Garvan's Breakthrough Medical Research 2007 – Arthritis & Immunology Research Program Update

Introduction

Garvan's Arthritis and Immunology researchers study aspects of immune function in normal and diseased situations. They hope to understand the mechanisms underlying diseases such as rheumatoid arthritis, lupus, diabetes, asthma and other autoimmune diseases and immunodeficiencies, as the basis for developing much needed new therapies to treat them. They also collaborate with other programs on cross-disciplinary projects such as finding links between immunology and metabolic systems, cancer and the nervous system.

2007 Major Highlights

Rheumatoid Arthritis
Together with Garvan spin-out company G2 Therapies, we have advanced a new therapeutic antibody, against one of the most potent inflammatory agents (c5a), towards human clinical trials. This was licensed to Novo Nordisk in early 2007 and **stage 1 human trials** are scheduled to begin in Europe in August 2008. Garvan scientists have developed and used this antibody to **cure rheumatoid arthritis in mice**. We are also developing other antibodies to be commercialized by G2 which focus on the actions of cytokine IL-21 (cytokines are chemical 'messengers'), and chemoattractant receptor GPR43 and other important immune molecules.

B cell mutations that may cause cancers and autoimmune diseases
B cells, the white blood cells the produce antibodies, form a key part of our immune defences. We must maintain exactly the right number of B cells to remain healthy. If there are too many, we risk developing cancers or autoimmune diseases. If there are too few, we are prone to infection. Our scientists have identified that two proteins made inside B cells, TRAF2 and TRAF3, are essential for controlling this important balance. Click here to read the press release about this finding.

How our bodies "remember" infection
We identified some of the genes which are involved in our bodies' capacity to "remember" infection, and fight it better the second time around – a key element to developing better vaccines . Until now, although scientists have known about B cell memory, we have not known how to manipulate it at a genetic level. The genes involved in regulating this response are negative regulators, effectively applying brakes to the production of B cells the first time an infection is experienced. The second time around, the genes responsible for applying the brakes are turned off. Having identified the genes which trigger or dampen this response might also help us better understand what happens in patients with immunodeficient diseases, such as people who don't create the antibodies that help them fight disease in the first place.

Lupus
Scientists in the Autoimmunity Research Unit discovered a new form of lupus in mice which may correspond to a conventional treatment-resistant form of the disease in humans thereby providing the basis for developing alternative kinds of treatment for some people. Click here to read the press release about this finding.

Type 1 Diabetes
We have found that the chemical messenger IL-21 plays a critical role in the immune response through stimulating the growth of the T cells that collaborate with B cells for antibody production. We also identified mutations in the IL-21 gene that trigger overproduction of the cytokine IL-21 and that pharmacological neutralization of IL-21 in mice inhibits IL-21-driven activation of immune cells, preventing Type 1 diabetes. We have also identified factors that improve the outcomes of islet (pancreatic insulin-producing cells) transplantations for sufferers of Type 1 diabetes.

Asthma
We have developed new therapeutic approaches for asthma that focus on inhibition of the cytokine GM-CSF. The antibody we have developed is now ready for toxicology studies and pre-clinical development.

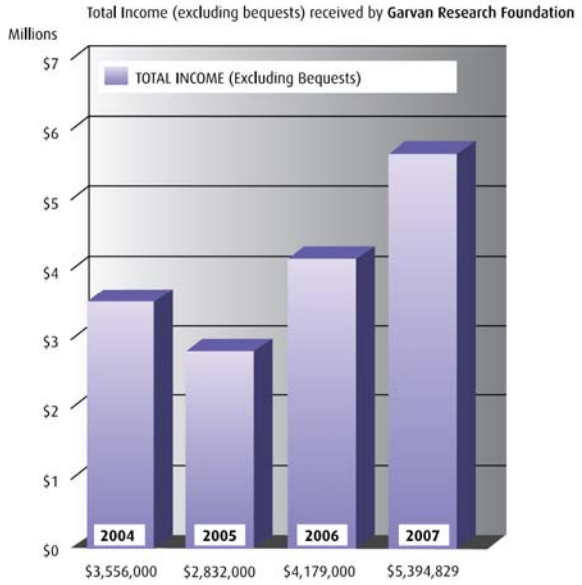
The Immune System in Cancer
Major factors predisposing people to cancer include exposure to viruses and ultraviolet radiation. Among the viruses is the Epstein Barr Virus (EBV) which causes glandular fever in healthy people but can occasionally be associated with tumours like lymphomas. A team has been studying EBV infection in a rare immune deficiency called XLP, since individuals with this are very prone to lymphoma. The work has provided definitive information on immunity to EBV which will improve our understanding of how such cancers develop as well as the chance of developing a protective vaccine.

Exposure to ultraviolet light greatly increases the risk of melanoma which has one of the highest incidences worldwide here in Australia. The only effective treatment is surgery and if the tumour spreads there is little else that can be done. Another Garvan team however, has come up with a completely new immunological approach to treatment. This involves the use of the potent stimulator of killer T cells known as interleukin-2. When this is combined with an antibody to prevent unwanted side effects, the combination is very effective in treating melanoma in an experimental model. Moreover, it is directly applicable to clinical use in this and probably other cancers as well.

GARVAN AT A GLANCE - 2007

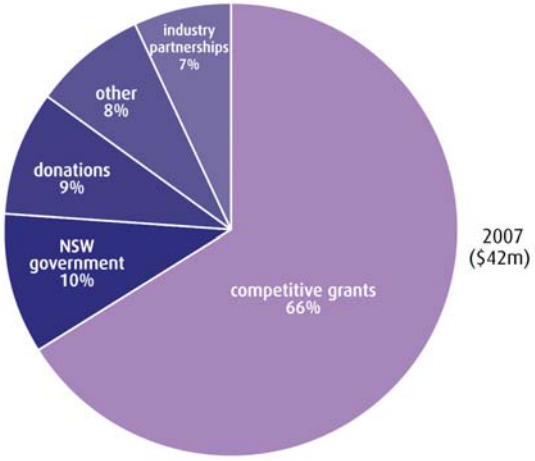
Garvan Research Foundation Income Growth

Garvan Research Foundation is the marketing and fundraising arm of Garvan Institute. In 2007 donations from the public (excluding bequests) increased by **30%** to over **$5.3 million.** In 2008 Garvan Research Foundation must raise at least **$7.6 million** from the public to help fund the Institute's planned research program.



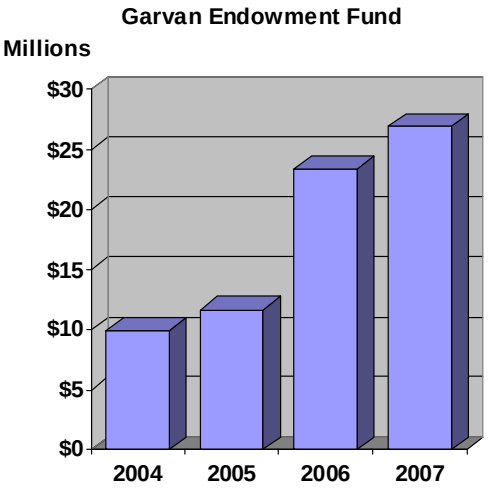
Garvan Institute Sources of Income

Donations from the public constituted **9%** of the Institute's total income for 2007. This excludes earnings from our Endowment Fund.



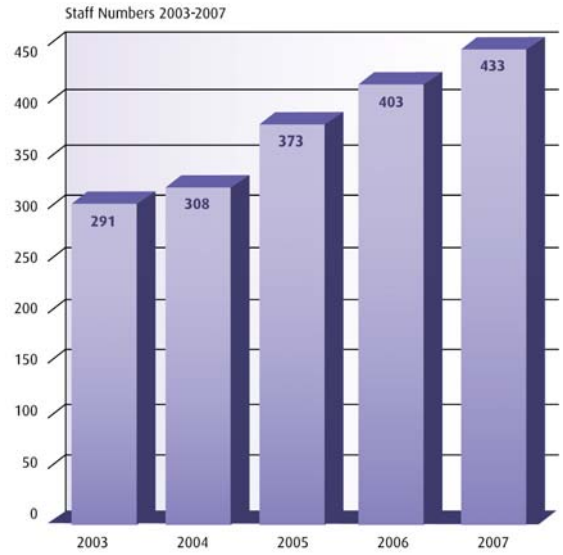
Endowment Fund Growth

Garvan's Endowment Fund gives Garvan the security of predictable funding into the future. The fund has grown from $10 million in 2004 to **$27million** in 2007.



Growth of the Institute's Research Capacity

Over the past 5 years the Garvan has significantly increased our research capacity across our 5 program areas. Our staff numbers have grown by almost 50% since 2003.



Garvan Publications

Breakthrough research by Garvan scientists appeared in **153** publications in 2007. 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 2007 Garvan achieved an **"average impact factor" of 8.2 for the top 80% of its publications**. This is an excellent result, well above the international benchmark.