Garvan's Breakthrough Medical Research 2008 - Cancer Research Update

Background

Although derived from normal cells, cancer cells have distinctive features that can be exploited to aid diagnosis, treatment, and prognosis. To do this, we need to know much more about the fundamental processes that govern cell behaviours: their division, their survival, and their differentiation into complex tissue structures. With this knowledge, we will be better able to stop the formation and early growth of cancers.

Garvan has one of the largest cancer research programs in Australia. As well as 7 teams conducting basic research into the cell and molecular biology of cancer, we have six translational research groups studying a number of the most commonly diagnosed and most lethal cancers: breast, colorectal (bowel), lung, ovarian, pancreatic and prostate. In 2008 scientists from the Cancer Research Program published **48 articles about new discoveries** in prestigious journals. Below are just some examples from the highlights of our work in 2008.

2008 Major Highlights

Breast Cancer

Tamoxifen is the most effective breast cancer treatment currently available. Dr Alex Swarbrick, working in collaboration with Nobel prize winner Prof J Michael Bishop has been researching why some aggressive cancers do not respond to this treatment. They have identified that the gene Id1 drives some of the more aggressive and metastatic varieties. By "turning off" Id1 in established breast tumours in mice, the growth of tumours was reduced, and in 40% of cases the tumours shrank away. The team will now focus on further manipulating Id1 to see if the potential of this exciting new discovery can be fully realised to extend or save the lives of hundreds of women.

Whilst around 70% of breast cancers are treatable with Tamoxifen, it's still the case that 30% or more of these women may not respond well to such anti-hormone therapy long term. Associate Professor Liz Musgrove and Professor Rob Sutherland have also been able to identify particular gene groupings in breast cancer patients that can provide us with a good indication of whether they will respond well to treatment with Tamoxifen. As a result of this new breakthrough, clinicians may soon be in a position to determine whether Tamoxifen or an alternative treatment plan is the best option for individual breast cancer patients.

In August, Professor Roger Daly and his team identified a way to 'switch off' Gab2 – a molecule which is a key player in the molecular processes that trigger breast cancer and certain forms of leukaemia. Gab2 performs a number of signaling roles in normal cells throughout the body, and is usually switched off when it's not needed. Our task has been to work out how the body switches off Gab2, so that we can mimic that process in abnormal cells.

Prostate Cancer

Garvan progressed the first trial of a biomarker for prostate cancer outcome in Australia during 2008. This follows the discovery in 2006 by Garvan researchers of a new marker for identifying aggressive prostate cancers. Men with low levels of the marker called AZGP1 in the prostate at the time of surgery have a greatly increased risk of developing life-threatening metastatic cancer – where the cancer spreads to other parts of the body such as the bones. This new marker has made it possible to identify men who would benefit from a more aggressive treatment at the time of surgery when the cancer may be curable. Men at a lower risk of metastatic disease will also benefit by deferring treatments that have a negative impact on quality of life. The new trials, if successful, will lead to the adoption of an AZGP1 test in clinical practice – representing a major advance in the treatment of prostate cancer sufferers.

In the advanced stages of the disease, called hormone-refractory prostate cancer (HRPC), where men have gone through almost all treatment options, there is at present only one chemotherapy agent, Docetaxel, which is proven to improve both symptoms and survival rates. Unfortunately only around 40% of patients respond to this treatment; and the drug is associated with significant side effects. Currently, there are no measures that assess a patient's suitability for this treatment. Garvan scientists have recently though identified the protein MIC-1 as a biomarker of resistance to the Docetaxel. The aim is to identify markers in blood plasma which can predict response to treatment with Docetaxel. In the clinic, this would allow much better patient selection for such treatment and avoid suffering in patients who do not benefit from the treatment.

Ovarian Cancer

Garvan scientists have determined that cancer cell DNA with altered patterns in a biochemical process called methylation can be found in the blood of women with ovarian cancer, paving the way for a new diagnostic approach.

Methylation is a normal biological process that regulates gene function. During tumor growth, however, methylation is abnormally accelerated, preventing (de-activating) protective genes which would otherwise slow or halt the disease from activating. These changes are called **epigenetic** changes.

During 2008 Dr Pip O'Brien and her Ovarian Cancer team identified a number of genes that are frequently methylated in ovarian cancer. A combination of these genes will form a methylation signature unique to ovarian cancer. These preliminary data led to a new grant from Cancer Australia to develop this further as a potential blood test for ovarian cancer based on the cancer cell DNA present in blood.

Pancreatic Cancer
Pancreatic cancer is the fifth leading cause of cancer death in Western societies, with a 5 year survival rate of less than 10%. The treatment and survival of patients with pancreatic cancer has not changed for over thirty years because there has been little research into the molecular and cell biology associated with it. Garvan's team led by Professor Andrew Biankin has recently identified that the S100A2 calcium-binding protein is a predictive biomarker for response to pancreatectomy in pancreatic cancer.

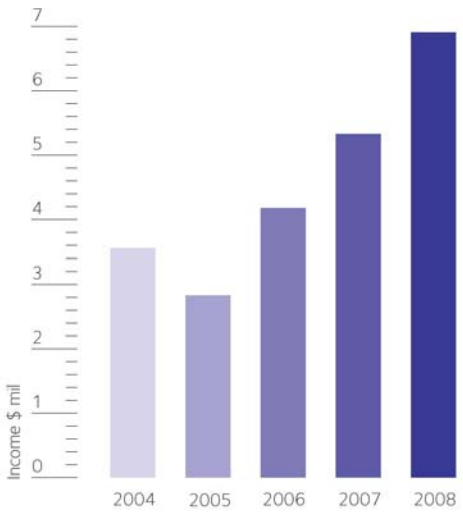
Lung Cancer
Garvan has identified ways in which the gene DLEC1 may be used as a biomarker for lung cancer, helping determine the prognosis of patients. Methylation causes the inactivation of DLEC1 in lung cancer. In 2008 the team's work confirmed that methylation is synchronized in two genes (DLEC1 and MLH1) during lung cancer development.

The team led by Dr Maija Kohonen-Corish also aims to test biopsies of a cohort of patients who were operated for lung cancer prior to the year 2000 to see if a defect in the gene SATB1 affects patient outcomes in lung cancer. This year they have developed a diagnostic test for this – the first difficult stage in this experiment.

GARVAN AT A GLANCE – 2008

Garvan Research Foundation Income Growth

Garvan Research Foundation is the marketing and fundraising arm of Garvan Institute. In 2007 donations from the public (excluding bequests) increased by **30%** to almost **$7 million.** In 2009 Garvan Research Foundation must continue to raise funds from the public to help fund the Institute's planned research program.

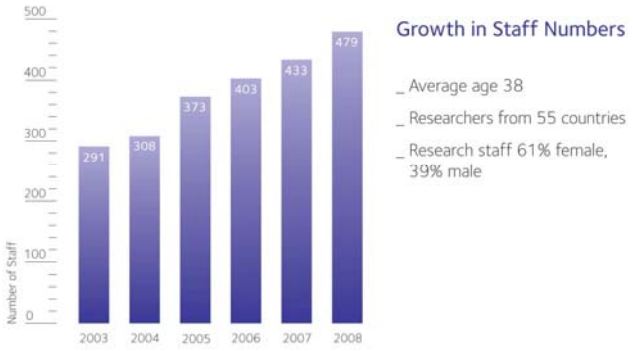


Garvan Institute Sources of Income

Donations from the public constituted **10%** of the Institute's total income for 2008. This excludes earnings from our Endowment Fund.

Growth of the Institute's Research Capacity

Over the past 6 years the Garvan has significantly increased our research capacity across our 5 program areas. Our staff numbers have grown by almost 65% since 2003.



Garvan Publications

Breakthrough research by Garvan scientists appeared in **185** publications in 2008. Each paper published constitutes a **new piece of knowledge**, and scientists aim to publish in the most highly regarded journal in their research field. Each journal has an "impact factor" which is a common measure of its relative importance within a specific discipline. Research organisations use "average impact factor" measurements to determine the overall significance of their research output. For example, in 2008 Garvan achieved an **"average impact factor" greater than 8 for the top 75% of its publications**. This is an excellent result, well above the international benchmark.