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Multipotent progress

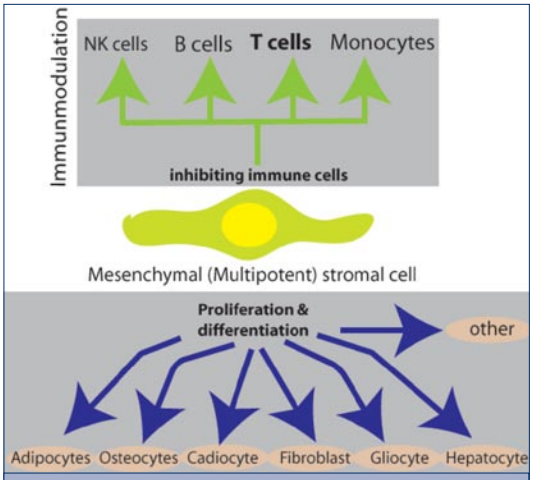
This tale has two stories. One story is about Mesenchymal Stromal Cells (MSCs) and a Phase I clinical trial in Perth which currently investigates their potential use as a novel treatment for Graft-Versus-Host-Disease (GVDH), a common and often fatal complication in patients that have received a bone marrow transplant.

The other story is about the **Research Infrastructure Support Services** (RISS), a small not for profit company supporting the Australian manufacture of human cell and cellular based products for transplantation. RISS operates under **the National Collaborative Research Infrastructure Strategy** (NCRIS), which was implemented in 2005 to increase Australian research capacity by providing $542 million over five years for major research facilities, supporting infrastructure and networks. The strategy is currently under review.

Both these stories make one tale as one leads to the other.

But let's reverse the chronological order and start with the medical story and the science behind it, at the centre of which are Mesenchymal Stromal Cells (MSC) – also referred to as Multipotent Stromal Cells – and their astonishing characteristics.

Discovered over 40 years ago they are present in a variety of tissues and constitute a form of multipotent stem cells as MSCs can develop *in vitro* into a number of different tissues. It is also known that when transplanted into a patient they tend to migrate to sites of inflammation and injury where they can play a role in the repair of damaged tissue and also act a immunosuppressants by tuning down the activity of immune cells, particularly T lymphocytes.



Mesenchymal stromal cells (MSC) can differentiate into highly specialised cell types that fabricate bone, neuron and other connective tissues (lower part); MSCs are also immunomodulatory, inhibiting function, differentiation and proliferation of a number of immune cells (upper part).

Another feature of MSCs is that they seem to be ignored by the host immune system even when the donor has an immunologically different (allogenic) background the patients immune system otherwise would react to. This 'immunological unresponsiveness' restricted to MSCs was recently confirmed by research at the Swedish Karolinska University Hospital.[1] Consequently, these cells can be clinically used as a 'ready-made' product irrespective of the immunological background of the donor. Fortunately, they can be extracted from various donor tissues, expanded to larger amounts in the laboratory and kept frozen until their use.

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The immune tolerance of MSCs still meets disbelief. "When you talk to clinicians and ethics committees, they can't get their mind around the fac that these cells can be given from one individual to another. They think it's crazy stuff," says ***Professor Richard Herrmann***, medical director of the **Ray & Bill Dobney Cell and Tissue Therapies** (CTTWA) facility at **Royal Perth Hospital** (RPH). He is currently conducting a Phase 1 clinical trial with patients that have developed GVHD after a bone marrow transplant and do not respond well to standard treatment with corticosteroids.

GVHD develops as immune cells from the donor bone marrow begin to attack the immunologically different tissue cells of the recipient. It is a common complication following bone marrow transplants and corticosteroids are usually given to systemically suppress the patient's immune reaction – with sometimes serious side effects, for example opportunistic infections. Still, patients that do not respond to the treatment have at present very poor survival chances. MSCs, with their potential capacity to suppress the immune reaction locally, at the site of the inflammation, may provide a life saving alternative.

Around the world scientists are investigating this, and US-based **Osiris Therapeutics Inc** has just completed a Phase III trial using MSCs in patients with acute GVDH. The company has yet to announce final results, although a preliminary announcement reported some success. Earlier studies, such as a Phase II trial with steroid-resistant, severe, acute GVHD at the Swedish Karolinska University Hospital showed a very clear response and, importantly, no adverse toxicities.[2]

Herrmann is convinced the therapy will make a difference for patients that currently have few options options left. So far nine patients were treated in the Phase I trial at the RPH, and the results have been promising. He remarks, though, that patients included in the study tend to be at a very late stage of their illness, often burdened with opportunistic infections as a consequence of steroid treatment. " ...it's like running a race horse in the mud," he says. The treatment has been, however, particularly successful in the case of a young leukaemia patient who received a bone marrow transplant in 2007 and then developed the GVDH complication. Lane Martino was the first patient in Western Australia to receive MSCs and has staged a positive recovery. He suffers relapses but responds well to repeated treatment, Hermann says, and the patient prefers the treatment to conventional treatment because of the absence of side effects.

A breakthrough? Yes, says Herrmann adding that although there may not be a permanent effect, one certainly can treat a patient.

He does not stop short in appraising the crucial support the project received, directly and indirectly, through RISS funding, which leads to the second story of the tale. "They are just fast tracking that kind of translational research," he says. He describes the impact of the RISS, as a small player in a relatively small field of research, as very solid, because of the flexibility but also the intimacy, the one to one contact with people like Stewart Hay, the chief executive of RISS. "These guys are very enthusiastic to get their funding working," he says.

Underlying this proactive approach is the general philosophy of the NCRIS funding strategy which aims to stimulate dialog between different groups, and to increase collaboration in the shared use of infrastructure to reduce unnecessary duplication, says RISS CEO ***Dr Stewart Hay***.

RISS support sets in at a different stage of a project cycle than the NHMRC, which mainly supports projects up to proof-of-concept stage. Through RISS clinicians can find support for trials at a critical stage before they may become attractive for venture capital, Hay says.

While the funding capacity of the agency, compared to the NHMRC, is small, the targeted impact in a relatively small sector can be crucial. However, Hay says the field is growing rapidly in Australia underlining the importance of centralised pieces of infrastructure to facilitate the different emerging applications for human cells and cellular products; also for locally translating research that has been done overseas.

Funded by the **Department of Innovation, Industry, Science and Research** (DIISR), RISS supports a number of facilities throughout Australia, foremost to meet and maintain critical regulatory requirements such as a **Therapeutic Goods Administration** (TGA) licence for the manufacturing of human cell and cellular based products. This includes the multidisciplinary **CTTWA** facility at the RPH, which was constructed in 2006 and provides a variety of cells and tissues, including MSCs, for the WA Health Service.

The set up asks for increased dialog across departments, as much of the baseline funding of hospitals is provided through the **Department of Health and Ageing** (DoHA), with additional funding for cellular based therapies from RISS through the DIISR. With the connection with DoHA the basic driver of RISS is working towards particular health outcomes. But this does not lose sight of potential commercial aspects.

Indeed, Hay's personal view is that the NCRIS funding strategy can provide substantial help for small and medium sized enterprises. Instead of the cash given directly to companies, for example through the now scrapped Commercial Ready program, SMEs can save substantial amounts in the development of a product through Government subsidies as they use NCRIS infrastructure and facilities.

"The Government is saying we provide you with infrastructure, provide you support pathways and give you substantial subsidies, sometimes in the order of 50%. If you take a product through to the clinic starting with the genomics, that could save you hundreds of thousands of Dollars."

[1]Sundin, M (2009) J Immunotherapy 32, 755-64. [2]Le Blanc K (2008) Lancet 371:1579-8

Ramaciotti Awards

The **Ramaciotti Foundations** are collectively one of the largest private contributors to biomedical research in Australia. Established in 1970, they have to date granted more than $47 million to research projects. Through the annual Ramaciotti Awards the foundations provide significant assistance to researchers in areas such as molecular biology, genetics and immunology.

Biomedical Research Award

The $1 million Ramaciotti Biomedical Research Award has been presented to a research team led by ***Professor Phillip Robinson*** and ***Professor Roger Reddel*** from the **Children's Medical Research Institute**, and ***Professor Adam McCluskey*** from **The University of Newcastle**. The grant will be used to create a **Centre for Kinomics**, a resource that will enable research teams throughout NSW to analyse current therapeutic drugs and improve on them. "Essentially, the equipment will allow scientists to identify the undesirable elements of existing therapeutic drugs - in particular the cause of negative side effects – and then use this information to develop new therapeutics," said Professor Robinson.

Philip Robinson	Roger Reddel	Adam McCluskey
		

Excellence in Biomedical Research Medal

Geoff McFadden

The discovery that malaria parasites contain chloroplasts similar to plants, a finding that has lead to a potential treatment for the disease, has won ***Professor Geoff McFadden*** from **Melbourne University** the prestigious Ramaciotti Medal.

Malaria infects approximately 300 million people each year and kills around one million, mostly in developing countries. "Exploiting the genetic link between malaria and plants, we have successfully applied herbicide-like compounds against the parasites, providing hope for a new and different way of treating the disease," said McFadden. The medal includes a cash prize of $50,000.

Establishment & Major Equipment Grants

The Ramaciotti Establishment and Major Equipment Grants, each worth $50,000, have been awarded to 30 recipients undertaking biomedical research. Establishment grants provide financial support for emergingresearchers, while equipment grants go towards the purchase of a major piece of equipment.

▶ **More information: www.perpetual.com.au/campaigns/ramaciotti_rama_awards.aspx**