10 YEARS:
10 STORIES OF IMPACT

CASE STUDY 4

T1DCRN investment leads to one of the world's first T1D gene therapy trials

One of the key challenges of islet transplantation is how to increase the survival rate of transplanted islets by preventing the immune system from attacking them.

Funding from the Australian Type 1 Diabetes Clinical Research Network (T1DCRN) has led to the development of a novel gene therapy system to protect transplanted islets. This system is now the focus of one of the world's first gene therapy trials in type 1 diabetes (T1D). If successful, this trial could lead to a significant expansion in the availability and effectiveness of islet transplantation.

Australian Type 1 Diabetes Clinical Research Network

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

WHAT PROBLEM DO WE NEED TO SOLVE?

Islet transplantation can restore some level of insulin production in those with T1D. However, because of the challenges with current transplantation technology, the procedure is currently restricted to a select group of people with T1D.

The T1DCRN is supporting work to address one of the key areas limiting the progress and expansion of islet transplantation to a broader group of people with T1D, namely how transplanted islets can be protected from attack by the host's immune system without the need for widespread immunosuppression.

WHAT WAS FUNDED BY THE T1DCRN, AND WHAT DID THEY FIND?

Funding from the T1DCRN has been key to understanding how to protect beta cells from immune attack. Since the start of the T1DCRN, JDRF has supported **Professors Shane Grey, Phillip O'Connell and their teams** over multiple increasingly progressive projects between 2011 and 2022 to find protective molecules to reduce inflammation and protect the transplanted beta cells from the immune system, in a bid to improve islet survival.

One of these projects involves Professor Grey's team, which has found that a protein called A20 found in islets is critical to regulating the inflammation process and modulating post-transplant mechanisms.

In 2019, the team published a ground-breaking study in a pre-clinical model which showed that increasing levels of A20 protein improved islet survival after transplantation.[24]

Subsequently, Professor Grey and collaborators developed a novel gene-therapy system called GARV-AAV2-A20 which uses a virus to deliver the A20 gene into human donor islet cells.

This allows donor cells to increase A20 protein levels, making them more resilient to a host immune attack and increasing their survival.

This could reduce both the number of islets needed to achieve independence from insulin and the need for immunosuppressive drugs following islet transplantation. Pre-clinical studies demonstrated that this approach may work, and Professor Grey now has approval to start one of the world's first gene therapy human clinical trials for T1D.

WHAT DOES THIS MEAN AND WHAT'S NEXT?

The trial will use the GARV-AAV2-A20 system on donor islets to increase production of A20 protein before they are transplanted into recipients using a Biodegradable Temporizing Matrix (BTM) intracutaneous technology. Recruitment will commence in mid-2024.

If successful, this trial would make islet transplantation available to a broader selection of people with T1D, in turn enabling them to produce insulin once again, and bringing many clinical and quality of life benefits.

> "JDRF funding was critical for allowing us to pioneer a new therapy approach for T1D. We've worked on this research for 20 years and to see it now reach a stage of translating to people is amazing. It's the beginning of a long journey, but it's an exciting step.
>
> **Professor Shane Grey,** Principal Investigator leading a project using a novel T1D gene-therapy system

24. Zammit N, et al. A20 as an immune tolerance factor can determine islet transplant outcomes. .JCI Insight. 2019;4(21):e131028. https://doi.org/10.1172/jci.insight.131028.