04 breakthrough

GARVAN NEWSLETTER APRIL 2007 / ISSUE 04

What's Inside

Garvan Institute Chairman Bill Ferris (R) with business partner Joe Skrzynski (L) and artist Janet Laurence in front of Janet's work entitled Illogical Discohesion (see story on pg 7)

This year's first issue tackles the hot topic of cancer immunotherapy, reports on the findings from our donor survey, and describes research (made possible by a generous family donation) into a rare genetic disorder.

Branwen Morgan, Editor

Making News

Garvan scientists have found that once men over the age of 60 have had a fracture, around one in three will have broken another bone within just a few years. This new research shows the chances of either men or women having a second break are not only much higher than the first, but they are equivalent – dispelling the common belief that osteoporosis affects mainly elderly women.

In other research we have shown that fats directly affect immune system function. In particular, we discovered that certain immune cells, called dendritic cells, which kick-start the immune system, only become active after exposure to fats. This suggests that targeting the dendritic cell's ability to respond to fats would have great potential as a treatment for inflammatory disorders such as rheumatoid arthritis where these cells are overactive.

Garvan's Business Development Unit, whose role is to help take Garvan's research findings one step closer towards the development of new treatments and diagnostic tests, has signed three new agreements with international biotech companies relating to prostate cancer diagnosis, bipolar treatment optimisation, and a new epilepsy treatment. New patents were filed in the areas of neuroscience, cancer and immunology.

Opinion

Garvan has a proud record in obesity and diabetes research, led for many years by the dedicated efforts of Professor Don Chisholm. Don first joined the Garvan in 1968 at the same time as he was a young Registrar at St Vincent's Hospital. In the past four decades, Don's work has had an enormous impact on our understanding of the development of insulin resistance – a hallmark of type 2 diabetes. His group was the first to demonstrate that the amount of abdominal (gut) fat, not total body (butt) fat, was the risk factor for diabetes and that this was determined by both genetics and lifestyle. This is leading to more effective, personalised, approaches to the prevention of obesity. In very recent times, Don's work has also shown that inflammation in people with type 2 diabetes contributes to their increased risk of cardiovascular disease – providing some exciting new clues to the prevention of this devastating condition.

In recognition of Don's contributions to diabetes research, an international symposium was held in March to honour his official retirement from hospital clinical duties (he will, fortunately, continue to play a major role in research and mentoring at Garvan). In testament to the Don's international standing, a most impressive group of diabetes researchers from around the world participated in a one day symposium – an opportunity for his friends and colleagues to recognise a man of enormous wisdom, dedication and humility who has committed his life to improving the quality of life of those suffering from diabetes and to helping ensure that future generations are not afflicted.

Garvan owes an enormous debt to Don Chisholm and we are proud to have had the opportunity to celebrate his amazing contributions to medical research.

Professor John Shine AO FAA
Executive Director

Donor Profile:
Curran Foundation funds Chair in Neuroscience

In late 2006, the Curran Foundation generously donated $1million to fund the establishment of an endowed Chair in Neuroscience at Garvan, to be known as the Curran Foundation Chair of Neuroscience Research. The Foundation typically raises funds for St Vincent's Hospital, but also maintains a close relationship with Garvan. The gift was supported by special project donations to the Curran Foundation, including $500 000 from Mr Paul Curran and $100 000 from Mr Lang Walker, both of whom have an interest in finding a cure for hearing loss.

Mr Charles Curran AC was Chairman of the Garvan Institute from 1988 to 1992 and remains deeply committed to the ongoing growth and development of the whole St. Vincent's campus. Due to our affiliation agreement with the University of New South Wales, named Chairs can be set up in perpetuity, their incumbents embracing research and teaching responsibilities and working across both institutions.

Hearing loss is just one of the exciting research areas in Garvan's Neuroscience program and our researchers' work with nerve stem cells taken from the nasal lining is showing more and more promise. The stem cells have successfully converted into new hearing cells in the lab. Now the challenge is to achieve the same in mice, and then in people.

Mr Charles Hulley AM (Chairman) and Mrs Trish Burns AM (Executive Director) present the Curran Foundation's gift to Professor John Shine AO FAA

did you know?

That 1% of detected breast cancers are found in men?

Quiz

1. **Are cytokines chemical messengers produced by immune cells or nerve cells?**
2. **Adult nerve stem cells can be accessed via the nose. True or False?**
3. **What type of immune cells make antibodies?**
4. **In which NSW town does Garvan have an osteoporosis study clinic?**

Answers:
1. Immune cells
2. True – they are from the nasal lining where cells responsible for our sense of smell are constantly being replaced
3. B cells
4. Dubbo

Donor Survey Update

Garvan would like to thank the hundreds of donors who responded to our recent survey. While we are still completing the compilation and analysis of the results, here are a few highlights:

The top 4 answers to the question "What inspired you to support Garvan?" gave us an insight into the drivers of your loyalty to Garvan:

1) I believe that only through medical research will we find cures for major diseases - 68%
2) I / a family member or a friend has suffered from a disease - 60%
3) I believe in the value of fundamental scientific research - 37%
4) I wish to contribute to finding cures for major diseases - 34%

We also discovered that is it particularly important to you that Garvan researches a range of major diseases, so this is an aspect of our work we will promote further.

Perhaps predictably, 18% of our donors work, or have worked, in a health or medical field and 12% in education – although many of you (63%) are now retired.

A very special thank you to the donors who advised that they are considering including, or have already included, Garvan in their will.

Researcher Profile: Professor Jonathan Sprent FRS FAA

Jon Sprent was born in England but, after several years in Canada, his family moved to Brisbane. Jon was ten years old at the time. He always wanted to be a scientist - stimulated by his father, a well-known parasitologist. After finishing medical school at the University of Queensland, he undertook a PhD at The Walter and Eliza Hall Institute in Melbourne with one of Australia's most famous scientists, Jacques Miller, at the same time as Garvan's Professor Tony Basten was working there as a post doctoral researcher. On completion of his PhD, Jon spent several years working in Switzerland and London before moving to the USA, where he remained for 30 years. Last year saw him being recruited back to Australia by his old lab mate Tony Basten. After spending the last 20 years at the prestigious Scripps Institute in San Diego, Jon decided that "pretty good science was happening in Australia" and that he had family reasons for making the move back. He now heads a research group called 'Cellular Immunity', which relates to the development and fate of T cells (white blood cells that participate in a variety of immune responses but are able to somehow distinguish between self tissue and foreign substances). Application of this work lies in harnessing the immune system to boost its attack on cancerous tumours and, conversely, dampening down the immune response to treat autoimmune diseases (see the immunotherapy feature on pg 4). It's hard to pick just one career highlight for Jon Sprent, but becoming a Fellow of the UK's Royal Society (the UK's premier scientific body) is definitely up there; so is being the only Australian ever to be elected President of the American Association of Immunologists, and being a joint recipient of the Canadian J Allyn Taylor International Prize in Medicine.

Ask Garvan...

1. What involvement does Garvan have in commercialisation of its discoveries?

Garvan is focused on the early discovery phase of research and development, and licenses its inventions to industry for further development. The most recent example of this is the licensing agreement with Novo Nordisk, potentially valued at USD 100m, made with our 'spin out' biotechnology company G2 to take our development of antibodies to the C5a receptor as a new anti-inflammatory agent into human trials (initially, for treatment of rheumatoid arthritis).

Wherever possible, Garvan tries to retain a significant interest in the commercial development of its discoveries through partnerships and equity participation. We currently hold about 30 patent families and partner with industry to take our discoveries from bench to bedside as quickly as possible. However, Garvan is fundamentally a 'public good' institution and has limits on the amount of significant resources it can divert to commercial activity.

2. How much of Garvan's $35 million budget goes directly to research?

Garvan is about research, thus about 85% of our budget goes directly to research. The only two exceptions are:

- $3.5m provided specifically for infrastructure support from the NSW government (electricity, water, office equipment and so on)
- cost of all Garvan salaries, and a small operational budget to run the Garvan Research Foundation, the Institute's marketing and fundraising arm.

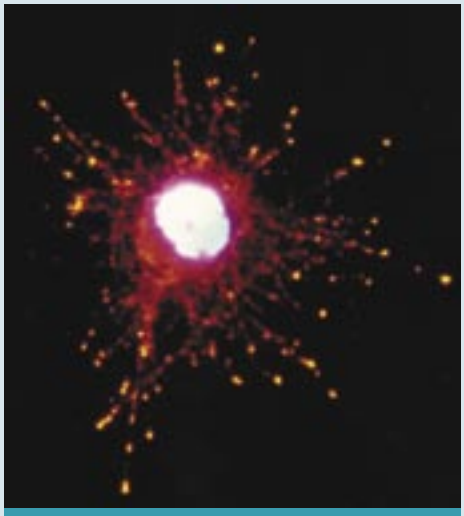
Immunotherapy

Immunotherapy is a simple word with a simple concept: to manipulate the immune system so that it can better fight diseases like cancer and prevent transplanted organ rejection and autoimmune disorders, such as type 1 diabetes or rheumatoid arthritis, where there is an over enthusiastic immune response. But behind the basic principle of immunotherapy there are multiple layers of complexity and holes in our understanding of the immune system's modus operandi. Garvan researchers are working hard to bridge this gap.

Tumours are masters of deception

Cancer immunotherapy is a particularly hot topic. How can we help our immune systems to recognise and destroy rogue tumour cells that have managed to escape normal growth controls?

One of the problems lies in the fact that cancer cells have only a few features that distinguish them from normal healthy tissue. As the cancer grows, however, it becomes more invasive and more 'visible', acquiring additional distinctive characteristics (new antigens) that the immune system can see. So, why can't we eradicate cancer? The reason is that there are several opposing forces at work, including the tumour's own tactics for evading detection and enabling stealthy growth.



The immune system needs to be given measures to enable it to counter a tumour's tactics for evading detection and for enabling stealthy growth

This is a breast cancer cell in its 'death throes', photgraphed by Dr Alison Butt.

The immune system's balancing act

To figure out how to deploy counter measures against a tumour's propensity for hiding, we need greater knowledge of immune system biology, in particular the roles of the individual immune cells that form our lines of defense.

There are many types of immune cells, but essentially the T cell and the B cell families are the masters of the immune system. They comprise the 'adaptive' half of the immune system that responds specifically to antigens (substances the body makes anitbodies to). T cells are primarily of two types: CD8+, which are capable of killing other cells (and are so-called cytotoxic T cells), and CD4+, also known as T helper cells because they help orchestrate antibody production (antibodies are proteins that specifically recognize a foreign substance). However, a small number of CD4+ cells have another function: to suppress the immune response. Known as T regulatory (Treg) cells, they are vital for dampening the over enthusiastic immune response that can lead to autoimmune disease (where the body mistakenly thinks its own tissue is foreign and attempts to destroy it). But, interestingly, they can also prevent the immune system destroying cancer cells. There are numerous documented reports of increases in the numbers of Treg cells in various cancers ranging from melanomas to ovarian, breast and colorectal cancers. This has led to the idea that reducing the numbers of Treg cells may help in the fight against cancer.

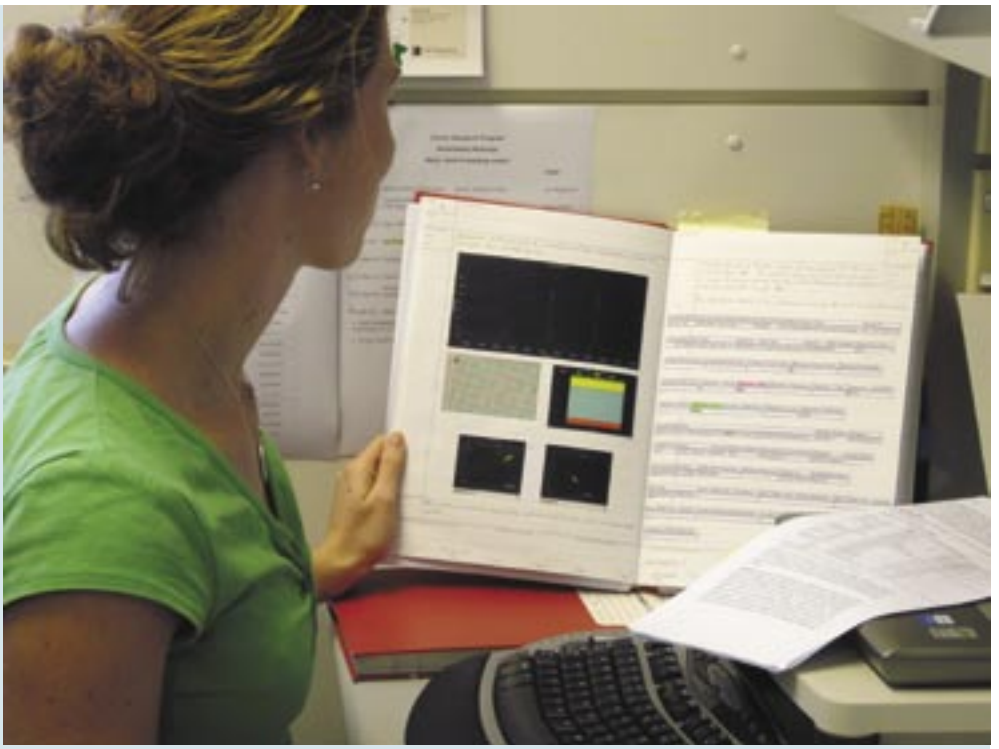
Key Cells of the Immune System

T cells: white blood cells that develop in the thymus gland, there are 2 sub categories:

- CD4+ (T helper cells) – 3 types: TH1, TH2 and Treg cells
- CD8+ (cytotoxic or 'killer' T cells)

B cells: Antibody-producing white blood cells, which mature in the bone marrow

Research teams led by Professor Fabienne Mackay and Dr Shane Grey are looking closely at how T cells are regulated. Fabienne's group,



together with Professor Herbert Herzog, previously reported finding the mechanism by which a brain hormone (neuropeptide Y) that is overproduced during times of stress affects the T helper cells. They were excited to discover that this same neuropeptide Y signalling pathway might be manipulated to prevent Treg cells dampening the immune system's response to cancer and are investigating this idea further. Shane's team believe that they have a way to reduce the numbers of Treg cells: by blocking a molecule that previously hadn't been implicated in Treg cell proliferation. They are using this same factor for another purpose too, to expand Tregs and prevent organ rejection.

Garvan's Professor Jon Sprent's research group is interested in how T cells are able to distinguish between self and foreign antigens and the life cycle of a T cell: what gets them going, what causes them to differentiate into one of the T cell sub populations (CD4+, CD8+, or Treg cells) and how, once a job is done, they are disposed of. There are two applications of this research. The first is to use knowledge gained to boost the numbers of CD8+ T cells that are capable of killing cancer cells and the second is to boost the numbers of Treg cells to prevent autoimmune disease – the opposite of what Grey's team is doing to promote cancer eradication i.e. deplete Tregs. The researchers have developed a simple but elegant method of exploiting the finding that both CD8+ and Treg cells respond differently to a signalling molecule (cytokine) called IL-2. They have made antibodies against IL-2 that can selectively block its action and are now testing to see whether the antibody that causes an expansion of the CD8+ killer cells has measurable outcomes in terms of reducing tumour size in animal models of cancer.

Dr Vanessa Hayes's Cancer Genetics team is also interested in the connections between the immune system and cancer, but they're trying to understand why in some people the immune system may be less effective at preventing or limiting cancer growth. They are searching for variations in the genes that regulate inflammation and those that code for cytokines, chemical messengers that regulate the intensity and duration of immune responses. It is hoped that these variations, called polymorphisms, can then be grouped and associated with an increased risk of breast or prostate cancer. Should an individual with an increased risk of cancer then develop it, the information could be used to personalise the treatment e.g. it could involve administering a medicine that boosts a particular immune response against the cancer, thereby compensating for the 'weakened' gene.

Boosting cancer detection

In addition to looking at inherited genetic changes, Vanessa's Cancer Genetics researchers are also interested in the gene mutations that a tumour acquires as it morphs from a normal healthy cell into a destructive mass. Knowing what these mutations are may help immunotherapists to design strategies to improve immunosurveillance - the ability of the immune system to keep a watchful eye over any abnormal activities.

Garvan's broad breadth of research enables these very exciting emerging medical fields to be tackled from numerous directions. This is one worth watching...

Staff Profile: John Dakin

John Dakin could have had a career as a professional golfer (his handicap stands at 2). Instead, after a short time as a pro, he turned to the more reliable profession of accounting and went on to make his mark at Lend Lease Ltd and MBF.

Now, after five years as Garvan's Chief Operating Officer, JD – as he is often known, to distinguish him from the other John (Shine) – is not slowing down. He is energised by his current pet projects: overseeing development of an offsite mouse breeding and holding facility in Moss Vale, NSW; creating a childcare centre for Garvan staff; and pursuing plans with St. Vincent's hospital for a cancer research centre.

Q. Why come to Garvan?
I'd been well aware of and impressed by the activities of Garvan for some time, so when I was approached I saw it as a great opportunity, as I wanted to work for an organisation that gives something back to the community.

Q. What have been your major challenges?
Ensuring that Garvan has a stable financial footing in a period of sustained growth, especially if you consider that the Institute has doubled in size in the last few years. Also, finalising plans for the development of a new precinct building in the old Garvan carpark area.

Q. What are you most proud of achieving in your time spent at Garvan?
Maintaining and enhancing the high level of service that my teams provide to the scientists in areas of IT, building operations, finance, human resources etc.

Donor Profile: Finding potential treatments for Prader-Willi Syndrome

Finding potential treatments for Prader-Willi Syndrome is being made possible by private family donations. Garvan is extremely grateful to those who are enabling us to tackle this challenging area of work

Most people have never heard of Prader-Willi Syndrome (PWS), as it only affects approximately one out of every 10 000 - 20 000 people and is believed to be under-diagnosed. It is caused by an abnormality on chromosome 15 and does not discriminate between sex or race.

The first symptom is usually an insatiable appetite that appears between the ages of two and six. These children often feel constantly hungry, their metabolic rate is lower than normal (so only 60% of the calories of a typical person is required) and their muscle development is weak. The combination of these problems increases the likelihood of secondary health risks later in life, such as obesity, heart disease and diabetes.

In addition to struggling with being overweight, people with PWS are often of normal to slightly-below-normal intelligence and short of stature. Many would be able to live independently if only there were effective treatments to curb their voracious appetite - known as 'the hunger'. Presently, no such treatment exists and current management of PWS involves living in homes where access to food is strictly controlled (padlocks on fridges and pantries) and there is strict supervision when outside the home.

Garvan researchers are investigating whether the naturally occurring hormones peptide YY (PYY) and pancreatic polypeptide (PP), both of which are secreted from the gut, might be involved in the development and possible treatment for increased appetite and obesity in PWS. They are testing their hypothesis that people with PWS have less circulating PYY or PP than those unaffected, and want to determine whether changes in these satiety hormones are linked to changes in body metabolism and composition. The team also plan to test a licensed medicine that may help improve the management of PWS and prevent the ensuing obesity with all its complications.

And there's another angle to this research. If long-term deficiency of PYY or PP can contribute to increased appetite or obesity, it might be possible to administer additional PYY or PP (either individually or in combination) to reduce appetite and control obesity in otherwise normal individuals.

Science As Art

"The most beautiful experience we can have is the mysterious - the fundamental emotion which stands at the cradle of true art and true science." Albert Einstein (Living Philosophies, 1931)

Art and Science converged at the Art Gallery of New South Wales on 12 February for an auction of artworks inspired by Garvan scientists. The auction revenue of over $50 000 will help support our research.

Every year at Garvan, researchers are encouraged to draw a different kind of inspiration from their work by creating an image, literally or loosely based on their work, to enter into the annual 'Science as Art' competition.

In 2005, the Garvan Research Foundation had the idea to take this competition to another level, and at the same time raise much-needed funds for research. Through Australian art curator Paul Sumner, various Sydney art luminaries were approached to judge the competition. Subsequently, the Sherman and Roslyn Oxley9 galleries were asked to identify five artists who would be interested in creating a science-inspired work that could be auctioned.

The chosen artists, Janet Laurence, Guan Wei, Lindy Lee, Julie Rrap and Robyn Backen were introduced to Garvan and randomly paired with one of the Garvan winners. They were given complete artistic license to produce their personal response to these sources of inspiration.

Over 250 people attended the auction, which was preceded by a panel discussion moderated by well-known arts reviewer, Andrea Stretton, and included arts journalist Peter Ross, Garvan's John Shine and Samantha Oakes, and artists Janet Lawrence and Julie Rrap. Panelists discussed the misty zone where science resembles art and intuition guides research.

Robyn Backen (R), pictured here with gallery owner Roslyn Oxley (L), investigated the way a brain slowly deteriorates with the onset of dementia. Her creation involved using a surgical scalpel to painstakingly remove surface sections of CDs, thus deleting the disc's memory

Young Garvan

Young Garvan's aim is to educate and inform the younger generation about the importance of medical research and to annually raise $55 000 to support a young scientist by awarding them the Young Garvan Postdoctoral Fellowship.

YG events include topical forums that have a discussion component.

The next forum, **Stem Cells: Unlocking Your Future** is on **Wednesday, April 18, 7pm,** with the pre-event reception beginning at 6.30pm.

To register, phone **(02) 9295 8110** or email **foundation@garvan.org.au**

"Young Garvan is a great cause and a great excuse to mingle! Its interesting and entertaining forums engage generation X on health issues that can affect us all and draw attention to the tireless work of the Garvan Institute. Their end of year parties are also a must in every social calendar!"

Kate Spencer of insurance and financial services company Promina Group Ltd.

breakthrough

Clinical research – help needed

From time to time, we need volunteers to take part in our clinical research studies. If you or someone you know is interested in helping in this way, please contact the following lead researchers on 9295 8100, or send an email.

Currently, we are in need of volunteers for the following projects:

- **How does Hepatitis C cause type 2 diabetes?**
  Healthy males between 25 and 55 years of age without hepatitis C
  Contact: Dr Kerry-Lee Milner, k.milner@garvan.org.au
- **Metabolism and risk of type 2 diabetes**
  Healthy males or females less than 60 years of age, who are willing to lose or gain weight
  Contact: Dr Leonie Heilbronn, l.heilbronn@garvan.org.au
- **Prader-Willi Syndrome study**
  Healthy volunteers between 18 and 45 years of age, who are overweight and between 140cm (4.5ft) and 160cm (5.2ft) in height
  Contact: Dr Alex Viardot, a.viardot@garvan.org.au

In memoriam Nov 06 - Mar 07

We gratefully acknowledge gifts received in memory of:

Annabel Catt
Mrs Karen Fitzgerald
Deborah George
Mrs Annunziata Inzitari
Elias Pertsinidis
John Arthur Thomas
John Samuel Thomson
Mrs Lorraine Rossely
Mrs Vesna Ryan
Tahmas Mardirossian
Patricia Moxham

Coming Up:

Our next seminar on Monday, April 30 (10am-12pm) is on Breast & Ovarian Cancer. Speakers include Garvan's Drs Catriona McNeil and Pip O'Brien, and Professor Neville Hacker from Sydney's Royal Hospital for Women

On Tuesday, July 17 (5pm-7pm) Dr Cecile King and Professor Fabienne Mackay will be two of the experts discussing the autoimmune diseases type 1 diabetes, lupus (SLE) and Sjogren's syndrome

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.

My Contact Details

Title _____ First name _____

Surname _____

Address _____

Suburb _____ State _____ Postcode_____

Daytime Phone _____

Email _____

Garvan Supporter Number (if known)_____

Please Send Me Further Information About:

☐ Giving to Garvan in my will (strictly confidential)
☐ Volunteering with Garvan
☐ Giving regularly to Garvan through my bank account

Please Change My Contact Details:

☐ I no longer wish to receive *breakthrough*
☐ I only wish to receive *breakthrough* by email
☐ I only wish to receive appeal mailings in May/June
☐ I do not wish to receive any appeal mailings

My Gift Details

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

☐ **$50** ☐ **$100** ☐ **$250** ☐ **$500** ☐ **$1000** ☐ **Gift of choice $** _____

☐ My **cheque/money order** made payable to **Garvan Research Foundation** is enclosed

OR Please deduct the above amount ☐ once ☐ monthly ☐ annually from my ☐ **Visa** ☐ **Mastercard** ☐ **Diners** ☐ **Amex**

Card Number |_|_|_|_| |_|_|_|_| |_|_|_|_| |_|_|_|_|

Expiry Date |_|_| |_|_|

2007BT01

Cardholder's Name _____

Signature _____

Please complete this coupon and mail it to:

Garvan Research Foundation,
Reply Paid 68593, Darlinghurst NSW 2010

Call: (02) 9295 8110 (9am to 5pm)

Fax: (02) 9295 8151
(you can use this coupon)

Online: www.garvan.org.au

GARVAN INSTITUTE