Garvan's Breakthrough Medical Research 2008 – Arthritis & Immunology Research Program Update

Introduction
Our immune systems are designed to protect us from life threatening infections and cancer. Sometimes however, they malfunction resulting in disease. The focus of the Immunology Research Program is therefore to study what happens to immune function in both normal and disease situations. In doing so, we hope to unravel the mechanisms underlying diseases such as rheumatoid arthritis, lupus, allergies including asthma and immunodeficiencies as the basis for developing much needed therapies to treat them. Since immune mechanisms are responsible for many human diseases, our location at Garvan means that we are ideally placed to collaborate with other programs on cross-disciplinary projects involving obesity, osteoporosis, cancer, and neurodegenerative diseases.

2008 Major Highlights

Rheumatoid arthritis
Together with Garvan spinout company G2 Therapies, we have advanced a new therapeutic antibody against one of the most potent inflammatory agents C5a, towards human clinical trials. G2 Therapies licensed the C5aR antibodies discovered at Garvan, to the Danish pharmaceutical company Novo Nordisk A/S in 2006. A first-in-man (phase 1) clinical trial of anti-C5aR in healthy volunteers commenced in 2008 with primary endpoints of safety and tolerability. This trial will be completed later in 2009. Planning for further trials, in lupus and rheumatoid arthritis patients, is well advanced. A series of other antibodies with anti-inflammatory properties are being developed to pass onto G2 Therapies for development including to IL-21 (see below) and a chemoattractant receptor, GPR43.

Curbing severe allergies including asthma
Allergic diseases like asthma, hay fever and eczema account for nearly 20% of visits by patients to their general practitioner. Most of these conditions are due to production of a special class of antibody known as IgE, which comes from white cells termed B cells. Normally this type of antibody is present in very small amounts and protects us from parasitic infections, but in people who are susceptible to allergic diseases, the levels are greatly increased leading to tissue inflammation and damage. According to our research, one of the key molecules involved in controlling IgE levels is the cytokine, IL-21. The next step is therefore to produce an antibody against IL-21, which will have the potential to reduce IgE levels and the severity of allergic reactions. An alternative approach to treating asthma in particular that is being developed is based on an antibody designed to neutralise the inflammatory mediator, GM-CSF, which is present in excess within the lungs. This antibody is now ready for toxicology studies and pre-clinical development. A feasibility study is being conducted in collaboration with a major pharmaceutical company with the aim of fully licensing it for pre-clinical and clinical development by the end of 2009.

Novel ways to boost vaccination or natural defences
Eight years ago, a new subset of T cells termed T follicular helper (TFH) cells was identified based in large part on work performed at the Garvan. This important class of T cells plays a critical role by communicating with and helping to activate B cells to generate antibodies, which are particularly effective at neutralizing and killing microorganisms and tumour cells. Recently, Garvan scientists have found that the molecule IL-21 (see previous section), which is produced by TFH cells, is also a growth factor for them. Without IL-21, the all-important TFH cells can neither develop nor survive. Thus, if you take a mouse genetically deficient in IL-21 and immunise it, TFH cells do not develop and you do not get antibody production. We believe that IL-21 directs the most finely tuned aspects of our immune responses and is therefore a novel target for the next generation of antibodies and vaccines.

By studying a rare immunodeficiency disease known as Job's Syndrome, Garvan scientists have identified a molecule called STAT3, which is crucial for protection against common microbes like Candida (monilin) and the golden staph. This work is very important since it could lead to development of much needed vaccines, given the limited efficacy of antibiotics, particularly in the case of penicillin-resistant staphylococcal infections.

B cell mutations that may cause cancers and autoimmune diseases
As mentioned above, B cells are the white blood cells that produce antibodies, and 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 such as lymphomas or leukaemias or generalised autoimmune diseases. On the other hand, if there are too few B cells, we become prone to infection. Early in 2008, Garvan scientists demonstrated that 2 proteins made inside B cells called TRAF2 and TRAF3 are essential for controlling this important balance and maintaining the integrity of our defences.

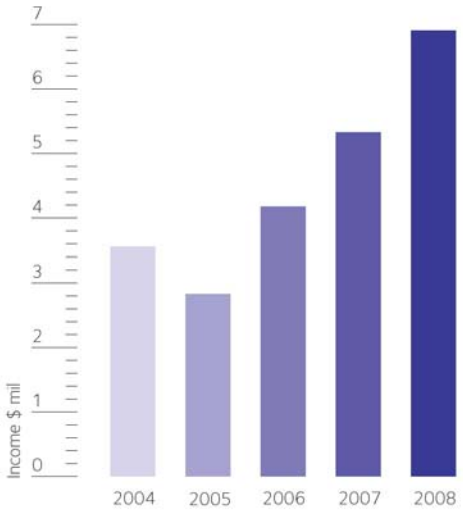
Type I diabetes
Garvan scientists have performed whole genome analyses on diabetic versus non-diabetic mice with a view to identifying new genes that may contribute to the susceptibility of humans to type I (insulin-dependent) diabetes. These genes are likely to work by causing infiltration of the insulin-secreting cells in the pancreas by various types of immune cells including the T cells and B cells mentioned previously.

A particularly exciting discovery published early in 2009 revealed that if the hormone BAFF which controls survival of B cells is blocked in mice prone to type I diabetes, none of them go on to develop disease. A phase I-II trial funded by the Diabetes Vaccine Development Center is planned for next year to test whether a BAFF blocker can prevent onset of disease in highly susceptible individuals.

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 raise at continue to raise funds from the public to help fund the Institute's planned research program.

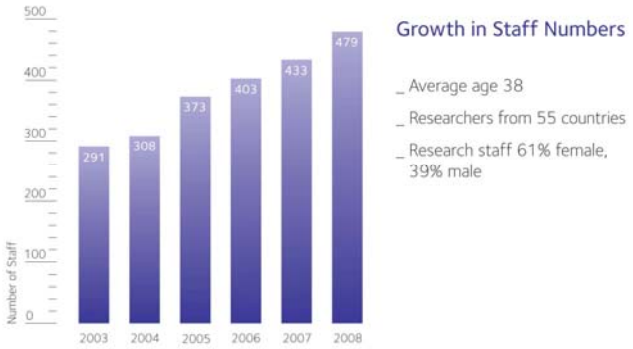


Garvan Institute Sources of Income

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.