Review Article

Pluripotent Stem Cell-Derived Cell Therapy for the Treatment of Type 1 Diabetes

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ABSTRACT

Type 1 diabetes (T1D) is a chronic autoimmune disease affecting millions of people worldwide. The condition results from the immune-mediated destruction of pancreatic β-cells, leading to insulin deficiency and lifelong dependency on insulin therapy. Despite advances in insulin delivery and glucose monitoring technologies, many patients struggle to maintain optimal glycemic control, and severe hypoglycemia remains a persistent risk. Islet transplantation offers a potential alternative but is limited by donor shortages and the need for lifelong immunosuppression. Pluripotent stem cells (PSCs), including embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), offer a renewable and scalable source of insulin-producing β-cells. These cells can be differentiated in vitro and have demonstrated glucose-responsive insulin secretion and the ability to reverse diabetes in animal models. Recent years have seen the translation of PSC-derived β-cell therapies into clinical trials, with several promising candidates including VX-880, VC-02, CTX-211 and OZTx-410 under investigation. These approaches include both allogeneic and autologous strategies as well as gene-edited and encapsulated cell delivery systems designed to enhance cell survival and minimize immune rejection. This article reviews the latest advances in PSC-based cell therapies for T1D with a focus on differentiation protocols, preclinical studies and ongoing clinical trials. It also discusses current challenges including immune protection, vascular integration, and scalability and outlines future directions for achieving a functional cure through regenerative medicine.

Keywords: Type 1 diabetes; pluripotent stem cells; β-cell replacement; iPSCs; ESCs; stem cell therapy; insulin; regenerative medicine

INTRODUCTION

Type 1 diabetes (T1D) is a chronic autoimmune disease in which the immune system mistakenly attacks and destroys insulin-producing β-cells within the pancreatic islets of Langerhans. The resulting insulin deficiency impairs glucose uptake by cells, leading to chronic hyperglycemia. Without insulin, the body cannot effectively use glucose for energy, necessitating lifelong insulin therapy for survival. As of 2022, approximately 8.8 million people globally were living with T1D, and the number is expected to almost double by 2040 (1) .

Despite significant advancements in insulin delivery technologies including pumps and continuous glucose

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Accepted August 16, 2025
https://doi.org/10.70251/HYJR2348.34303310

monitors, maintaining optimal glycemic control remains difficult for many individuals with T1D. Around 40% of patients fail to meet recommended glycemic targets, and 20% experience severe hypoglycemic episodes annually (2). While islet transplantation offers potential therapeutic benefits, their broader use is limited by donor shortages and the lifelong need for immunosuppressive therapy to prevent graft rejection (3).

Over the past decade, pluripotent stem cells (PSCs) have emerged as a promising new avenue for generating a renewable supply of functional β-cells for transplantation to cure T1D (4). Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are the main two types of PSCs, and they possess the remarkable ability to differentiate into virtually any cell types including insulin-producing β-cells. This differentiation capability has significant implications for developing cell replacement therapies aimed at restoring endogenous insulin production and achieving long-term glycemic stability in T1D. The recent advances in the differentiation of PSCs to functional insulin-producing β-cells and explore their potential for use in cell replacement. This review highlights recent advances in PSC differentiation toward insulin-producing β-cells and explores their clinical potential in cell-based therapies for T1D.

RATIONALE FOR PSCS-BASED CELL THERAPIES

PSCs are characterized by their ability to self-renew and differentiate into nearly all cell types of the body, making them a powerful tool in both basic research and regenerative medicine. ESCs are derived from the inner cell mass of the early blastocyst, while iPSCs are reprogrammed from adult somatic cells through defined transcription factors (5). PSCs, especially iPSCs, have been widely used in developmental biology and disease modeling, offering unprecedented opportunities to study human disease mechanisms, screen drugs and develop personalized therapies. Clinically, PSCs hold potential for generating specific tissues and organs for transplantation, potentially reducing the need for donor organs (6).

Significant progress has been made in developing protocols to efficiently differentiate PSCs into insulin-producing β-cells, with the goal of replacing damaged or nonfunctional pancreatic cells in patients with T1D. More recently, rapid advancements in stem cell technologies and differentiation strategies have brought these therapies closer to clinical application, with increasing success in generating functionally mature β-like cells. Encouragingly, PSCs-derived β-cells have entered clinical trials with preliminary results demonstrating their ability to secrete insulin in response to glucose levels (NCT02239354, NCT05791201). By targeting the root cause of T1D (β-cell loss), this approach offers a potential cure rather than mere symptom management. In contrast to traditional islet transplantation, which is severely limited by donor organ scarcity and the need for multiple donors per recipient, PSC-derived β-cells provide a renewable and scalable alternative. These cells can be produced in large quantities with high consistency and reproducibility, offering a theoretically unlimited supply for transplantation. By reducing dependence on cadaveric donors, PSC-based therapies hold promises for broadening access to cell replacement treatments and reshaping the future of diabetes care.

PRE-CLINICAL STUDIES OF PSCS-DERIVED BETA CELLS

Preclinical studies using diabetic animal models have been instrumental in evaluating the safety, functionality and therapeutic potential of PSC-derived insulin-producing β-cells. Kroon *et al* developed a method to successfully differentiate human ESCs into early pancreatic precursor cells which were then transplanted into immune-deficient mice (7). Within the in vivo environment, these precursor cells continued to mature, benefiting from the physiological cues and vascularization provided by the host. Over time, the transplanted cells developed into fully functional, insulin-producing β-cells capable of sensing glucose levels and secreting insulin accordingly. Remarkably, these mature cells were able to restore and maintain normoglycemia in diabetic mice which demonstrates robust glucose responsiveness and long-term glycemic control (7). Additionally, Rezania *et al* reported a robust seven-stage protocol for differentiating human ESCs into insulin-producing cells which expressed key markers of mature pancreatic β-cells and displayed glucose-stimulated insulin secretion comparable to that of human islets during static in vitro assays (8). Further analysis using single-cell imaging and dynamic glucose stimulation revealed dramatic similarities between the ESCs-derived insulin-producing cells and primary human β-cells. Importantly, the ESCs-derived insulin-producing cells reversed diabetes in mice within 40 days, approximately four times faster than pancreatic

progenitors which required 23 weeks (8). Although the ESCs-derived insulin-producing cells are not fully equivalent to mature β-cells, their glucose responsiveness and rapid therapeutic efficacy in vivo make them a promising alternative to pancreatic progenitors or cadaveric islets for the treatment of diabetes.

In addition to the successful differentiation of human ESCs into insulin-producing β-like cells, significant progress has been made using human iPSCs as well. Yabe *et al*. established a six-stage protocol for differentiating human iPSCs into functional β-cells by mimicking human ESC differentiation strategies (9) (Figure 1). A key enhancement was the inclusion of the compound CHIR99021, which significantly improved definitive endoderm induction. Importantly, transitioning from monolayer to spheroid culture markedly increased insulin secretion efficiency. When transplanted into diabetic mice, the iPSC-derived β-cells effectively lowered blood glucose levels and formed islet-like structures, underscoring their strong therapeutic potential for diabetes treatment (9). Moreover, Velazco-Cruz *et al*. developed an enhanced six-stage differentiation protocol to generate functional β-like cells from human iPSCs (10). Key innovations included precise modulation of transforming growth factor β signaling, optimization of cellular cluster size and the use of enriched serum-free media. These modifications yielded stem cell-derived β (SC-β) cells that not only expressed essential β-cell markers but also exhibited dynamic glucose-stimulated insulin secretion, which closely resemble native pancreatic β-cell function (10). *In vitro* analyses demonstrated that SC-β cells responded robustly to glucose. Upon transplantation into streptozotocin-induced diabetic mice, these cells significantly improved glucose tolerance within 10 days with sustained function observed over several months (10). These findings underscore the therapeutic potential of SC-β cells for diabetes treatment and provide valuable insights for refining differentiation protocols to produce clinically relevant β-cells.

In summary, both ESCs and iPSCs have shown immense promise as renewable sources for generating insulin-producing β-cells for the treatment of T1D. Unlike traditional insulin therapy, which only manages the symptoms of the disease, PSC-based cell therapies aim to replace the damaged β-cells to restore insulin production. Preclinical studies have consistently demonstrated that stem cell-derived β-like cells can recapitulate many of the key features of native pancreatic β-cells, including glucose sensing and regulated insulin secretion. When transplanted into diabetic animal models, these cells not only survive and integrate into host tissue but also restore normoglycemia and improve glucose tolerance for extended periods, in some cases even months after transplantation.

CLINICAL TRIALS OF PSCS-DERIVED BETA CELLS FOR DIABETES TREATMENT

In the ongoing quest to find a functional cure for T1D, several clinical trials have been initiated to explore the potential of PSCs-derived cell therapies to restore insulin

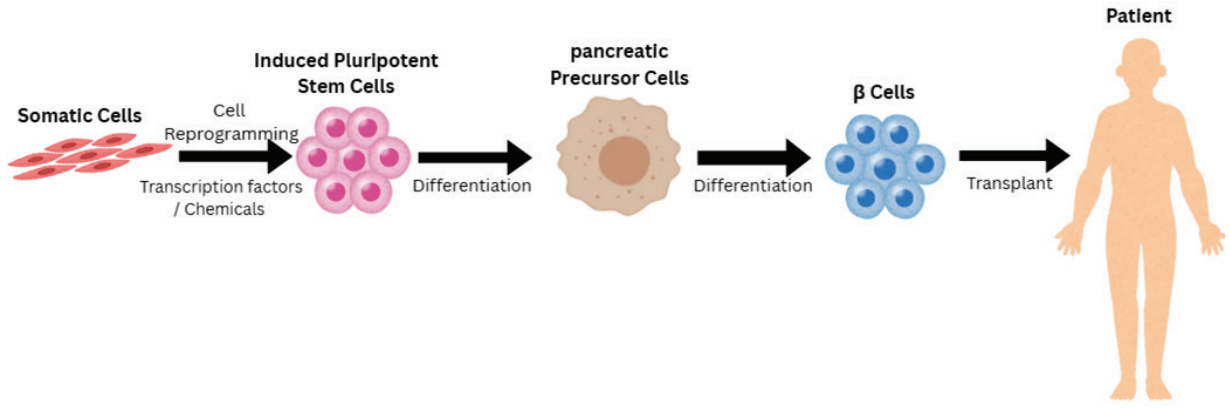

Figure 1. Differentiation of induced pluripotent stem cells (iPSCs) reprogrammed from somatic cells to generate β cells for Type 1 diabetes therapy. Somatic cells are reprogrammed into induced pluripotent stem cells (iPSCs) using transcription factors or chemical methods. These iPSCs are then differentiated into pancreatic precursor cells, which are further matured into functional β cells. The β cells are transplanted into the patient to restore insulin production in diabetes treatment.

production (Table 1). These studies aim to move beyond traditional insulin injections into regenerative medicine that could offer patients independence from daily management routines. Broadly, PSC-based therapies for T1D can be categorized into two main types: allogeneic and autologous cell therapies.

Allogeneic Cell Therapy for T1D Treatments

Allogeneic cell therapy involves the transplantation of insulin-producing cells derived from PSCs that originate from a donor rather than the patient. These cells are genetically distinct from the recipient's immune system, which typically necessitates immunosuppressive therapy or protective encapsulation to prevent immune rejection. This approach allows for large-scale manufacturing of standardized cell products and has become the focus of several industry-led clinical trials seeking to deliver off-the-shelf and therapeutic-grade β-cell replacements.

VC-01. ViaCyte's VC-01 developed by Vertex

Table 1. Clinical Trials for T1D Using PSC-Derived β Cells

Product	Sponsor	Clinical Phase	Cellular Grafts	Transplant Sites	Immuno-suppression	Main Outcome	Clinical Trial #
VC-01	ViaCyte	1/2	ESC-derived pancreatic endoderm cells (PEC-01)	Subcutaneous	Not expected to be required	VC-01 explants at 12-week showed minimal cell survival	NCT02239354
VC-02	ViaCyte	1/2	ESC-derived pancreatic endoderm cells (PEC-01)	Subcutaneous	Yes	Insulin production did not reach therapeutic levels	NCT03163511
VX-880	Vertex	1/2	ESC-derived islet cells	Intrahepatic via the portal vein	Yes	More than 3 of 12 participants are insulin independent	NCT04786262
CTX-211	CRISPR Therapeutics	1	Modified ESC-derived pancreatic endoderm cells for immune evasion (PEC211)	Unspecified	Not expected to be required	Anticipated in 2025	NCT05565248
VX-264	Vertex	1/2	ESC-derived islet cells	Subcutaneous	Not expected to be required	Anticipated in early 2025	NCT05791201
E-islets	Shanghai Changzheng Hospital	1/1b	iPSC-derived islet cells	Intrahepatic via the portal vein	Yes	Insulin-independence after 11 weeks post-transplantation	NCT05294822
CiPSC-islets	Tianjin First Center Hospital	1	CiPSC-derived islet cells	Beneath the anterior rectus sheath	Yes	Insulin-independence from 75 days post-transplantation	ChiCTR2300072200
OZTx-410	Kyoto University Hospital	1/1b	iPSC-derived islet cells	Subcutaneous	Yes	Anticipated in 2030	jRCT2053240146

Pharmaceuticals Incorporated in USA was one of the earliest clinical products to test an allogeneic PSC-derived therapy for T1D (NCT02239354). It employed pancreatic progenitor cells differentiated from human ESCs, which were encapsulated in a non-vascularizing, immune-isolating device designed for subcutaneous implantation. This device was intended to protect the transplanted cells from immune rejection while supporting graft viability and function for up to two years. Early findings from the Phase 1/2 clinical trial of VC-01 provided proof-of-concept that pancreatic progenitor cells could survive, engraft and mature in vivo within the encapsulation device. In some patients, detectable levels of C-peptide were observed, indicating insulin production and partial differentiation of the implanted cells toward functional endocrine lineages (NCT02239354). However, results from the trial revealed that viable cell survival declined significantly within 12 weeks post-implantation. Histological analysis indicated that this failure was likely due to hypoxia caused by the formation of multinucleated giant cells surrounding the device, which impaired oxygen diffusion. As a result, VC-01 did not provide meaningful or sustained therapeutic benefit in most patients.

VC-02. To address the limitations of VC-01, ViaCyte developed VC-02, a second-generation product consisting of pancreatic progenitor cells (PEC-01) derived from the CyT49 human ESC line, delivered via a vascular-permissive device known as PEC-Direct. Unlike the immune-isolating encapsulation used in VC-01, the PEC-Direct device allows for direct vascularization of the implanted cells, aiming to enhance oxygenation, support cell survival and promote maturation into insulin-producing islet cells (11).

Initial trial results of VC-02 offered encouraging signs of biological activity (NCT03163511). In several patients, the implanted PEC-01 cells demonstrated survival and partial engraftment with detectable C-peptide levels indicating insulin production. Histological analysis confirmed the presence of insulin- and glucagon-expressing cells within the grafts, suggesting progression toward functional islet cell phenotypes. These findings provided proof-of-concept that ECS-derived pancreatic progenitors could survive, vascularize, and mature in vivo in an immunosuppressed setting. However, despite these improvements, the overall clinical efficacy remained limited. After one year, C-peptide levels in most patients were only around 1% of normal physiological levels, and no consistent therapeutic effect was observed. The trial's modest outcomes were largely attributed to incomplete differentiation of PEC-01 cells into mature β cells as well as fibrosis-induced inhibition of vascular ingrowth, which impaired the long-term function and integration of the grafts (11).

VX-880 (Zimisele) and VX-264. To overcome the limitations observed with earlier products, Vertex Pharmaceuticals in USA developed VX-880 (now known as zimisele), a more advanced cell therapy using fully differentiated human ESC-derived islet cells. In this ongoing Phase 1/2/3 clinical trial (NCT04786262), VX-880 is delivered via intraportal infusion to patients with T1D and impaired awareness of hypoglycemia or a history of severe hypoglycemia.

The most recent update of VX-880 clinical trial results was presented at the European Association for the Study of Diabetes annual meeting in September 2024, demonstrating compelling benefits across all participants who received the full therapeutic dose. These include measurable insulin production as indicated by C-peptide levels (a biomarker of endogenous insulin secretion), elimination of severe hypoglycemia and significantly improved glucose control within one year of follow-up. Impressively, 11 out of 12 participants have reduced or eliminated their need for external insulin. Furthermore, all four participants with more than one year of follow-up after receiving the full dose achieved the primary endpoint of eliminating severe hypoglycemic events and met the secondary endpoint of insulin independence. While long-term durability and safety are still under evaluation, these initial outcomes suggest that VX-880 holds considerable promise as a transformative therapy for T1D and represents a major step forward in the development of stem cell-based treatments for T1D (12).

Compared to VX-880 which requires chronic immune-suppressing drugs to prevent rejection of the transplanted islet cells, VX-264 employed the same human ESC-derived islet cells but delivered them within an implantable encapsulation device designed to shield the cells from immune attack while allowing for the exchange of oxygen, nutrients, and insulin. The encapsulated therapy aimed to restore insulin production without the need for immunosuppression, making it more broadly applicable and safer for long-term use. VX-264 entered a Phase 1/2 clinical trial in early 2023 (NCT05791201), enrolling adults with T1D. Participants underwent surgical implantation of the encapsulated islet cells, and researchers monitored insulin production, glycemic control, and safety outcomes.

Despite the sound scientific rationale and favorable safety profile, VX-264 failed to demonstrate clinical

efficacy. By 90 days post-implantation, participants showed no significant increase in C-peptide levels, suggesting insufficient insulin production, possibly due to poor vascularization, inadequate nutrient exchange, or early cell death within the device. As a result, in March 2025, Vertex discontinued the VX-264 program. Although the therapy did not achieve its intended outcome, the trial provided valuable insights into the challenges of device-based cell encapsulation and will inform future innovations.

CTX-211. One of the major obstacles facing allogeneic human ESC-based therapies for T1D is the immune rejection of transplanted cells. To address this challenge, CRISPR Therapeutics has developed CTX-211, a first gene-edited human ESC-derived cell replacement therapy designed to restore endogenous insulin production without the need for chronic immunosuppression. CTX-211 utilizes pancreatic endoderm cells (PEC211) derived from human ESCs. These cells are precisely engineered using CRISPR-Cas9 technology to disrupt genes involved in immune recognition, rendering the cells immune-evasive. As a result, they can be transplanted with a reduced risk of immune-mediated rejection. The gene-edited cells are delivered in a retrievable, perforated implant that supports vascularization, enhances cell viability, and allows for future removal if needed. This device is implanted subcutaneously, offering a less invasive and more manageable treatment for patients.

To evaluate the safety, tolerability and therapeutic potential of this strategy, a Phase 1/2 clinical trial (CT05565248) is currently ongoing in Canada. Initiated in early 2023, the study aims to enroll approximately 40 adults with T1D. Participants receive PEC211 cells via the implanted device, and investigators are monitoring key outcomes including C-peptide production, glucose control, insulin independence and overall metabolic improvement. Although clinical results have not yet been released, CTX-211 represents a significant advance in the field. If successful, it could become one of the first therapies to reestablish durable, physiologic insulin secretion using stem cell-derived beta cells combined with gene editing, potentially transforming the treatment landscape for T1D.

OZTx-410. Kyoto University Hospital, in collaboration with Orizuru Therapeutics, has developed OZTx-410, an implantable sheet of pancreatic islet cells derived from human iPSCs. These sheets are composed of purified iPSC-derived pancreatic endocrine cells (iPICs) engineered to recapitulate native islet architecture and secrete insulin in response to blood glucose fluctuations. OZTx-410 sheets are fabricated into thin, implantable constructs designed for subcutaneous placement. This approach offers a less invasive and potentially retrievable graft compared to conventional intraportal islet infusion, aiming to simplify transplantation and reduce procedural risks. The cell sheets are produced using closed-system manufacturing processes with iPSC lines sourced from Kyoto University's CiRA Foundation.

To evaluate the safety and therapeutic potential of OZTx-410, a Phase 1/1b clinical trial (jRCT 2053240146) was initiated at Kyoto University Hospital in early 2025. The first patient has already undergone successful implantation of the cell sheet via a small abdominal incision, with no significant safety concerns reported during the initial post-operative period. Participants will be followed for up to five years to assess safety as the primary endpoint, along with secondary measures including insulin production, glucose control and metabolic function. While clinical efficacy data remain pending, OZTx-410 represents a novel, scalable cell therapy platform that could provide a safer and more manageable option for restoring endogenous insulin secretion in T1D patients.

Autologous cell therapy for T1D Treatments

Compared to the allogeneic approach, autologous cell therapy refers to the use of insulin-producing cells derived from iPSCs reprogrammed from the patient's own somatic cells. Because these cells are genetically identical to the patient, autologous therapy significantly reduces the risk of immune rejection and often eliminates the need for long-term immunosuppressive treatment.

In 2022, a clinical trial was initiated at Shanghai Changzheng Hospital in China to explore a personalized autologous cell therapy using islet cells derived from iPSCs reprogrammed from T1D patients own somatic cells (NCT05294822). In this study, a patient's iPSCs-derived islet cells are implanted into the liver via a minimally invasive portal vein infusion. Primary endpoints include changes in C-peptide, insulin requirements, and blood sugar levels, while secondary measures assess daily insulin use, incidence of severe hypoglycemia, and changes in glucagon levels, another key hormone in glucose homeostasis. The trial results indicated that, despite the complication of residual endogenous insulin secretion, the patient achieved insulin independence 11 weeks after transplantation, having required 20 units of insulin daily prior to the procedure. Additionally, the patient's HbA1c, a measure of average blood glucose

levels over the previous two to three months, decreased from 6.6% before the transplant and remained within the normal range for at least 52 weeks post-transplant (6). These findings suggest the promise of autologous iPSC-derived islet cell therapy for insulin-dependent diabetes, though further studies are needed to validate long-term safety and efficacy.

Recently, Tianjin First Central Hospital in China initiated a pioneering clinical trial (ChiCTR2300072200) evaluating chemically induced iPSC (CiPSC)-derived islet-like cells for T1D treatment. CiPSC-islets are generated by reprogramming patient-derived adipose cells into CiPSCs, which are subsequently differentiated into insulin-secreting islet-like clusters. The CiPSC-derived islet cells were transplanted subcutaneously beneath the abdominal anterior rectus sheath. The trial enrolled a 25-year-old female patient with longstanding insulin-dependent T1D and a complex clinical history including previous liver transplants. Post-transplantation, the patient achieved sustained insulin independence beginning 75 days after the procedure. Glycemic control improved significantly with time-in-target glucose range increasing from 43.18% to 96.21% by four months, alongside normalization of HbA1c levels. No transplant-related adverse events were observed over one year of follow-up. Although immunosuppressive therapy was required due to the patient's transplant history, ongoing research aims to develop immune-protective strategies to obviate the need for chronic immunosuppression. This study represents a significant milestone as the first reported case of CiPSC-derived islet transplantation successfully restoring endogenous insulin production in a T1D patient.

CONCLUSION

The development of PSC-derived insulin-producing β-cells marks a pivotal advancement in regenerative medicine with profound implications for the treatment of T1D. By replacing lost β-cell function rather than simply managing hyperglycemia with exogenous insulin, these cell-based therapies aim to restore endogenous insulin production and achieve durable glycemic control. Preclinical studies have established the functional capabilities of both ESC- and iPSC-derived β-like cells, demonstrating their ability to respond to glucose and reverse diabetes in animal models. Building on this foundation, early-phase clinical trials are now validating the safety and efficacy of these therapies in humans with T1D, with some participants achieving insulin independence and improved metabolic outcomes.

The rapid evolution from pancreatic progenitors to fully differentiated and even gene-edited β-cells reflects the growing sophistication of stem cell technologies and differentiation protocols. Efforts to overcome challenges such as immune rejection, limited vascular integration, and cell viability are beginning to yield more consistent and clinically meaningful results. Autologous approaches which utilize iPSCs reprogrammed from patients' own somatic cells, offer an exciting avenue to minimize immunological barriers. However, it takes much longer to complete the whole therapeutic procedure. In contrast, allogeneic strategies allow large-scale manufacturing of standardized cell products which allow delivering off-the-shelf and therapeutic-grade β-cell replacements to T1D patients right away. However, the allogeneic approach is often associated with host immune rejection which requires long term usage of immunosuppression drugs and this issue could be overcome by the newly developed gene-editing tools such as Crisp/Cas9.

As research progresses, the scalability, reproducibility and clinical refinement of PSC-derived β-cell therapies are expected to expand access and move closer to achieving a functional cure for T1D. The collective insights gained from ongoing clinical trials not only underscore the therapeutic potential of these approaches but also guide the next generation of treatments designed to transform long-term outcomes for individuals with T1D.

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