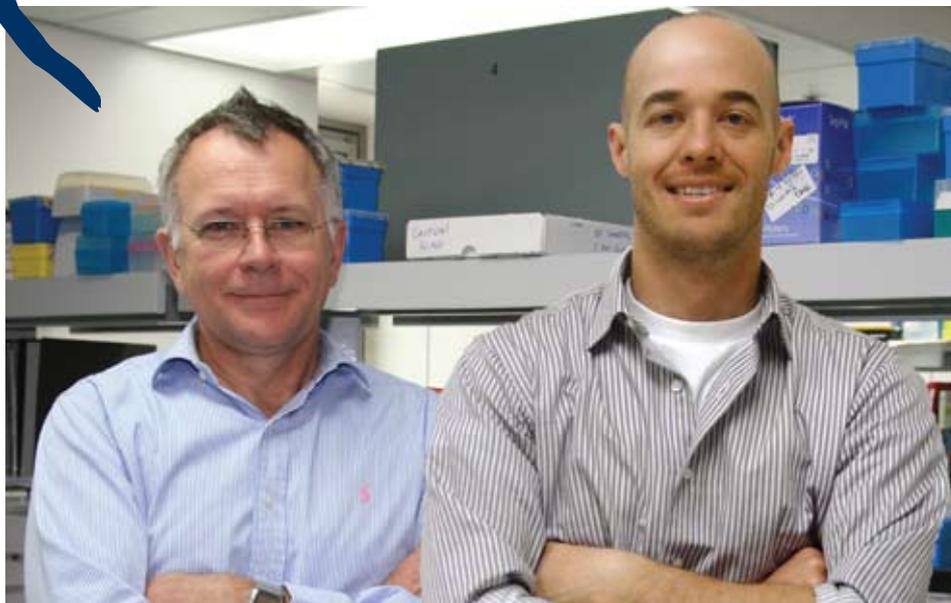


breakthrough

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Professor David James and Dr Kyle Hoehn

Garvan scientists, led by Dr Kyle Hoehn and Professor David James, have found that overeating may stimulate the conversion of the oxygen in the air we breathe into toxic free radicals, leading to insulin resistance and type 2 diabetes. Until now, no-one has identified the central mechanism, or cellular switch, that initiates insulin resistance. They have also found that neutralising this 'conversion pathway' may reverse insulin resistance in animals. This is encouraging because identifying the mechanistic origin of insulin resistance is a very important first step for developing diabetes therapies in the future.

making news

➤ Researchers in the Diabetes and Obesity Program have shown that a diet rich in coconut oil protects against 'insulin resistance' (an impaired ability of cells to respond to insulin) in muscle and fat. The diet also avoids the accumulation of body fat caused by other high fat diets of similar calorie content. These findings are important because obesity and insulin resistance are major factors leading to the development of type 2 diabetes.

➤ The work of Professor Susan Clark is featured in the National Health and Medical Research Council *10 of the Best Research Projects 2009* booklet. Professor Clark's expertise is epigenetics, a branch of research that seeks to

understand changes that occur in the function of genes without a change in the genome sequence. Her research into identical twins has shown that even though they have an identical genome sequence their epigenome sequence can vary leading to subtle changes in the twins' appearance and disease susceptibility.

➤ Drs Dominique Gatto and Robert Brink have solved an important mystery about what drives B cells; a finding that among other things could be used to help improve the body's reaction to vaccination. B cells, which make antibodies, can either make high quality antibodies over a period of several weeks

or quickly make low quality antibodies, sacrificing quality for speed. Until now no-one has understood what drives B cells to make this choice. The researchers have demonstrated that the presence or absence of a cell surface receptor, EB12, is the determining factor.

➤ Garvan researchers believe they may have identified a master regulator that tips our bodies into autoimmunity when our immune systems overreact, and into immunodeficiency when they underreact. Understanding the mechanisms involved is a promising step in the development of drugs to control diseases such as rheumatoid arthritis and lupus.

opinion



We like to think of Garvan's research as without borders, and nowhere is this better illustrated than in the range of our scientific collaborations throughout Australia, North and South America, Europe and Asia. All Garvan senior scientists have spent extensive periods working overseas, and we strive to enable all our researchers to interact regularly with international colleagues at key conferences. In this we are greatly assisted by a generous annual in-kind donation by Qantas.

There are many examples of the calibre and outcomes of the international collaborations we enjoy. Prof Jonathan Sprent worked at California's Scripps Research Institute and at the University Hospital of Lausanne in Switzerland to develop a novel complex designed to enhance the immune system to fight cancer. The complex combines Interleukin-2 (IL-2), a cytokine or chemical messenger, with an IL-2 antibody, and has now been tested in mice for cancer treatment and found to be effective.

Prof John Eisman collaborated with the Icelandic genetics company, deCode, in a genome-wide search project. Twelve genetic variations in the human genome were identified that are important in bone mineral density and fragility fractures. The discovery of genes linked to osteoporosis will allow researchers to develop better prognostic models, and clinicians to identify individuals with high risk of fracture for intervention.

Each year, we invite a pre-eminent overseas researcher to visit as the Garvan International Fellow, thanks again to Qantas' support. In 2009 this will be Prof Stephen O'Rahilly, from Cambridge UK, a pioneer in the genetic basis of obesity and type 2 diabetes. We look forward to hosting his visit in December.

Professor John Shine AO FAA
Executive Director

QuickQuiz

1. What area of the brain is affected in the neurodegenerative condition Parkinson's disease?
2. How many neurons are there in the human brain?

Answers: 1. Basal Ganglia 2. 100,000,000,000 (100 billion).

Researcher Profile: Dr Tri Phan



What are some of the recent findings from your work?

We found that a specialised cell in the lymph node captured dangerous particles from the lymph and alerted another cell to make protective antibodies against them. To do this these cells had to hold the particles on their surface and not ingest and destroy them. This is an exciting finding because we think that some pathogens and cancer cells that spread to the lymph node exploit these specialised cells as a 'safe haven' to hide from destruction by the immune system.

What is the biggest challenge in your area of research?

Faster, deeper, brighter! We are always trying to improve the intravital two-photon microscopy technology to allow us to image biological processes at faster scanning speeds, at greater depth, at higher resolution and with brighter colours. This will allow us to unlock the secrets to biological processes that have been hidden away deep in the tissues. Such transformative research requires very expensive equipment and we have been extremely fortunate to find a generous donor to help us.

What do you enjoy doing away from the research lab?

Dressing my 3-year old son up as an astronaut and making space shuttles and launching balloon rockets with him.

What is the current focus of your research?

We are interested in how cells of the immune system come together to generate a protective immune response. This involves rare cells navigating their way around the body to find and interact with other cells that can alert them to the presence of infectious pathogens or cancer cells within a lymph node. Therefore our work depends on a revolutionary technology – intravital two-photon microscopy – that allows us to directly see the behaviour of immune cells in an intact lymph node where the architecture and all the environmental cues that determine the immune response are preserved.



Regular Gifts from a Constant Traveller



John D. Head

Steadfast supporter John D. Head first became aware of Garvan as a frequenter of Darlinghurst's cafe Coluzzi Bar for 25 years. This exposure was enhanced through close friendships with medically oriented friends allowing John an entrée into the standard of research conducted within the institute.

Prior to this however, John's attitude towards philanthropy was shaped by personal experiences in third world countries, through which he travelled for the better part of 11 years. "You realise just how good our system is. We have access to amazing clinicians and facilities which is made possible not only through government grants, but through generous giving."

John signed up for Garvan's regular giving program in 1998, a program he feels to be mutually beneficial. He prefers to channel his donations through our regular giving program noting: "I don't miss the small amounts of money each month, compared

to a large donation at tax time". For Garvan, it means we are better positioned to financially forecast for the essential novel projects and core facilities not covered by government grants.

Further to John's significant contribution, the Garvan would like to thank John Head Snr who also gives to the Garvan; and family and friends who gave in memory of John's late mother Hope Head.

"As a family we had talked about some of these issues beforehand. My mother had a particular interest in Alzheimer's as her sister was afflicted at an early age, so she asked that we donate to Garvan rather than buy flowers. It was the Garvan's own good work that convinced them."

To find out more about monthly giving, please call the Garvan Research Foundation on **1300 73 6677** or visit www.garvan.org.au/support-us.

askGARVAN

What is the relationship between Garvan and the Sisters of Charity?

The young Mary Aikenhead established the Sisters of Charity to work for the poor of Ireland by offering education, visiting the sick in their homes, and setting up hospitals, schools and a refuge. The Sisters arrived in Australia in 1838 and founded St Vincent's in 1857 and the Garvan in 1963. Subsequently, the Garvan was established as an independent medical research institute under its own Act of Parliament in 1984.

Today, the Sisters remain closely involved with the institute. Their values of excellence, justice, dignity, compassion and unity underpin the work of our 500 staff, who reflect the diverse cultural, ethnic and religious make-up of modern Australia. Research carried out at Garvan is required, under the Act, to be consistent with the tenets of the Sisters. In governance terms, the Sisters occupy a position on both the Institute and Foundation Boards.

The Sisters also support our research in a myriad of ways. Most recently, eleven Sisters participated in the Nuns' Run to raise funds for the Garvan St Vincent's Cancer Centre. Sister Paulina Pilkington, who sits on the Foundation Board and was not able to do the run, secured a donation of crates of fresh apples for all the participants who crossed the finishing line.

Cancer Centre Update

Our capital campaign to raise the funds for construction and basic fit-out of the Garvan St Vincent's Cancer Centre is now complete, thanks to a \$70m capital grant from the Federal Government; \$35m in philanthropic pledges; a \$2.5m grant from the Australian Cancer Research Foundation; and the funds raised through the Nuns' Run. We are very grateful to everyone who has contributed to enable this vision to be realised.

We are still waiting on project approval from the Department of Planning, with the findings from the assessment due in December. Demolition of existing buildings on the Victoria Street site should take place in the first half of 2010, with construction beginning in September and the building ready for occupation in mid 2012.

The design brief for the Centre is still being finalised, but a number of core elements are in place. On ground level of the Centre, visitors will find both the Wellness Centre

and the chemotherapy unit (ambulatory care). The Wellness Centre will feature a range of evidence-based complementary therapies that patients can access. Treatment chairs in the chemotherapy unit will face outwards towards a lovely garden planted in Chaplin Lane. Other levels of the Centre will house consulting rooms and a range of state of the art scientific facilities, such as the molecular genetics and cell culture laboratories.

feature story:

Garvan Unlocks the Potential of the Brain to Fight Disease

Garvan researchers investigating brain activity are finding novel ways to approach a range of debilitating diseases such as osteoporosis, eating disorders, obesity and immune disorders. Their research has led to several recent breakthroughs and a better understanding of how the brain, notably the hypothalamus, regulates appetite, body weight, immune function and bone development. The impact of chronic stress on all these processes is a particular focus, especially the ways in which the negative effects of stress can be avoided.

Garvan's Neuroscience program, led by Professor Herbert Herzog, is exploring the significant role of a molecule made by the brain called neuropeptide Y (NPY). This molecule is abundant in the hypothalamus and widely distributed throughout the body. Interestingly, NPY is one of only a few brain proteins that has been conserved for millions of years of evolution, suggesting that it plays a very specific and critical role in the body.

NPY and appetite control

A key focus for Prof Herzog and Dr Amanda Sainsbury-Salis in the Neuroscience program is to understand NPY's role in the regulation of appetite, satiety, energy distribution and energy storage and what goes wrong in conditions such as obesity or the other extreme anorexia nervosa. They hope their work will lead to new, targeted therapies for these debilitating diseases.

The intricate NPY system may hold the key. Certain proteins such as NPY enhance appetite and induce feeding while other peptides, such as leptin, act as a satiety factor. Defects in the pathways that regulate these processes may be responsible for wasting conditions such as anorexia nervosa as well as the metabolic resistance to weight loss known as the 'famine reaction' - the

evolutionary survival mechanism that kicks in to protect us from wasting away in times of limited food supply.

The finely tuned NPY system operates much like a lock and key, where the NPY molecule acts as the key to unlock receptors on the surface of cells which regulate normal functioning. Initial research by the program looked to identify the receptors responsible for the feeding drive. It was found that receptors Y1 and Y5 were critical for stimulation of the feeding response, while the receptor Y2 reduces appetite. This provides a good starting point to search for new treatment options and cures for eating disorders and obesity. By blocking the receptors it may be possible to either stimulate or decrease appetite and make it easier to lose or gain weight.

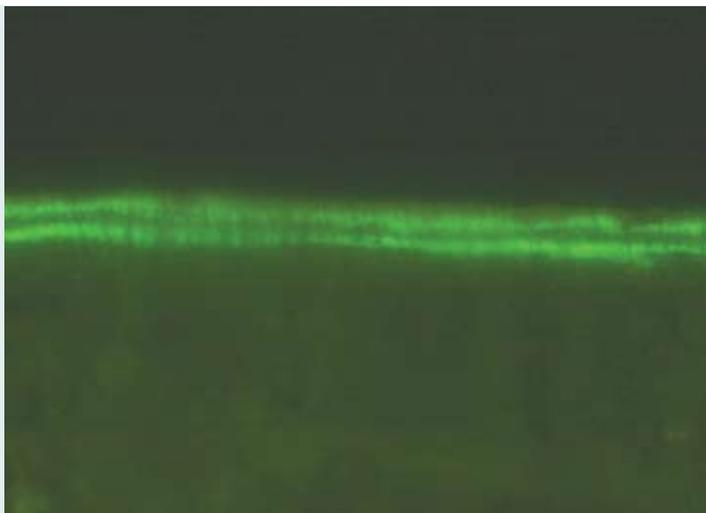
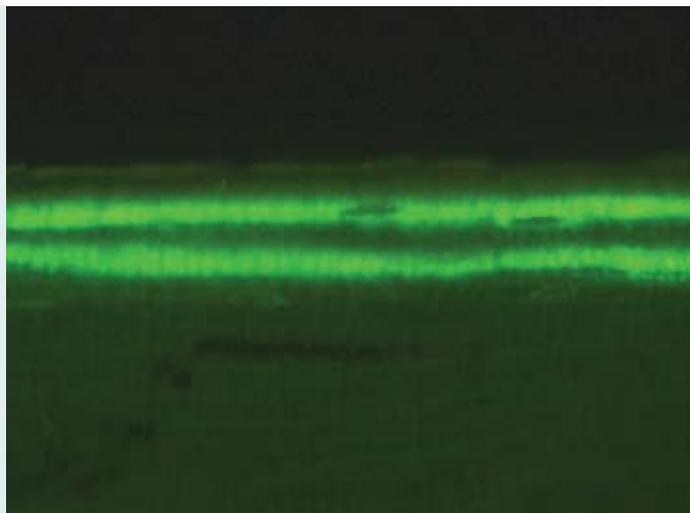
Studies have also shown that a gut-derived hormone called peptide YY (PYY), another member of the NPY family which promotes satiety, is abnormally high in people with anorexia. Apart from inducing nausea, high PYY levels were also found to be associated with decreased body weight, body mass index and bone composition in people with anorexia. The Neuroscience group has also shown that mice with high levels of PYY have decreased fat and bone mass, suggesting that the loss of body fat and bone tissue in young people with anorexia may be caused by these circulating PYY levels. Their aim

is to determine whether methods to block PYY levels in anorexia patients may have beneficial effects in restoring body weight, body composition and food intake.

Stress and obesity

We have known for some time that there is a connection between chronic stress and obesity, but how this works has been unclear. We have also known that NPY plays a role in other chronic stress-induced conditions, such as susceptibility to infection. Garvan Neuroscience researchers investigating the pathways, or chain of molecular events, linking chronic stress and obesity were able to shed light on this mystery when they identified the exact mechanisms that trigger stress-induced obesity.

When we are under stress, NPY levels increase in the body in an attempt to control heart rate and blood pressure. These are normal and healthy physiological responses designed to keep us alert and ready for action. When the stress passes, the body calms down and NPY levels return to normal. However, if stress is constant, or chronic, blood pressure remains high and the body starts to think that this new level is normal. In the long term, if chronic stress continues, the body loses the ability to respond to the stressful situation effectively;

**Control****Active**

These images illustrate the amount of bone formed during a single week, as demarcated by the two fluorescent labels, in control and treated bones. They highlight the 6 fold increase in the speed of bone formation resulting from activation of the NPY-mediated pathway to bone.

and if you add a high fat and high sugar diet into the equation, which is what many people indulge in as a response to stress, obesity will result. There is not much that can be done about the increased levels of NPY caused by stress. However, it may be possible to intervene to prevent the damage it causes. If we can interfere before NPY causes fat to amass, it could be beneficial for people suffering with cardiovascular disease, diabetes and cancer (which all have links with obesity).

Garvan researchers, in collaboration with scientists at Georgetown University (Washington D.C), found a direct connection between stress, a high calorie diet and unexpectedly high weight gain. Stressed and unstressed mice were fed normal diets and high calorie (high fat and high sugar, or so called 'comfort food') diets. The mice on normal diets did not become obese. However, stressed mice on high calorie diets gained twice as much fat as unstressed mice on the same diet. The novel and unexpected finding was that when stressed and non-stressed mice ate the same high calorie foods, the stressed animals used and stored fat differently.

The underlying cause for this intriguing discovery goes back to the NPY system. In the case of chronic stress, the researchers demonstrated that NPY (which is released from sympathetic neurons when stressed) can 'unlock' Y2 receptors in the body's fat cells, stimulating the cells to grow in size and number. By blocking these receptors in mice, they showed that stressed mice on high calorie diets do not become obese. Even more surprisingly, they found that

adverse metabolic changes linked to stress and obesity, like glucose intolerance and fatty liver, became markedly reduced.

These findings suggest that future therapies targeting the Y2 receptor directly on fat cells may result in a reduction of fat cells, benefiting millions of people around the world who have lived with high levels of stress for so long that their bodies think it's 'normal'.

NPY and bone health

There are currently no therapies available to reverse the effects of osteoporosis. It is a condition commonly known as the silent thief due to the gradual deterioration of bone structure leading to 'fragility' fractures. Often a person does not know they have a problem until a fracture occurs. Through a novel collaboration between Garvan researchers in the Neuroscience and Bone programs the link between body weight and bone mass is being explored, with some very promising results for the 2 million people affected by osteoporosis in Australia.

Clearly, a person with more body weight will need stronger bones to carry them around, compared to a person with reduced body weight. Also, in a starving situation, the body is more likely to put energy into essential body functions rather than bone formation. It is now clear, through research at Garvan by Dr Paul Baldock with Prof Herzog, that the pathways regulating bone formation and strength are controlled by the NPY system. If nutritional energy is low, thereby increasing NPY levels in the brain, bone growth is blocked to conserve energy. However, under obese conditions when nutritional energy

is plentiful, NPY is reduced in the brain and bone growth is accelerated.

Garvan researchers are now working to identify which receptors, or 'locks', in the NPY system are responsible for this process; as well as how stress effects the process. It is clear that stress (which elevates NPY) has a negative impact on bone growth. Initial research using mice models indicates that again the Y2 receptor has a role to play. Mice placed under stress have dramatic bone loss if the Y2 receptor is blocked. This suggests that the Y2 receptor could be an attractive target for new osteoporosis therapies. New compounds that inhibit Y2 might protect against stress-induced bone loss, and increase bone growth.

NPY and the immune system

In another collaboration, between the Neuroscience program and Autoimmunity Unit, Prof Fabienne Mackay and Prof Herzog discovered a clear link between the NPY and immune systems – explaining why we are more likely to fall ill during stressful periods.

When we are stressed nerves release a lot of NPY which gets into the bloodstream where it inhibits the cells in the immune system that look out for and destroy pathogens (bacteria and viruses) in the body – leaving us more prone to illness. Understanding the connection between NPY and the immune system offers major opportunities for therapeutic intervention.

Staff Profile: Christina Hardy

Director Business Development & Legal Affairs



What do you enjoy about working at Garvan?

Seeing breakthrough discoveries progress towards clinical development - it's a long journey and Garvan research is at the very beginning! Each discussion with a researcher, no matter how senior or junior, leads to me learning more about how

disease can occur in our bodies and what we can do to either prevent it, diagnose it early or treat it.

Describe a typical day.

First of all, I respond to emails, many of which have come in overnight from international companies interested in opportunities with Garvan. I usually have several meetings throughout the day with senior researchers discussing high priority projects. We involve the researchers in our commercial discussions and so we spend time discussing how a particular opportunity can be maximised. We also invest in maintaining a broad network of contacts which importantly includes my counterparts in other research institutes and universities in Australia. We are always looking for ways to collaborate externally to add to the technologies that the researchers can access to further progress discoveries to a clinical

outcome. Liaising with patent attorneys to ensure that the discoveries are patented is also an important focus for our office.

What challenges are there working at Garvan?

The early, but vital, stage of the research means that we have to work really hard at identifying the right commercial partner to take our research forward, no matter where they are located. Because we are at the discovery end of the pipeline, setting up the right commercial relationship is critical, and with organisations which are similarly aligned in their objective.

What do you enjoy doing away from Garvan?

Yoga, swimming, playing the piano and spending time with my family occupy the rest of my time. I'm also involved in some other non-profit activities, including trying to build a hospital in East Timor. That could sound like work, but it isn't.

Perpetual Trusts Support Garvan Research

A number of Garvan research teams will benefit from funding received from charitable moneys managed by Perpetual Trustee.

The Signal Transduction Group, headed by Professor Roger Daly, was awarded \$50,000 by the Baxter Charitable Foundation and the Elaine Haworth Charitable Foundation towards the establishment of a Tissue Processing Facility within the Cancer Program. This equipment will accelerate identification of molecular markers that can be used to stream patients into the most effective treatment regime. In addition, it is hoped that this work will assist in the development of novel targeted therapies that avoid the side effects of chemotherapy.

Associate Professor Antony Cooper received \$70,000 in funding to continue his work into Parkinson's disease from the Estate of the Late Olga Mabel Woolger. This will support research to find the causes of neuronal dysfunction. His work will look at how PARK9 function interacts with other naturally occurring substances in the body to cause Parkinson's disease; and this new information may identify alternate therapeutic targets to develop novel treatments for this debilitating condition.



Steve North (L) and Tonnia Johanson (R) from Perpetual with Associate Professor Antony Cooper

Dr Kharen Doyle's Neural Adult Stem-Cell Group (headed by Garvan Executive Director, Professor John Shine) was awarded \$35,735 (Estate of the Late Olga Mabel Woolger) to continue research into potential neuroreplacement therapies. The overall aim of this research is to isolate and purify olfactory neuronal stem cells (found in the lining of nasal passages), multiply them and convert them into particular types of nerve cells, which can then be used to replace brain tissue that has degenerated as in Parkinson's disease.

In addition, \$50,000 was awarded by The Clive and Vera Ramaciotti Foundation for Biomedical Research to Dr Maija Kohonen-Corish and Dr Laurent Pangon to further their research into the role of a newly identified biomarker (called the MCC defect) for the development of colorectal cancer, with the ultimate aim of developing new therapies and targeted treatments.

We are very grateful to these donors and Perpetual for such support.



GSK Supports Garvan Diabetes Research

Garvan's Associate Professor Katherine Samaras has been announced as the GlaxoSmithKline (GSK) Don Chisholm Diabetes Research Fellow. The Research Fellowship is dedicated to funding vital research into the causes, processes and treatments for type 2 diabetes, one of Australia's most common and serious diseases – and is named in honour of Professor Don Chisholm, one of Garvan's most distinguished scientists and clinicians, and a world-renowned expert on type 1 and type 2 diabetes.

Assoc Professor Samaras will use the Research Fellowship to explore the link between obesity and diabetes. In particular, she will examine the mechanisms by which weight loss improves type 2 diabetes. This research will be



Assoc Prof Katherine Samaras with Prof Don Chisholm

conducted through a trial that charts the progress of obese patients with diabetes, both prior to and following gastric-banding surgery. The results will help doctors and patients to predict which patients will benefit the most from such surgery by identifying biomarkers in the blood.

The GSK Don Chisholm Fellowship will also allow Assoc Professor Samaras and her team to explore the molecules that regulate blood sugar and how they can help to reverse diabetes in patients, giving researchers a better understanding of how this reversal process might take place and the time frame in which it can occur.

In Celebration Gifts – A different way to support Garvan's work

When you next celebrate a birthday, wedding, anniversary or any other special event, why not ask your guests to make a donation to Garvan in lieu of a gift. This is a wonderful way to mark the occasion, and at the same time to make a contribution to breakthrough medical research.

In Celebration Envelopes for your Guests

Garvan can provide personalised "In Celebration" donation envelopes for you. Guests can then fill these out before, during or after your event and mail them directly to us. We will then receipt your guest and let you know the total raised on our behalf.

In Celebration Online

You can download a Garvan In Celebration donation form from our website or guests can make a donation online at www.garvan.org.au/support-us.

All donations \$2 and over are tax-deductible. To find out more please contact Mona Saade at Garvan Research Foundation on **1300 73 66 77**.



