

Celebrating 50 years of the Garvan's life-saving medical research, Her Excellency Professor Marie Bashir AC CVO, the Governor of New South Wales, and Professor John Mattick cut the 50th birthday cake at a February event held for long-serving Garvan staff. ▶

Making *NEWS*

How the immune system positions its gate keepers

Garvan immunologists, Dr Dominique Gatto and Associate Professor Robert Brink, published work in the March edition of the prestigious Nature Immunology journal outlining the gate-keeper role of dendritic cells. Dendritic cells express the cell surface receptor EB12, without which the gate-keepers fail to marshal information about invading microbes to other immune cells. In the absence of EB12, dendritic cells do not develop and the adaptive immune response is disabled.

Forget about plaque when diagnosing Alzheimer's disease

Plaques are not an early hallmark for Alzheimer's disease say a team of Garvan neuroscientists led by Dr Bryce Vissel. In mice with Alzheimer's disease, subtle memory problems appear around the same time as significant nerve cell loss and inflammation. In contrast, the plaques form long after memory loss becomes significant. This finding will impact the current debate about how best to diagnose and treat Alzheimer's disease.

Brains rewire themselves after injury

The brain is able to form complex new circuits after damage, often far from the damaged site, to compensate for lost function. In collaboration with US scientists, Dr Bryce Vissel reported this startling demonstration of brain plasticity in the journal PNAS in May. The brain re-wiring was observed in the frontal cortex, a site distant from the damaged hippocampus - the brain's learning and memory centre.

A step towards better understanding of pancreatic cancer

The protein Sirtuin-1, known for helping cells live longer, also has a role in pancreatic cancer. Garvan researcher, Dr Ilse Rooman has studied Sirtuin-1 in mice and in cell cultures from human tumours. She found that blocking this key protein may help prevent pancreatic cancer, as well as prevent the further growth of established tumours.

Cellular garbage and insulin resistance

The first step on the road to diabetes is the development of insulin resistance. Diabetes and Obesity researchers at Garvan, led by Professor David James, have shown how the insulin-triggered protein FOXO regulates the cleaning up of cellular junk. In the pre-diabetic state, the junk disposal unit may be blocked. Keeping FOXO switched on in the appropriate organs may prevent diabetes and other diseases associated with obesity and insulin-resistance from developing.



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From the CEO

It has been a wonderful experience for me to meet so many of our generous supporters and friends at one of the many 50th Anniversary celebrations we have hosted so far this year.

At our major seminars, smaller supporter engagement events, monthly public tours and research updates, I have been delighted to speak with so many donors and learn more about why you have chosen to support our work. Many people have spoken about a personal connection to a particular research project, and just as many of a general belief in the overall value of medical research.

Certainly the output from our researchers here at Garvan is continuing at a great pace. In her speech at our recent AGM, The Hon Jillian Skinner MP, NSW Minister for Health and NSW Minister for Medical Research, made reference to that old adage, "publish or perish." She highlighted that she was, "proud to see that, in 2012, Garvan published more than 224 peer reviewed research papers, the top 80% in major journals. This remains above internationally accepted benchmarks and is testament to the excellence and commitment of Garvan researchers."

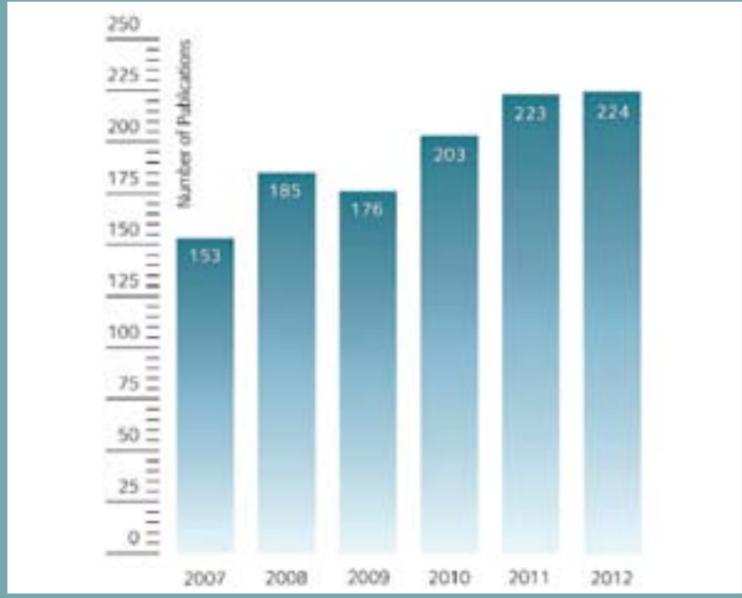
A graphical analysis of our publication record is reproduced from our Annual Report on this page, highlighting Garvan's ongoing success in this area. This record of achievement and breakthrough is only possible thanks to your ongoing support of our novel projects, equipment and staffing needs.

In this, our 50th Anniversary year, a very warm thank you for your ongoing support of Garvan's work and mission.



Yours sincerely,
Andrew Giles
Garvan Research Foundation

Scientific Publications



Dr John Schubert, AO

Garvan bids fond farewell to Chairman Bill Ferris and extends a warm welcome to Dr John Schubert

In April, the Garvan Institute of Medical Research farewelled Mr William D. Ferris, AC, Chairman of the Board since 2001. In his 12 years of service, Bill made an outstanding contribution and the Institute achieved many significant breakthroughs under his guidance. Bill was instrumental in overseeing The Kinghorn Cancer Centre from conception to completion. He also served on the panel of the McKeon Strategic Review of Health and Medical Research in Australia.

Garvan extends a warm welcome to Dr John Schubert, AO, following his election to the position of Chairman of the Board.

"I am very pleased indeed to welcome and congratulate John Schubert as the new Chairman of the Garvan Institute," said outgoing Chairman, Bill Ferris.

"From his successful time as chief executive of the Pioneer group to his public company directorships and leadership of the Great Barrier Reef Foundation, John brings a wealth of experience and wisdom to the Garvan boardroom," he said.

On taking up his position as Chairman, John commended Bill Ferris on his outstanding achievements.

"Bill has done a wonderful job as Chairman over the last 12 years, not only for Garvan but for medical research in Australia. The achievements Garvan made while Bill was Chairman of the board were huge," said Dr Schubert.

"Garvan is exceptionally well placed to take advantage of this period of time given the diseases it concentrates on and its expertise in genomics," he said, "I was delighted to be able to take up the position."

Garvan's Longest Serving Scientists

Research institutes are places of discovery where great minds gather and wrestle with the unknown - the mysteries of the processes underpinning human biology, thought and disease.

Garvan has been home to many inspiring scientists and clinicians, who have made enormous contributions to the knowledge of human biology and disease, and the effectiveness of medical treatment. As part of our 50th birthday celebrations, in this issue of *breakthrough* we profile some of Garvan's most distinguished and long-serving scientists from the Diabetes and Obesity team - Garvan's longest running research program.



(46 yrs) Professor Ted Kraegen joined Garvan as a PhD student in 1967, and has played a central role in the development of both the Institute and its world class Diabetes and Obesity Program. Professor Kraegen's early work involved creating an artificial pancreas (which initially took up half a room). Nowadays, as head of the Diabetes and Metabolism Group he and his team are currently trying to understand the enzyme that controls whether fat is used or stored once it enters the muscle cell.

The author of over 170 academic papers, Professor Kraegen cites his proudest achievement as his part in discovering that abnormal fat metabolism was the major cause of defective insulin action in diabetes and obesity. This finding was based on numerous highly cited publications produced over the period 1985-1991. Professor Kraegen has partnerships with a number of pharmaceutical companies to examine drugs that activate this enzyme and which could reduce fat accumulation. And his group is also delving into traditional Chinese medicines with collaborators in Shanghai to identify new insulin-sensitising agents that could be more useful than current therapies.



(38 yrs) Professor Lesley Campbell AM a third generation female doctor with an early interest in endocrinology, began working at St Vincent's Hospital in 1974 as a Senior Medical Registrar. She joined Garvan to work as a clinical researcher in the artificial pancreas team led by Professor Kraegen. Professor Campbell now heads the Appetite and Adiposity in Type 2 diabetes and Prader Willi Syndrome Group in the Metabolic Diseases Program, and her work in diabetes and obesity has resulted in the publication of nearly 150 papers. Professor Campbell nominates her current work as her proudest achievement. This research involves defining subtle abnormalities in people (while they are still healthy) who will later get Type 2 diabetes. This could eventually be used for diagnosis, prevention and early treatment. Professor Campbell was awarded a Member of the Order of Australia in 2008 for her service to medicine as a clinician, academic and researcher in the field of endocrinology, to the development of the Diabetes Centre at St Vincent's Hospital, Sydney, and through professional organisations.



(37 yrs) Professor Don Chisholm AO Senior Principal Research Fellow, returned to Garvan in 1978 after an earlier initiation to research at the Institute from 1968 - 1969; on return he advanced Professor Kraegen's insulin delivery device for hospital use. Professor Chisholm was head of the Diabetes Research Program from 1978 to 2003 and was foundation director of the Diabetes Centre at St Vincent's Hospital from 1980 to 1991.

Professor Chisholm has authored over 250 papers and notes that one of his most satisfying career achievements was his involvement in the growth and development of the Diabetes Research Program. In 1999, he was awarded an Officer of the Order of Australia for service to medicine and medical research as a leader in the fields of diabetes research, patient care, medical education and the organisation of medical services. The key research goal of Professor Chisholm's team is to identify the molecular mechanisms by which visceral fat (fat tissue near the abdominal organs) generates insulin resistance.

Erratum: In the last edition of *breakthrough* it was incorrectly implied that Prof Don Chisholm [with Prof Ted Kraegen] was involved in the 1970s in work on the low dose insulin infusion treatment of diabetic ketoacidosis and "Artificial Pancreas". This work was principally driven by Prof Kraegen under the supervision of Prof Les Lazarus and with the clinical involvement of Drs Warren Kidson, John Casey and [later] Prof Lesley Campbell.

Feature story: “Junk” DNA and the human genome

Did you know that if the DNA of one cell were stretched end to end it would reach nearly two metres in length? Every one of us has a unique, slightly different sequence of 3 billion DNA units (or letters) in long double helix strands. These strands of DNA are tightly coiled into the nucleus of the cell in structures called chromosomes. The genome is our complete set of DNA. A gene is a section of DNA that encodes the instructions for the cell to make proteins. When a gene is activated it is copied to make a different but related molecule called RNA, which transports the instructions to be translated into the amino acids that build proteins. This was the understanding for most of the 20th century.

The massive Human Genome Project (1990 – 2003) not only found that we had approximately the same number of conventional genes as the humble *C. elegans* nematode worm — the first multicellular organism to have its genome completely sequenced — but that most of the human genome (about 98%-99%) appeared to code for nothing much at all.

“Because only a tiny fraction — around 1.5% — of the human genome encodes proteins, the rest of it was assumed to be junk,” explains Professor John Mattick, Garvan’s Executive Director. Professor Mattick was a postdoctoral researcher in the late 1970s when he started mulling over the mystery of why complex organisms had so much non-coding DNA.

“I realised that not only did these non-protein-coding sections produce RNA, but if those RNAs were functional, it would mean that there was another type of information being expressed from our genome, and that the genetic system in humans was much more sophisticated than we expected,” explains Professor Mattick.

“We now realise that the genome is extraordinarily complex, and the deeper we drill down, the more surprises we find. Indeed, what was dismissed as junk because it was not understood almost certainly holds the secret to understanding human development and human cognition. It is also likely to hold the secret to understanding many complex diseases.”

It seems that Professor Mattick was right, and the long tracts of our genome lying within and between the genes are important after all.

For example, short segments of non-coding DNA are used to produce RNA known as microRNAs which rather than creating proteins, target and break down other RNA molecules. And long segments of non-coding RNAs (long non-coding RNAs, or lncRNAs) play roles in regulating how genes are switched on and off. Interestingly, vast non-coding tracts of DNA are made up of viruses that once randomly inserted themselves in our genome, often many hundreds of generations ago.

Long non-coding RNA and schizophrenia

Researchers at Garvan are now turning their attention to the specific roles that non-coding RNA plays in health and disease. Earlier this year, the Mattick lab, in collaboration with groups from Queensland, Japan and the US, found that non-coding RNAs may play a role in schizophrenia.

The particular lncRNA involved in schizophrenia is called ‘Gomafu’, and it is regulated by the changing patterns of neuronal electrical activity. Gomafu’s job is to alter the expression of proteins in neurons. When neurons in the brain are activated, Gomafu levels drop dramatically. Professor Mattick’s team found that levels of Gomafu were abnormally low in the post-mortem brains of people with schizophrenia.

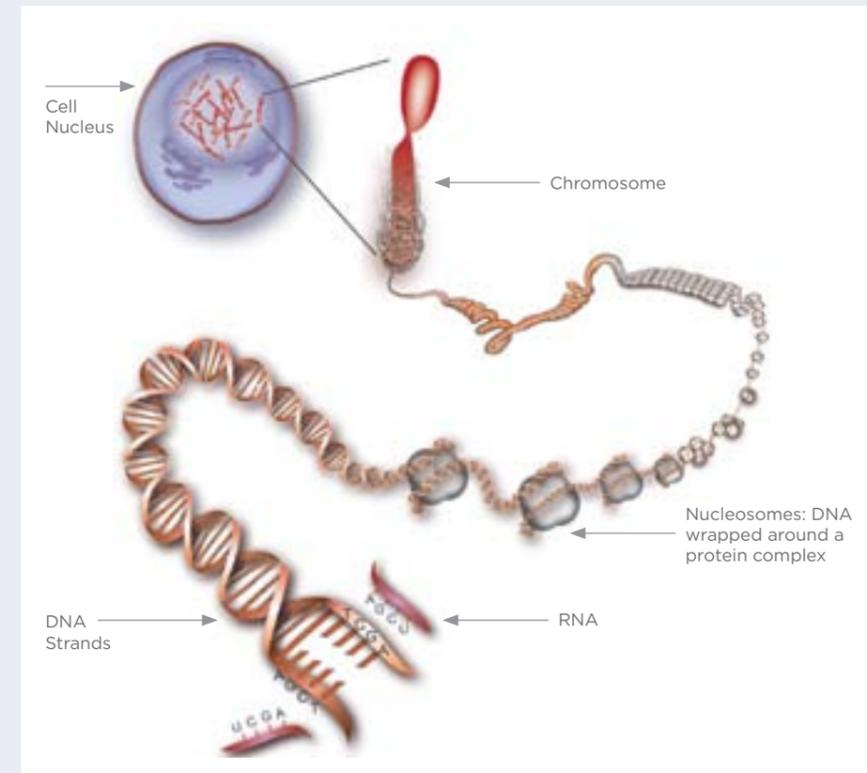
“You can imagine that if the schizophrenic brain is firing differently – and Gomafu levels are consistently lower – it would cause havoc within the cell, with all sorts of genes and proteins free floating and available to act, whereas in a normal brain they would be tethered to Gomafu,” says Dr Barry, one of the collaborators.

Professor Mattick adds, “Knowing now that long non-coding RNAs are regulated by neuronal activity and associated with schizophrenia gives us insight into the cause of the disease and new pathways to treatment in the future.”

MicroRNA and cancer therapy

Non-coding RNAs also play a role in the development of cancer, says Dr Alex Swarbrick who heads the Garvan Cancer Program’s Tumour Progression Group. Dr Swarbrick and his team found one particular non-coding RNA known as microRNA 380 to be produced at high levels in the aggressive childhood cancer neuroblastoma, in a proportion of adult brain cancers and in melanoma. In many cancer types, a critical tumour suppressor known as P53 is disabled by genetic mutation. However, Dr Swarbrick’s team found that in neuroblastoma, P53 is instead disabled by the action of microRNA 380. When they blocked microRNA 380 in the laboratory, P53 was reactivated, cancer cells died and experimental tumours became much smaller. “We’ve shown if we can block the microRNA we also greatly inhibit the ability of those tumours to grow and multiply,” explains Dr Swarbrick.

Earlier this year, Dr Swarbrick, Professor Mattick and a large team of international researchers found that microRNAs are key regulators of tumour angiogenesis — a process by which new blood vessels are recruited to feed the growing tumour. The team was able to show that targeting specific microRNAs prevented new blood vessel formation and slowed tumour growth, a finding that may eventually be translated to the clinic.



Whole genome sequencing

The advent of whole genome sequencing heralds the next chapter in the story of our understanding of human genetics and its role in health and disease, or ‘genomic medicine’. Whole genome sequencing is a laboratory technique that reads the complete DNA sequence of an individual’s genome — it includes both the coding (known genes) and non-coding sequences.

Knowing the complete DNA sequence of an individual’s genome does not, on its own, provide useful clinical information, but this may change over time, explains Dr Marcel Dinger, head of the new Centre for Clinical Genomics, who has also identified important lncRNAs in melanoma and breast cancer. “With genome sequencing you capture a lot of information for free. The information you return to the patient is what is clinically interpretable at that time, for example, mutations in genes involved in disease or genes that interact with particular drugs. The remainder of the sequences from the non-coding parts of the genome, which we don’t yet understand, we then return to the researchers. This information is of huge value to research.”

Whole genome sequencing and osteoporosis

Whole genome sequencing techniques and bioinformatics (the analysis of the extremely complicated biological data generated by the sequencing) will be used in a study by Professor John Eisman and his team in Garvan’s Bone Research Program. The team run the Dubbo Osteoporosis Epidemiology Study (DOES), which began in the late 1980s, and is the longest running, large-scale epidemiological study of osteoporosis in men and women in the world. It focuses on identifying risk factors for fractures in both men and women as well as identifying new genes that are important to bone health.

This particular study aims to look at genetic data from people enrolled in the DOES who have a high bone density. Using the very latest in technology, the team will perform whole genome sequencing with the objective of identifying the genes that are implicated in high bone mass. Identifying the genes involved in high bone mass may point towards what is going wrong in individuals with osteoporosis (i.e. low bone mass). Once this is complete, analysis of the information will commence, and Garvan researchers will add another new chapter to the ever evolving human genome story.

Ask Garvan

What is the Centre for Clinical Genomics?

Led by Dr Marcel Dinger, Head of Genome Informatics, the Centre for Clinical Genomics (CCG) will be Australia’s first accredited facility providing both research and clinical services for cancer and other complex diseases. Using a whole genome approach, clinicians and researchers will be able to look at various aspects of disease: diagnosis, susceptibility, predictive signs and how individuals may react to specific drug treatments. Already operating on a research basis, and housed at The Kinghorn Cancer Centre (TKCC), the centre will shortly receive clinical accreditation and begin testing patient samples.

What type of equipment is used at the Centre for Clinical Genomics?

Scientists at the CCG will use multi-million dollar next-generation sequencing equipment. The equipment allows the whole genome to be sequenced in one day using DNA extracted from a patient’s blood or tissue sample. Complex data analysis is then carried out on the genome sequence.

What are the plans for the Centre in the future?

The establishment of the CCG is an exciting development for Garvan and TKCC and will form a platform for the rapid development of genomic medicine, placing Garvan and TKCC at the frontier of personalised, integrative medicine.



Preparing fragmented DNA using magnetic beads for next generation sequencing at the Centre for Clinical Genomics.

Garvan Celebrates 50 Years

Garvan in the Community



Long serving Garvan staff at the Government House celebration



(L to R): Mr Charles Curran AC (Chair 1988-1993), Professor John Shine AO FAA (Executive Director 1990-2011), Mr Peter Wills AC (Chair 1993-2001), Professor Leslie Lazarus AO (Director 1968-1989), Mr Bill Ferris AC (Chair 2001-2013), Professor John Mattick AO FAA (Executive Director 2012 -). Taken at NSW Government House on 17th February 2013 at the celebration of Garvan's 50th Anniversary.



(L to R): Prof John Mattick, Executive Director, Garvan Institute, Tanya Plibersek, Federal Health Minister, Delta Goodrem, Bill Ferris, outgoing Garvan Chairman and Jillian Skinner, NSW Minister for Health and Medical Research at the Garvan Gala held on 25th May 2013.

Actor Samuel Johnson attempts 15,000km unicycle world record in the name of sibling love

Australian actor Samuel Johnson, best known for his roles in *Crackerjack*, *Underbelly II*, *Rush* and as Evan in *The Secret Life of Us*, is on an inspiring crusade around the country on his unicycle. His mission is to raise early breast cancer detection awareness and funds for Garvan breast cancer research.

Samuel's sister, Connie, is 36 and the mother of two little boys, Willoughby and Hamilton. She has metastatic breast cancer that has spread to her lungs and bones and a life expectancy of only 6-12 months. However, she is determined to make every last day count and is working incredibly hard, alongside Samuel, to raise awareness and funds.

Samuel expects it will take close to a year to cover his 15,000km target distance and hopefully break the current Guinness unicycling world record of 14,686.82km. He set off from Melbourne on February 15 and as *breakthrough* went to press he had covered over 6,000km and raised over \$500,000.

"The generosity has been mind-blowing, but it has become very emotional," said Samuel, "I'm lost for words for the amount of people who have fought this disease and lost loved ones to it."

"For every bit of support I receive, I say thank you, not from me, but from my sister Connie," he said.

To follow Samuel and Connie on their inspiring and courageous journeys visit www.loveyoursister.org.



Rose Family February 2013

Giving a Voice to Ovarian Cancer

Each year, 1200 Australian women are diagnosed with ovarian cancer and tragically, 800 will die. This is because ovarian cancer is mostly diagnosed at late stage whereupon the cancer has spread beyond the ovaries.

Mrs Margaret Rose AM is an ovarian cancer survivor and a passionate advocate for ovarian cancer research. As Chairman and Patron of Garvan's Ovarian Cancer Working Party, Mrs Rose is helping raise much needed funding for an early-detection test for this deadly disease.

Most recently, Mrs Rose has donated a luxury two bedroom apartment in the prestigious Rose Property Group *Breakfast Point* development. Proceeds from this immensely generous gift will support Garvan's Dr Goli Samimi and her efforts to develop a screening program in order to significantly increase life-expectancy for this insidious disease.

For more information or to make a donation please contact Relationship Manager, Mara-Jean Tilley on (02) 9295 8513 or m.tilley@garvan.org.au.

Garvan's Breakthrough Fund

The aim of Garvan's Breakthrough Fund is to build an endowment from which the Garvan can recruit the world's very best researchers into professorial and senior fellowship positions. These outstanding researchers will be free to work on a range of basic scientific discoveries that will pave the way for the development of new tools and techniques in the fight against the world's most complex diseases. In bringing the best minds together into a multi-disciplinary translation research program Garvan is superbly positioned to put the latest breakthroughs directly to work. The Breakthrough Fund was launched at Garvan's Chairman's Dinner on 25th February.



(L - R) Fred Murrell, Ian Haigh and Professor John Mattick unveil a plaque commemorating The Alan Elder Trust's inaugural leadership gift of \$2m to launch the *Breakthrough Fund*.



Russell and Sue Scrimshaw announced a major legacy gift on the night to build the capacity of Garvan's Neuroscience research through the *Breakthrough Fund*.



Garvan Extends Public Engagement Program To Rural Australia

In 2013, Garvan is celebrating 50 years of breakthrough medical research with a new pilot awareness and education program in partnership with corporate sponsor, Ridley AgriProducts, entitled *Healthy Families, Healthy Communities*.

Through this initiative, Garvan and Ridley are extending Garvan's Public Engagement Program into rural and regional Australia, sharing important messages about health and medical research with the community.

The first year of this three year pilot - *Cancer in the Community* - explores cancer; the facts and the fiction and important new research being undertaken in this area.

For more information or to be notified of upcoming forum dates and locations please contact Relationship Manager, Mara-Jean Tilley on (02) 9295 8513 or m.tilley@garvan.org.au.



Clinical Studies

Metabolism – Genetics of Obesity Study

Do you think you could be overweight? Volunteers are needed to screen for a gene that links to obesity at the Garvan Institute. It involves only one visit during which measurements and a blood test will be taken. If you are suitable, you may enter the second part of the study to receive a full metabolic assessment. **For further enquiries please contact Dr Daniel Chen (02) 9295 8557 or d.chen@garvan.org.au, or Jen or Renee, (02) 9295 8215 or j.evans@garvan.org.au (St Vincent's Human Research Ethics Ref HREC/10/SVH/133).**

Pre-diabetes Study

We are looking for healthy male volunteers who have close relatives with Type 2 diabetes for a study investigating the role of the autonomic nervous system activity in the development of the disease. The study involves visiting the Garvan Institute in Darlinghurst for one morning during working hours. **If you are willing, aged 50 to 60 years and healthy, please contact Lynne (02) 9295 8231 or Dorit (02) 9295 8309 or email crf@garvan.org.au (St Vincent's HREC Ref 12/102).**

Osteoporosis Study

Are you female and over 60? Have you had a vertebral (spinal) fracture due to osteoporosis? We are looking for volunteers to be part of a clinical trial that compares a new osteoporosis treatment to a current medication. Both are designed to stop further fractures. **For further information please contact Dr Yvonne Selecki on (02) 9295 8276 or y.selecki@garvan.org.au, or Vanessa Travers on 9295 8269 or email v.travers@garvan.org.au (Southern Health HREC Ref HREC/12/SHA/6).**

Coming Up

Garvan Public Seminars

Thursday 14 November – Diabetes in Modern Australia.

For more information or to register for Public Seminars visit, www.giving.garvan.org.au/seminars or phone (02) 9295 8110. Seminars are free, but registrations are essential.



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In Memoriam February - July 2013. Donations have been made in memory of:

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