Editorial Commentary | Clinical Studies

Insulin-producing cells derived from expandable stem cell-derived endoderm are effective for the treatment of type 2 diabetes

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Type 2 diabetes (T2D) is primarily triggered by a combination of genetic, lifestyle, and environmental factors (1). Initially, insulin resistance in the peripheral tissues increases demand of insulin to promote glucose uptake and generate energy, which causes over work for insulin producing β cells. This eventually leads to the gradual attenuation of β cell function to secrete insulin in response to nutritional stimuli, along with the loss of functional β cells, promote to the irreversible progression of T2D (2). Current management strategies emphasize glycemic control through medications, such as insulin, combined with strict dietary management to monitor blood sugar levels. Despite these measures, a definitive cure remains a significant unmet need (3). In the recent article in *Cell Discovery* entitled "Treating a type 2 diabetic patient with impaired pancreatic islet function by personalized endoderm stem cell-derived islet tissue", Wu *et al.* reported the intrahepatic implantation of autologous human endoderm stem cells (EnSCs)-derived islets (E-islets) in T2D patients who had impaired insulin secretion (4). This pilot clinical study showed that the stem cell derived islets can be used for treating human T2D.

Previously, the authors developed EnSCs from human pluripotent stem cells (hPSCs), characterized by definitive endoderm cell properties and self-renewal capability (5). They generated the patient's own human induced pluripotent stem cells (hiPSCs) and then created EnSCs, which were differentiated into functional pancreatic islet cells. Notably, these EnSCs exhibit self-renewal, allowing the expansion of cell numbers without losing endoderm characteristics. This process significantly reduces the time required to generate insulin compared to the use of typical hiPSCs. Importantly, EnSC-derived islets, referred to as E-islet cells, are capable of secreting hormones such as insulin and glucagon, which are crucial for regulating blood sugar levels.

The authors first explored the potential allogenic tolerance of E-islets in a preclinical animal model. Using patient-derived peripheral blood mononuclear cells (PBMCs), they created humanized mice and evaluated the allogenic responses of E-islets derived from the same patient. The patient-specific E-islets survived and functioned under the kidney capsules of diabetic immunocompromised mice humanized with the patient's own PBMCs, but were rejected by those humanized mice with PBMCs from an unrelated volunteer.

Following the preclinical results in mouse and monkey models, the authors initiated a human clinical trial. They focused on a 59-year-old male patient with a 25-year history of T2D. After undergoing a kidney transplant in June 2017, the patient's pancreatic islet function deteriorated, requiring multiple daily insulin injections from November 2019. To address this issue, Wu *et al.* (4) pioneered a novel stem cell treatment using E-islets. In July 2021, the

patient underwent autologous islet cell transplantation. Remarkably, within 11 weeks post-transplantation, the patient achieved insulin independence. Over the following year, oral diabetes medications were gradually reduced and eventually discontinued. Long-term follow-up examinations revealed restored pancreatic function, eliminating the need for exogenous insulin or oral medications. Additionally, the patient maintained normal kidney function, suggesting a potential long-term cure for both T2D and complications from the kidney transplant. This groundbreaking achievement marks a paradigm shift in treating human T2D. Recent clinical studies led by ViaCyte have provided evidence that hPSC-derived pancreatic progenitors can differentiate and mature into functional insulin- or glucagon-producing cells (6-8), offering the first clinical evidence of stem cell therapy for treating type 1 diabetes (T1D). More recently Vertex announced positive results from ongoing phase 1/2 study of encapsulated hPSC-derived human islets (VX-880) for the treatment of T1D patients (presented at the American Diabetes Association 84th Scientific Sessions). Compared to these prior studies, the current study used more terminally differentiated islet aggregates for treating T2D.

Although, the successful application of stem cell therapy in T2D presents a potential path to a cure, encouraging further research into large-scale implementation and long-term efficacy (9), there are still challenge remaining. Recent studies of fine-tuning multiomics analyses of hiPSC-derived islets identified that the immaturity persists in *in vitro* generated islets (10-12). These immaturity of stem cell-derived islets may limit the reproducible generation of high-quality human islets in a dish (13), and it may influence the clinical outcome of variability. E-islet cells may also face several potential pitfalls and concerns. One major issue is the variability in how patients respond to stem cell therapy due to genetic, environmental, and lifestyle factors, which could affect the treatment's overall effectiveness. Specially, there are huge genetic and metabolic differences in individual T2D compared to T1D. The presented clinical trial was conducted using a combination therapy that included known T2D treatments such as metformin, insulin, and an α-glucosidase inhibitor, along with immunosuppressants like mycophenolate mofetil and tacrolimus. It is currently unknown whether the E-islets alone effectively improves glycemic controls under severe insulin resistance patients, which most of T2D patients under that condition. For T1D, in addition to alloresponses, autoimmune responses that recognize insulin and other β cell-specific proteins as antigens pose an additional burden for the prolonged survival of transplanted islets (14). Although T2D patients do not exhibit autoimmune responses, other types of β cell toxicity, such as human islet amyloid deposits, oxidative stresses, endoplasmic reticulum (ER)-stress, or cytokine-induced β cell inflammation (15-17), may lead to T2D-like β cell dysfunction in transplanted islets. Since hPSCs are highly amenable to various genome editing technologies, such as clustered regularly interspaced short palindromic repeats/Caspase 9 (CRISPR/Cas9), transcription activator-like effector nucleases (TALENs), and zinc-finger nucleases (ZFNs), enabling precise modifications to modulate gene expression, designing stress-resistant E-islets may need to be investigated in future studies.

Additionally, the long-term safety and potential side effects of this therapy are still unknown, with risks such as uncontrolled stem cell proliferation or differentiation into unwanted cell types, potentially leading to complications like tumors. The cost and complexity of the procedures for extracting, cultivating, and transplanting stem cells are also significant barriers, requiring specialized facilities and expertise that could limit accessibility, particularly in low-resource settings. Furthermore, ensuring the consistency and safety of stem cell therapy across diverse patient populations is complex and requires further research to optimize protocols. The current clinical trial was conducted on patients who had undergone kidney transplantation before participating in this trial. There is a lack of consideration and information regarding the immunosuppressive treatment associated with the kidney transplant, its duration, and its effect on endogenous β-cell function and metabolic control. Although the authors reported that insulin requirements were gradually reduced until complete withdrawal by the end of week 11, and oral antidiabetic medications were tapered starting at week 44 and discontinued by week 48 (acarbose) and week 56 (metformin), a more comprehensive data set and analysis are needed. This analysis should focus on basal and meal-stimulated β cell function and glucose control before and after the stem cell transplant, as well as the associated insulin treatment (including dose and regimen) and daily carbohydrate intake. This is crucial because the recipient still retains a functional pancreatic β cell mass. These concerns highlight the necessity for additional clinical trials and careful consideration before this novel treatment approach can be widely adopted.

The successful application of stem cell therapy offers a path towards a potential cure, paving the way for further research

into the large-scale implementation and long-term efficacy of this novel approach. If these preliminary results are confirmed in larger and longer-term studies, this could revolutionize the treatment of T2D, dramatically improving the quality of life for millions of patients worldwide. Researchers are now focusing on optimizing protocols for stem cell extraction, cultivation, and transplantation, as well as ensuring the safety and consistency of the treatment across diverse patient populations. While further clinical trials are warranted to validate these findings, this case study undoubtedly sparks hope for a future free from the burden of diabetes.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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