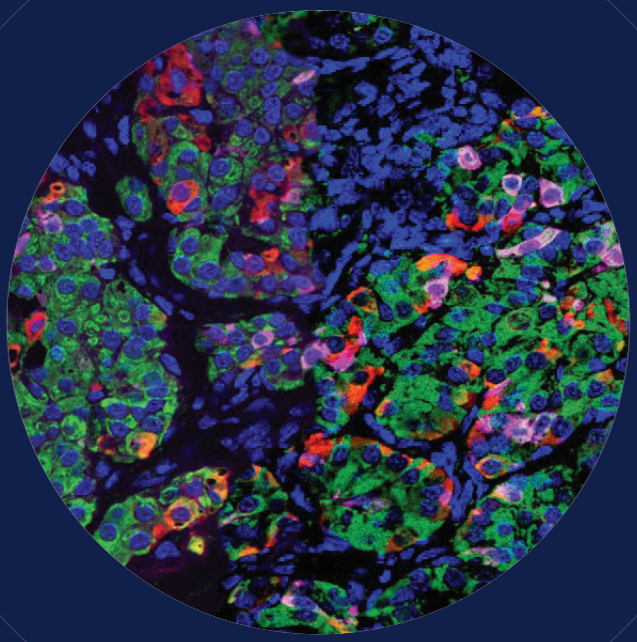

10 YEARS:
10 STORIES OF IMPACT

CASE STUDY 3

Driving breakthroughs in islet transplantation

Islet transplantation is a procedure that replaces pancreatic islets, which contain beta cells, to restore the ability to make insulin in people with established type 1 diabetes (T1D). Many recipients of the treatment globally have achieved independence from daily insulin administration. However, it is not yet widely available due to the challenges and safety of the procedure.

The Australian Type 1 Diabetes Clinical Research Network (T1DCRN) has funded some of Australia's best transplantation researchers to make islet transplantation simpler, more effective, and available to a broader selection of people with T1D. New approaches to the therapy such as the use of stem cells, protection from the demands of post-transplant immune suppression, and safer processes for islet infusion are being tested globally and in Australia. A new clinical trial testing skin as a site for transplantation is underway with support from the T1DCRN, and may offer a revolutionary approach towards islet transplantation.

Australian Type 1 Diabetes Clinical Research Network

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

WHAT IS THE PROBLEM WE NEED TO SOLVE?

Islet transplantation is a procedure in which islets, which are clusters of cells in the pancreas including beta cells, are removed from a donor pancreas, and transplanted—typically into the liver—of a recipient with T1D. The goal of the procedure is to restore insulin production and regulate blood glucose levels naturally.

Islet transplantation is not a cure for T1D, but can lead to independence from insulin administration, significantly improve quality of life, and reduce the risk of long-term complications associated with the condition.

Despite the promise of this procedure, it remains complex and faces significant challenges, limiting its widespread use as a T1D therapy. These include:

1 The need for immunosuppression

As for any other transplant, islet transplantation requires lifelong immunosuppression to prevent the body from attacking transplanted islets and to prevent the recurrence of islet destruction. Immunosuppression increases susceptibility to other infections and health complications, meaning the therapy is out of reach for children and many adults.

2 Transplantation site challenges

The liver is not an ideal site for transplantation as the environment in the liver does not provide optimal conditions for the survival and function of transplanted islets. In addition, the procedure requires invasive surgery under general anaesthetic, and monitoring of the transplanted cells is challenging.

3 Transplantation methodology

The isolation and culture of islets from donors prior to transplantation inflames the cells, increasing the chances of transplant failure. Success often requires multiple infusions from different donors, and many people revert to a requirement for exogenous insulin within a few years.

4 Scarcity of islets

The demand for transplanted cells greatly outstrips the limited supply of islets from organ donation, with an urgent search for new sources of beta cells underway, including those derived from stem cells.

EARLY ISLET TRANSPLANTATION PROGRESS

In 2006 the Australian Government dedicated $30 million to establish the Islet Transplantation Program (ITP).

The ITP, administered by JDRF and delivered by world-recognised clinicians, established a consortium that united three transplantation centres across Sydney, Melbourne, and Adelaide, to progress islet transplantation and make the procedure more accessible.

Thanks to the program's investment and progress, islet transplantation has been a nationally funded clinical treatment for people with T1D under the National Funded Centres program since 2012.

So far, 103 people with T1D have received islet transplantations, many of whom became insulin independent for over five years.

However, due to the challenges outlined, the procedure is currently approved only for people who have difficulty controlling their blood glucose levels with insulin therapy, experience severe hypoglycaemia unawareness (inhibited ability to detect when blood glucose levels are dropping dangerously), and have not responded well to other diabetes treatments.

> There is an anxiety around having T1D, and if this treatment is effective, that anxiety will go. I also have a daughter with T1D, and I hope that this will be a cure for me, and for her.
>
> Islet transplantation **clinical trial participant**

WHAT IS BEING FUNDED BY THE T1DCRN, AND WHY?

The T1DCRN has funded a program of work that builds on the early success of the ITP and aims to address the current limitations of islet transplantation to help make the procedure simpler and more widely available to people with T1D.

A team of distinguished experts in transplantation, immunology, and islet biology have been supported by the T1DCRN to combine their expertise. **Professors Philip O'Connell**, **Thomas Kay**, **Toby Coates**, **Shane Grey**, **Wayne Hawthorne**, **and Stephen Alexander** are among the world's foremost authorities in this area.

They are part of an international consortium driving ground-breaking advancements and shaping the future of islet transplantation.

The advancements to date, made possible through T1DCRN support, include:

- results that prove that islet transplantation, when compared to traditional insulin therapies, leads to superior glucose management, and reduces the risk of hypoglycaemia when compared to continuous insulin infusion or multiple daily insulin injections[17]
- results that showcase islet transplantation restores the lost awareness of hypoglycaemic episodes[18]
- the development of innovative assays that significantly advance monitoring and personalised care for people with T1D in the field of transplantation[19]
- exciting early results from an ongoing clinical trial suggesting that less toxic existing immunosupressive drugs (belatacept and sirolimus) hold great promise in increasing insulin independence and enhancing islet function
- **Professor Anandwardhan Hardikar**, now at the University of Western Sydney, discovering unique molecular signatures that can potentially predict beta cell death[20]
- **Professor Peter Thorn**, University of Sydney, working to improve insulin secretion and glucose sensitivity of islets.[21,22]

17. Holmes-Walker DJ GJ, et al. Islet transplantation provides superior glycemic control with less hypoglycemia compared to continuous subcutaneous insulin infusion (CSII or multiple daily insulin injections (MDI). Transplantation. June 2017 2017;101(6):7.

18. Lee MH, et al. Mortality in People With Type 1 Diabetes, Severe Hypoglycemia, and Impaired Awareness of Hypoglycemia Referred for Islet Transplantation. Transplant Direct. Nov 2018;4(11):e401. doi:10.1097/txd.0000000000000841

19. Jimenez Vera E, et al. Standardisation of flow cytometry for whole blood immunophenotyping of islet transplant and transplant clinical trial recipients. PLoS One. 2019;14(5):e0217163. doi:10.1371/journal.pone.0217163

20. Wong WK, et al. The long noncoding RNA MALAT1 predicts human pancreatic islet isolation quality. JCI Insight. Jul 30 2019;5(16)doi:10.1172/jci.insight.129299

21. Gan WJ, Do OH, Cottle L, et al. Local Integrin Activation in Pancreatic β Cells Targets Insulin Secretion to the Vasculature. Cell Rep. Sep 11 2018;24(11):2819-2826.e3. doi:10.1016/j.celrep.2018.08.035

22. Ma W, et al. Arp2/3 nucleates F-actin coating of fusing insulin granules in pancreatic β cells to control insulin secretion. J Cell Sci. Mar 30 2020;133(6)doi:10.1242/jcs.236794

Sustained funding through the T1DCRN has also enabled **Professors Toby Coates and John Greenwood** to develop an innovative islet transplantation protocol using NovoSorb™ BTM (Biodegradable Temporizing Matrix).

This material is a biodegradable matrix historically used for severe burns and allows for intracutaneous islet transplantation. Using the BTM for this application is a world first and demonstrates the power of multidisciplinary collaboration and innovative thinking in bringing truly novel ideas to T1D research.

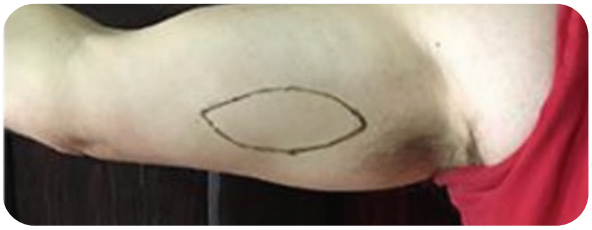

Figure 1: Site of intracutaneous BTM transplant in arm of recipient

The intent of this method is to improve islet survival by increasing oxygen supply to the transplant site and means the transplanted islets can be more easily retrieved. Importantly for participants, it also offers a less invasive procedure than what is currently available in the clinic and does not require general anaesthetic.

Results from rigorous pre-clinical testing, published in a leading academic journal, *Diabetes,* showed that the BTM helped transplanted islets to thrive.[23]

WHAT HAS THIS PROJECT DELIVERED AND WHY IS IT IMPORTANT?

These results show that the BTM skin-based approach has potential as a transformative islet transplantation alternative for people with T1D.

This approach is now being tested in a first-in-human clinical trial at the Royal Adelaide Hospital. A select number of adults involved in the trial will receive islet transplantations utilising this new method and will be monitored over the course of 12 months to assess if the procedure is safe and track the progress of participants.

> Our research project is aiming to create a future where more people with T1D can access islet transplants, so that they will be able to make insulin for themselves again. We know islet transplantation offers real promise and making it a simpler and more accessible procedure could transform how – and how many – people can benefit from it.
>
> **Professor Toby Coates,** Principal Investigator

23. Rojas-Canales D, et al. Intracutaneous Transplantation of Islets within a Biodegradable Temporizing Matrix (BTM) as an Alternative Site for Islet Transplantation. Diabetes. 2023;doi:10.2337/db21-0841