BioDrugs (2025) 39:261–280
https://doi.org/10.1007/s40259-025-00703-7

REVIEW ARTICLE

Islet Cell Replacement and Regeneration for Type 1 Diabetes: Current Developments and Future Prospects

Arthur Rech Tondin[1,2] · **Giacomo Lanzoni**[1,2]

Accepted: 5 January 2025 / Published online: 7 February 2025

Abstract

Type 1 diabetes (T1D) is a chronic autoimmune disorder characterized by the destruction of insulin-producing beta cells in the pancreas, leading to insulin deficiency and chronic hyperglycemia. The main current therapeutic strategies for clinically overt T1D – primarily exogenous insulin administration combined with blood glucose monitoring – fail to fully mimic physiological insulin regulation, often resulting in suboptimal or insufficient glycemic control. Islet cell transplantation has emerged as a promising avenue for functionally replacing endogenous insulin production and achieving long-term glycemic stability. Here, we provide an overview of current islet replacement strategies, ranging from islet transplantation to stem cell-derived islet cell transplantation, and highlight emerging approaches such as immunoengineering. We examine the advancements in immunosuppressive protocols to enhance graft survival, innovative encapsulation, and immunomodulation techniques to protect transplanted islets, and the ongoing challenges in achieving durable and functional islet integration. Additionally, we discuss the latest clinical outcomes, the potential of gene editing technologies, and the emerging strategies for islet cell regeneration. This review aims to highlight the potential of these approaches to transform the management of T1D and improve the quality of life of individuals affected by this condition.

Key Points

Islet cell transplantation is a promising approach for replacing beta cells and restoring endogenous insulin production in patients with type 1 diabetes (T1D), offering the potential for long-term glycemic stability.

In addition to islet transplantation, which has gained clinical approval in multiple regions of the world, newer approaches such as transplantation of stem cell-derived islets and stimulation of regeneration from endogenous progenitors are rapidly advancing.

Advancements in differentiation protocols, bioengineering, and immunomodulation strategies are improving the protection of transplanted or regenerated islet cells while addressing challenges related to achieving durable islet function and integration.

Outcomes from recent preclinical and clinical studies highlight the transformative potential of these islet cell replacement and regeneration therapies for managing T1D.

Extended author information available on the last page of the article

1 Type 1 Diabetes (T1D)

Today, approximately 9 million people live with type 1 diabetes (T1D). This number is expected to grow to between 13.5 and 17.4 million by 2040 [1]. The burden of T1D on human health and healthcare systems is substantial and is projected to increase rapidly in the coming years. T1D is an autoimmune disease characterized by an immune attack against insulin-producing beta cells. This autoimmune attack causes patients to lose insulin production and control of glucose metabolism, leading to chronic hyperglycemia and generalized inflammation. The standard treatment for T1D patients is exogenous insulin administration, which needs to be diligently managed by the patient throughout life. Although insulin therapy allows patients to manage the disease, the lack of beta cell endocrine function results in secondary complications such as retinopathy, nephropathy, neuropathy, and cardiopathy. These complications markedly diminish the quality of life of T1D patients and place a significant strain on healthcare system [1]. Approximately 6% of T1D patients experience recurrent severe hypoglycemic events (SHEs) and impaired hypoglycemia awareness, conditions that can put the life of a patient at immediate risk. To address the limitations of conventional exogenous insulin treatment, pancreas and pancreatic islet transplantation have

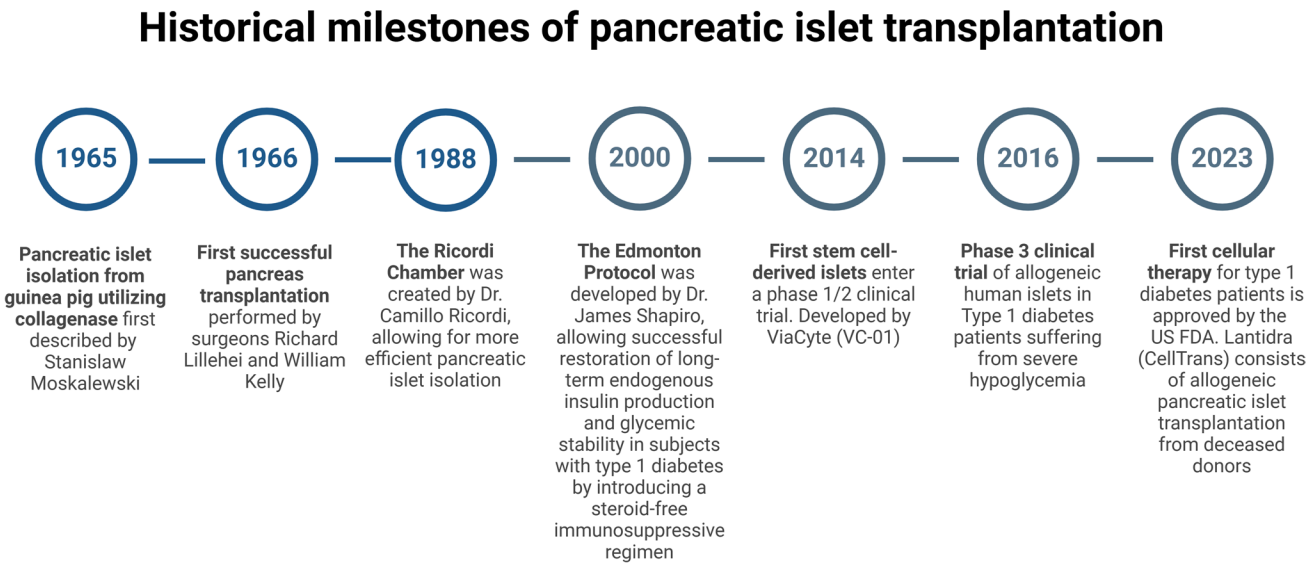

Fig. 1 Historical milestones of pancreatic islet transplantation. *FDA* Food and Drug Administration

been developed. These transplantation strategies enable the treatment of and potentially fully reverse the symptoms of diabetes. However, the scarcity of organ donors poses a significant limitation to these procedures. Additionally, because such transplantations occur in the allogeneic setting, recipients require immunosuppressive therapy. This chronic and systemic adjuvant treatment can lead to toxicity, increased risks of infection and tumor development, and ultimately a decreased quality of life for patients.

Research in beta cell replacement has focused on developing scalable solutions, such as stem cell-derived islets, combined with localized immunosuppression. Here, we present the key recent advancements in this field.

2 Cell-Based Therapies for T1D

2.1 Pancreatic Islet Transplantation for T1D

Pancreatic islet transplantation has laid the groundwork for islet cell replacement strategies for T1D and has evolved substantially since its early days (Fig. 1).

The first successful pancreas transplant in 1966 was a landmark achievement in diabetes care [2]. Pancreas transplantation has evolved extensively, but it continues to be limited by its nature as an invasive surgical procedure. Islet transplantation was developed as a less invasive alternative, focusing on the replacement of islet cells, with fewer potential side effects. Significant strides in islet cell transplantation were made by pioneers such as Dr. Camillo Ricordi, who developed the Ricordi Method for islet isolation in the late 1980s. This method enabled islet purification with minimal damage to the islets, protecting islets from further enzymatic action as they are freed, with minimal human involvement in the process of enzymatic digestion, and with high yield and purity of isolated islets. This work was a steppingstone for a more efficient method of pancreatic islet isolation intended for clinical islet transplantation [3]. In the year 2000, Dr. James Shapiro introduced the Edmonton protocol, which uses a steroid-free immunosuppressive regimen that greatly enhanced outcomes of islet transplantation. The international trial of the Edmonton protocol for islet transplantation demonstrated that insulin independence was achievable in 44% of T1D patients 1 year post-transplantation. While long-term sustainability posed challenges, with 31% of recipients maintaining insulin independence at 2 years follow-up, the study's execution across nine international centers showcased its potential. Despite encountering common manageable adverse events such as mouth ulceration and anemia, the trial confirmed the transformative potential of islet transplantation in significantly improving glycemic control and preventing severe hypoglycemia [4]. This research enabled advancements in immunosuppressive therapies to enhance patient outcomes and reduce toxicity, paving the way for future innovations [4]. These innovations made islet transplantation a feasible alternative to pancreas transplantation. Over the years, advancements in islet purification and immunosuppression have further improved graft survival and insulin independence. The advancements in the isolation of donor-derived pancreatic islets via the Ricordi method [5] and the transplantation of islets in combination with improved immunosuppressive regimens enabled this

therapeutic modality to be tested in a series of large multicenter clinical trials [5–7]. In a National Institutes of Health (NIH)-supported phase 3 clinical trial, islet transplantation was found to be more effective than intensive insulin therapy in enhancing metabolic control and reducing severe hypoglycemic episodes in patients with T1D [7]. A recent phase 3 study confirmed that allogeneic islet transplantation is a safe and effective treatment for patients with T1D and unstable glucose control despite intensive insulin treatment and supported the indication in the post-renal transplant setting [8]. Islet transplantation permits achievement of glycemic targets in the absence of severe hypoglycemia for recipients with impaired awareness of hypoglycemia, with acceptable safety of immunosuppression, in both settings of islet-alone and islet-after-kidney transplantation [9]. Despite ongoing challenges such as limited availability of donor-derived islets and the need for lifelong immunosuppression, recent studies indicate long-term benefits of islet transplantation in reducing hypoglycemia and improving glycemic control for transplant recipients.

Islet transplantation is now a clinically approved therapeutic modality for T1D patients with impaired awareness of hypoglycemia in multiple countries.

2.2 Stem Cell-Derived Islets for T1D

The widespread application of islet transplantation is significantly constrained by the limited availability of pancreata from deceased donors. Nevertheless, millions of individuals with T1D stand to benefit from islet cell replacement therapy. To overcome the challenge of the scarcity of donor-derived islets, researchers have investigated human pluripotent stem cells (hPSCs) as a scalable source for generating islet cells. Certain products developed in this rapidly advancing field have recently progressed to the stage of clinical trials. Here, we highlight the potential of stem cell-derived islets in developing sustainable and effective diabetes treatments. We will further discuss the risks, the open questions that need to be addressed, and the ethical considerations connected with these novel forms of cell therapy for T1D.

Leveraging knowledge from the field of embryology and development, a series of studies centered on pluripotent stem cells have provided robust protocols for in vitro differentiation of islet cells. In a pioneering study, D'Amour et al. [10] developed a five-stage differentiation protocol to generate pancreatic hormone-expressing endocrine cells from human embryonic stem cells (hESCs), marking one of the first significant advancements in stem cell therapy for diabetes. This protocol had the goal of mimicking the stages of in vivo pancreatic development, guiding hESCs through definitive endoderm, gut-tube endoderm, pancreatic endoderm, and endocrine precursor stages. Key steps include the use of Activin A and Wnt3a to induce definitive endoderm, followed by fibroblast growth factor 10 (FGF10) and KAAD-cyclopamine to inhibit hedgehog signaling and promote the formation of cells with the characteristics of primordial gut-tube. Subsequent stages involve retinoic acid to stimulate the development of posterior foregut cells and further differentiation into pancreatic endoderm and endocrine precursors. The final differentiated cells expressed key pancreatic markers such as insulin, glucagon, and somatostatin, and demonstrated insulin secretion in response to multiple secretory stimuli. This protocol appeared to be the first demonstrating convincing maturation of scalable stem cells into insulin-producing cells, paving the way for advanced cell replacement therapies in diabetes. In a subsequent study, Kroon et al. [11] evolved the protocol to differentiate hESCs, utilizing fibroblast growth factors (FGFs) and bone morphogenetic proteins (BMPs) to establish pancreatic progenitors. Retinoic acid was confirmed to promote commitment of these progenitors, and inhibition of the Sonic hedgehog (Shh) pathway, a known inhibitor of pancreatic development, resulted necessary for proper maturation. Transplantation of these cells at the stage of pancreatic endoderm progenitors into immunodeficient mice enabled their maturation into functional insulin-producing beta cells. This in vivo environment, which provided vascularization, enabled the cells to mature and respond to physiological levels of glucose. The glucose-responsive insulin secretion observed in these cells matured in vivo demonstrated their therapeutic potential, restoring and maintaining normoglycemia in diabetic mice models. The field of stem cell research received a major impulse from the groundbreaking studies by Dr. Takahashi and Yamanaka that discovered that mature cells can be reprogrammed to become pluripotent. These studies enabled the generation of induced pluripotent stem cells (iPSCs) from adult cells using key transcription factors: Oct4, Sox2, Klf4, and c-Myc [12, 13]. Leveraging this technology, Maehr et al. [14] developed iPSC from patients with T1D and stimulated them to generate insulin-producing cells. This study supported the feasibility of autologous islet cell therapy, where a patient's own cells could be reprogrammed and used for treatment, thereby minimizing the risk of immune rejection. The researchers reprogrammed skin cells from T1D patients into iPSCs. These iPSCs were then differentiated into insulin-producing pancreatic beta cells that exhibited insulin secretion in response to glucose levels at levels similar to those of natural pancreatic beta cells. The technology for generation of iPSCs was leveraged to generate cell lines derived from primary human pancreatic tissue acquired through organ donation [15]. In this approach, pancreatic cells were isolated and reprogrammed using non-integrating vectors. A cell line was selected because of its preferential

differentiation toward endodermal lineage and loss of mesodermal potential. With an improved differentiation protocol, the selected cell line generated populations of greater than 60% insulin-expressing cells that secreted insulin in response to glucose and were capable of reversing diabetes in rodents. The cell line, generated following current Good Manufacturing Practice (cGMP) methods, appeared as a candidate for insulin-producing cells for diabetes treatment [16]. In a milestone development aimed at refining the differentiation protocol, Pagliuca et al. [17] generated highly functional pancreatic in vitro from hPSCs, and confirmed the function in vivo. The differentiation process utilized specific growth factors and signaling molecules such as Activin A, Wnt3a, FGF10, and retinoic acid to replicate the natural development of pancreatic cells. The cells in output from the in vitro differentiation protocol exhibited key markers of beta cells maturation, including insulin, PDX1, and NKX6.1, and demonstrated glucose-responsive insulin secretion. When transplanted into diabetic mice, these cells effectively normalized blood glucose levels. This advancement provided a scalable and renewable source of insulin-producing cells, with significant potential for developing cell-based therapies for T1D. Nostro et al. [18] developed a method to generate NKX6.1+ pancreatic progenitors from hPSCs in an efficient way. The protocol utilizes epidermal growth factor (EGF) and nicotinamide signaling, along with retinoic acid and FGF10. This protocol inhibited BMP and hedgehog signaling to stimulate the formation of pancreatic endodermal cells expressing PDX1 and NKX6.1. These progenitors matured into endocrine cells in vitro, showing strong expression of NGN3 and differentiating into insulin-producing beta cells upon transplantation into immunocompromised mice. The study demonstrated glucose-responsive insulin secretion and successful differentiation into multiple pancreatic endocrine lineages, highlighting an efficient method to generate enriched beta cell progenitors from pluripotent stem cells. In 2016, Millman et al. [19] demonstrated the successful generation of functional pancreatic beta cells from iPSCs derived from skin cells of T1D patients. This study utilized an advanced differentiation protocol involving growth factors such as Activin A, Wnt3a, FGF10, and retinoic acid to guide the iPSCs through stages of pancreatic development. The resultant beta cells expressed critical markers including insulin, PDX1, NKX6.1, and MAFA, and exhibited glucose-responsive insulin secretion both in vitro and in vivo. When transplanted into diabetic mouse models, these cells effectively controlled blood glucose levels, demonstrating their functional maturity. Notably, there were no significant functional differences between beta cells derived from T1D patients and those from non-diabetic individuals, underscoring the potential for personalized cell-based therapies. This approach provided a scalable and renewable source of beta cells for potential therapeutic use but also offered a robust platform for studying beta cell biology and screening new diabetes treatments, marking a significant advancement in the field. Molakandov et al. demonstrated that selection for CD26− and CD49A+ cells from stem cell-derived islet-like clusters improves therapeutic activity in diabetic mice [20]. These cells were derived from a clinical-grade line of hESCs, with a differentiation protocol adapted to up-scalable bioreactors. The team identified CD49A (integrin alpha1) as a marker for cells that express insulin (or C-peptide) and NKX6.1. Depletion of CD26+ (dipeptidyl peptidase 4, DPP4), which was found on NKX6.1− cells, followed by enrichment for CD49A+ cells increased insulin+/NKX6.1+ cell fraction to ~70%. The CD26−/CD49A+ enriched islet-like clusters exhibited improved function in diabetic mice and maintained prolonged blood C-peptide levels. Jeyagaran et al. [21] presented a significant advancement in the forward programming of human iPSCs towards beta-like cells using the transcription factors NGN3, PDX1, and MAFA. This approach addressed the limitations of prolonged differentiation timelines and heterogeneity in pancreatic endocrine cell populations, which are major hurdles in the development of stem cell-based therapies for T1D. By utilizing an inducible lentiviral system, the team upregulated the expression of NGN3, PDX1, and MAFA in human induced pluripotent stem cells (hiPSCs), demonstrating glucose-responsive insulin secretion within *5* days of induction. The extension of the culture period in three-dimensional (3D) spheroid formations maintained the expression of NGN3 and MAFA, though PDX1 expression was lost, indicating the need for precise temporal control of these markers. Comparative analysis revealed that the hiPSC-derived spheroids resemble fetal pancreatic tissues functionally, highlighting the necessity for further optimization in maturation protocols. A recent study conducted by Augsornworawat et al. [22] demonstrated that hPSCs can be stimulated to mature in beta-like cells that release insulin following the same response profile and in amounts similar to true beta cells. The study utilized single-cell transcriptome profiling to track changes in stem cell-derived beta cells (SC-β cells) after being transplanted into the kidney capsules of diabetic mice over 6 months. The results indicated that the transplanted SC-β cells underwent significant transcriptional changes, maturing to closely resemble adult beta cells. They also expressed essential maturation genes like MAFA, CHGB, and G6PC2, which are usually absent in cells differentiated solely in vitro. Furthermore, these SC-β cells exhibited improved functionality, demonstrated by increased secretion of insulin and islet amyloid polypeptide (IAPP) proteins, which iscrucial for effective glucose regulation in

diabetes management. This study provided a valuable resource for understanding human islet cell maturation and offered insights that could refine differentiation strategies for beta cells and other islet cell types in future developments.

These findings highlight the promise of stem cell-derived islets as a viable and sustainable solution for T1D treatment. Advances in technologies and protocols have led to major milestones, includinging the functional maturation of beta cells following transplantation. Ongoing clinical trials are assessing the safety, efficacy, and scalability of these beta cell replacement approaches.

2.3 Chemically Induced Pluripotent Stem Cells (CiPSCs)

Human chemically induced pluripotent stem cells (hCiPSCs) represent a transformative development in regenerative medicine, potentially offering a scalable, safe, and efficient alternative to traditional reprogramming methods. Unlike genetic approaches, hCiPSCs are generated solely through small-molecule cocktails, which avoids risks like genomic integration and oncogenic transformation, making them ideal for clinical applications [23].

Recent advances have refined differentiation protocols, enabling the production of functional islet-like aggregates containing beta cells, alpha cells, and delta cells at efficiencies comparable to native human islets. These hCiPSC-derived islets display robust insulin secretion in response to glucose stimulation, as well as high expression of mature pancreatic markers such as MAFA and UCN3, essential for beta cell function [24].

Preclinical studies in diabetic models, including nonhuman primates, demonstrated that transplantation of hCiPSC-derived islets effectively restored glycemic control, reduced exogenous insulin requirement, and significantly improved C-peptide secretion [25].

Moreover, novel transplantation strategies, such as placement under the abdominal anterior rectus sheath, have been shown to enhance vascularization, functional maturation, and long-term viability of grafts, overcoming limitations of traditional intraportal infusion [25]. A recent clinical study demonstrated a significant advancement in T1D treatment through the use of autologous chemically induced pluripotent stem cell (CiPSC)-derived islets. Patient-specific CiPSCs were generated from adipose-derived mesenchymal stromal cells (ADSCs) [26]. These CiPSCs were differentiated into islet-like cells through a six-stage stepwise protocol optimized to mimic pancreatic development. The resulting islet aggregates contained approximately 60% beta cells, alongside alpha-like and delta-like cells, and were tested for genetic stability, tumorigenicity, and glucose responsiveness. The differentiated islets were transplanted beneath the abdominal anterior rectus sheath, a site chosen for its reduced inflammation risk and ease of monitoring. Remarkably, the patient achieved insulin independence within 75 days and sustained over 98% time-in-range glycemic control for a year, with glycated hemoglobin (HbA1c) reduced to non-diabetic levels [26]. While the approach used patient-specific CiPSCs, the patient was receiving immunosuppressive drugs in connection with previous allogeneic organ transplantation. There is the possibility that such immunosuppression may inhibit a recurrence of T1D autoimmunity.

Despite this important achievement, several challenges remain that could limit the broader application of CiPSC-derived islets. One key issue is scalability. While the differentiation protocol used to generate islet-like cells showed high efficiency, translating this process into a scalable, cost-effective production system for widespread clinical use poses significant logistical and economic challenges for millions of patients in the autologous setting. Ensuring batch-to-batch consistency, maintaining the safety of the cells, and meeting clinical-grade manufacturing standards must be addressed to support larger-scale applications.

3 Immunomodulation and Immune Evasion Strategies for Allogeneic Islet Cell Transplantation

The development of immunomodulation strategies for allogeneic islet transplantation has yielded significant success over the years (Fig. 2). Various approaches have shown potential in furthering islet graft survival and function while minimizing the need for chronic immunosuppression.

3.1 Improved Pharmacological Immunosuppression and Immunomodulation

The CD40-CD40 ligand (CD40L, also referred to as CD154) pathway has a critical role in graft rejection. Studies on anti-CD40L-based immunosuppression showed effectiveness in preventing islet and kidney allograft rejection in nonhuman primates, but development toward clinical applications stalled due to antibody interaction with platelets and thromboembolic complications. AT-1501 (Tegoprubart) was developed as an engineered anti-CD40L-specific monoclonal antibody characterized by reduced binding to Fcγ receptors on platelets to minimize these risks, while maintaining CD40L binding activity. Anwar et al. tested AT-1501 in cynomolgus macaque islet transplants and rhesus macaque kidney transplants. AT-1501 monotherapy achieved long-term graft survival, indicating strong immunosuppressive potential [27]. Post-islet transplant, AT-1501 improved C-peptide

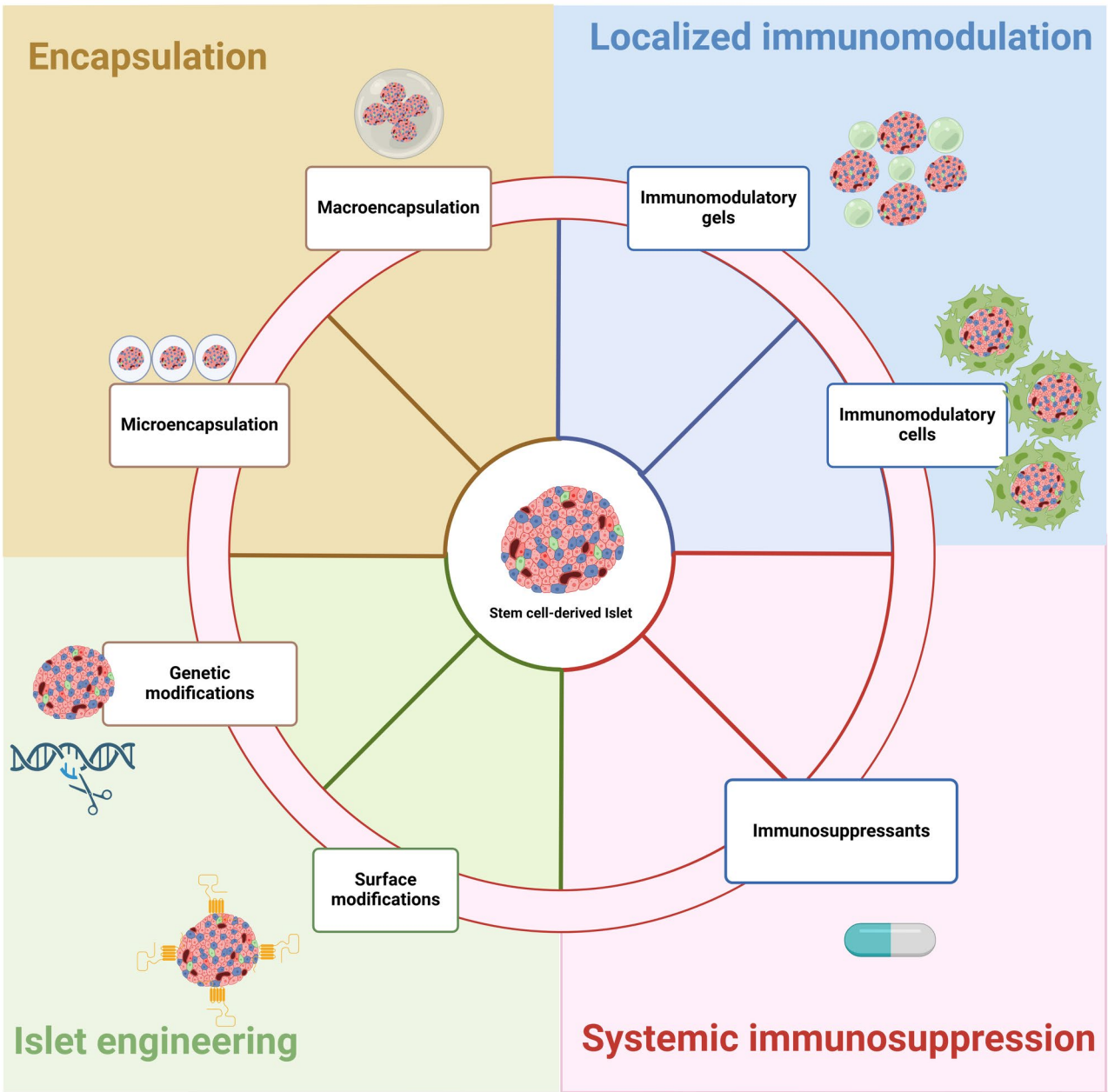

Fig. 2 Strategies to improve the outcomes of islet and stem cell-derived islet transplantation

levels, appetite, and weight gain and reduced cytomegalovirus reactivation compared to traditional immunosuppression. These findings support AT-1501 as a safe, effective agent for promoting islet and kidney allograft survival. A clinical study investigating this approach was recently initiated (NCT06305286).

3.2 Surface-Engineered Islet Cells to Evade the Immune Response

Traditional allogeneic donor transplants for T1D are hindered by immunosuppression-related morbidity and gradual loss of islet function. One way to overcome this challenge is through the engineering of islet cells to evade the immune system. Presentation of Fas ligand (FasL) on the surface of

islet cells could impart a pro-apoptotic signal in activated effector T cells, thus inhibiting a T cell-mediated attack against the graft. A study conducted by Yolcu et al. [28] investigated the potential of engineering pancreatic islets with a streptavidin-Fas Ligand (SA-FasL) protein to induce localized immune tolerance in diabetic mice. The team demonstrated that islet cells modified with SA-FasL protein, which persisted on their surface for over a week, were able to establish euglycemia indefinitely in diabetic syngeneic mice, demonstrating both endocrine cell functionality and a lack of acute toxicity. Furthermore, when these engineered islets were transplanted into allogeneic recipients alongside a brief rapamycin treatment, a robust localized tolerance mediated by CD4+ CD25+ FoxP3+ regulatory T (T_{reg}) cells was imparted in the totality of recipients. Depletion of T_{reg} cells led to immediate graft rejection, highlighting their critical role in maintaining immune tolerance. These results show the potential of ex vivo engineering of islets with immunomodulatory proteins.

3.3 Genetically Engineered Stem Cell-Derived Islet Cells to Evade the Immune Response

Multiple strategies are under investigation to engineer universal donor cells that can evade immune detection, thus minimizing the need for immunosuppressive therapies in transplantation [29]. The manipulation of human leukocyte antigen (HLA) molecules, which are pivotal in immune recognition and rejection processes, is a central goal. A knockout of the Beta-2 microglobulin (B2M) inhibits HLA class I expression, thereby avoiding cytotoxic T cell responses. However, in absence of HLA class I, natural killer (NK) cells would build a "missing self" response. To counteract this response, immunomodulatory HLA molecules can be utilized, such as HLA-E, HLA-F, or HLA-G. To inhibit T cell activity and promote immune tolerance, other natural immune evasion tactics can be leveraged, such as the expression of immune checkpoint molecules programmed cell death ligand 1 (PD-L1) and CTLA4-Ig. Hence, to create robust universal cells, there is a need for multifactorial approaches that combine HLA engineering with other immunomodulatory techniques. Preclinical studies demonstrate the efficacy of engineered cells in evading immune detection and surviving long term in allogeneic transplantation models [29]. Building on the concept of engineering islets for enhanced immunomodulation, Yoshihara et al. [30] explored the development of human islet-like organoids (HILOs) from iPSCs as a potential treatment for insulin-dependent diabetes. Transplanted HILOs effectively restored glucose homeostasis in diabetic NOD-SCID mice and, with PD-L1 overexpression, achieved prolonged function in immune-competent diabetic mice by evading immune rejection. Additionally, intermittent interferon gamma (IFNγ) stimulation induced sustained PD-L1 expression, enhancing immune protection [30].

A comprehensive study to address the immune rejection of stem cell-derived islets in the context of insulin-dependent diabetes therapy was performed by Sintov et al. [31]. Utilizing whole-genome Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and single-cell RNA sequencing (scRNA-seq), they identified key genetic modifications that could reduce immunogenicity. By using single-cell transcriptional analysis, the team identified "alarm" genes that drive the immunogenicity of stem cell-derived islets. These alarm genes appear to be involved in the regulation of antigen presentation and inflammatory responses. Among the most upregulated genes were B2M, HLA-A, HLA-B, HLA-C, HLA-F, TAP1/2, CD74, PSMB9, STAT1, JAK1/2, IRF1/2, and IL32. These genes play critical roles in T cell activation and inflammation. More importantly, the study revealed that the interferon (IFN) pathways significantly contribute to the immune response against stem cell-derived islets. Targeting IFNγ-induced mediators, such as chemokine ligand 10 (CXCL10), improved stem cell-derived islet survival in immune-challenged environments. By depleting CXCL10, the stem cell-derived islets showed enhanced resistance to allogeneic rejection in humanized mice models, highlighting the potential for genetic engineering in developing hypoimmunogenic stem cell-derived islet grafts.

In another study, Gerace et al. [32] engineered stem cell-derived islets to promote localized immune tolerance. The team initially focused on modifying stem cell-derived islets to overexpress PD-L1 and HLA-E, aiming to inhibit T cell activation and NK cell-mediated destruction. However, these modifications alone were insufficient, as the stem cell-derived islets were rapidly rejected upon xenotransplantation. To enhance immune evasion, the researchers developed stem cell-derived islets that secreted a combination of immunomodulatory cytokines: interleukin-10 (IL-10), transforming growth factor beta (TGFβ), and a modified IL-2 (IL-2 mutein N88D), designed to selectively expand T_{reg} cells. This strategy created a local immunosuppressive environment at the graft site, significantly improving stem cell-derived islet survival and function. In vitro studies demonstrated enhanced resistance to immune cell-mediated destruction, and in vivo experiments showed that these cytokine-secreting stem cell-derived islets could normalize blood glucose levels and maintain graft survival in diabetic and NOD mice.

More recently, Hu et al. reported that allogeneic transplantation of genetically engineered hypoimmune pseudo-islets ($B2M^{-/-}$, $CIITA^{-/-}$, $CD47^{+}$) in diabetic nonhuman primates resulted in successful engraftment, stable endocrine function, and insulin independence without triggering any detectable immune response, even without

immunosuppression [33]. Notably, these cells were transplanted in a fully immunocompetent diabetic nonhuman primate, achieving stable endocrine function and insulin independence without immunosuppression. The cells were engineered to disrupt major histocompatibility complex (MHC) class I and II functions and overexpress CD47, rendering them hypoimmune. Diabetes was induced in the nonhuman primate using streptozotocin, followed by insulin injections to manage glucose levels. After 78 days, hyperimmune pseudo-islets were transplanted intramuscularly, leading to insulin independence within a week, with normalized serum C-peptide levels and tightly controlled blood glucose for 6 months. Immune analysis post-transplantation showed no T cell recognition, graft-specific antibodies, or NK cell and macrophage killing. Furthermore, the targeted deletion of the hypoimmune pseudo-islets led to recurrence of diabetes and return to exogenous insulin dependence, which confirmed the transplant as the source of insulin independence. This study demonstrated the potential for hypoimmune pseudo-islets to provide an immunosuppression-free treatment for type 1 diabetes mellitus, achieving immune evasion and stable insulin independence in diabetic nonhuman primates [33, 34].

These studies indicate that the modification of islets or stem cell-derived islets through genetic engineering can induce localized immune tolerance and enhance graft survival without the need for continuous immunosuppression. Future research should address the safety and genetic stability of these engineered cells, the long-term effects of their engineered phenotype, and include mechanisms, such as safety switches, to remove the cells in case of uncontrolled growth.

3.4 Combination of Islet Cells with Immunomodulatory Cells

Mesenchymal stem cells (MSCs) are multipotent stromal cells under investigation for their immunomodulatory and regenerative properties. These cells can modulate immune responses, reduce inflammation, and promote tissue repair, making them promising candidates for therapeutic applications in various contexts, including autoimmune disorders, diabetes mellitus, and organ transplantation. Investigations are underway to determine the ideal MSC tissue source, transplant setting, and timing for use in combination with islet cell transplantation. A study by Kenyon et al. utilized a preclinical model of allogeneic islet cell transplantation in diabetic nonhuman primates, cynomolgus monkeys [35]. The study investigated the use of bone marrow-derived MSCs in combination with reduced levels of immune suppression as adjuvant treatment for allogeneic islet transplantation. Transplantation of pancreatic islets was performed with significant mismatch of major histocompatibility antigens. The goal was to evaluate the effects of MSCs from different sources (recipient, donor, or unrelated third party) and the timing of treatment. MSCs and islets were co-transplanted, with additional MSC infusions administered during the first month post-transplantation. MSC treatment was found to prolong islet survival and improve metabolic control, particularly when MSCs were derived from the recipient and when MSCs were both co-transplanted and administered with multiple infusions in the first month post transplantation. Immunological analyses showed that recipient MSCs significantly downregulated memory T cells, decreased anti-islet donor T cell proliferation, and increased the ratio of T_{reg}:$T_{conventional}$ cells, despite not preventing alloantibody formation [35].

Drs. Gooch and Westenfelder reported a study focused on Neo-Islets for the treatment of dogs with spontaneous autoimmune T1D [36]. Neo-Islets are 3D organoids composed of culture-expanded islet cells and MSCs. The study involved nine diabetic pet dogs receiving allogeneic Neo-Islets at a dose of 2×10^5/kg body weight, administered intraperitoneally under ultrasound guidance. Multiple parameters were monitored: blood glucose levels, HbA1c, exogenous insulin requirements, chemistry, lipids, complete blood counts, urinalysis. Baseline measurements for each dog served as control, followed by monthly assessments for 3 months and biannual evaluations for 3 years. The results indicate that allogeneic Neo-Islet treatment is safe, with no adverse events attributed to the investigational therapeutic. Moreover, the investigational treatment appears to be effective over the 3-year follow-up period. Notably, serum glucose, HbA1c, fructosamine levels, and exogenous insulin needs decreased after treatment. Neo-Islets appear to produce up to 1.2 insulin U/kg body weight. Importantly, Neo-Islets were implanted without using anti-rejection drugs, suggesting that the MSCs could impart key immunomodulatory effects [36]. Further preclinical research and clinical trials will be necessary to validate these results and optimize protocols for human application.

4 Encapsulation and Devices for Allogeneic Islet Cell Transplantation

Pancreatic islet encapsulation has been explored as a strategy to address immune rejection issues in islet transplantation for T1D treatment. Significant advancements have been made in the design and functionality of encapsulation devices, enhancing the viability and performance of transplanted islets. Key advancements include the development of more biocompatible materials, improved microencapsulation techniques, the incorporation of immunomodulatory agents, and innovative oxygenation strategies. However, certain challenges remain, such as material degradation,

managing the immune response, ensuring adequate nutrient and oxygen diffusion, scalability and manufacturing, and maintaining the functional longevity of the implanted cells.

4.1 Macroencapsulation

In the macroencapsulation strategy, islets are combined and placed into a single large device, built using materials intended to bolster islet graft survival.

A macroencapsulation device that has been widely utilized is the TheraCyte™ device [37]. Kumagai-Braesch et al. [38] investigated the immunoprotective capabilities of the TheraCyte™ device in preventing islet allograft rejection in an allogeneic rat model, focusing on immunized recipients. The study involved Lewis rats as donors of allogeneic islets and diabetic Wistar-Furth rats, either non-immunized or pre-immunized, as recipients. The results indicated that non-encapsulated islets had very short survival, averaging less than 10 days. The survival was shorter in immunized recipients compared to non-immunized ones (mean survival of 5.3 ± 2.7 days vs. 9.3 ± 1.6 days, respectively). However, when islets were encapsulated within the TheraCyte™ device, graft function was maintained throughout the six-month study period in both immunized and non-immunized rats. Oral glucose tolerance tests conducted 1 month post-transplantation indicated similar metabolic functions between the two groups, with comparable insulin and blood glucose levels. Additionally, the study observed a higher number of IFNγ-producing CD8+ T cells in immunized Wistar-Furth rats, indicating sustained donor-specific alloreactivity. Despite the presence of alloantibodies and alloreactive CD8+ T cells, the TheraCyte™ device successfully protected the encapsulated islet grafts in immunized recipients.

4.2 Macroencapsulation Devices Tested in Clinical Trials

Few devices for pancreatic islet encapsulation have been explored in the clinical setting.

4.2.1 Encaptra®, VC-01™, VC-02™

Viacyte's Encaptra® Drug Delivery System, a modified version of the TheraCyte™ device, was designed to provide long-term biocompatibility and stability in the subcutaneous space. This device was intended for complete encapsulation of stem cell-derived islet progenitor cells, preventing cell escape and teratoma formation while protecting against alloimmunity and autoimmunity [39]. In 2014, ViaCyte started its first clinical trial in T1D patients (NCT02239354) testing pancreatic endoderm cells (PEC-01) derived from CyT49 hESCs in combination with the device, yielding the VC-01™ combination product. This investigational product was tested in the absence of anti-rejection drugs. The device appeared to be safe, but hypoxia-induced necrosis affected most of the encapsulated cells. ViaCyte subsequently evolved the design of the device by adding several large pores across the membrane to enable vascularization. This evolved design removed the immunoisolatory function, bringing back the requirement for immunosuppression, but enabled cell engraftment, in vivo maturation, and beta cell function [40, 41]. Preliminary data from a phase 1/2 study showed that PEC-01 cells implanted in T1D patients matured in insulin-releasing islet cells. In 17 participants, PEC-01 cells were implanted in VC-02™ macroencapsulation devices, resulting in engraftment and insulin expression in 63% of devices within 3–12 months. Positive C-peptide was observed in 35.3% of participants, with adverse events mainly related to surgical procedures and immunosuppression. These findings were among the first to show that pluripotent stem cells could provide a scalable, renewable alternative to traditional islet transplants in humans [40]. In the phase 1/2, open-label, multicenter trial aimed at optimizing cell engraftment (ClinicalTrials.gov identifier: NCT03163511), the VC-02™ combination product was implanted in T1D patients with undetectable endogenous insulin production (C-peptide levels below the limit of detection of 0.03 nmol/L). In this trial, the function of the engrafted and matured beta cells could be detected in four out of ten patients at 6 months post-implantation. Although the amounts of insulin release did not reach clinically significant levels in most recipients, the patient with the highest C-peptide (0.23 nmol/L) increased time in range via continuous glucose monitoring from 55 to 85% at month 12 [42]. In this patient, at month 6 post-transplantation, the beta cell mass in sentinel devices was 4% of the initial cell mass. This observation indicates that substantial modifications will be necessary for improving engraftment and efficacy of the VC-02™ combination product.

4.2.2 βAir Device

Considering that oxygen has an essential role in islet survival and function [43], improving oxygen permeability in encapsulation materials will be key to improve transplantation outcomes. Pedraza et al. [44] addressed the challenge of preventing hypoxia-induced cell death in beta cells and islets. The team developed a hydrolytically activated, oxygen-generating biomaterial using polydimethylsiloxane (PDMS) encapsulated solid calcium peroxide (CaO_2). The encapsulation in PDMS restrained the rapid hydrolytic reactivity of CaO_2, enabling a sustained oxygen release over 6 weeks at an average rate of 0.026 mM per day. This biomaterial was evaluated using a beta cell line (MIN6) and pancreatic rat islets, demonstrating that the PDMS-CaO_2 disks could eliminate hypoxia-induced dysfunction and death,

maintaining metabolic function and glucose-dependent insulin secretion at levels comparable to normoxic controls. Additionally, the presence of PDMS-CaO_2 disks enhanced beta cell proliferation under hypoxic conditions for over 3 weeks. The study highlighted the potential of these materials to prevent detrimental oxygen gradients in 3D tissue-engineered constructs, supported by mathematical simulations. Carlsson et al. [45] conducted a phase 1 clinical study to evaluate the safety and efficacy of the bioartificial pancreas βAir device, from Beta O_2, which incorporates a refillable oxygen tank to address the critical issue of oxygen supply in macroencapsulation for islet transplantation. The study involved transplanting macroencapsulated human islets within the βAir device into four patients with type 1 diabetes mellitus. Each patient received one or two βAir devices containing between 155,000 and 180,000 islet equivalents (IEQ). The patients were monitored for three to 6 months, and the devices were subsequently recovered. The results demonstrated that the βAir device successfully prevented immunization and rejection of the transplanted islets, and the implanted beta cells survived within the device. However, the study observed only minute levels of circulating C-peptide, indicating limited metabolic control. Additionally, fibrotic tissue formation with immune cell infiltration was noted around the device. While the device supported islet viability and insulin secretion in vitro, the in vivo function was significantly compromised, with recovered devices showing blunted glucose-stimulated insulin responses and amyloid formation in the endocrine tissue [45].

4.2.3 Cell Pouch

Sernova's Cell Pouch™ is a microporous pouch made of polypropylene membranes designed for islet transplantation without immunoprotection. It has multiple parallel cylindrical chambers prefilled with polytetrafluoroethylene (PTFE) plugs, which are removed post-implantation for islet introduction. In a 2012 study (NCT01652911), Sernova's device was implanted subcutaneously in three T1D patients for 53 days. After removing the PTFE plugs, allogeneic pancreatic islets (~6000 IEQ/kg) were introduced, and immunosuppression was initiated. Despite initial C-peptide release, the graft failed [46]. In a 2018 study (NCT03513939), immunosuppression was started a month after implantation, and islets were introduced a month later. By July 2019, the first recipient showed no major adverse events, with well-vascularized devices [46, 47].

4.2.4 Shielded Living Therapeutics

Sigilon Therapeutics, which was recently acquired by Eli Lilly, developed the Shielded Living Therapeutics™ sphere (SLTx), consisting of cell clusters in an alginate matrix with a triazole-thiomorpholine dioxide (TMTD) coating. This modification is intended to inhibit host fibrotic reactions. In preclinical studies, human SC-β cells were encapsulated and implanted into the intraperitoneal space of immunocompetent diabetic mice. This combination product normalized blood glucose for 174 days [48]. A related encapsulation product from Sigilon Therapeutics was tested in a clinical trial for hemophilia (NCT04541628), using SIG-001 spheres with genetically modified cells expressing human factor VIII. When a patient developed inhibitors to factor VIII, a laparoscopic procedure was performed to retrieve the implanted spheres. The spheres were found to have fibrosed, and the encapsulated cells appeared non-viable. Hence, in view of T1D applications, the issue of fibrosis and engraftment may still need to be fully addressed.

4.2.5 VX-264

Semma Therapeutics developed an investigational cell therapy consisting of fully differentiated stem cell-derived islet cells loaded in a device with two semipermeable membranes of polyvinylidene fluoride. The device presents cross-membrane channels to improve vascularization. With a molecular weight cut-off of approximately 500 kDa, the device prevents the entry of immune cells and IgM antibodies but allows IgG antibodies, which are around 150 kDa, and cytokines to pass through [46, 49]. Semma Therapeutics was recently acquired by Vertex Pharmaceuticals, Inc., who further developed the cell therapy. Vertex`s VX-264 investigational treatment consists of differentiated islet cells that are encapsulated in an immunoprotective device and surgically implanted in the body. The device is designed to shield the cells from the body's immune system and is intended to remove the need for immunosuppression. VX-264 is being tested in a phase 1/2 clinical trial, which is currently enrolling (NCT05791201).

4.2.6 Biovascular Pancreas

Recently, an innovative approach for islet transplantation, termed the Biovascular Pancreas (BVP) has been developed [50, 51]. This method addresses challenges associated with traditional islet transplantation into the portal vein, such as inflammatory reactions, hypoxia, and peri-islet thrombosis. The BVP consists of an acellular biological vascular graft with an outer layer coated with an islet-populated hydrogel, designed to create an oxygen-rich environment for the embedded islets when connected to arterial circulation. This method is designed to enhance islet viability and functionality by ensuring adequate blood flow through the BVP lumen. In previous studies, the BVP demonstrated the ability to restore normoglycemia in diabetic rodent models with as few as 1500 IEQ per rat. Recent advancements include the

generation of BVPs using 6-mm inner-diameter human acellular vessels coated with a fibrin layer loaded with primate islets. These were tested in nonhuman primates (cynomolgus macaque), where the BVP was implanted as an aortic bypass graft. Over a two-week period, the BVP supported islet viability and insulin secretion, marking the first successful primate implantation of the BVP. The promising results of this study suggest that the BVP has significant potential to improve the viability of transplanted islets, which will be further evaluated in subsequent long-term in vivo studies [50, 51].

4.2.7 Immunomodulatory and Immunoprivileged Hydrogels

Novel approaches are being developed to enable islet transplantation without chronic immunosuppression. Lei et al. [52] tested microgels presenting SA-FasL in combination with islets as a method to enhance immune acceptance of islet allografts in nonhuman primates. The team co-transplanted allogeneic islets with SA-FasL-presenting microgels into the omentum of diabetic nonhuman primates, administering only a short course of Rapamycin as immunosuppression. The results demonstrated robust glycemic control, sustained C-peptide levels, and long-term graft survival exceeding 6 months when islets were combined with SA-FasL microgels. The SA-FasL microgels significantly prolonged islet graft survival compared to controls. Enhanced presence of FoxP3+ T_{reg} cells at the graft site indicated localized immune tolerance without affecting systemic T cell responses. Recipients maintained excellent glycemic control, had normal insulin and C-peptide levels, and showed no significant adverse effects. This study highlighted the potential of SA-FasL-presenting microgels in achieving durable islet allograft survival without chronic immunosuppression, paving the way for more effective and safer beta cell replacement therapies for T1D. Our team recently reported that the SA-FasL immunomodulatory microgels can be safely combined with human stem cell-derived islets, without detrimental effects on the diabetes reversal function of the cells in a preclinical model of diabetes. In our study, IsletRx stem cell-derived islets manufactured by Kadimastem Ltd (Israel) were shipped intercontinentally via air to Miami (USA) and implanted in diabetic immunodeficient NSG mice with or without SA-FasL microgels (iTOL-100, iTolerance Inc.). Over 3 months, body weight, glycemia, and human C-peptide levels were monitored. The study showed that IsletRx successfully engrafted, demonstrated maturation over time, and released substantial amounts of human C-peptide, normalizing blood glucose levels within a month at a dose of 9000 IEQ per recipient. Importantly, iTOL-100 did not negatively impact islet function or maturation. This suggests that IsletRx could be a globally available stem cell-derived islet and could be utilized in combination with local immunomodulatory gels (iTOL-100) [53]. In another recent and important work, Stover and colleagues explored physically immuno-protective hydrogels for allogenic islet transplantation, aiming to overcome the limitations of systemic immunosuppression [54]. Synthetic hydrogels were evaluated for robustness and islet function both in vitro and in immunocompetent diabetic animals without any immunosuppression. The study involved encapsulating rat and human donor islets in next-generation, shape-agnostic hydrogels and implanting them in the peritoneal space of streptozotocin-induced diabetic immunocompetent mice and rats. The functionality of the encapsulated islets was assessed over time through measurements of blood glucose, C-peptide, and HbA1c levels. The results demonstrated that the hydrogels successfully excluded IgG, maintained good islet function in vitro, and showed visible blood vessels early post-implant. Encapsulated rat islets provided rapid and sustained blood glucose control for over 140 days in immunocompetent mice and over 110 days in immunocompetent rats. Human donor islets encapsulated in the hydrogels also had extended functionality in mice, Yorkshire pigs, and Gottingen minipigs, as indicated by reduced blood glucose levels and increased C-peptide and HbA1c levels. A dose-dependent effect on in vivo function was observed, despite similar in vitro glucose-stimulated insulin secretion (GSIS) indices. Upon explantation, the encapsulated islets showed indicators of good function and viability, while the hydrogels exhibited minimal tissue response, good robustness, and integrity [54].

4.3 Microencapsulation and Conformal Coating

The microencapsulation technology for islets involves encasing the cell clusters within a hydrogel polymer, creating an encapsulation structure with a very thin layer [55]. Synthetic polymers offer tunable properties, easy synthesis, and superior mechanical properties, making them suitable for creating hydrogels, solid scaffolds, and microparticles. However, due to low biocompatibility and biodegradability, challenges remain, as synthetic polymers can often trigger chronic inflammatory or immunological reactions and may pose toxicity concerns [56]. Among the various materials tested for microencapsulation, alginate has shown considerable promise—being a biocompatible hydrogel that creates a semipermeable barrier allowing for nutrient and hormone exchange while preventing immune cell infiltration [57–60]. Alagpulinsa et al. [61] investigated a novel method to improve the survival and function of SC-β cells for the treatment of T1D without the need for systemic immunosuppression. The study focused on using alginate microencapsulation combined with the chemokine CXCL12 to protect and enhance the functionality of these cells when

transplanted into immunocompetent mice. The results demonstrated that incorporating CXCL12 into alginate microcapsules significantly improved the GSIS and long-term viability of the encapsulated beta cells. This approach led to prolonged glycemic correction in diabetic mice for over 150 days without inducing a fibrotic foreign body response, which is a common issue with other encapsulation methods. Furthering the development of microencapsulation utilizing alginate, Wang et al. [62] developed an islet encapsulation system intended to address both challenges of oxygenation and immune protection for therapeutic cells. The system, termed the Inverse Breathing Encapsulation Device (iBED), leverages a gas-solid reaction between carbon dioxide (CO_2) and lithium peroxide (Li_2O_2) to produce oxygen (O_2) autonomously from CO_2 from cellular respiration. Encapsulation was achieved using alginate. The O_2 generation is separated from the aqueous cellular environment by a gas-permeable membrane, ensuring cell survival under hypoxic conditions. This system was validated through O_2 measurements and imaging, demonstrating enhanced cell survival and function in hypoxic conditions. In vivo experiments showed that the device restored normoglycemia in diabetic mice for over 3 months and maintained functional islets in minipigs for 2 months. Hence, the iBED system appears promising to address the dual challenges of oxygenation and immune protection.

4.3.1 Zwitterionic Modifications of Alginate Microcapsules

Capsules with different chemistries can trigger foreign body reactions after implantation; hence, modifications of the capsules are being investigated to minimize this risk. Zwitterionic modifications of capsules are gaining popularity. Previous studies have shown that zwitterionic modifications in hydrogels reduce foreign body reactions, through antifouling properties avoiding absorption of non-specific proteins to the implanted materials [63, 64]. In addition, zwitterionic modifications could reduce cellular overgrowth and fibrosis around the implants [65]. In a work sponsored by Novo Nordisk, Liu et al. [66] developed the Safe, Hypo-immunoreactive, Islet Encapsulation, Long-term-functional Device (SHIELD) to encapsulate islets and human SC-β cells. The device utilized a nanofibrous membrane with a zwitterionic alginate hydrogel coating, designed to mitigate fibrosis while ensuring excellent mass transfer and long-term cell viability. Notably, SHIELD successfully maintained normoglycemia in diabetic mouse models for extended periods, demonstrating functionality for up to 399 days with rat islets and 238 days with human SC-β cells. Furthermore, the results were validated in canine models, demonstrating scalability and potential for clinical application.

4.3.2 Emulsion Cross-Linking Method for Conformal Coating

In a recent study by Tomei and colleagues [67], an emulsion cross-linking method was investigated for conformally coating islets with polyethylene glycol (PEG). The new method addresses significant limitations of previous coating techniques, which involved low pH exposure and viscosity enhancers that compromised islet viability and functionality. The emulsion method maintains a physiological pH and eliminates the need for viscosity enhancers, resulting in improved cytocompatibility and biocompatibility. In vitro and in vivo studies demonstrated that emulsion method-coated islets exhibit superior viability, insulin secretion, and scalability compared to the more traditional direct method-coated islets [67].

It is clear that encapsulation and device technologies for islet cell transplantation have paved the way for potential breakthroughs in the treatment of T1D, but key challenges remain. Issues such as material degradation, biocompatibility, and managing the immune response without chronic immunosuppression need to be addressed. Ensuring adequate nutrient and oxygen diffusion is crucial for maintaining cell viability and function of the mass of implanted islet cells. In addition, optimizing scalability and manufacturing processes will be paramount to enable clinical applications. Continued research and innovation are vital to overcome these obstacles and fully realize the potential of islet transplantation in T1D management.

5 Adult Beta Cell Progenitors: Differentiation and Regeneration

5.1 Adult Beta Cell Progenitors

An improved understanding of beta cell development, maturation, and replication could allow novel therapeutic strategies based on the potential of endogenous cells. Razavi et al. [68] conducted a pivotal study that shed light on the impact of diabetes on the proliferation of adult pancreatic multipotent progenitor cells (PMPs), as well as on their differentiation into insulin-producing beta cells. This study, which utilized both murine models and human samples, demonstrated that hyperglycemia and beta cell metabolic stress are critical factors in enhancing PMP proliferation and directing their maturation into functional insulin-secreting beta cells. Wang et al. [69] provided evidence that the peribiliary glands (PBGs) within bile duct walls and pancreatic duct glands (PDGs) along the major pancreatic ductal structures harbor a continuum of progenitor cells across maturational lineages, from pluripotent stem cells marked by NANOG, OCT4, and SOX2, to fully differentiated pancreatic endocrine cells. The

study revealed that biliary tree stem cells (BTSCs) obtained from bile duct tissue can differentiate into functional pancreatic islet cells, capable of regulating glucose levels. This differentiation appeared enhanced in a 3D culture environment, forming neoislets that closely mimic the ultrastructural and functional properties of native islets. The biliary tree, large pancreatic ducts, and PDGs could serve as a reservoir for pancreatic progenitors contributing to lifelong pancreatic organogenesis, maintaining structural and functional relationships related to organ development [70]. The identification of these stem and progenitor cell niches, along with the recognition that pancreatic progenitors may be replenishing pancreatic islet cells throughout adult life, offer a transformative framework for developing regenerative therapies for diabetes. In a recent significant study, Dominguez-Bendala and colleagues [71] utilized dynamic scRNA-seq on live human pancreatic slices (HPSs) to elucidate the process of islet endocrine cell neogenesis. The research showed that under bone morphogenetic protein 7 (BMP-7) stimulation, pancreatic ductal cells exhibit a blurring of maturational compartment boundaries and initiate a differentiation trajectory through a ducto-acinar intermediate stage. By demonstrating the conversion of ductal cells into insulin-producing endocrine cells through an intermediate ducto-acinar stage, this groundbreaking longitudinal analysis confirmed the dynamic and plastic nature of human pancreatic cells and suggested potential regenerative therapies for diabetes in connection with BMP-7 stimulation [71].

More recently, Darden et al. investigated expandable human pancreatic progenitor cells capable of generating islet organoids in vitro and in vivo. Using scRNA-seq on dissociated pancreatic tissue from normal and pancreatitis human pancreata, they identified islet progenitor cell populations, gene signatures, and unique markers. Validation involved quantitative polymerase chain reaction (qPCR) and flow cytometry. Progenitor cells marked by Procr, CD9, and RGS16 were flow-sorted and expanded to produce functional islet-like organoids. Undifferentiated progenitor cells and differentiated organoids were transplanted into streptozotocin-induced diabetic nude mice to assess function. Within 28 days, undifferentiated cells migrated to the damaged pancreas and produced human islet organoids in vivo. Differentiated cells produced insulin and glucagon in vitro and restored islet function in vivo. Hence, Procr+, CD9+, and RGS16+ islet progenitor cells showed regenerative properties, highlighting their potential in islet cell replacement and regeneration [72].

In a recent study, Al-Hasani et al. [73] investigated the potential of enhancer of zeste homolog 2 (EZH2) inhibitors, specifically the Food and Drug Administration (FDA)-approved GSK126 and tazemetostat, to promote the regeneration of beta-like cells in samples from donors with T1D. The study demonstrated that transient stimulation of exocrine cells from juvenile and adult T1D donors with these EZH2 inhibitors resulted in a phenotypic shift towards beta-like cell identity. This shift was facilitated by changes in chromatin states, particularly modifications involving H3K27me3 and H3K4me3. The reprogrammed pancreatic ductal cells exhibited insulin production and secretion in response to physiological glucose challenges ex vivo. These findings highlight the potential of EZH2 inhibitors as novel modulators of ductal progenitor differentiation and propose a promising approach for restoring beta-like cell function in diabetic patients. The study's results suggest that targeting EZH2 could be a viable strategy for enhancing beta cell regenerative capacity.

As previously discussed, investigators have developed methods for generating pancreatic islets from early-stage stem cells, often resulting in protocols that are both time-consuming and costly. Starting with pancreatic progenitors could offer a more efficient approach that may significantly accelerate the process [74]. Moreover, pancreatic progenitor cells could be stimulated in vivo, within the pancreas of a patient, to form new insulin-producing cells.

5.2 Beta Cell Regeneration

Beta cell regeneration is another mechanism targeted for therapeutic intervention. This approach allows for non-invasive treatments to be developed. Recent advancements in the understanding of beta cell regeneration have unveiled promising pathways for diabetes therapy.

Dor et al. [75] employed a tamoxifen-inducible Cre/lox genetic lineage tracing system to elucidate the source of new beta cells in adult mice. The findings from this study indicated that adult beta cells are primarily generated through the duplication of pre-existing beta cells rather than stem cell differentiation. The study suggested that no substantial numbers of new islets are formed postnatally, and that the significant turnover and expansion of beta cell mass in adult life is primarily deriving from the proliferation of beta cells. These results highlight the intrinsic capability of beta cells to maintain and restore their population.

Molecules and growth factors with the ability to stimulate beta cell proliferation have been studied extensively, but few have shown sufficient promise to reach the stage of clinical trials for T1D. One notable exception is related to the recent work on harmine. Dr. Stewart and his team have conducted pioneering studies on the regenerative potential of harmine, a dual tyrosine-regulated kinase 1A (DYRK1A) inhibitor, in human pancreatic beta cell regeneration [76]. Harmine has shown promise in enhancing beta cell proliferation and function, with therapeutic potential for both T1D and type 2 diabetes. The study indicates that harmine boosts beta cell numbers, restores insulin secretion, and normalizes

glycemic control. Importantly, harmine appears especially efficacious when combined with glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) like exenatide, significantly enhancing human beta cell mass by four- to sevenfold, as demonstrated in a mouse xenograft model [77]. This combination therapy achieved beta cell increase through enhanced cell proliferation, function, and survival without causing dedifferentiation or affecting alpha cell mass. The studies further identified the islet prohormone VGF is non-acronymic as a mediator of increased beta cell survival. The safety profile of harmine is favorable, showing no significant off-target effects, adverse proliferation, or histological changes in non-target tissues, and no hypoglycemia in treated mice. Provided that the autoimmune condition can be addressed, these advancements could enable the development of an affordable treatment to restore beta cell mass, offering a promising solution for T1D management.

6 Recent Clinical Developments in Islet Cell Replacement Therapy

6.1 US Food and Drug Administration Approval of CellTrans's Donislecel (Lantidra)

Recently, in June 2023, the first cellular therapy for T1D was approved by the US FDA [78]. Donislecel, a product developed by CellTrans Inc., consists of isolated islets from deceased donors, intended for transplantation into T1D patients who are unable to maintain good glycemic control through traditional insulin therapy and with impaired glycemia unawareness. These islet cells are infused into the hepatic portal vein, where they can establish themselves in the liver and begin to produce insulin endogenously, thereby helping to regulate blood glucose levels more effectively [79, 80]. The FDA's approval of donislecel was grounded on findings from two non-randomized controlled single-arm trials. In a recent update, Rios et al. presented the efficacy and safety results of donislecel, evaluated in two core clinical studies, UIH-001 (phase 1/2) and UIH-002 (phase 3). Patients who were screened for an appropriate benefit-risk profile received one to three administrations of donislecel. Out of 30 patients treated, 19 (63%) achieved the composite efficacy endpoint of HbA1c $\leq$ 6.5% and the absence of SHEs through one year after the last transplant. Additionally, 20 out of 30 patients (67%) were insulin-independent at one-year post-transplant. Importantly, the improvements in glycemic control persisted, with two-thirds of patients maintaining good glycemic control after 6 years. Donislecel demonstrated a safety profile consistent with the known risks associated with the transplant procedure and the long-term use of immunosuppressants [81].

The approval of donislecel represents a significant milestone in the treatment of T1D, offering an option for patients who struggle with traditional insulin therapy and hypoglycemia unawareness.

6.2 Clinical Trials of Stem Cell-Derived Islets

In 2014, the FDA approved the first clinical trial for stem cell-derived islets. In that trial, an investigational product consisting of hESC-derived pancreatic endoderm encapsulated was tested: ViaCyte's VC-01™. However, the trial for the modified device VC01-103 was terminated due to inadequate functional engraftment [41]. Subsequently, ViaCyte initiated a new trial using a different cell product, PEC-01, encapsulated in an open macroencapsulation device, VC-02™. The open system allowed re-vascularization and immune system access, necessitating immunotherapy [40]. A multicenter trial reported by Shapiro et al. [40] demonstrated insulin expression and C-peptide production in T1D participants who received PEC-01 cells. Preliminary findings from this phase 1/2 open-label trial involved 17 participants with T1D who received subcutaneous implants of PEC-01 cells in VC-02™ devices. The study found that 63% of the explanted VC-02™ units showed successful engraftment and insulin expression at 3–12 months post-implantation. Six out of the 17 participants (35.3%) showed positive C-peptide production, indicating functional insulin secretion as early as 6 months post-implant. Most adverse events were related to surgical procedures and immunosuppression, with a few potentially linked to the investigational product.

Separately, Ramzy et al. [82] reported on a single-center trial using the ViaCyte system with 15 patients who received subcutaneous PEC-01 cell implants within a macroencapsulation device. Over 1 year, the implants were well tolerated without teratoma formation or severe graft-related adverse events. Patients showed increased fasting and glucose-responsive C-peptide levels, with some developing meal-stimulated C-peptide secretion. The explanted grafts contained cells with a mature beta cell phenotype, immunoreactive for insulin, islet amyloid polypeptide, and MAFA.

More recently, Keymeulen et al. [42] reported that in one study group, ten patients with undetectable baseline C-peptide received two to three times the cell doses (PEC-01) in ViaCyte encapsulation devices with enhanced perforation patterns. After over a year, results showed that three patients achieved clinically significant C-peptide levels ($\geq$ 0.1 nmol/L) correlating with improved glucose control and reduced insulin requirements. However, beta cell mass in the best responder was only 4% of the initial implant, suggesting a need for further optimization.

ViaCyte led the way for the further development and exploration of stem cell-derived pancreatic islets. In July 2022, the company was acquired by Vertex Pharmaceuticals, which is now leading clinical trials utilizing stem cell-derived islets.

6.3 Observations in the Clinical Trial of Vertex's VX-880

VX-880 is an investigational allogeneic stem cell-derived, fully differentiated pancreatic islet cell replacement therapy developed by Vertex Pharmaceuticals Inc. VX-880 is currently being evaluated in a phase 1/2 clinical trial for patients with T1D with impaired hypoglycemic awareness and severe hypoglycemia (NCT04786262) [83]. Initial observations in this trial have been reported between 2022 and 2024 [84, 85]. At baseline, all patients in the study had undetectable fasting C-peptide (indicating negligible levels of endogenous insulin secretion), had a history of recurrent SHEs in the year prior to screening, and required an average of 39.3 units of insulin per day. The preliminary observations in this trial suggest that VX-880 with immunosuppression has a safety profile consistent with that of immunosuppressive agents used, the infusion procedure, and complications from long-standing diabetes. All 12 patients who received a full dose of VX-880 in a single infusion exhibited islet cell engraftment and glucose-responsive insulin production by day 90. SHEs were abated, and glycemic control was significantly improved. All patients achieved the ADA-recommended target of HbA1c levels below 7.0% and spent over 70% of their time within the glucose range of 70–180 mg/dL, with 11 out of 12 patients significantly reducing or completely eliminating the need for exogenous insulin. Based on these results, the trial has advanced and expanded to enroll approximately 37 participants. These observations indicate that VX-880 has potential to restore insulin production, improve glycemic control, and provide insulin independence in patients with T1D.

6.4 Vertex VX-264 - NCT05791201

In 2023, Vertex received the approval of the FDA to conduct a phase 1/2 clinical trial for its other product, VX-264, which employs a unique strategy. It uses the same pancreatic islet stem cells as VX-880, but these cells are encapsulated within a surgically implantable canal-arterial protective device to shield them from the recipient's immune system [86]. The completion of the study is aimed for May 2026 (NCT05791201).

6.5 Regulatory Approach to Pancreatic Islet Cell Transplantation

In the USA, allogeneic islet transplantation is regulated by the FDA as a biological drug under the Biologics License Application (BLA) pathway [87]. This classification mandates extensive clinical trials, consistency in manufacturing, and strict adherence to safety and efficacy standards. While this regulatory framework is intended to maximize quality and long-term safety, it comes with significant challenges, including high costs, approval delays, and limited accessibility. For example, the orphan drug designation granted to Lantidra (CellTrans), the first FDA-approved allogeneic islet product, gives 7 years of market exclusivity, which restricts competition and potentially limits broader patient access [88].

Many in the field propose a shift in the oversight of islet transplantation to the framework used for organ transplants, governed by the Health Resources and Services Administration (HRSA) and the United Network for Organ Sharing (UNOS). This model would integrate clinical oversight and quality assurance tailored to the unique characteristics of islets, facilitating broader access while maintaining safety standards [89]. Such updates could enable the USA to align with international practices where islet allotransplantation is a recognized standard of care. Countries like Canada, Australia, and several European nations regulate islets as tissue or organs, exempting them from drug-related constraints and allowing reimbursement through national healthcare system.

6.6 Risks and Challenges in Developing Stem Cell-Derived Islets for Therapeutic Applications

Although stem cell-derived islet cell therapy represents a promising approach for treating diabetes mellitus, a range of issues must be addressed to deliver safe, efficacious, and scalable therapies. The use of allogeneic cells raises the challenge of alloimmune responses and graft rejection. While immunosuppression can mitigate these issues, it introduces risks such as increased susceptibility to infections and tumors, along with organ toxicity. Moreover, T1D autoimmunity could recur, attacking the engrafted islets. A wide array of strategies have been studied regarding preventing immune attacks and rejection, but the risks associated with most of these strategies remain unclear, and further research is needed to refine their safety and efficacy [29, 90]. Repeat transplantation might be an option in the case of graft loss, but it is not ideal, due to the associated risks and logistical challenges. Another important concern is whether residual pluripotent stem cells persist in the transplanted products, which could lead to tumorigenesis or teratoma formation. To mitigate these risks, strategies to increase the safety

have been proposed, including reprogramming of somatic cells into iPSCs, selection of "pure" differentiated pancreatic cells, depletion of contaminant PSCs in the final cell product, and control or destruction of tumorigenic cells with engineered suicide genes [91, 92]. From a manufacturing point of view, although multiple observations suggest that high-yield, precise, and advanced differentiation of hPSCs into functional beta cells is possible, many protocols appear to be difficult to replicate in full. Additionally, the risk of off-target differentiation exists. While it is unclear whether such misdirected cells would be harmful, they are often detected in the cell preparations in output from differentiation protocols. These observations highlight the importance of rigorous quality control in the manufacturing process and the need to quantify the risks associated with implanting such cells. Achieving efficient differentiation of stem cells into fully functional, insulin-producing beta cells remains a substantial challenge, impacting the reproducibility and costs of the cell manufacturing. Incomplete or suboptimal differentiation can result in cells that fail to respond adequately to glucose levels, diminishing therapeutic effectiveness, or, worse, that can give rise to unexpected or undesired tissues in vivo.

The potential need for a retrievable implantation device and transplant site [93] or the eventual need for direct interaction with recipient tissues further complicate the strategies. All of these factors could influence both differentiation outcomes and therapeutic efficacy. The duration and sustained function of transplanted islet cells will be critical for long-term disease management. Microenvironmental factors, immune responses, fibrosis, and the potential need for a supportive graft microenvironment could affect the viability and function of engrafted cells. Research into the best implantation sites and surgical strategies is ongoing, as these factors appear to influence outcomes significantly.

The use of embryonic stem cells continues to raise ethical concerns, and navigating the global regulatory landscape for stem cell therapies adds a layer of complexity. In combination strategies, such as those involving immune-evasion, encasing, and retrievable devices, safety analyses may need to dissect the risks of the non-cellular components. Safety of adjuvant immunosuppressive regimens has always been a concern, and when these are combined with potentially tumorigenic or improperly differentiated cells, the risk-benefit analysis reaches yet another layer of complexity.

Several questions remain unanswered. Should the cells be encapsulated or implanted directly to enable contact with recipient tissues? What is the best graft environment to ensure engraftment and sustained function? Could the risks of rejection or autoimmune recurrence be entirely mitigated, or will ongoing advancements in pharmacology, gene editing, and biomaterials provide a partial solution? These challenges highlight the need for further research and innovation in the field, with close consideration of the safety implications.

7 Discussion

Advancements in islet cell replacement therapy show significant promise for treating T1D. The recent FDA approval of donislecel makes donor-derived islet transplantation a viable clinical option for T1D patients with poorly controlled glycemia and impaired glycemic awareness. However, long-term graft survival remains a challenge, and the scarcity of donor pancreata limits widespread application. Millions of patients with T1D could benefit from islet cell replacement therapy. To address the donor shortage, hPSCs are being investigated as a scalable source for generating islet cells. The field has made significant progress, reaching early-stage clinical trials. Optimized protocols for stem cell differentiation have enhanced glucose responsiveness and insulin release in the derived beta cells. Early-phase clinical trials, such as the one testing Vertex's VX-880, suggest substantial efficacy of stem cell-derived islets in T1D. Safety and efficacy in the long term need to be further explored.

Remaining concerns revolve around the manufacture, scalability, and post-transplantation safety of stem cell-derived islets. Developing cost-effective, large-scale manufacturing methods for stem cell-derived islets is crucial for making this therapy accessible. The dose required for human trials is still not clearly defined. However, the established standards for achieving insulin independence in allogeneic islet transplantation from deceased donors [94, 95] can be considered to estimate the amount of stem cell-derived islets cells. To achieve such a sizeable number, the differentiation protocol for stem cell-derived islets will need to be tailored for scalability. An efficient solution to this issue is incorporating 3D culture utilizing bioreactors throughout the differentiation steps [96]. Furthermore, it will be relevant to pair large-scale manufacturing with islet cryopreservation. Many groups are investigating efficient methods to cryopreserve islets, aiming for good viability and the ability to ship globally [97, 98].

The fate of stem cells post-transplantation is always a point of concern due to the risk of continued proliferation and tumor formation [99]. In stem cell-derived islets, a significant concern is the possibility that highly proliferative uncommitted progenitors or residual pluripotent stem cells could be present in the final stem cell-derived islet product, potentially leading to tumor formation. Interestingly, Dr. Nostro's group showed that a pancreatic progenitor population enriched via glycoprotein GP2 can prevent teratoma formation in vivo [100]. It is also crucial to consider additional measures to ensure the safety of stem cell-derived transplantation. These include preventing the cells from differentiating into unintended cell populations and

implementing safety switches to destroy the graft if adverse outcomes occur [101].

Additionally, the need for immunosuppression in allogeneic transplantation remains a challenge, needing exploration of immunomodulation strategies. Significant advancements have been made in addressing this issue since the early days of pancreatic islet transplantation, where high doses of steroids were used to avoid graft rejection [102]. The Edmonton protocol developed by Dr. James Shapiro and colleagues was a steppingstone to different approaches for immunosuppression [4, 103]. Nowadays, the focus has turned to localized immunosuppression using various approaches, such as co-transplanting islets with immunomodulatory agents [52], encapsulating islets via macro- and microencapsulation methods [38, 54, 61], and engineering islets to evade the immune system [32, 104].

8 Conclusion

Approximately 9 million people worldwide are living with T1D. The vast majority of these individuals manage their metabolism through exogenous insulin treatment and regular blood glucose monitoring, which is crucial for regulating blood glucose levels and preventing complications. However, this treatment modality is also very demanding for patients. Islet cell replacement therapy offers a transformative approach to managing T1D. The transplantation of donor-derived pancreatic islets, now clinically approved in multiple countries, laid the groundwork for beta cell replacement therapies. Advancements in stem cell-derived islets, immune modulation, and encapsulation techniques present a promising future for T1D treatment. Ongoing research and clinical trials need to address challenges related to the safety, scalability, and immune tolerance of these cell therapies, aiming to fully realize their potential.

Declarations

Funding This research was supported by the Diabetes Research Institute Foundation at the University of Miami. The authors acknowledge the critical support and resources provided by these institutions, which have significantly contributed to the advancement of this work. The content is solely the responsibility of the authors and does not necessarily represent the official views of the University of Miami or the Diabetes Research Institute Foundation.

Conflict of Interest The authors declare that they have no conflicts of interest to disclose.

Availability of Data and Material Data Availability The list of references is presented in full.

Data Sharing Not applicable as no datasets were generated or analyzed for this review.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Both authors have reviewed and approved the final manuscript and consent to its publication.

Code Availability Not applicable.

Author Contributions ART: Conceptualization, research, analysis, and writing of the review. GL: Conceptualization, analysis, writing, and editing of the review.

References

1. Gregory GA, Robinson TIG, Linklater SE, Wang F, Colagiuri S, de Beaufort C, 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(10):741–60.
2. Squifflet JP, Gruessner RW, Sutherland DE. The history of pancreas transplantation: past, present and future. Acta Chir Belg. 2008;108(3):367–78.
3. Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. Diabetes. 1988;37(4):413–20.
4. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med. 2006;355(13):1318–30.
5. Ricordi C, Goldstein JS, Balamurugan AN, Szot GL, Kin T, Liu C, et al. National Institutes of Health-Sponsored Clinical Islet Transplantation Consortium Phase 3 Trial: Manufacture of a Complex Cellular Product at Eight Processing Facilities. Diabetes. 2016;65(11):3418–28.
6. Lablanche S, Vantyghem MC, Kessler L, Wojtusciszyn A, Borot S, Thivolet C, et al. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. Lancet Diabetes Endocrinol. 2018;6(7):527–37.
7. Hering BJ, Clarke WR, Bridges ND, Eggerman TL, Alejandro R, Bellin MD, et al. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care. 2016;39(7):1230–40.
8. Markmann JF, Rickels MR, Eggerman TL, Bridges ND, Lafontant DE, Qidwai J, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. Am J Transplant. 2021;21(4):1477–92.

9. Rickels MR, Eggerman TL, Bayman L, Qidwai JC, Alejandro R, Bridges ND, et al. Long-term Outcomes With Islet-Alone and Islet-After-Kidney Transplantation for Type 1 Diabetes in the Clinical Islet Transplantation Consortium: The CIT-08 Study. Diabetes Care. 2022;45(12):2967–75.
10. D'Amour KA, Bang AG, Eliazer S, Kelly OG, Agulnick AD, Smart NG, et al. Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol. 2006;24(11):1392–401.
11. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol. 2008;26(4):443–52.
12. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126(4):663–76.
13. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131(5):861–72.
14. Maehr R, Chen S, Snitow M, Ludwig T, Yagasaki L, Goland R, et al. Generation of pluripotent stem cells from patients with type 1 diabetes. Proc Natl Acad Sci U S A. 2009;106(37):15768–73.
15. Southard SM, Kotipatruni RP, Rust WL. Generation and selection of pluripotent stem cells for robust differentiation to insulin-secreting cells capable of reversing diabetes in rodents. PLoS ONE. 2018;13(9): e0203126.
16. Southard SM, Kotipatruni RP, Rust WL. Correction: Generation and selection of pluripotent stem cells for robust differentiation to insulin-secreting cells capable of reversing diabetes in rodents. PLoS ONE. 2019;14(10): e0224944.
17. Pagliuca FW, Millman JR, Gurtler M, Segel M, Van Dervort A, Ryu JH, et al. Generation of functional human pancreatic beta cells in vitro. Cell. 2014;159(2):428–39.
18. Nostro MC, Sarangi F, Yang C, Holland A, Elefanty AG, Stanley EG, et al. Efficient generation of NKX6-1+ pancreatic progenitors from multiple human pluripotent stem cell lines. Stem Cell Reports. 2015;4(4):591–604.
19. Millman JR, Xie C, Van Dervort A, Gurtler M, Pagliuca FW, Melton DA. Generation of stem cell-derived beta-cells from patients with type 1 diabetes. Nat Commun. 2016;7:11463.
20. Molakandov K, Berti DA, Beck A, Elhanani O, Walker MD, Soen Y, et al. Selection for CD26(-) and CD49A(+) Cells From Pluripotent Stem Cells-Derived Islet-Like Clusters Improves Therapeutic Activity in Diabetic Mice. Front Endocrinol (Lausanne). 2021;12: 635405.
21. Jeyagaran A, Urbanczyk M, Layland SL, Weise F, Schenke-Layland K. Forward programming of hiPSCs towards beta-like cells using Ngn3, Pdx1, and MafA. Sci Rep. 2024;14(1):13608.
22. Augsornworawat P, Maxwell KG, Velazco-Cruz L, Millman JR. Single-Cell Transcriptome Profiling Reveals beta Cell Maturation in Stem Cell-Derived Islets after Transplantation. Cell Rep. 2020;32(8): 108067.
23. Wang J, Sun S, Deng H. Chemical reprogramming for cell fate manipulation: Methods, applications, and perspectives. Cell Stem Cell. 2023;30(9):1130–47.
24. Du Y, Liang Z, Wang S, Sun D, Wang X, Liew SY, et al. Human pluripotent stem-cell-derived islets ameliorate diabetes in non-human primates. Nat Med. 2022;28(2):272–82.
25. Liang Z, Sun D, Lu S, Lei Z, Wang S, Luo Z, et al. Implantation underneath the abdominal anterior rectus sheath enables effective and functional engraftment of stem-cell-derived islets. Nat Metab. 2023;5(1):29–40.
26. Wang S, Du Y, Zhang B, Meng G, Liu Z, Liew SY, 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(22):6152-64.e18.
27. Anwar IJ, Berman DM, DeLaura I, Gao Q, Willman MA, Miller A, et al. The anti-CD40L monoclonal antibody AT-1501 promotes islet and kidney allograft survival and function in nonhuman primates. Sci Transl Med. 2023;15(711):eadf6376.
28. Yolcu ES, Zhao H, Bandura-Morgan L, Lacelle C, Woodward KB, Askenasy N, et al. Pancreatic islets engineered with SA-FasL protein establish robust localized tolerance by inducing regulatory T cells in mice. J Immunol. 2011;187(11):5901–9.
29. Lanza R, Russell DW, Nagy A. Engineering universal cells that evade immune detection. Nat Rev Immunol. 2019;19(12):723–33.
30. Yoshihara E, O'Connor C, Gasser E, Wei Z, Oh TG, Tseng TW, et al. Immune-evasive human islet-like organoids ameliorate diabetes. Nature. 2020;586(7830):606–11.
31. Sintov E, Nikolskiy I, Barrera V, Hyoje-Ryu Kenty J, Atkin AS, Gerace D, et al. Whole-genome CRISPR screening identifies genetic manipulations to reduce immune rejection of stem cell-derived islets. Stem Cell Reports. 2022;17(9):1976–90.
32. Gerace D, Zhou Q, Kenty JH, Veres A, Sintov E, Wang X, et al. Engineering human stem cell-derived islets to evade immune rejection and promote localized immune tolerance. Cell Rep Med. 2023;4(1): 100879.
33. Hu X, White K, Young C, Olroyd AG, Kievit P, Connolly AJ, et al. Hypoimmune islets achieve insulin independence after allogeneic transplantation in a fully immunocompetent non-human primate. Cell Stem Cell. 2024;31(3):334-40e5.
34. Hu X, White K, Young C, Olroyd AG, Kievit P, Connolly A, et al. 333-OR: Hypoimmune islet cells mediate insulin independence after allogeneic transplantation in a fully immunocompetent nonhuman primate without immunosuppression. Diabetes. 2024;73(Supplement_1).
35. Kenyon NS, Willman MA, Han D, Leeman RS, Rabassa A, Diaz WL, et al. Extended survival versus accelerated rejection of non-human primate islet allografts: Effect of mesenchymal stem cell source and timing. Am J Transplant. 2021;21(11):3524–37.
36. Gooch A, Westenfelder C. 334-OR: Allogeneic neo-islets reduce insulin need by up to 1.2 U/kg bw in autoimmune type 1 diabetes dogs over three years without requiring antirejection drugs, enough to meet human type 1 diabetes mellitus needs. Diabetes. 2024;73(Supplement_1).
37. Kirk K, Hao E, Lahmy R, Itkin-Ansari P. Human embryonic stem cell derived islet progenitors mature inside an encapsulation device without evidence of increased biomass or cell escape. Stem Cell Res. 2014;12(3):807–14.
38. Kumagai-Braesch M, Jacobson S, Mori H, Jia X, Takahashi T, Wernerson A, et al. The TheraCyte device protects against islet allograft rejection in immunized hosts. Cell Transplant. 2013;22(7):1137–46.
39. Tomei AA, Villa C, Ricordi C. Development of an encapsulated stem cell-based therapy for diabetes. Expert Opin Biol Ther. 2015;15(9):1321–36.
40. Shapiro AMJ, Thompson D, Donner TW, Bellin MD, Hsueh W, Pettus J, et al. Insulin expression and C-peptide in type 1 diabetes subjects implanted with stem cell-derived pancreatic endoderm cells in an encapsulation device. Cell Rep Med. 2021;2(12): 100466.
41. Butler PC, Gale EA. Reversing type 1 diabetes with stem cell-derived islets: a step closer to the dream? J Clin Invest. 2022;132(3)42:1507–1514
42. Keymeulen B, De Groot K, Jacobs-Tulleneers-Thevissen D, Thompson DM, Bellin MD, Kroon EJ, et al. Encapsulated stem cell-derived beta cells exert glucose control in patients with type 1 diabetes. Nat Biotechnol. 2024 Oct;42(10):1507-1514.

43. Komatsu H, Kandeel F, Mullen Y. Impact of Oxygen on Pancreatic Islet Survival. Pancreas. 2018;47(5):533–43.
44. Pedraza E, Coronel MM, Fraker CA, Ricordi C, Stabler CL. Preventing hypoxia-induced cell death in beta cells and islets via hydrolytically activated, oxygen-generating biomaterials. Proc Natl Acad Sci U S A. 2012;109(11):4245–50.
45. Carlsson PO, Espes D, Sedigh A, Rotem A, Zimerman B, Grinberg H, et al. Transplantation of macroencapsulated human islets within the bioartificial pancreas betaAir to patients with type 1 diabetes mellitus. Am J Transplant. 2018;18(7):1735–44.
46. Dang HP, Chen H, Dargaville TR, Tuch BE. Cell delivery systems: Toward the next generation of cell therapies for type 1 diabetes. J Cell Mol Med. 2022;26(18):4756–67.
47. Bachul P, Generette GS, Perez-Gutierrez A, Borek P, Wang L-J, Golab K, et al. 307.5: modified approach allowed for improved islet allotransplantation into pre-vascularized Sernova Cell PouchTM Device - Preliminary Results of the Phase I/II Clinical Trial at University of Chicago. Transplantation. 2021;105(12S1):S25.
48. Vegas AJ, Veiseh O, Gurtler M, Millman JR, Pagliuca FW, Bader AR, et al. Long-term glycemic control using polymer-encapsulated human stem cell-derived beta cells in immune-competent mice. Nat Med. 2016;22(3):306–11.
49. Thanos C, Lavin DM, Bintz BE, Bhatnagar D, Mills J, Billings M, inventorsCELL HOUSING DEVICE2019.
50. Han EX, Wang J, Kural M, Jiang B, Leiby KL, Chowdhury N, et al. Development of a Bioartificial Vascular Pancreas. J Tissue Eng. 2021;12:20417314211027710.
51. Kural MH, Nash KM, Naegeli KM, Qian H, Wang J, Kirkton RD, et al. 335-OR: Preliminary Results of Islet Survival in a Novel Biovascular Pancreas Implanted in Primates. Diabetes. 2024;73(Supplement_1).
52. Lei J, Coronel MM, Yolcu ES, Deng H, Grimany-Nuno O, Hunckler MD, et al. FasL microgels induce immune acceptance of islet allografts in nonhuman primates. Sci Adv. 2022;8(19):eabm9881.
53. Rech Tondin A, Yolcu ES, Herring SK, Hester DM, Gadea Y, Vega G, et al. 2024-LB: Reversal of Diabetes by Human Stem Cell–Derived Islets Implanted with an Immunomodulatory Microgel in a Retrievable Site. Diabetes. 2024;73(Supplement_1).
54. Stover H. 226-OR: Immunoprivileged Hydrogels Recover Normoglycemia for Extended Duration in Immunocompetent Diabetic Animals. Diabetes. 2024;73(Supplement_1).
55. Espona-Noguera A, Ciriza J, Canibano-Hernandez A, Orive G, Hernandez RMM, Saenz Del Burgo L, et al. Review of advanced hydrogel-based cell encapsulation systems for insulin delivery in type 1 diabetes mellitus. Pharmaceutics. 2019;11(11).
56. Kavand A, Noverraz F, Gerber-Lemaire S. Recent advances in alginate-based hydrogels for cell transplantation applications. Pharmaceutics. 2024;16(4).
57. Bochenek MA, Veiseh O, Vegas AJ, McGarrigle JJ, Qi M, Marchese E, et al. Alginate encapsulation as long-term immune protection of allogeneic pancreatic islet cells transplanted into the omental bursa of macaques. Nat Biomed Eng. 2018;2(11):810–21.
58. Ludwig B, Reichel A, Steffen A, Zimerman B, Schally AV, Block NL, et al. Transplantation of human islets without immunosuppression. Proc Natl Acad Sci U S A. 2013;110(47):19054–8.
59. Soon-Shiong P, Heintz RE, Merideth N, Yao QX, Yao Z, Zheng T, et al. Insulin independence in a type 1 diabetic patient after encapsulated islet transplantation. Lancet. 1994;343(8903):950–1.
60. de Vos P, Faas MM, Strand B, Calafiore R. Alginate-based microcapsules for immunoisolation of pancreatic islets. Biomaterials. 2006;27(32):5603–17.
61. Alagpulinsa DA, Cao JJL, Driscoll RK, Sirbulescu RF, Penson MFE, Sremac M, et al. Alginate-microencapsulation of human stem cell-derived beta cells with CXCL12 prolongs their survival and function in immunocompetent mice without systemic immunosuppression. Am J Transplant. 2019;19(7):1930–40.
62. Wang LH, Ernst AU, Flanders JA, Liu W, Wang X, Datta AK, et al. An inverse-breathing encapsulation system for cell delivery. Sci Adv. 2021;7(20).
63. Zhang L, Cao Z, Bai T, Carr L, Ella-Menye JR, Irvin C, et al. Zwitterionic hydrogels implanted in mice resist the foreign-body reaction. Nat Biotechnol. 2013;31(6):553–6.
64. Xiao Z, Wei T, Ge R, Li Q, Liu B, Ji Z, et al. microfluidic production of zwitterion coating microcapsules with low foreign body reactions for improved islet transplantation. Small. 2022;18(29): e2202596.
65. Liu Q, Chiu A, Wang LH, An D, Zhong M, Smink AM, et al. Zwitterionically modified alginates mitigate cellular overgrowth for cell encapsulation. Nat Commun. 2019;10(1):5262.
66. Liu W, Flanders JA, Wang LH, Liu Q, Bowers DT, Wang K, et al. A safe, fibrosis-mitigating, and scalable encapsulation device supports long-term function of insulin-producing cells. Small. 2022;18(8): e2104899.
67. Stock AA, Gonzalez GC, Pete SI, De Toni T, Berman DM, Rabassa A, et al. Performance of islets of Langerhans conformally coated via an emulsion cross-linking method in diabetic rodents and nonhuman primates. Sci Adv. 2022;8(26):eabm3145.
68. Razavi R, Najafabadi HS, Abdullah S, Smukler S, Arntfield M, van der Kooy D. Diabetes enhances the proliferation of adult pancreatic multipotent progenitor cells and biases their differentiation to more beta-cell production. Diabetes. 2015;64(4):1311–23.
69. Wang Y, Lanzoni G, Carpino G, Cui CB, Dominguez-Bendala J, Wauthier E, et al. Biliary tree stem cells, precursors to pancreatic committed progenitors: evidence for possible life-long pancreatic organogenesis. Stem Cells. 2013;31(9):1966–79.
70. Lanzoni G, Cardinale V, Carpino G. The hepatic, biliary, and pancreatic network of stem/progenitor cell niches in humans: A new reference frame for disease and regeneration. Hepatology. 2016;64(1):277–86.
71. Doke M, Alvarez-Cubela S, Klein D, Altilio I, Schulz J, Mateus Goncalves L, et al. Dynamic scRNA-seq of live human pancreatic slices reveals functional endocrine cell neogenesis through an intermediate ducto-acinar stage. Cell Metab. 2023;35(11):1944–60.
72. Darden C, Kuncha J, Mattke JD, Lawrence MC, Naziruddin B. 223-OR: Characterization of Regenerative Adult Islet Progenitor Cells from Human Pancreatic Tissue. Diabetes. 2024;73(Supplement_1).
73. Al-Hasani K, Marikar SN, Kaipananickal H, Maxwell S, Okabe J, Khurana I, et al. EZH2 inhibitors promote beta-like cell regeneration in young and adult type 1 diabetes donors. Signal Transduct Target Ther. 2024;9(1):2.
74. Ma X, Lu Y, Zhou Z, Li Q, Chen X, Wang W, et al. Human expandable pancreatic progenitor-derived beta cells ameliorate diabetes. Sci Adv. 2022;8(8):eabk1826.
75. Dor Y, Brown J, Martinez OI, Melton DA. Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. Nature. 2004;429(6987):41–6.
76. Ackeifi C, Wang P, Karakose E, Manning Fox JE, Gonzalez BJ, Liu H, et al. GLP-1 receptor agonists synergize with DYRK1A inhibitors to potentiate functional human beta cell regeneration. Sci Transl Med. 2020;12(530).

77. Rosselot C, Li Y, Wang P, Alvarsson A, Beliard K, Lu G, et al. Harmine and exendin-4 combination therapy safely expands human beta cell mass in vivo in a mouse xenograft system. Sci Transl Med. 2024;16(755):eadg3456.
78. Administration USFaD. FDA Approves First Cellular Therapy to Treat Patients with Type 1 Diabetes 2023 [Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-cellular-therapy-treat-patients-type-1-diabetes. Accessed Jul 7 2024.
79. Affan M, Dar MS. Donislecel-the first approved pancreatic islet cell therapy medication for type 1 diabetes: a letter to the editor. Ir J Med Sci. 2024;193(1):231–2.
80. Giri O, Goldman JD. Donislecel: First Cellular Therapy to Treat Patients With Brittle Type 1 Diabetes. Clin Diabetes. 2024;42(2):337–40.
81. Rios P, Mcgarrigle JJ, Lamonica G, Li Y, Cook J, Joshi I, et al. 35-OR: Lantidra, First FDA-approved cellular therapy to treat type 1 diabetes. Diabetes. 2024;73(Supplement_1).
82. Ramzy A, Thompson DM, Ward-Hartstonge KA, Ivison S, Cook L, Garcia RV, 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(12):2047–61.
83. (NLM) TNLoM. A phase 1/2 study to evaluate the safety, tolerability, and efficacy of VX-880 in subjects who have type 1 diabetes mellitus with impaired hypoglycemic awareness and severe hypoglycemia 2021 [
84. Markmann JF, Naji A, Rickels MR, Alba M, Marigowda G, Ross L, et al. 259-OR: stem cell–derived, fully differentiated islet cells for type 1 diabetes. Diabetes. 2022;71(Supplement_1).
85. Reichman TW, Ricordi C, Naji A, Markmann JF, Perkins BA, Wijkstrom M, et al. 836-P: Glucose-dependent insulin production and insulin-independence in type 1 diabetes from stem cell–derived, fully differentiated islet cells—updated data from the VX-880 clinical trial. Diabetes. 2023;72(Supplement_1).
86. Karpov DS, Sosnovtseva AO, Pylina SV, Bastrich AN, Petrova DA, Kovalev MA, et al. Challenges of CRISPR/Cas-based cell therapy for type 1 diabetes: how not to engineer a "Trojan Horse". Int J Mol Sci. 2023;24(24).
87. Stabler CL, Russ HA. Regulatory approval of islet transplantation for treatment of type 1 diabetes: implications and what is on the horizon. Mol Ther. 2023;31(11):3107–8.
88. Witkowski P, Philipson LH, Buse JB, Robertson RP, Alejandro R, Bellin MD, et al. Islets transplantation at a crossroads-need for urgent regulatory update in the United States: perspective presented during the Scientific Sessions 2021 at the American Diabetes Association Congress. Front Endocrinol (Lausanne). 2021;12: 789526.
89. Witkowski P, Philipson LH, Kaufman DB, Ratner LE, Abouljoud MS, Bellin MD, et al. The demise of islet allotransplantation in the United States: A call for an urgent regulatory update. Am J Transplant. 2021;21(4):1365–75.
90. Ho BX, Teo AKK, Ng NHJ. Innovations in bio-engineering and cell-based approaches to address immunological challenges in islet transplantation. Front Immunol. 2024;15:1375177.
91. Pellegrini S, Zamarian V, Sordi V. Strategies to Improve the Safety of iPSC-Derived β Cells for β Cell Replacement in Diabetes. Transpl Int. 2022;35:10575.
92. Harding J, Vintersten-Nagy K, Nagy A. Universal Stem Cells: Making the Unsafe Safe. Cell Stem Cell. 2020;27(2):198–9.
93. Berman DM, Molano RD, Fotino C, Ulissi U, Gimeno J, Mendez AJ, et al. Bioengineering the endocrine pancreas: intraomental islet transplantation within a biologic resorbable scaffold. Diabetes. 2016;65(5):1350–61.
94. Pisania A, Weir GC, O'Neil JJ, Omer A, Tchipashvili V, Lei J, et al. Quantitative analysis of cell composition and purity of human pancreatic islet preparations. Lab Invest. 2010;90(11):1661–75.
95. Ryan EA, Lakey JR, Paty BW, Imes S, Korbutt GS, Kneteman NM, et al. Successful islet transplantation: continued insulin reserve provides long-term glycemic control. Diabetes. 2002;51(7):2148–57.
96. Pollock SD, Galicia-Silva IM, Liu M, Gruskin ZL, Alvarez-Dominguez JR. Scalable generation of 3D pancreatic islet organoids from human pluripotent stem cells in suspension bioreactors. STAR Protoc. 2023;4(4): 102580.
97. Zhan L, Rao JS, Sethia N, Slama MQ, Han Z, Tobolt D, et al. Pancreatic islet cryopreservation by vitrification achieves high viability, function, recovery and clinical scalability for transplantation. Nat Med. 2022;28(4):798–808.
98. Scheibner K, Lickert H. Awaking sleeping islets for a cure of diabetes. Med. 2022;3(5):279–80.
99. Heslop JA, Hammond TG, Santeramo I, Tort Piella A, Hopp I, Zhou J, et al. Concise review: workshop review: understanding and assessing the risks of stem cell-based therapies. Stem Cells Transl Med. 2015;4(4):389–400.
100. Aghazadeh Y, Sarangi F, Poon F, Nkennor B, McGaugh EC, Nunes SS, et al. GP2-enriched pancreatic progenitors give rise to functional beta cells in vivo and eliminate the risk of teratoma formation. Stem Cell Reports. 2022;17(4):964–78.
101. Hogrebe NJ, Ishahak M, Millman JR. Developments in stem cell-derived islet replacement therapy for treating type 1 diabetes. Cell Stem Cell. 2023;30(5):530–48.
102. Warnock GL, Kneteman NM, Ryan EA, Rabinovitch A, Rajotte RV. Long-term follow-up after transplantation of insulin-producing pancreatic islets into patients with type 1 (insulin-dependent) diabetes mellitus. Diabetologia. 1992;35(1):89–95.
103. Shapiro AM, Gallant HL, Hao EG, Lakey JR, McCready T, Rajotte RV, et al. The portal immunosuppressive storm: relevance to islet transplantation? Ther Drug Monit. 2005;27(1):35–7.
104. Hu X, Gattis C, Olroyd AG, Friera AM, White K, Young C, et al. Human hypoimmune primary pancreatic islets avoid rejection and autoimmunity and alleviate diabetes in allogeneic humanized mice. Sci Transl Med. 2023;15(691):eadg5794.

Authors and Affiliations

Arthur Rech Tondin[1,2] · Giacomo Lanzoni[1,2]

✉ Giacomo Lanzoni
glanzoni@med.miami.edu

[1] Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, FL, USA

[2] Department of Biochemistry and Molecular Biology, University of Miami Miller School of Medicine, Miami, FL, USA