



How to create indestructible insulin-producing cells

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Scientists at the Garvan Institute of Medical Research now have further support in their quest to create indestructible insulin-producing cells for transplant into people with Type 1 diabetes.

Dr Shane Grey, head of Garvan's Gene Therapy and Autoimmunity Group, has received \$350,000 from the Juvenile Diabetes Research Foundation, as part of their Australian Islet Transplantation Program. The grant will help him genetically modify cells enabling them to defy the body's attempts to reject or kill them after transplant.

'Islets of Langerhans' are clusters of different types of cells in the pancreas, including the beta cells that make insulin. Each pancreas has around 1 million islets, which maintain the body's blood sugar levels in exquisite balance. A transplant involves removing the islets from a deceased donor pancreas - and transplanting them into a recipient.

"Our aim is to find a way of making beta cells unassailable," said Grey. "Transplanted in their natural state, without any form of gene therapy, beta cells are attacked by the body's immune response. Even if heavy duty immunosuppressive drugs are given to a patient, that person still has Type 1 diabetes - the autoimmune disease that destroyed their insulin-producing cells in the first place."

So how does Grey's group propose to create beta cells that escape detection? First they must silence the genetic signals that tell the body the cell is an 'intruder'. Then they must create a defence system within the cell to protect it from autoimmune attack.

"In autoimmune diseases the target cells, in this case insulin-producing beta cells, not only say 'Here I am'. They emit biochemical signals that scream 'Here I am, come and get me! Oh, and by the way, here's a cricket bat to hit me with,'" said Grey.

"We have already taken one step in the right direction by creating a gene that emits a protein known as A20 which appears to protect beta cells from immune attack. When mice are engineered to have diabetes and also express A 20 in their beta cell transplants, those mice successfully continue to produce insulin."

"This tells us two things about the potential of this protein. First, we may be able to achieve the same effect in human beta cells for transplant. Second, we may be able to stave off Type 1 diabetes in its very early stages, before it properly takes hold."

"The JDRF grant will allow us to test whether our genetic-engineering approach will protect beta cell transplants in mice with Type 1 diabetes. This would be a very important step and pave the way for large animal studies - in non-human primates and pigs - in preparation for a human clinical trial."

Background information

2007/08 ITP basic research project (\$350,000 over two years)

Generating islet graft tolerance by targeting apoptosis and NF- κ B activation

Dr Shane Grey, Senior Research Fellow Garvan Institute of Medical Research, Sydney

Islet transplantation is a potential cure for Type 1 diabetes, however the widespread clinical applicability of this treatment is hampered by the requirement for a large number of islets, and the requirement for toxic immunosuppressive drugs. A major problem in islet transplantation is that the immune system treats the newly transplanted islets as 'foreign'. This effectively means the islets will be treated like an infection and destroyed. We know however, that the immune system receives signals or 'cues' from the body to help it to 'decide' how to respond to these situations. i.e with a destructive immune response or a kind of indifference, which is often referred to as 'tolerance'. We have been exploring the way islets respond when they are transplanted, and together with other groups we have found the islets can provide cues that encourage the subsequent immune attack. If we could prevent those cues we may be able promote successful islet transplantation with less toxic immunosuppression.

Australian Islet Transplantation Program (ITP)

The transplantation of insulin-producing islet cells has emerged as the most promising avenue for a cure. The Australian Islet Transplantation Program (ITP), was established by the JDRF in 2005 with funding from the Department of Health and Ageing and is designed to help take islet transplantation from being an experimental procedure to one broadly available for people with diabetes. Involving both clinical and scientific expertise, the Australian ITP is one of only a handful of programs with this capability in the world. Now consisting of three clinical centres and a number of molecular facilities based in Sydney, Adelaide and Melbourne, the ITP is on the verge of perfecting this relatively non-invasive technique.

ITP basic research program

The basic research component of the ITP has been created as a supplement to the clinical program. It will complement existing clinical knowledge to provide valuable new therapeutic strategies to eliminate the need for life-long immunosuppressive therapy, increase long-term tissue survival and improve health-related quality of life. Specifically, research projects funded under the program aim to develop new ways of preventing transplant rejection without the use of harmful immune-suppression regimes and identify ways to bypass the unique immune system properties connected with this autoimmune disorder.

The Juvenile Diabetes Research Foundation

The Juvenile Diabetes Research Foundation is the world's largest not-for-profit supporter of diabetes research, investing more than \$130 million in the search to find a cure for type 1 diabetes each year. Type 1 diabetes is a disease which strikes people suddenly, makes them dependent on multiple daily injections of insulin to survive and at risk of devastating health complications like blindness, kidney failure, heart disease and amputation. The mission of JDRF is constant: to find a cure for diabetes and its complications through the support of research.

Type 1 diabetes

Type 1 (or juvenile) diabetes affects 140,000 Australians and incidence is increasing every year. Typically striking young people, it results in the destruction of insulin-producing cells in the pancreas, leaving the sufferer on a daily regime of painful injections and finger-prick tests. Unlike type 2 diabetes, type 1 cannot be prevented and is not associated in any way with obesity or lifestyle. While insulin keeps people alive, it is not a cure and does not prevent the onset of the serious disease complications that dramatically shorten life expectancy. Research programs such as the ITP offer the best hope for curing this debilitating condition and minimize the estimated ongoing health burden to the community.

ABOUT GARVAN

The Garvan Institute of Medical Research was founded in 1963. Initially a research department of St Vincent's Hospital in Sydney, it is now one of Australia's largest medical research institutions with approximately 400 scientists, students and support staff. Garvan's main research programs are: Cancer, Diabetes & Obesity, Immunology and Inflammation, Osteoporosis, and Neuroscience. The Garvan's mission is to make significant contributions to medical science that will change the directions of science and medicine and have major impacts on human health. The outcome of Garvan's discoveries is the development of better methods of diagnosis, treatment, and ultimately, prevention of disease.

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