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The new 'face' of Garvan's website

It has been a busy few months, with exciting progress in all Garvan's research programs. Our August feature story explains how cells can get stressed and how this might be linked to Parkinson's and motor neurone disease. We have also undertaken Garvan's first multi-state appeal mailing, the launch of our new website and the publishing of our annual report.

 Branwen Morgan,
Editor

Making News

■ Professor Ken Ho and Dr Anne Nelson announced their finding that human growth hormone has no effect on muscle mass or sports performance. The results are from the first large-scale scientific study designed to evaluate the effects of human growth hormone, and have also been used to help develop a reliable new doping test.

■ A prestigious scientific journal published Professor Herbert Herzog's research that explains how neuropeptide Y (NPY), a molecule the body releases when stressed, can 'unlock' Y2 receptors in the body's fat cells, stimulating the cells to grow in size and number. By blocking

those receptors, it may be possible to prevent fat accumulating or make fat cells die. This finding has obvious potential to curb the obesity epidemic.

■ Dr Alison Butt's team received some media attention in relation to their work on the avocado toxin persin and how it kills breast cancer cells grown in the laboratory – their next step is to test the finding in animal models.

■ Professor David James was elected Fellow of the Australian Academy of Science in recognition of the contributions he has made to the understanding of insulin action and diabetes. He discovered the glucose transporter GLUT4, the key

molecule that transports sugar from the blood stream into muscle and fat cells, and identified key steps in the insulin regulation of glucose transport, both now major therapeutic targets in diabetes.

■ Professor John Shine celebrated twenty years at Garvan. Since John joined the Institute, staff numbers have quadrupled (from 113 to over 400), and income has grown tenfold. Through his professional activities, vision, and capacity to comprehend the social and ethical implications of scientific discoveries, John has helped build the reputation of the Garvan as a research body of international stature.



Opinion



One of the more immediate outcomes of the human genome database and our rapidly developing insight into complex diseases such as cancer, mental illness and diabetes, is the identification of 'disease biomarkers'.

Biomarkers are normal molecules that are found in altered levels in disease and can be used to indicate the presence and extent of a disease. For example, our researchers recently discovered a new prostate tissue biomarker called AZGP1 that can help identify which men are at the highest risk of life-threatening metastatic disease – where the cancer spreads to other parts of the body such as the bones.

Men who have low levels of AZGP1 in the prostate at the time of their initial surgery have a much greater risk of developing metastatic cancer. This means that these men could benefit from more aggressive treatment such as radiotherapy or chemotherapy around the time of surgery, when they still have potentially curable cancer, and that patients with a low risk of developing metastatic disease will have the option of deferring treatments that have a negative impact on quality of life. This tailoring of treatment options for individual prostate cancer sufferers is something that is not currently possible.

Biomarkers are also proving to be valuable indicators of how individuals respond to various treatments. In clinical trials, biomarkers are rapidly becoming very useful surrogate measures for assessing the efficacy of potential new therapies. Moreover, substituting biomarkers for clinical endpoints (such as increased lifespan) can dramatically reduce the time and cost taken to complete a clinical trial. The discovery of more biomarkers for complex diseases promises to greatly improve our capacity to develop innovative treatments and to more effectively tailor treatments to individual patients. This is something a number of Garvan researchers are firmly focused on doing.

Professor John Shine AO FAA
Executive Director

Donor Profile: In memory of Leslie McAllister

The Garvan Research Foundation first came into contact with Leslie McAllister in early 2003, when she visited as part of a tour group. Subsequently, we received notification from Leslie that she had been diagnosed with pancreatic cancer at the age of 76. With what her family and friends say is typical big-heartedness, Leslie decided that she wanted to support Garvan's pancreatic cancer research program by organising a residuary bequest in her will. Very sadly, the next we heard of Leslie was that she had passed away.

Leslie was brought up in Mosman. An articulate and numerate child, she showed many of the skills and personality traits that would later define her career as an adult. She started out as a secretary with the Rural Bank of NSW; became a Bank accountant; and eventually, was appointed manager of the Nelson Bay branch in 1981. This event was of real historical significance as Leslie was the first female manager of a Rural Bank branch and the second female bank manager in Australia. Subsequently, when the Rural became the State Bank, Leslie was appointed manager of the Sydney Spit Junction branch where she remained until retirement in 1986.



Thanks to Leslie's extremely thoughtful action, and the continued support from others interested in defeating pancreatic cancer, Dr Andrew Biankin and team can now look forward to expanding their pancreatic cancer research

Leslie was also a person who was very active in community life. She became a member of QUOTA, a community service club, while in Nelson Bay. When she moved back to Sydney, she became the only member of Manly QUOTA who at one stage or another filled all of the executive positions of Treasurer, Secretary, Vice President and President. Leslie also served with the Lupus Association, initially lending her financial skills and then becoming President - a position she held for 6 years. Leslie will be remembered as a strong, warm and generous lady who will be sadly missed by all who knew her.

did you know?

The autoimmune disease lupus is known as a 'great imitator' because it mimics so many other diseases and conditions; thus doctors often find lupus difficult to diagnose

Quiz

1. Why are mitochondria so important?
2. Long-term stress can make some people gain weight. True or False?
3. Which nerve cells die first in Parkinson's disease?

Answers:
1. They are a cell's batteries and the source of all the cell's energy
2. True, a recent study that Herbert Herzog helped conduct describes the phenomenon of stress-related obesity
3. Dopaminergic neurons, which are responsible for motor control

Donor Update

Thank you to all our loyal and new donors who contributed to our New Projects, Garvan Institute Associate and May/June appeals. You have contributed more than \$400,000 to Garvan's breakthrough medical research.

More than 400 donors contributed to our New Projects Fund, which supports new and innovative projects early in their development, before we are able to successfully apply for government grant funding. Donors who pledge to make ongoing gifts to this vital Fund receive a yearly update and yearly briefing on the projects' progress.

Become a Garvan Institute Associate

Welcome also to those supporters who have joined us as Garvan Institute Associates, following the launch of the program in April. Associates pledge to contribute to our work every month via automatic deduction from their credit card or bank account. This is a convenient way to make donations and play a vital role in helping us make new discoveries. You can pledge any amount you choose and you can alter your contributions at any time.

Regular giving (pledge) programs like the New Projects Fund and Garvan Institute Associate program allow our scientists to plan their work secure in the knowledge of ongoing funding. They are also cost-effective for Garvan to administer. For further information, or to join a regular giving project, please call **1300 73 66 77**.

Researcher Profile: Dr Cecile King



Born and raised in Western Australia, Cecile did her PhD at the Institute of Child Health in Perth, researching asthma and allergy. She then moved to California to study type 1 diabetes at the Scripps Research Institute, a move that sparked her interest in autoimmune diseases. In early 2005, Cecile set up the mucosal autoimmunity lab at Garvan. "I have always found autoimmunity, the question of why the body loses tolerance to itself, fascinating," says Cecile. "And we're making some extraordinary discoveries at the moment, including

revealing the existence of lymphoid structures in tissue being attacked by an autoimmune disease. These are mini-outposts of inflammation, similar to the clusters of immune cells formed when they attack an invader, and we believe they are aggressive in nature".

Cecile's research team is particularly concerned with the role of a cytokine (a small messenger protein) called interleukin 21 (IL 21) that is found in the immune system and is associated with a variety of autoimmune diseases, particularly type 1 diabetes. So far, the group has discovered that if you block IL 21 in mice, the aggressive lymphoid structures disappear and diabetes can't develop. The next step is to determine whether or not people react in the same way as mice to the neutralisation of IL 21. "If they do, we will be able to treat a plethora of autoimmune diseases, and even reverse them. It would be a pharmacological phenomenon," adds Cecile.

Ask Garvan...

1. What is the current focus of Garvan's pancreatic cancer research?

There are four main aspects: to gain a better understanding of the characteristics of precursor lesions of pancreatic cancer, because early detection is critical for increasing survival times; to develop better methods of selecting patients for surgery, because surgery is only suitable for 10-20% of pancreatic cancer patients and many of these still succumb rapidly to the disease (n.b. our scientists have identified several candidate molecular markers that are now being tested for their ability to predict a patient's response to surgery); to develop an antibody-mediated method for diagnosis and therapy aimed at a cell surface receptor called retinoic acid induced 3 (RAI3) receptor; and to manage the network of clinicians and scientists, known as the NSW Pancreatic Cancer Network, which was set up by Garvan to coordinate pancreatic cancer care and research across ten teaching hospitals and research institutions.

2. What is the DVDC and how is it linked to Garvan?

The Diabetes Vaccine Development Centre (DVDC) is a joint initiative of the National Health and Medical Research Council (NHMRC) and the New York based Juvenile Diabetes Research Foundation International. It has recently moved from the University of Melbourne to Garvan. DVDC will now operate as part of Garvan, but will maintain separate branding. The Centre is conducting clinical trials of a vaccine against type 1 diabetes that has proved to be effective in mice. A pilot trial in high-risk children and young adults has found that the vaccine is safe and causes immune changes in humans like those in the mice that were protected from getting diabetes. The trial, which is taking place at a number of centres across Australia and New Zealand, is currently recruiting participants. If you have a relative with type 1 diabetes you may be eligible to take part. For more information about the trial and to register interest please call 1300 138 712.

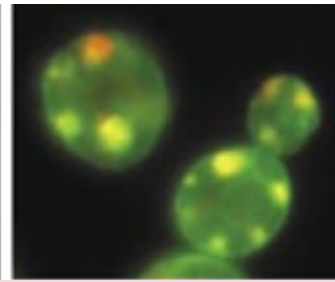
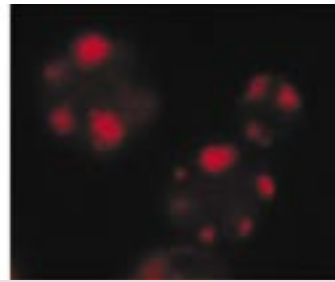
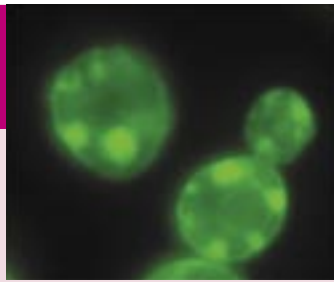


Cell Stress

Cell stress is not a concept many of us are familiar with, yet it is a primary reason for cell death and neurodegenerative diseases such as Parkinson's, motor neurone disease and diabetes. But what sort of things would make a cell 'stressed'? Our cells are protein factories, and proteins are the products of our genes. Like any efficient factory, a cell can become stressed when one part of its product supply chain malfunctions, is blocked, or when too many product orders are placed within a short period of time. As nerve cell regeneration is limited compared with other tissues and organs, any damage to brain cells can have serious consequences.

Role of proteins

Some of our proteins have structural functions, others have signalling and communication roles and yet others catalyse reactions such as those involved in producing energy for the cell. When proteins are first assembled, they are just a series of amino acids in a linear chain. Most will then undergo a series of modifications before they are ready to take on a specific function, much like a sheet of metal that is destined to become a car door panel – it has to be shaped and painted before being welded to the rest of the car body. Each protein has a particular lifespan – so cells are constantly making and replacing proteins.



Toxic by-products

The chemical process of modifying proteins creates potentially toxic by-products that must be disposed of. For example, when proteins are folded and bonded together to create something that is 3-dimensional, the creation of 'disulfide bonds' leads to production of reactive oxygen species (such as super oxide, O_2^-). The presence of these by-products causes 'oxidative stress'. Luckily, our cells usually produce sufficient enzymes and antioxidants to turn these by-products into harmless, easily excreted substances.

One of the questions asked by scientists like Garvan's Associate Professor Antony Cooper is: why don't beta pancreatic cells that are designed to produce lots of the protein insulin (which contains 3 disulfide bonds), and are therefore under considerable stress, produce more antioxidants to offset potential damage for the increased 'factory pollution'? The current theory is that short-lived potentially damaging reactive oxygen species actually have a role as signalling molecules. In fact, if an enzyme to eradicate these reactive oxygen species is increased in diabetic mice, the mice actually get worse. And, in the brain, there is pretty good evidence for nitric oxide, another reactive oxygen species, having an important role.

Cooper's group work with two systems: yeast cells and nerve-

like PC12 cells grown in culture. Surprisingly, yeast cells (like baker's yeast) are very similar to our own cells. In addition, they are easy to work with and the protein manufacturing, assembly and transport systems in particular are comparable.

Parkinson's disease

The team became interested in Parkinson's disease because the disease results in the progressive death of the neurons that make the neurotransmitter dopamine, the metabolism of which - because of its chemical nature - increases oxidative stress. A clue as to where to start their investigation into why these cells die came from the knowledge that, in a small number of patients, there is one mutant gene (called P, which encodes a protein called α -synuclein) that very clearly causes Parkinson's.

The mutant α -synuclein protein forms aggregates (clumps) called Lewy bodies, which are seen in the brain tissue of people with Parkinson's disease. But forming insoluble protein aggregates doesn't in itself make something toxic. And given that the α -synuclein genetic mutations are present at birth, the model has to account for the disease symptoms not showing up until late in life. So, what does α -synuclein normally do? It has a role in coating synaptic vesicles, which are little lipid-based containers

that contain neurotransmitters (like dopamine) whose role is to carry signals between nerve cells. However in Parkinson's disease, α -synuclein interferes with critical transport within the neurons. Interestingly, α -synuclein by itself has no defined structure in the test tube, and has different forms, so it is difficult to pinpoint its targets.

The questions that need to be answered are: what is the lethal α -synuclein species, why is it causing a failure in protein trafficking and what genes may help a cell with mutations in α -synuclein survive? It's like studying a line of dominos and trying to find the first one that has caused all the others to fall over. But, if the link between mutant α -synuclein and the death of the dopaminergic neurons can be found, it could lead medical researchers to find other genetic mutations that also cause Parkinson's because they could be interfering with the same cellular pathway.

Motor neurone disease

However, there's a confounding factor to all this logic. Lewy bodies are also present in the brains of people who have died with other neurological diseases, which makes Cooper believe that the loss of dopaminergic neurons in Parkinson's patients are just the first symptoms detected, because the mutant α -synuclein is more prone to forming aggregates there. Cooper's group is using the yeast system to test how α -synuclein might be adversely affecting a cell. They can look at what genes in the

system are perturbed in response to the genetic changes instigated and, by using clever molecular techniques to attach a fluorescent marker to proteins of interest, see what proteins are collecting where. They have observed that if the yeast cells produce the mutated α -synuclein protein, they will be dead within a matter of hours. They are still investigating why.

Cooper group's newest project, however, is to look at what causes motor neurone disease (MND, a.k.a. Lou Gehrig's disease or amyotrophic lateral sclerosis). Once again the first clues come from patients where a specific gene defect has been linked to the disease. The clinical features too are interesting. The motor neurons also accumulate protein aggregates, but unlike in Parkinson's where they are comprised largely of α -synuclein, these ones are of a protein called superoxide dismutase-

and effect. SOD1 is an enzyme that neutralises the reactive oxygen species that cause oxidative stress. So perhaps the mutations instead cause the enzyme to produce reactive oxygen species and this leads to enhanced stress levels rather than reduced ones? A model for MND would also have to account for the spreading nature of the disease, as it starts in one part of the nervous system and gradually affects motor neurons that control the function of various organs – such as those that innervate the lung muscles. Cooper is now applying the α -synuclein yeast approach to ask why cells with SOD1 mutations die and what genes could be altered in order to delay motor neuron death and slow down the onset of symptoms.

Because of the essence of what neurons are designed to do - communicate via a variety of signals - they are incredibly sensitive to

Dr Antony Cooper and team are taking their knowledge of cell stress and its role in diabetes and using it to understand the possible cause of neurodegenerative diseases – another example of how Garvan's interdisciplinary capabilities are paying off

1 (SOD1). Interestingly, if this protein is 'knocked out' in mouse models there appears to be no effect, rather it appears that the disease results from the presence of mutations in the protein that are obviously acting to change its function. The problem is that it is not just one mutation in this gene that is linked to MND and so it is not easy to link cause

transport problems within the cell and between each other. Only by dissecting and examining the complexities of these fundamental biological processes will we ever truly be able to comprehend and potentially cure these devastating neurological conditions.



Staff Profile: Natasha and Ebony – *our receptionists*

If you call or visit Garvan, either Natasha or Ebony, who manage our busy reception desk and switchboard, will usually greet you. Both work part-time, both are outgoing, and both agree that meeting people is the best part of the job.

Natasha has been with us since 2003, Ebony since February of this year. Natasha hails from an insurance industry background, which she left when it became too bureaucratic. She went on to become a receptionist at the Woollahra Sailing Club and the Royal Sydney Golf Club before joining Garvan – whose location, nature and hours of work, were appealing.

Ebony's background is extremely varied. She studied events management and one day hopes to become a nurse. Being at Garvan means she is in the right environment to learn about medical-related career paths, as well as a variety of other things from medical terminology to computers. She is now starting to help out in other departments, where she is getting to better know staff. Part-time work also gives Ebony time to ride horses, her main passion, and compete in dressage, cross country and show jumping. Until recently, Ebony filled in what was left of her 'spare time' by working as a horse-riding instructor.

Donor Profile: Alcoa/Garvan health education partnership

By teaming up with the Garvan Institute, Alcoa Australia Rolled Products (Alcoa ARP) at Yennora in Western Sydney provided their employees with opportunities to learn first hand about the latest breakthroughs in medical research. On-site interactive presentations, delivered in May during work hours, included information about prostate cancer, osteoporosis and diabetes research and how Alcoa staff could assess and manage their risks of developing these health problems. By conducting seminars for the employees at their place of work, Garvan was able to extend its PACE (public awareness and community education) program into the corporate sector. The seminars were supported financially by Alcoa and were collaboratively designed to meet the needs of their predominantly ageing male workforce. Alcoa ARP at Yennora is Australia's largest recycler of aluminium products, recycling over 70 000 tonnes of aluminium per year, including 550 million cans. Recycling reduces industry requirements for natural resources, diverts waste from landfill, and uses only 5% of the energy required to make new aluminium from scratch. The business recently won the Excellence in Sustainability Award at the 2007 Western Sydney Business Awards.

An additional Alcoa Foundation grant is supporting the free 2007 Garvan Public Seminar Series. Since its inception in 1952, the Alcoa Foundation, which is based in the US, has invested more than \$410 million in community quality of life projects worldwide.



Alcoa employees conduct self-assessments during an interactive Garvan presentation

Cafe Opening

We were delighted to express our gratitude for gifts in cash and kind to five members of the Schirato family (owners of Vittoria Coffee) in attendance at the opening of our new staff café, de novo, on June 7. Mr Les Schirato (CEO of Vittoria Coffee) is noted for his support of charitable causes, and when asked to assist Garvan with this project, responded immediately. A generous donation by Vittoria Coffee enabled us to outfit our café to a high standard. By providing a comfortable, modern environment in-house, Garvan hopes to encourage staff to congregate and meet in de novo, which will simultaneously facilitate cross-disciplinary dialogue. In addition to significant financial support, Mr Schirato donated coffee-making machines and Vittoria-branded cups and saucers.

Annual General Meeting

The Hon Verity Firth MP accepted the invitation to speak at our April AGM just days after receiving her portfolio and being sworn in to the new State Government ministry. Ms Firth MP, the Minister for Women, Minister for Science and Medical Research, Minister Assisting the Minister for Health (Cancer) and Minister Assisting the Minister for Climate Change, impressed Garvan staff with her insightful comments and her enthusiasm for medical research.



The 'Jointventure' project challenged 30 well-known "artists", from the arts, sport, fashion and entertainment to create their own Stanley. Above is the Stanley decorated by Jo Nevill of Paper Couture



Members of the Schirato family attend the opening of Garvan's new staff café, de novo

'Jointventure' fundraiser

On June 29, thirty 'Stanleys' were among the prizes auctioned at the Jointventure fundraiser in Sydney's Surry Hills, to raise more than \$30 000 for Garvan's research into the painful inflammatory disease, rheumatoid arthritis. 'Stanley' is the jointed wooden human figure used in Seven Network's 1970s children's show Romper Room. Jointventure is the brain-child of Sarah Lamond, a graphic and interior designer, inspired by her best friend's stoic struggle with the disease since age 7. We are extremely grateful to all those who contributed to this great event. If you would like to propose a community fundraising project to raise money for Garvan, please contact our Fundraising Coordinator on (02) 9295 8110.

Running to stop the hunger

On April 15, Mark Ranucci and David Stevens completed the Canberra marathon to raise money to support research into effective treatments for the appetite disturbances that characterise Prader-Willi syndrome. Mark's daughter, Charlie (who is almost 18 months old) suffers from this condition. To date, they have raised a total of \$33 546 for Garvan's work in this area – thank you!

Dubbo's 18th birthday/conga line



On May 2, 477 of Dubbo's senior citizens formed a conga line and danced through a local park. Apart from being fun, they did this for three reasons: to celebrate the 18th birthday of Garvan's Dubbo Osteoporosis Epidemiology Study, to publicise a very

generous donation from Amgen (\$240 000) and to try and get into the Guinness Book of World Records – which they would have done if they'd been able to verify everyone's birthdate on the day.

Free Wills Days for Supporters



The Public Trustee
is there for you

Thanks to a long-standing relationship between Garvan and the Public Trustee NSW, Garvan's NSW supporters are invited to have their wills prepared by the Public Trustee at no charge. This service is available to those who wish to nominate the Public Trustee as executor. If you don't have a will, or if you need to review your will, this is an opportunity to have the legal documentation drawn up on the spot, by experts, to ensure that your wishes will be carried out.

Professional will-makers from the Public Trustee will conduct 45-minute private and confidential appointments at Garvan (384 Victoria Street, Darlinghurst, Sydney) on September 25 and 26.

There is no obligation whatsoever to include Garvan as a beneficiary in your will. Should you choose to include Garvan and you let us know, we will be very grateful and delighted to welcome you as a Garvan Partner for the Future.

To make an appointment, or for further information, please call Monica Schneider on (02) 9295 8117. Once you have made your booking we will send you details on what to bring and how to prepare for the day.

In memoriam Apr 07 - Jun 07

We gratefully acknowledge gifts received in memory of:

Andrew Bristow
Gail Bushby
Deborah George
Max Gore
Rosly Milne

Vasilis Natsis
Lorraine Ryan
Lady Marie Sutton
June Viles

Acknowledgement

Thanks to Fitness First for the free gym memberships given to the participants involved in our 'Metabolism and type 2 diabetes' clinical research study.

Coming Up:

Our next seminar on **Tuesday, August 7** (10am - 12pm) is on **Osteoporosis** and will be hosted by Garvan's Professor John Eisman. Speakers include Garvan's Dr Jackie Center, Professor Markus Seibel (Concord Hospital), A/Professor Rod Baber (Royal North Shore Hospital) and Dr Chris White (Prince of Wales Hospital and the Royal Hospital for Women).

On **Monday, September 17** (10am - 12pm), join us for our **'Ageing Brain'** seminar and hear from expert scientists and clinicians about Parkinson's disease, Alzheimer's disease, and how adult stem cell research is being explored as a potential therapy for brain diseases.

Also, mark **Wednesday, October 17** (6pm - 8pm) in your diaries as it's the date for our **mental health disorders** seminar, where we shall discuss depression, bipolar disorder, and anorexia.

Garvan's 2007 free public seminars series is being sponsored by the Alcoa Foundation.

Call 9295 8110 to register, or visit our website www.garvan.org.au
Bookings are essential

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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