GARVAN NEWSLETTER AUGUST 2010 / ISSUE 14

breakthrough 10

Spend a day with our superstars of science and quiz some of the sharpest minds in medical research at **Garvan Open Day, 9am – 3pm on Sunday 24th October**. Open Day offers an opportunity to meet our scientists face to face and find out about their breakthrough research and what it means for your health. See the Open Day program of activities on page 7.

inside this issue

making news

Australia is making a substantial contribution to the International Cancer Genome Consortium, a global body cataloguing the genome of the 50 most common cancers, by tackling pancreatic cancer. Garvan is taking a leading role in the Australian project arm, through our expertise in **pancreatic cancer research**. Garvan's Prof Andrew Biankin is a co-leader of the project with Prof Sean Grimmond from the University of Queensland.

Healthy people with a genetic predisposition to **type 2 diabetes** gain more weight overeating over the short term than their non-genetically-prone counterparts. The Garvan study highlighted how a person's genes could make them more likely to become overweight and at a higher risk of related health problems including type 2 diabetes.

Garvan researchers showed that the reduced expression of the HIF-1 alpha gene in beta cells (the insulin-producing cells of the pancreas), with the resulting reduction of HIF-1 alpha protein, helps explain the impaired ability of the pancreas to produce insulin in people with **type 2 diabetes**. They also showed that a drug already used to treat rare inherited disorders increased levels of HIF-1 alpha protein and may restore insulin production.

Garvan researchers demonstrated for the first time the positive effect of **growth hormone** on athletic performance. Their study showed a .4 second improvement in a 10 second sprint, enough to turn a last-place Olympic athlete in a sprint event, running or swimming, into a Gold medal winner.

Prof Rob Sutherland, Director of Garvan's Cancer Research program, has been awarded an Officer of the Order of Australia (AO) for distinguished service to medicine as an international contributor to the research of cancer, the development of Australia's research capacity and through leadership roles in advisory bodies. Prof Sutherland has also been honoured with the Cancer Institute NSW Premier's Award for Outstanding Cancer Researcher.

opinion

New technologies are taking medical research further than we ever thought possible. The human genome project completed in 2003, which identified all the genes in human DNA, took 13 years and cost USD2.7 billion. Today, the same amount of data can be processed in a week at a fraction of the cost. These advances in technology are already revolutionising the way we approach cancer research.

A new global project involving leading cancer researchers from around the world known as the International Cancer Genome Consortium (ICGC) has set about cataloguing the genetic changes of the 50 most common cancers – 500 genomes from each cancer type (25,000 genomes) - and making their findings available on the internet.

Identifying whole cancer genome sequences will allow researchers to pinpoint the exact molecular aberrations of each tumour, and will therefore make it easier to target them with the most appropriate treatment. This approach to understanding the specific biology of a cancer in order to match it with the best drug is known as personalised medicine.

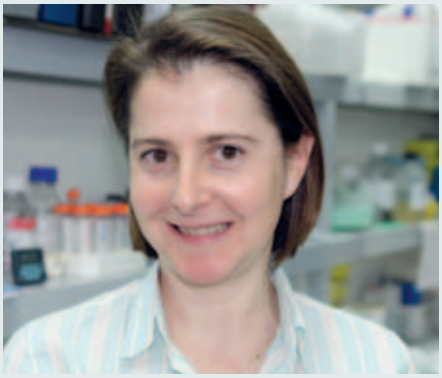
One of the first things made possible through the Consortium's work will be the ability to investigate the efficacy of treatments previously unexplored with certain cancers. For example, if an existing therapy targets molecular aberrations in one cancer but its effects have not been tested in other cancers, there is now a rapid way of identifying which of the unexplored cancers is a possible new target.

Garvan is playing a leading role in this project through our expertise in pancreatic cancer research (see cover page for details).

Exciting times ahead – watch this space.

Professor John Shine AO FAA
Executive Director

Researcher Profile:
Dr Dorit Samocha-Bonet



What is the current focus of your work?
We study the effect of the amino acid glutamine on blood sugar control in type 2 diabetes patients. Defective insulin secretion from the insulin producing cells in the pancreas is a key feature of type 2 diabetes. Hormones secreted from the gut in response to a meal trigger insulin secretion from the pancreas and contribute to a decrease in glucose rise in response to a meal. One such hormone is glucagon-like protein-1 (GLP-1) and we have found previously in healthy individuals and type 2 diabetes patients that when glutamine is taken with a meal, blood concentrations of GLP-1 and insulin are increased and glucose elevation after a meal is reduced. We are currently recruiting type 2 diabetes patients to study the effect of adding extra glutamine to a meal twice daily for 4 weeks.

We expect to establish that glutamine improves blood sugar control in type 2 diabetic patients. This may help increase the compliance to treatment and translate to a decrease in diabetes complications such as cardiovascular disease.

What are some of the recent findings from your work?
We have recently reported that healthy people with a family history of type 2 diabetes are more susceptible to the adverse effects of overeating over the short term than their non-genetically prone counterparts. In response to 28 days of overeating, the people with a family history of diabetes gained on average over a kilogram more than the rest (3.4 kg as opposed to 2.2 kg).

We also found that the moderate weight gain resulted in an increase in insulin resistance without induction of inflammation in abdominal fat. This is an important finding as it reveals that in humans, insulin resistance induced by short term overeating and moderate weight gain is not triggered by inflammation in abdominal fat.

What is the biggest challenge in your area of research?
One of the biggest challenges is recruiting volunteers to our studies. We recruit people via advertisements and we mainly need type 2 diabetes patients, their healthy siblings/offspring as well as healthy people without a family history of diabetes. The people I meet through recruitment to our studies have a common denominator of devotion and care to others. Some of them are relatives of type 2 diabetes patients and are familiar with the disease and its outcomes. Their motivation stems both from the state-of-the-art tests we perform to evaluate their health status and their desire to contribute to disease research.

What do you enjoy doing away from the lab?
I enjoy spending time with my kids and husband and catching up on their school and social activities. We enjoy going to the cinema on a cold weekend. I also love to explore Australia's landscape, preferably driving. Our last road trip, from Perth to Adelaide through the Nullarbor Plain and the Great Australian Bight, was a bonding adventure and the views were simply breathtaking. I also enjoy reading books.

Cancer Centre Breaking New Ground

L to R - Richard Harpham, Chairman of the Trustees of Mary Aikenhead Ministries, Sr Annette Cunliffe; Paul Robertson, Chairman of St Vincent's Hospital; Minister Jodi McKay; Jill Kinghorn; His Eminence Cardinal Pell; Minister Tony Kelly and Bill Ferris, Garvan Chairman

They say rain is a sign of good luck. If true, The Kinghorn Cancer Centre has truly been blessed, and not only by His Eminence Cardinal Pell. The ground breaking and blessing ceremony on 26th May, officiated by the Cardinal, was a very wet affair. However, despite the mud underfoot, the event was well attended and marked with the 'turning of the sod' by members of the official party including Jill Kinghorn together with Minister for Planning, Tony Kelly and Minister for Science and Medical Research, Jodi McKay.

An engraved memorial shovel was presented to both Mrs Kinghorn and Sister Annette Cunliffe, representing the Trustees of St Vincent's, to mark our gratitude for their respective gifts of $25 million and the land for the cancer centre site.

A *loving* celebration

John and Bloom de Largie Dálton on their wedding day

There are many decisions to be made when planning a wedding; and Garvan is extremely grateful that, for their special day, John and Bloom de Largie Dálton decided to request their guests make a donation to our cancer research in lieu of gifts.

Bloom, recently diagnosed with cancer, wanted to celebrate her marriage to John by contributing to medical research. John, sharing her sentiments, immediately thought of the Garvan. "The Garvan was the first name to spring into my mind; I had heard so much about their work. We both felt this was the right thing to do, especially since we have everything we need," said John.

"We were very impressed when we received the personalised *In Celebration* envelopes to send to our guests; and we found the process very easy with the help of Mona Saade in the Garvan Research Foundation. Our guests were also impressed and enjoyed giving to such a worthwhile cause. Bloom and I were very pleased to see how much was contributed," he added.

Thanks to the generosity of John, Bloom and their guests, Garvan received over $3,400 towards cancer research.

If you are celebrating a special event why not ask your guests to make a donation to Garvan in lieu of a gift? Garvan can provide personalised envelopes which guests can complete before, during or after the event and mail to us. We will then send your guest a receipt and let you know the total raised on your behalf. You can also download an *In Celebration* form from our website or guests can make a donation online at www.giving.garvan.org.au.

For more information contact Mona Saade at Garvan Research Foundation on 1300 73 66 77.

feature story: Fighting Obesity

Australia is one of the most overweight developed nations, with the latest statistics showing 62 per cent of Australian adults are now overweight or obese, as well as one in four children.

And unfortunately these statistics show no sign of abating, giving rise to claims that obesity is the major health crisis of our times. The impact of obesity on our health is substantial: high rates of type 2 diabetes (almost 300 Australians develop type 2 diabetes every day), heart disease, fatty liver disease, inflammation and some cancers.

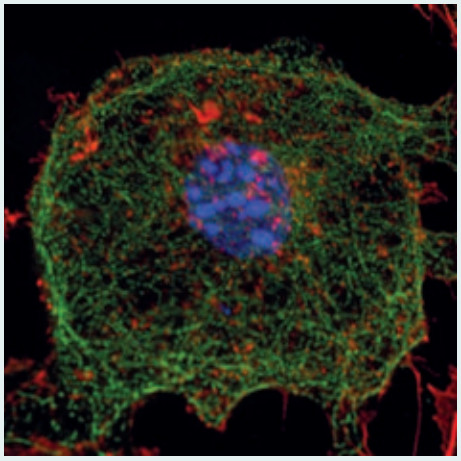
So what is driving this rapid change in obesity rates? Over the last 50-60 years our modern Western society has engineered most physical activity out of our lives; contributing to a sedentary lifestyle where most things can be achieved at the push of a button. In addition, there has been a marked increase in the calorie density of many foods, and at the same time these foods are more accessible and cheaper than ever before. These two recent environmental changes, specific to the Western world - decreased physical activity and increased calorie intake - have ensured that people with the intrinsic ability to put on weight over time can do so far more easily than their predecessors.

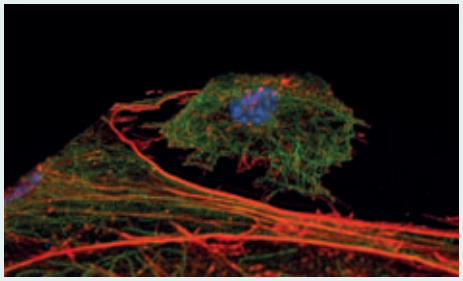
But this is not the whole story. Genetic influences on our appetite and weight are profound and contribute to our susceptibility to be overweight or obese. The work of Garvan's 2009 International Fellow Professor Stephen O'Rahilly from Cambridge University has shown that gene mutations in appetite regulatory pathways will promote over consumption of food. While these mutations account for a small percentage of all obesity cases, these findings highlight how the genetic regulation of food intake impacts on obesity. It is most likely that the common varieties of obesity are not due to mutations, but to genes that have assisted in our survival through wars and famines over the course of human history. During these times, people with the ability to source food, conserve energy and with stronger drives to eat no matter how little food was available, were more likely to survive. This means in populations where there have been multiple cycles of famine, people are more genetically prone to obesity if they acquire a sedentary Western lifestyle.

Over the last two decades Garvan researchers have contributed substantially in the area of genetics and obesity. Using precise measures of fatness, with measures of abdominal (or visceral fat), our researchers have shown that 50-60 per cent of difference in fatness between one person and the next is due to genetic factors. Our research is well aligned with the compelling evidence for the influence of genes on body weight from earlier international twin studies.

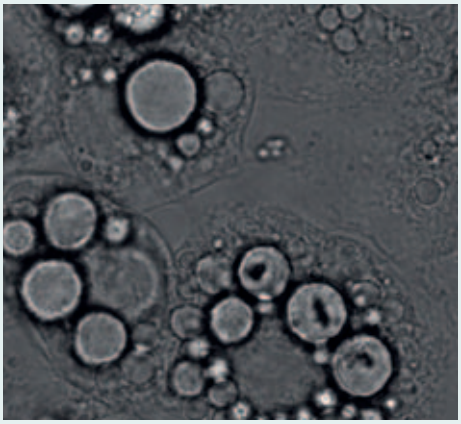
Other studies have shown that twins raised apart are more likely to resemble each other in body weight than their adoptive family. Another intriguing twin study showed the amount of weight gained was almost the same in adult twin pairs who had been overfed. However, the amount of weight gained was very different between different twin pairs, highlighting that the unique genetics of each twin pair greatly influenced how much weight could be gained in the same overfeeding conditions.

It is clear from these studies that our genetic make up will influence exactly how much weight we gain or lose when we are exposed to the same set of circumstances. Some people will gain a lot more weight in our current environment than others. This is likely to be the effect of multiple genes influencing different aspects of appetite regulation and how efficiently we store and metabolise fat. The genes responsible for this may have once saved our lives, but in modern Western society they can now promote weight gain and make it harder for us to burn off the extra calories. There is also strong evidence suggesting that each individual has a predetermined trajectory when it comes to body weight. We are inclined to defend a particular 'threshold' of body weight - if we fall below this set point the brain receives messages that we are hungry in order to restore equilibrium.





Fat cells imaged under a microscope



Fat cells imaged under a microscope showing the fat droplets inside the cell

This is evidence of the strong biological regulatory systems operating to maintain our body fat stores. This is why it is so difficult for many people, with the genes to carry more weight, to successfully achieve long term weight loss.

Even modest weight loss reverses many of the damaging changes seen in the immune cells of obese people, particularly those with type 2 diabetes

Obesity and disease

So how does obesity make us sick? Obesity produces a number of metabolic disturbances that lead to type 2 diabetes, heart disease and some cancers particularly breast, prostate and oesophagus. In the case of people with type 2 diabetes a large proportion will also be overweight or obese. However, not all people who are obese will develop the disease. For people genetically predisposed to diabetes, being overweight or obese is the strongest accelerant towards disease onset. In some cases a modest amount of weight gain can be enough to induce diabetes. This is because obesity worsens insulin resistance and inflammation, and both of these promote eventual exhaustion of the insulin-producing beta cells in the pancreas, which is the stage at which diabetes develops. Research at the Garvan has also shown that abdominal obesity - weight carried around the waist or being apple-shaped - particularly promotes type 2 diabetes.

How is Garvan tackling the problem of obesity?

Garvan researchers were the first to show that higher levels of physical activity protect people who carry genes for obesity from being overweight. Work by Associate Professor Katherine Samaras in Garvan's Diabetes and Obesity program has also shown for the first time that even modest weight loss reverses many of the damaging changes seen in the immune cells of obese people, particularly those with type 2 diabetes.

Excess body fat, in particular abdominal fat, promotes immune cells to become activated and 'pro-inflammatory'. These immune cells circulate in the blood and can promote coronary heart disease and other obesity-related illnesses. With a modest weight loss of about 6kgs in morbidly obese people following a calorie restricted diet, Associate Professor Samaras found that the pro-inflammatory nature of circulating immune cells was reduced back to that found in lean people. This important finding indicates that substantial health improvements can be achieved even if there is modest weight reduction. The study also showed that the activation status of immune cells found in fat tissue predicted how much weight people would lose following a calorie restricted diet and gastric banding surgery. Those with more activated immune cells lost less weight. This may help us better understand why some people lose weight more easily than others. Associate Professor Samaras has also shown that following gastric banding, type 2 diabetes can resolve very quickly in obese patients, even if their obese condition remains.

Garvan researchers in the Neuroscience program are tackling obesity from another perspective – that of brain chemistry. Professor Herbert Herzog and Dr Amanda Sainsbury-Salis have shown that the hormone peptide YY (PYY), released naturally from the gut, could be used to treat obesity and type 2 diabetes. After a meal, PYY is released into the blood from the gastrointestinal tract. PYY then acts on the brain, contributing to a feeling of satiety and inhibiting the desire to continue eating. The researchers were able to show that long-term increases in PYY can induce and maintain lower body fat levels in mice - a critical effect required for weight loss medications.

In another study, Garvan researchers decided to take a radically new direction in weight loss research. Aware of the ineffectiveness of current weight loss drug therapies that try to stop the brain from sending hunger signals to the body, they decided to take the brain out of the equation. The brain acts as the master controller of appetite and energy expenditure - telling us when we are hungry, when we have had enough to eat, instructing one group of cells to burn fat, another to conserve it. This regulation occurs through the neuropeptide Y (NPY) system, when neurotransmitters in the brain send signals to receptors throughout the body. However, if we block the hunger signals to the brain, we are so hard-wired to eat that the brain finds alternate pathways for the signal. Therefore, Garvan researchers decided to bypass the brain and instead prevent peripheral tissues from receiving the hunger signals. They found if they blocked NPY receptors (Y1) in the peripheral tissues of mice fed with high calorie diets, those mice were resistant to gaining weight and fat. These findings show the potential for the development of drugs or antibodies to block Y1 receptors in humans.

While the obesity statistics look grim, the encouraging message is that a modest amount of weight loss can have significant beneficial effects on health, and that this can be achieved through diet and increases in physical activity.

Garvan's next FREE public seminar will focus on type 2 diabetes and obesity and will feature a presentation by Associate Professor Katherine Samaras. See back page for full details and how to register.

Researcher Profile: Dr Adam Cole

What is the current focus of your work?
Protein phosphorylation is a communication system utilized by *every* cell in the body to coordinate every cellular function. It is mediated by enzymes called kinases, which modify their target proteins by putting a phosphate molecule onto them. This changes the protein's activity, causing changes to the cell's behaviour (e.g. shape, strength, movement, survival). Defects in these pathways can lead to cancer and mental disorders. The Neurosignalling Group focuses on three important brain kinases called Cdk5, GSK3 and PCTK2 that are important regulators of neurotransmission (communication between neurons).

Efficient neurotransmission is essential for healthy brain function, including thinking, learning, moving, emotions and memory. Cdk5 and GSK3 are associated with the development of Alzheimer's disease, while virtually nothing is known about the third kinase (PCTK2), providing great opportunity for new discoveries. We hope to better understand how these proteins regulate neurotransmission in healthy brains, but also why changes to their activity contribute to brain dysfunction during ageing and in dementias such as Alzheimer's disease.

What are some of the recent findings from your work?
We previously discovered a brain protein called CRMP2 that is excessively modified in the brains of Alzheimer's disease patients. This occurs early in the disease process and might also be specific for Alzheimer's disease, since it was not detected in other forms of dementia. Therefore, CRMP2 shows great promise as a diagnostic biomarker for early and specific detection of Alzheimer's disease. However, CRMP2 is not easily detected outside the brain, limiting its use for screening/diagnostic purposes. More recently, we discovered a similar brain protein called β-adducin that is also found in red blood cells. Since blood is more accessible for diagnostic purposes, this poses the exciting possibility that β-adducin might serve as an early stage, blood-based biomarker for Alzheimer's disease. If so, this would greatly assist clinicians to more accurately diagnose patients with Alzheimer's disease at an *earlier stage*, when patients are more receptive to drug therapy.

What is the biggest challenge in your area of research?
Studying the complexities of the brain is enormously challenging. I was trained as a biochemist, so we focus our research at the biochemical or molecular level. This type of research can lead to important initial discoveries, but it is important to extend these studies beyond the test tube and to investigate their effects on brain *function*. Obtaining funding for our work is also always a challenge.

What do you enjoy doing away from the lab?
I enjoy weekends with my wife and three young children, usually pushing them on a swing in the park. We are new to Sydney, so we are still exploring this spectacular city and very much looking forward to experiencing the beaches in summer. I am less enthusiastic about the upcoming City 2 Surf, which I have entered for the first time, but am looking forward to treating myself to fish and chips after the race.

Knights Supporting Diabetes

L to R Chev Stephen Vassallo, Garvan's Dr Katherine Tonks, Chev Joseph Borg, Chev Sydney JP Borg and Dr Jerry Greenfield

When the Australasian Priory for the Sovereign Order of St John of Jerusalem Knights of Malta donated to type 2 diabetes research at the Garvan, some of the Knights didn't stop at financial assistance in their support of the cause. To assist a clinical study by Dr Jerry Greenfield, the Knights gave a generous $2,000 donation; and some even volunteered to participate in the study.

The research by Dr Greenfield, in collaboration with Prof David James' research group, is investigating what goes wrong in human muscle in the early stages of type 2 diabetes, leading to limited glucose uptake. The Knights, who are an Order committed to charitable works in aid of the sick, poor and disadvantaged, were particularly drawn to Garvan's goal to better understand disease and develop cures. "We believe that the Garvan is a unique, amazing and wonderful institution, which helps future generations live a healthier life," says Chevalier Sydney Borg.

Open Day Is Back

GARVAN OPEN DAY www.giving.garvan.org.au/openday

Back by popular demand, we are once again opening our doors for **Garvan Open Day on Sunday 24th October**; and this time it will be bigger than ever. So big in fact, we are attempting to enter the Guinness Book of World Records by building the world's longest DNA model, and we will have the model on display for all visitors to the Garvan on Open Day.

There will be more tours, more seminars and we are open for longer – from 9am – 3pm. If you can't make it along, we have also catered for you. You can watch the Breakthrough Talks and panel discussion on ***What Will it Take to Cure Cancer?*** through a live webcast on the Garvan website at **www.garvan.giving.org.au/openday**

Open Day is a unique opportunity to meet leading experts in the fields of cancer, diabetes, osteoporosis, immune and brain disorders research, and hear about the latest breakthroughs in these areas.

Open Day activities are:

Panel discussion: What Will it Take to Cure Cancer?: facilitated by Channel Nine's Peter Overton 10am – 11am.

Breakthrough Talks:

- Type 2 diabetes 11:30am
- Immune function 12:30pm
- Osteoporosis 1:30pm
- Neurodegenerative disorders 2:30pm

Tours: Throughout the day.

Interactive Disease Mini-Expo: Throughout the day.

Refreshments (including great coffee from Vittoria) will be available for purchase from our rooftop café.

We look forward to welcoming you, your friends and family to the Garvan – we are located at 384 Victoria Street Darlinghurst (easily accessible by car, bus and train). Open Day is FREE, registration is not required. For more information call **(02) 9295 8110** or visit **www.giving.garvan.org.au/openday**

Experience Garvan through our new website

We have made some great changes to the supporter sections of our website. So now it's even easier to stay connected with all the latest news and breakthroughs at the Garvan, made possible by your valued support.

When you visit **www.giving.garvan.org.au** you can:

- Watch videos of our scientists, staff and volunteers
- Visit our 'this week in the lab' scientist's blog
- Read donor case studies
- Sign up to become a member of our online community and
  - o receive regular e-newsletters
  - o view your donations online
  - o update your details and research interests
- Register for Garvan events
- Create your own personal fundraising pages
- Listen to podcasts of our seminars

We are always aiming to improve how we communicate with you so please let us know what you think! Call **1300 73 66 77** (9am to 5pm) or email **foundation@garvan.org.au**

Host a Garvan High Tea

A New Way to Help Raise Funds For Garvan

Treat your friends, family or colleagues to an enticing high tea any time in September and at the same time raise vital funds for Garvan's work.

Hosting a Garvan High Tea is easy. Simply:

1. Register to host a high tea at **www.giving.garvan.org.au/hightea** or call **1300 73 66 77**
2. Create your own personal high tea fundraising page when you register online
3. Invite your friends and ask them to support your high tea with a donation to Garvan
4. Have fun!

You will find everything you need to get started and host your own fabulous high tea on our website, from recipes by well-known Sydney chefs to high tea tips.

breakthrough 10

Diabetes Study

Are you interested in improving the control of your diabetes? We study the effect of the amino acid glutamine on glucose control in type 2 diabetes.

We are looking for people with type 2 diabetes for less than 5 years, males and females aged 40-75 years, only on Metformin (ie not taking insulin or other diabetes medications). For more information contact Jen or Ashley on (02) 9295 8215 or (02) 9295 8233, email j.evans@garvan.org.au or a.douglas@garvan.org.au.

For more details go to www.garvan.org.au, click on Research>Clinical Studies>Diabetes. (St Vincent's Human Research Ethics Ref H07/059 version 1)

Coming up

Diabetes Public Seminar
10am – 12pm Thursday 19th August

Our next event will focus on **type 2 diabetes** risk factors, latest research and treatments. **Seats are limited** and registration is essential. Call **(02) 9295 8110** or visit **www.giving.garvan.org.au**

All seminars are available to listen or download on the Garvan website – visit www.garvan.org.au/news-events/podcasts.

Open Day Sunday 24th October

We look forward to welcoming you and your friends and family to our FREE Open Day, from 9am – 3pm Sunday 24th October. Full details are on page 7 or visit www.giving.garvan.org.au/openday.

Both events will be held at the Garvan Institute, 384 Victoria Street Darlinghurst.

In memoriam: March – June 2010

We gratefully acknowledge gifts received in memory of:

Gordon Adamson
Efstathios Amanatidis
Don Baird
Bob Baiza
Diana Bowman
Ralph Burley
Sydney Carleton
David Carter
Denise Cobcroft
Daphne Hilda Commerford
Florence Elizabeth Davies
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Rhoderick Donald Walker
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John F Williamson

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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- ☐ 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

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

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Donations of $2 and above are tax deductible.

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