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COMMENTARY



# Toward a cure for diabetes: iPSC and ESC-derived islet cell transplantation trials

Insulin-producing pancreatic β-cells located within the islets of Langerhans are predominantly destroyed due to autoimmune mechanisms in type 1 diabetes. This ultimately leads to a complete loss of endogenous insulin secretion, forcing people with type 1 diabetes into an insulin-dependent state where insulin therapy becomes crucial for survival. As of 2022, an estimated 8.8 million people worldwide were living with type 1 diabetes, and this number is projected to nearly double to 17.4 million by 2040[1]. In recent years, insulin pumps integrated with glucose sensors have been increasingly used to automatically adjust insulin delivery based on real-time blood glucose levels. However, despite these technological advancements, accurately responding to the dynamic fluctuations in glucose remains challenging. Achieving and maintaining normoglycemia continues to be difficult, as these devices often struggle to fully replicate the body's rapid changes in glucose metabolism[2]. In fact, despite the use of the above-mentioned cutting-edge diabetes technologies, more than 40% of individuals with type 1 diabetes still do not reach the glycemic target of HbA1c below 7%. Additionally, around 20% of them experience severe hypoglycemic events annually, and one-third report hypoglycemia unawareness[3]. Pancreas and islet transplantation offers a promising treatment option that aims restoring physiological insulin secretion by re-establishing pancreatic β-cell function, potentially leading to a cure for type 1 diabetes. While advancements in immunosuppressive therapies and glycemic management strategies have significantly improved transplantation outcomes, a critical challenge remains: the shortage of donors, which results in long waiting periods for those in need. In response to this issue, regenerative medicine using induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs) has been gaining increasing attention as a potential solution[4] (Figure 1). In 2006, it was discovered that mouse somatic cells could be reprogrammed into iPSCs, which exhibit self-renewal and pluripotency—characteristics like ESCs—through the forced expression of a specific set of transcription factors (i.e., Oct4, Sox2, Klf4 and c-Myc). Just a year later, the same breakthrough was achieved in human cells, marking a revolutionary milestone in medical science. Initially, these iPSCs were primarily used for disease modeling and drug discovery. Today, they are increasingly being explored for experimental cell transplantation, opening new possibilities in regenerative medicine by generating replacement cells for those lost to disease while avoiding the ethical concerns associated with ESCs derived from fertilized eggs. Significant global progress has been made in developing pancreatic islet cell transplantation therapies utilizing iPSCs in addition to ESCs (Table 1)[5]. Transplantation of pancreatic endoderm cells differentiated from ESCs or iPSCs have been attempted with the expectation that differentiation into islet cells would progress in vivo.

In the United States, ViaCyte conducted a clinical trial involving the transplantation of human ESC-derived pancreatic endoderm cells (PEC-01) into the subcutaneous space using a small device. In the VC-01 transplant, which utilized an immune-isolating device that prevented vascularization, the surviving cells became sparse within 12 weeks in most cases. This was believed to be due to hypoxic conditions caused by multinucleated giant cells surrounding the device (ClinicalTrials.gov ID: NCT02239354). To address this issue, the VC-02 device, which allows for vascularization, was developed and used for subcutaneous transplantation of PEC-01 cells. However, during the 1-year observation period, C-peptide levels remained at only ~1% of normal ranges, and no clear therapeutic effect for type 1 diabetes was observed (ClinicalTrials.gov ID: NCT03163511). The failure was ultimately attributed to the improper differentiation of the transplanted PEC-01 cells into functional islet cells and inhibiting vascular ingrowth due to extensive fibrosis[6]. Later, Vertex Pharmaceuticals in the United States initiated a clinical trial (ClinicalTrials.gov ID: NCT04786262) to administer more differentiated human pluripotent stem cell-derived islet cells (VX-880) to individuals with type 1 diabetes via intraportal infusion. At the 180-day follow-up, seven of 10 participants achieved insulin independence, while two demonstrated approximately a 70% reduction in insulin requirements. While the long-term outcomes remain uncertain, these early results are highly encouraging. A recent review paper suggests that the starting pluripotent stem cells are ESCs[7]. Another promising approach, VX-264, involves delivering the same islet cells encapsulated within a surgically implanted device, potentially eliminating the need for immunosuppression (ClinicalTrials.gov ID: NCT05791201).

Researchers have investigated the transplantation of pancreatic endoderm cells derived from allogeneic iPSCs. Capitalizing on the ability of iPSCs to be generated from somatic cells, two reports from China have documented successful islet transplants derived from patient-specific iPSCs. Wang *et al.*[8] reported the world's first autologous transplantation of islet cells derived from a type 1 diabetes patient's iPSCs (Chinese Clinical Trial Register Registration Number:

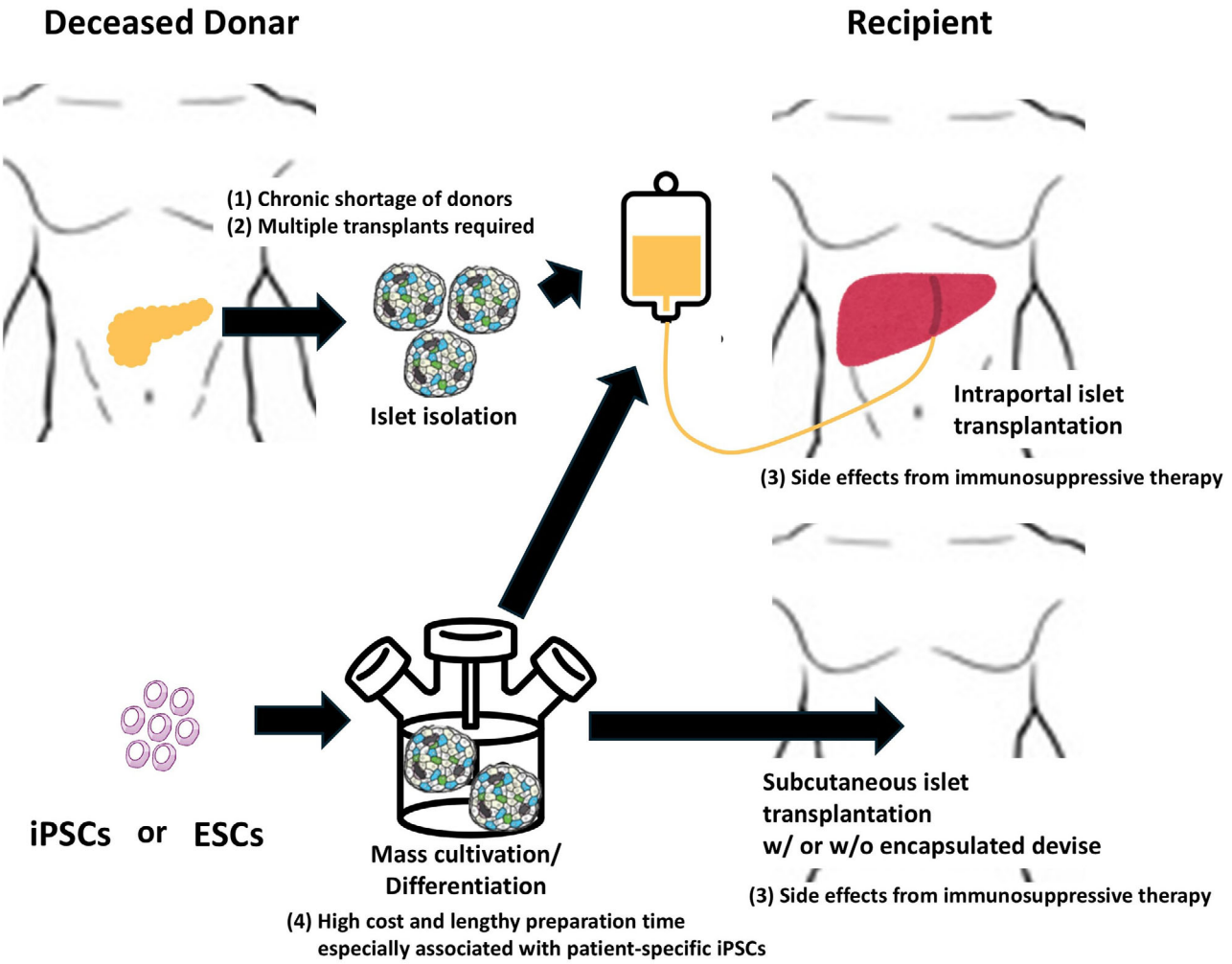


**Figure 1** | Islet cell transplantation: Methodologies and challenges to overcome. Transplantation of pancreatic islets from deceased donors presents a promising treatment avenue aimed at restoring physiological insulin secretion by re-establishing pancreatic β-cell function, primarily for patients with type 1 diabetes. Despite its potential, several significant challenges persist. These include the limited availability of donors, leading to prolonged waiting periods for patients in need (1), the necessity for multiple transplantations to achieve satisfactory outcomes (2), and the risk of side effects from immunosuppressive therapy (3). Advancements in regenerative medicine, particularly through the use of induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs), are garnering substantial attention as potential solutions to these challenges. Clinical trials exploring the safety and efficacy of intraportal islet transplantation using ESC-derived islet cells, as well as subcutaneous islet transplantation using ESC-derived or patient-specific iPSC-derived islet cells, with or without encapsulation devices, have shown promising initial results. Nonetheless, significant obstacles remain. These include potential adverse effects from immunosuppressive agents (3) and the high cost and lengthy preparation time associated with patient-specific iPSC-derived islet cells (4). To address these barriers, ongoing research focuses on the development of genetically modified ESC- or iPSC-derived islet cells with immune evasion properties, as well as the creation of more efficient, cost-effective protocols for the differentiation and expansion of these cells. The promising outcomes from recent clinical trials suggest that transplantation of iPSC- or ESC-derived islet cells could pave the way for more effective and broadly accessible treatment options. This progress holds potential not only for individuals with type 1 diabetes but may also extend to type 2 diabetes treatment in the future.

ChiCTR2300072200). The iPSCs were generated from a 25-year-old woman with 11-year history of type 1 diabetes using a proprietary chemical reprogramming method. These chemically induced iPSCs (CiPSCs) were then differentiated through a six-stage protocol into islet cell clusters, consisting of approximately 60% insulin-producing β-cells and 13% pancreatic endocrine progenitor cells. In preclinical safety trials, the islet cells were transplanted into 244 immunodeficient mice, with no evidence of teratoma or malignant tumor formation. Using an 18-gauge needle with ultrasound guidance, the CiPSCs-derived islet cells were transplanted beneath the anterior rectus sheath of the woman who had previously

**Table 1** | Clinical cell transplantation therapy for type 1 diabetes.

| Product | Sponsor Clinical Trials Registry ID | Clinical phase | Recipient | Donor | Starting cells | Cellular grafts | Transplant sites | Transplantation devices | Immunosuppression | Main outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| VC-01 | ViaCyte NCT02239354 | 1/2 | T1D | Allo | ESCs | ESC-derived pancreatic endoderm cells (PEC-01) | Subcutaneous | Immunoisolation devices | Not expected to be required | VC-01 explants at 12-week showed minimal cell survival, likely due to hypoxia |
| VC-02 | ViaCyte NCT03163511 | 1/2 | T1D | Allo | ESCs | ESC-derived pancreatic endoderm cells (PEC-01) | Subcutaneous | Macroencapsulation devices allowing for direct vascularization of the cells | With | Insulin production did not reach therapeutic levels |
| VX-880 | Vertex NCT04786262 | 1/2 | T1D | Allo | ESCs | ESC-derived islet cells | Intrahepatic via the portal vein | Without | With | More than 3 of 12 participants are insulin independent |
| CTX-211 | CRISPR Therapeutics NCT05565248 | 1 | T1D | Allo | ESCs | Modified ESC-derived pancreatic endoderm cells for immune evasion (PEC211) | Unspecified | Perforated device | Not expected to be required | Anticipated in 2025 |
| VX-264 | Vertex NCT05791201 | 1/2 | T1D | Allo | ESCs | ESC-derived islet cells | Subcutaneous | Channel array devices for vascularization while providing immune protection | Not expected to be required | Anticipated in early 2025 |
| E-islets | Shanghai Changzheng Hospital NCT05294822 | 1/1b | IDDM | Allo | iPSCs | iPSC-derived islet cells | Intrahepatic via the portal vein | Without | With | A single reported participant: Insulin-independence after 11 weeks post-transplantation |
| CiPSC-islets | Tianjin First Center Hospital ChiCTR2300072200 | 1 | T1D | Auto | CiPSCs | CiPSC-derived islet cells | Beneath the anterior rectus sheath | Without | With | A single reported participant: Insulin-independence from 75 days post-transplantation |
| OZTx-410 | Kyoto University Hospital jRCT2053240146 | 1/1b | T1D | Allo | iPSCs | iPSC-derived islet cells | Subcutaneous | Without | With | Anticipated in 2030 |

Allo, allogeneic; Auto, autologous; CiPSCs, chemically induced pluripotent stem cells; E-islets, endoderm stem cell-derived islets; ESCs, embryonic stem cells; IDDM, insulin-dependent diabetes mellitus; iPSCs, induced pluripotent stem cells; PEC, pluripotent stem cells-derived pancreatic endoderm cells; T1D, type 1 diabetes.

undergone two liver transplants due to cryptogenic cirrhosis and had lost a pancreas transplant due to thrombotic complications. Immunosuppression was maintained with tacrolimus, mycophenolate mofetil, and methylprednisolone, while the IL-2 receptor inhibitor basiliximab and the tumor necrosis factor-α inhibitor etanercept were administered during the transplantation. While insulin injection of 43 units/day was required before the transplantation, insulin independence status was achieved 75 days after the transplantation, which sustained for 1 year. Indices related to glycemic control were improved substantially: HbA1c, 7.6% to <5.7% within 120 days; fasting glucose levels, from 210 ± 59 mg/dL to <126 mg/dL within a year; time in range (TIR; 70–180 mg/dL) on continuous glucose monitoring, from 43.18% to >98% within a year. Importantly, she experienced no severe hypoglycemic events after the transplantation, in contrast to three episodes in the previous year. After insulin withdrawal, C-peptide levels stabilized between 297.9 and 350.9 pmol/L. A 75 g oral glucose tolerance test revealed impaired glucose tolerance 75 days after the transplantation, which improved to normal glucose tolerance by 180 days after the transplantation. Ultrasound and magnetic resonance imaging monitoring confirmed the absence of abnormal graft growth, teratomas, or tumors. She experienced only mild adverse effects, including a brief hospitalization for an upper respiratory infection. The clinical trial is ongoing, with two additional participants enrolled. This study marks the first successful autologous transplantation of islet cells derived from iPSCs and achieved near-normal glucose metabolism, representing a paradigm shift from care to cure in type 1 diabetes management. Last year, a group from China conducted an autologous transplantation of pancreatic islet-like cells (E-islets) derived from iPSCs of an individual with type 2 diabetes who had previously undergone a kidney transplant (ClinicalTrials.gov ID: NCT05294822)[9]. Although the assessment is complicated by the subject's residual endogenous insulin secretion, insulin independence was achieved 11 weeks after the transplantation despite the daily insulin dose of 20 units prior to the transplant. Additionally, the subject's HbA1c dropped from 6.6% pre-transplant and have remained within the normal range for ≥52 weeks post-transplant. In the case of autologous iPS cell transplantation, the preclinical safety tests and procedures needed to establish and differentiate individual iPSCs entail significant financial and time costs for each patient (Figure 1). To address this, we initially adopted the approach of transplanting allogeneic iPSCs, which have established safety profiles, while administering immunosuppressive drugs to prevent rejection. An investigator-initiated clinical trial is set to commence in early 2025 at Kyoto University Hospital (Japan Registry of Clinical Trials Trial ID: jRCT2053240146), supported by the Japan Agency for Medical Research and Development (Grant Number JP24ym0126125). The trial will involve the transplantation of Orizuru Therapeutics' OZTx-410 into the abdominal region of three individuals with insulin-deficient type 1 diabetes at high risk for severe hypoglycemia. OZTx-410, which is a sheet of pancreatic islet-like cells, differentiated from clinical-grade iPS cells provided from CiRA foundation (Kyoto, Japan).

To date, no fatal events have been reported in clinical cell transplantation therapies for type 1 diabetes related to the persistence of undifferentiated cells, tumorigenesis, or unregulated pancreatic hormone secretion due to aberrant differentiation when using stem cells. However, as the observation periods have been relatively short, typically spanning only a few years, continuous and careful monitoring will remain essential. Additionally, our understanding of the differences in rejection rates across transplantation sites in allogeneic transplantation and the potential recurrence of autoimmune responses against β-cells remains limited. In the two reported cases from China involving autologous transplantation of pancreatic islets derived from iPSCs, the subjects were under immunosuppressive therapy due to prior organ transplants. Therefore, it remains unclear whether pancreatic islets derived from autologous iPSCs can truly evade immune rejection. So far, even in clinical trials using donor-derived islets, there have been few cases of successful transplantation outside the portal circulation[10]. Since islet cells are transplanted beneath the anterior rectus sheath in the case of Wang *et al.*[8], it is interesting from the perspective that it can be sufficiently effective even when transplanted to local site that directly access to systemic circulation, not portal circulation. Nevertheless, once the safety of such clinical trials is firmly established, cell transplantation therapies for type 1 diabetes could offer new hope for more effective and widely accessible treatments —not only for type 1 diabetes but potentially for type 2 diabetes in the future. It is no exaggeration to say that we are making significant strides toward the potential eradication of diabetes.

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Not applicable.

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## REFERENCES

1. Gregory GA, Robinson TIG, Linklater SE, *et al*. Global incidence, prevalence, and mortality of type 1 diabetes in 2021 with projection to 2040: A modelling study. *Lancet Diabetes Endocrinol* 2022; 10: 741–760.
2. Latres E, Finan DA, Greenstein JL, *et al*. Navigating two roads to glucose normalization in diabetes: Automated insulin delivery devices and cell therapy. *Cell Metab* 2019; 29: 545–563.
3. Sherr JL, Laffel LM, Liu J, *et al*. Severe hypoglycemia and impaired awareness of hypoglycemia persist in people with type 1 diabetes despite use of diabetes technology: Results from a cross-sectional survey. *Diabetes Care* 2024; 47: 941–947.
4. Sakurai T, Kubota S, Kato T, *et al*. Advances in insulin therapy from discovery to β-cell replacement. *J Diabetes Investig* 2023; 14: 15–18.
5. Kieffer TJ, Woltjen K, Osafune K, *et al*. Beta-cell replacement strategies for diabetes. *J Diabetes Investig* 2017; 9: 457–463.
6. Ramzy A, Thompson DM, Ward-Hartstonge KA, *et al*. Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes. *Cell Stem Cell* 2021; 28: 2047–2061.
7. Butler PC, Gale EA. Reversing type 1 diabetes with stem cell-derived islets: A step closer to the dream? *J Clin Invest* 2022; 132: e158305.
8. Wang S, Du Y, Zhang B, *et al*. Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient. *Cell* 2024; 187: 6152–6164.e18.
9. Wu J, Li T, Guo M, *et al*. Treating a type 2 diabetic patient with impaired pancreatic islet function by personalized endoderm stem cell-derived islet tissue. *Cell Discov* 2024; 10: 45.
10. Gala-Lopez BL, Pepper AR, Dinyari P, *et al*. Subcutaneous clinical islet transplantation in a prevascularized subcutaneous pouch – Preliminary experience. *CellR4* 2016; 4: e2132.

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