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# After 45 Years of Pancreatic Islet Transplantation, Is It Time to Seriously Consider Molecular Alternatives to Cure Type 1 Diabetes?

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## Abstract

Type 1 diabetes (T1D) is caused by the autoimmune destruction of the insulin-producing beta (β)-cells of the pancreas resulting in hyperglycaemia and life-threatening complications. The promise of a β-cell replacement therapy has yet to be fulfilled due to the shortage of donor pancreata and the requirement for lifelong immunosuppression to prevent recurrent autoimmunity and allograft rejection, both of which pose significant clinical risks. Therefore, islet/ pancreas transplantation is unlikely to be a realistic cure for most patients. In this opinion summary, we build on our laboratory's work and that of other researchers demonstrating the successful genetic engineering of surrogate β-cells from hepatocytes that are capable of synthesising and secreting insulin in response to physiological metabolic cues, akin to pancreatic β-cells. We propose that these advances highlight the feasibility of clinical translation and provide proof-of-principal that a patient's own hepatocytes could ultimately be reprogrammed in *vivo* towards a β-cell phenotype. This approach bypasses the challenges of both donor tissue availability and immune-mediated rejection that complicate allogeneic islet and pancreas transplantation.

## Introduction and Background

Type 1 diabetes (T1D) is caused by the autoimmune destruction of the insulin-producing pancreatic beta (β)-cells. It is the most common chronic disease of childhood in developed nations and its incidence continues to rise each year. Current treatment constitutes multiple daily insulin injections and blood glucose monitoring. Tight glucose control achieved through intensive insulin therapy can delay, but not eliminate, complications such as nephropathy, retinopathy, cardiovascular disease, and neurological impairment, which collectively contribute to significant morbidity and mortality. Since the 1970s pancreatic (β)-cell replacement has been considered a promising approach for the treatment of T1D, where pancreatic islets, purified from either an allogeneic or xenogeneic donor pancreas are administered to the patient, most commonly through portal vein infusion [1]. However, this procedure is limited by a shortage of donor pancreata and the requirement for lifelong immunosuppression, with its associated adverse side effects, together with a number of other unresolved issues, including limitations in encapsulation technology. Microencapsulation technology isolates islets in a thin layer of biomaterials, such as alginate, which allow the exchange of nutrients, insulin and other substances, improving immuno-rejection. However, studies have encountered several challenges, including pores blockage or obstruction, reduced cell viability and cell death and diminished insulin response to glucose levels [1].

Before the clinical onset of T1D, islet autoantibodies signal the initiation of silent and progressive destructive autoimmune processes, often appearing months or even years before hyperglycaemia develops. This pre-symptomatic phase presents a unique opportunity for early intervention. Indeed, population-based screening programs for T1D have been shown to reduce the incidence of diabetic ketoacidosis at diagnosis by enabling earlier detection [2]. To date the most successful studies aimed at delaying T1D onset has been the administration of anti-CD3 monoclonal antibodies, such as Teplizumab [3]. So far, immunotherapies have not had ultimate successes in altering T1D disease course. Their benefits are typically short term and long term favourable immune responses or regulation has remained difficult to sustain.

Thus, alternative therapeutic strategies are urgently needed. Gene therapy, whereby an "artificial β-cell", capable of synthesising and secreting insulin in response to the physiological metabolic signals, is generated by genetically engineering the patient's own cells. This approach would circumvent the issues of tissue rejection inherent to both allogeneic transplantation of islets and pancreas. Our laboratory (and others) has shown that a number of cell types can be used for the genetic engineering of artificial β-cells [4-15], but hepatocytes are particularly useful as they as they derive from the same endodermal precursors as pancreatic cells and possess similar characteristics to pancreatic β-cells, including an ability to process and secrete proteins, and a glucose sensing system (glucose transporter 2 [GLUT2] and glucokinase [Gck] [ 6-8,12,14,15].

### Recent Work from Our Laboratory

Our team and others have established that specific combinations

of β-cell transcription factors exert a synergistic effect in stimulating β-cell transdifferentiation, storage of insulin in granules, regulated insulin secretion to glucose and other β-cell secretogogues, and, most importantly, permanent reversal of diabetes [5,6,13]. Additionally, and very importantly, this transdifferentiation process does not result in recurrent autoimmune reactions against the surrogate β-cells [14]. Together, these findings highlight that only approaches combining immune regulation with enhanced β-cell survival have the potential to delay, prevent and ultimately cure T1D.

A recent study investigated a novel gene therapy approach that prevented disease development by replacing pancreatic β-cell function with insulin-producing cells generated through hepatic transdifferentiation [14]. In this model, a clinically applicable third-generation lentiviral vector (based on the pRRLSIN.cPPT.PGK-GFP. wpre vector) was used to deliver a cocktail of β-cell transcription factors: pancreatic and duodenal homeobox 1 (*Pdx1*), neuronal differentiation 1 (*ND1*), and MAF BZIP Transcription Factor A (*MafA*) to the portal vein of 5-6-week-old non-obese diabetic (NOD) mice. At the experimental endpoint of 30-weeks, all (100%) of the treated NOD mice remained normoglycemic, exhibited normal intraperitoneal glucose tolerance responses and demonstrated an ability to regulate blood glucose as effectively as the non-diabetic controls. A range of pancreatic markers, including somatostatin, Glut 2 and, most importantly mouse insulin (*Ins1* and *Ins2)*, were detected in the liver, and liver function tests remained normal. Collectively, these findings showed that expression of these β-cell transcription factors induced partial pancreatic transdifferentiation and prevented the onset of hyperglycemia and impaired glucose tolerance, as the transduced hepatocytes effectively assumed β-cell function. Immunohistochemistry confirmed that endogenous β-cells had been destroyed by the autoimmune process. As lentiviral vectors permanently transduce cells, this approach therefore holds substantial promise as a potential clinical therapy, particularly if applied in individuals at early stages of Type 1 diabetes.

## Author Contributions

Both authors contributed to the writing and review of the manuscript and approved the final version.

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## Disclosure Provenance and Peer Review

Nothing to report.

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