garvan's Neuroscience Division) and colleagues will use next-generation whole genome sequencing and bioinformatic analysis to identify genetic differences that associate with bipolar disorder. The team will compare the genome sequences of individuals with bipolar disorder and members of their families with the genome sequences of unrelated healthy individuals, in order to identify genes that contribute to the development of bipolar disorder.

This genomic information will be critical to identify the molecular basis of bipolar disorder – and the Garvan team hopes it will ultimately lead to targeted therapies for its treatment.

Lara Bourguignon, Chair of the MLC Community Foundation, which is providing financial support for the study, says, "We are extremely proud to be supporting such ground-breaking and critical research. Our philanthropic mission is to support the mental health and wellbeing of all Australians, and this work has the potential to not only benefit thousands of Australians and their families but also people right across the globe which is truly exciting."

Together, Garvan and the MLC Community Foundation hope to improve mental health outcomes for all Australians.

Is it possible to be obese and healthy?

For the majority of people who are obese, excess weight brings with it a myriad of additional, often life-threatening, health issues. These can include diabetes, cardiovascular disease, high blood pressure, fatty liver and even some types of cancer.

However, a small proportion of obese people remain healthy, somehow evading some of these obesity-related health issues.

Associate Professor Jerry Greenfield and Dr Dorit Samocha-Bonet are working to uncover the ways in which people who are obese, yet metabolically healthy, differ from the majority of metabolically unhealthy obese individuals. This research is helping to pave the way to a future of personalised medicine in obesity.

Bucking the trend

Garvan's Associate Professor Greenfield and Dr Samocha-Bonet lead a team studying obese individuals who are metabolically healthy, hoping to gain understanding of the underlying mechanisms that protect these individuals from disease. Why and how do these people 'buck the trend'?

Getting to grips with what's different about these 'metabolically healthy' obese individuals could give us a clearer understanding of what causes Type 2 diabetes, and could ultimately lead to better, and more targeted treatments.

To shed light on this, the Garvan team compared obese individuals who were insulin-resistant to individuals who were obese and insulin-sensitive.

To explain – for those who are insulin-sensitive, the body's tissues (particularly

to insulin's "take up glucose now" message. As a result, blood glucose

remains high, which can, in the long-term, cause tissue damage. Insulin-resistance is not only considered to be a precursor for diabetes, it also plays a key role in other metabolic imbalances associated with obesity, including dyslipidaemia (abnormal amounts of fat or cholesterol in the blood), and increased blood pressure.

For the first time, the Garvan team has shown that different patterns of insulin resistance (in muscle, in liver, in both, or neither) have different implications for the health of obese individuals.

Associate Professor Greenfield points out that it has been known for some time that some obese individuals seem to stay metabolically healthy. "However, there has been no consensus about what 'metabolically healthy' actually means, so it hasn't been easy to understand how and why these people are different.

"Our own approach is to define metabolically healthy obesity in clearly measurable terms. We

look at whether or not obese individuals also have a key complication of obesity: a resistance to the hormone insulin, which regulates the level of sugar in the blood after a meal. We consider that obese

individuals who are not insulin-resistant, but instead remain sensitive to insulin, can be thought of as being metabolically healthy."

To conduct a detailed measurement of insulin-sensitivity, Garvan researchers recruited 64 obese individuals and used the 'gold standard' measurement technique – the hyperinsulinaemic-euglycaemic clamp. This test can take between three and seven hours, and measures how each participant's blood glucose levels respond to insulin.

Dr Dorit Samocha-Bonet said, "The power of the clamp technique is that you can simultaneously look at how the muscle and the liver respond to insulin. In this study, for the first time, we took the data generated by the clamp and divided the participants into groups – those who were resistant to insulin at both muscle and liver; those who were insulin-resistant at one tissue and insulin-sensitive at the other; and those who were insulin-sensitive at both.

"Previously, in a study where we compared insulin-sensitivity between obese and lean individuals, we found that in about 10 per cent of obese individuals, insulin-sensitivity was similar to that measured in the lean control group."

Elevated fat in the liver (not caused by excessive alcohol intake) is also shown to be an important marker for metabolically abnormal, or insulin-resistant people. Obese people who are insulin-sensitive have very little fat in the liver, similar to those levels measured in the healthy control group.

Associate Professor Greenfield said, "This is a fascinating observation, because it clearly shows that obesity and insulin-resistance (and therefore diabetes) need not go hand-in-hand. It also confirms that we are working with a group of genuinely metabolically healthy obese individuals."

Personalising treatment

The researchers went on to measure a number of key readouts of metabolic health. Dr Samocha-Bonet explains, "We found that obese individuals who are sensitive to insulin in either muscle or liver are healthier in some respects than the group that is insulin-resistant at both sites.

"They have lower blood pressure, lower deep abdominal fat and less fat within the liver.

"So, we now know that it's not enough to label an individual as being

'insulin-resistant'. More specifically, they can be insulin-resistant at muscle, or at liver, at both, or neither – and that is likely to have an effect on their metabolic health."

Associate Professor Greenfield added, "The results of our study have identified some of the key metabolic factors that may protect an obese person from developing diabetes and related metabolic diseases.

"By demonstrating that impairment of insulin action in the liver and muscle are independently associated with detrimental metabolic effects in humans, we have potentially paved the way for earlier detection and treatment of people most at risk of developing metabolic disease.

"It's early days, but we are taking the first steps toward a personalised approach to the treatment of obesity and Type 2 diabetes."

A lifetime's protection?

Another question being pursued by Garvan researchers is, does insulin-sensitivity in obese people offer a lifetime of protection against other related health complications?

In the Insulin Sensitivity in Obesity Study (2013-2017), Garvan researchers aim to find out if insulin-sensitive obesity is sustained over time and, if so, what metabolic factors predict this.

If not, they want to know what causes the change from being insulin-sensitive to insulin-resistant over time.

The team has previously tested 120 men and women with a range of body weights and insulin-sensitivity levels.

Now, five to six years after they were originally tested, the participants have had meticulous measurements taken, including insulin-resistance, abdominal fat distribution and liver fat. The aim is to compare the data collected with the original results.

Dr Samocha-Bonet said, "Discovering if there are long-term protective effects associated with being obese and insulin-sensitive is fascinating.

"I feel it will have a significant impact on the way we prioritise treatment, and the way we manage the health implications associated with obesity in the future."

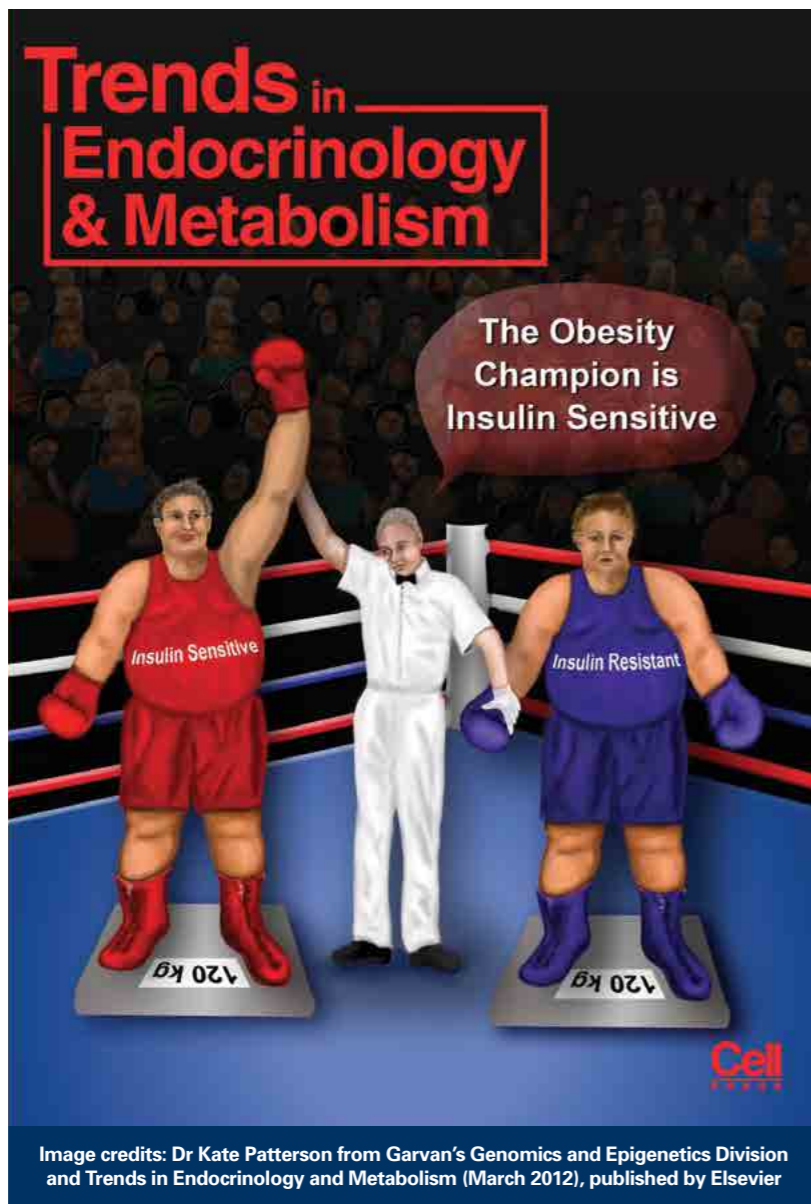


Image credits: Dr Kate Patterson from Garvan's Genomics and Epigenetics Division and Trends in Endocrinology and Metabolism (March 2012), published by Elsevier

muscle and liver) respond to the presence of insulin appropriately, taking up glucose from the bloodstream. In contrast, the tissues of insulin-resistant individuals are less able to respond

Ask Garvan

Q: What is personalised medicine?

A: Personalised medicine is the future of health and medicine. It uses uniquely personal information about an individual, such as genetic information, to help guide health-related decisions.

Q: How will personalised medicine change the way we are diagnosed and treated?

A: When personalised medicine becomes a reality, information from an individual's genome – their complete set of DNA – will be read, and analysed. This information can be used to diagnose illness, estimate disease risk or to predict how an individual may react to therapies.

Understanding an individual's risk of developing disease may make it possible to intervene early to monitor, minimise or ideally, prevent disease. If a person has already been diagnosed with a disease, the information contained in their genome can also help to identify the most effective treatment methods, and to predict how the individual might react to the treatment (i.e. maximising effectiveness, while minimising side-effects).

Q: How is Garvan involved in accelerating personalised medicine?

A: Garvan researchers are already using genome-sequencing technology to conduct medical research, identifying genes and changes to genes that cause or influence some of the major diseases affecting society today. This information is vital to improving our understanding of disease, how it progresses and laying the foundation on which a personalised approach to medicine will be based.

In celebration

Clive Water's birthday

Nina Leibovitch's birthday

Jenny Grogan's birthday





Staff Profile: Dr Meredith Ross

Can you give us a brief outline of your recent work history?

I come to the Science Communications position from a diverse background in biochemistry, science/medical publishing and science education. My PhD was in mitochondrial reactive oxygen species production and targeted drug delivery, with Mike Murphy at the Medical Research Council in Cambridge, UK. After a short postdoc, I left the lab to become Associate Editor of *Journal of Cell Science* (also in Cambridge).

Then, several years later, I moved back to my native New Zealand to a position at Waikato University, developing multimedia resources for New Zealand's Science Learning Hub and Biotechnology Learning Hub. I have long had my eye on Garvan as one of the most exciting places to do, and write about science in Australasia – so I'm thrilled to be here.

What does your work at Garvan involve?

The core purpose of my job is to raise the profile of Garvan's research. I do this by working with Garvan's researchers when they publish a high-profile paper, win an award or receive grant funding, set up a new collaboration, or speak at a major conference.

I get the word out about all these things by liaising with the mainstream media, where appropriate, and by publishing articles on the Garvan website and social media channels.

What inspires you about your work?

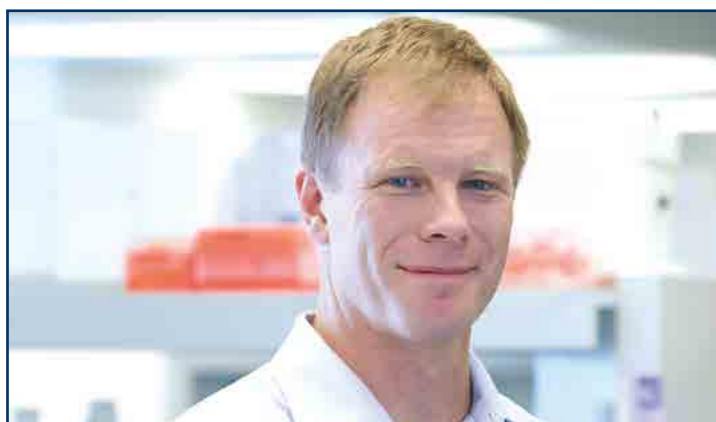
Throughout my career, I have focused on the communication of science to audiences beyond the research community. I'm passionate about helping members of the public to understand how science and medicine can impact them and their loved ones.

In an era of next generation sequencing, big data and rapid technological advances (in imaging, for instance), it's more important than ever that we keep the wider community up to speed on what's happening in the lab and the clinic.

What do you enjoy doing in your spare time?

With two daughters (aged 6 and 3), my spare time is limited! As a family, we spend a lot of time exploring Sydney and its surrounds – we've only been on this side of the Tasman for a year, so there's still a lot we have yet to explore.

I like to read (particularly Australasian fiction – Peter Carey is an all-time favourite) and take photos. I also have a hobby Twitter account (@SydneyWords) where I document my explorations of Sydney.



Staff Profile: Professor Robert Brink

What is the current focus of your work?

Our focus is on the processes by which the body regulates its production of antibodies – the highly evolved molecules that target the destructive capabilities of the immune system. Antibodies are great things to have when they zero in on viruses, bacteria and the like, but can cause real problems when they attack the body itself, as in diseases like lupus and rheumatoid arthritis.

We recently identified a new type of cell that can produce these problematic "autoantibodies" and we are currently looking at how these cells are involved in autoimmune diseases and how we could control them.

What is the biggest challenge in your area of research?

Every scientist will tell you the biggest challenge is obtaining the regular funding required to keep your research going. We have done well to maintain competitive funding for some time now, but with every funding round, the task becomes harder.

In the last few years, NHMRC funding rates have dropped from 25% to 10%. Having built a track record over some time, we are in a relatively good position. However, I do worry about the struggles faced by our many talented young researchers in establishing their careers.

What inspires you about Garvan's work?

The opportunity to work with the best and brightest is one of the joys of working at Garvan. In particular, the opportunity for more basic scientists, like myself, to collaborate with those in the clinical sphere.

A great example of this is the new facility we have developed to quickly and cheaply transpose disease-causing mutations from humans to mice, fast-tracking research and testing of potentially curative therapies.

What do you enjoy doing away from the lab?

I enjoy spending time with my wife, the kids (when they are around) and the dog. In general I like being outdoors doing pretty much anything, as well as trawling YouTube for all the songs I used to listen to in the 70's and 80's!



Left to right: Neale Whitaker, Richard Reid, Alphie Sadsad and Chris Paspaley at FashionLab. Photographer: Jesse Taylor

Fashion Targets Breast Cancer hits the mark

The return of the Fashion Targets Breast Cancer campaign, in support of the Garvan's breast cancer research, has been a success.

The campaign saw limited edition t-shirts, designed by renowned New Zealand fashion designer, Karen Walker, sold through THE ICONIC, Australia's leading online fashion retailer.

The campaign was celebrated recently at FashionLab, an exclusive evening of fashion, food and fundraising, hosted at Paspaley Pearls' flagship Sydney boutique. FashionLab was MC-ed by Neale Whitaker, Editor in Chief of *Vogue Living* and judge on Channel Nine's *The Block*.

Neale was joined by a panel of experts including international guest, style expert and personality Richard Reid who talked guests through a fashion show featuring Australian designer Carla Zampatti. Make-up tips were provided by Bobbi Brown Make-up Director, Alphie Sadsad, and Chris Paspaley introduced guests to beautiful jewellery from Paspaley's latest collections.

Thank you to all who purchased a Fashion Targets Breast Cancer t-shirt this year. Keep an eye out for the campaign in 2016, including a brand new t-shirt design.

Updating your summer wardrobe? Don't forget to purchase your Karen Walker-designed Fashion Targets Breast Cancer t-shirt at www.theiconic.com.au

Thank you Tulip Time!

The Garvan Institute of Medical Research and Love Your Sister would like to express heartfelt thanks to all those who visited us at Tulip Time.

We thoroughly enjoyed the opportunity to meet so many of you and share the latest in our cutting edge research.

Also, a huge thanks to the festival organisers and those who took part in the Ride for a Reason.

Love Your Sister's Samuel Johnson and friends at Tulip Time ▶



Mr Iñaki Berroeta, CEO Vodafone and Garvan's Dr Samantha Oakes at the launch of DreamLab

DreamLab – available now!

Garvan and the Vodafone Foundation recently celebrated the launch of DreamLab – a world first Smartphone app that allows Australians to use the power of their phone to help speed up Garvan's cancer research.

When your Smartphone is fully charged, it will process a tiny research problem and send the result back to the cancer team at Garvan.

It's like working on a giant crossword, with everyone solving a different clue.

Supporting cancer research has never been simpler!

Download the DreamLab app now from Google Play.

The app is currently only available for Android devices.

We hope the DreamLab app will be available for Apple devices in the near future.

For more information, visit vodafone.com.au/dreamlab



In Memoriam July to October 2015. Donations have been made in memory of:

Pat Arthur	Paul Hawker	Vassie Papaioannou
Mary W Bennett	Margaret Hayes	Leo Papast
Emile and Lucie Bernard	Helen M Henry	Marilyn Pearsall
Ian Birks	Theo Hill	Merril Phillips
Doreen Booth	Pamela J Hodson	Ross Ponder
Gregory J Bounds	Carolina Hoecher Pizarro	Barry Price
Alan Bullot	Ash Huggett	Cath Raadts
Linda Childs van Wijk	Jerry Ioannou	Colin Reid
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Betty M Colman	Phillip Jackson	Robert J Rice
Barbara Cooper	Anne Jensen	Barry Roberts
Natale G Corrente	John Jewell	Ignazio Rontondo
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Elizabeth A Harris	Jayne O'Callaghan	George Zisopoulos
John H Harris	Kenneth W Palmer	

Coming Up

2016 free public seminars

Wednesday 20 April – 10am – Pancreatic, ovarian and other rare and neglected cancers

Wednesday 4 September – 6pm – Genomics and the revolution in medical research

Friday 28 October – 10am – Immune disorders

Space at these free public seminars is limited, so bookings are essential. To book, phone 1300 73 66 77 during business hours, or visit www.garvan.org.au

Clinical Studies

Ovarian cancer study

We are looking for volunteers with NO personal history of cancer to donate approximately 50-80 mL of blood to be used to optimise experimental protocols and/or biobanked for future use in cancer vs controls comparisons. This work is part of a project aimed at developing a blood-based test for early ovarian cancer. To volunteer, or for more information, contact Dr Kristina Warton 0438 649 073 or email k.warton@garvan.org.au (St Vincent's HREC Ref SVH14/257).

Brown fat and blood pressure study

Brown fat is a special kind of fat which burns fat in the body. We are looking for volunteers who have high blood pressure to participate in a trial investigating the effect of a medication on brown fat. Participants must be aged 18 to 45 years and currently on one blood pressure medication. For further information please contact Dr Paul Lee (02) 9295 8416 or email p.lee@garvan.org.au (St Vincent's HREC Ref 14/SVH/105).

Impact of medication on ability to process a meal

Volunteers are needed for a study testing an approved medication on your body's ability to process a meal. We are looking for healthy men and women, aged 22-65 years. The study involves one short (1 hour) and 2 longer (4 hours each) morning visits to the Garvan Institute in Darlinghurst. Participants will be provided breakfast and reimbursed for travel. For further information, please call (02) 9295 8215 or email crf@garvan.org.au (St Vincent's HREC Ref 14/157 Version 1 Meal Study).

BE PART OF PROGRESS

Please use this coupon if you would like to make a donation to Garvan's breakthrough medical research, or if you would like further information. We would love to hear from you.

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Yes! I want to help Garvan make progress with a gift of

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