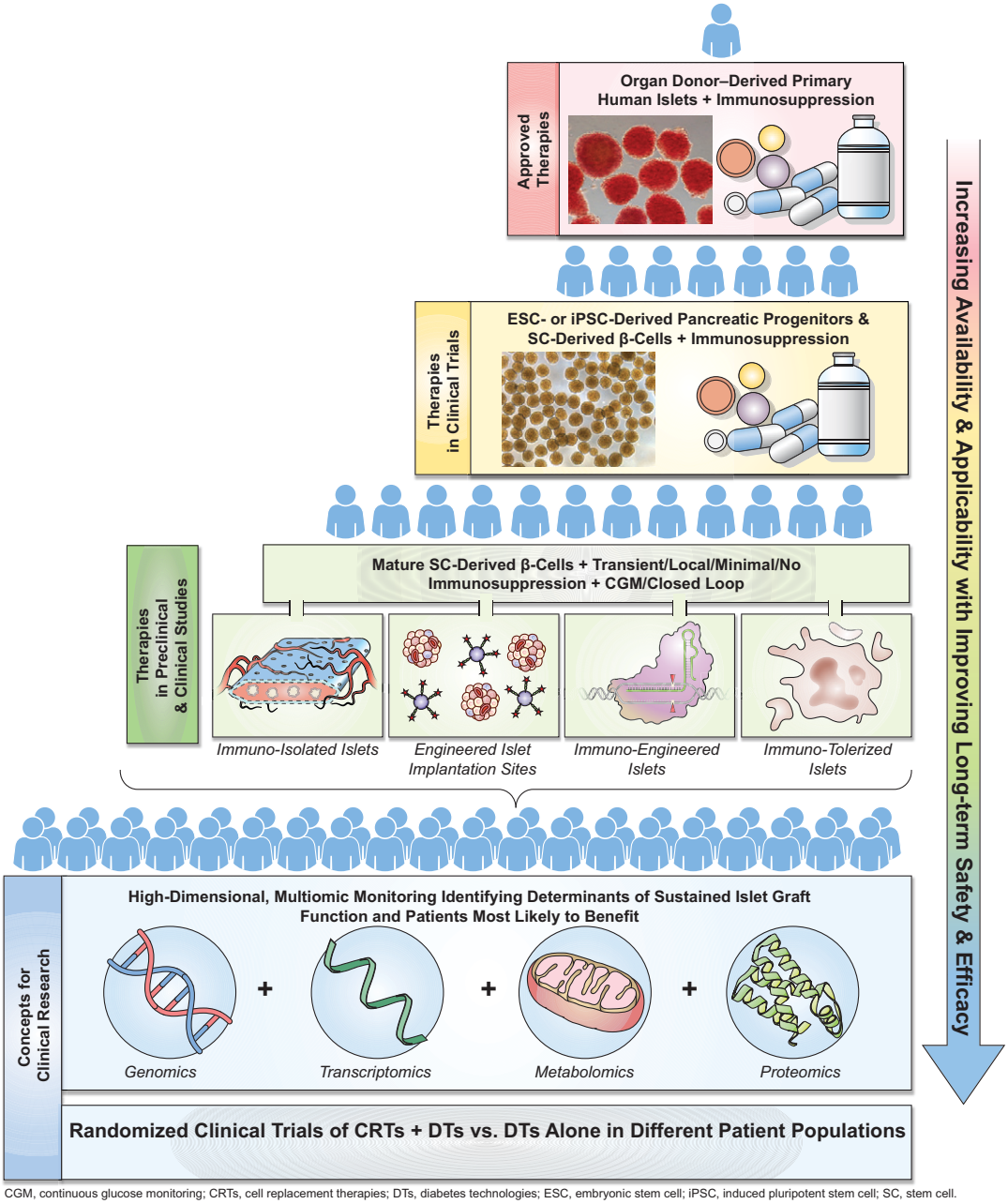
diabetes®
American Diabetes Association®

Advances in Cell Replacement Therapies for Diabetes

Bernhard J. Hering, Michael R. Rickels, Melena D. Bellin, Jeffrey R. Millman, Alice A. Tomei, Andrés J. García, Haval Shirwan, Cherie L. Stabler, Minglin Ma, Peng Yi, Xunrong Luo, Qizhi Tang, Sabarinathan Ramachandran, Jose Oberholzer, Camillo Ricordi, Timothy J. Kieffer, and A.M. James Shapiro

Diabetes 2025;74(7):1068–1077 | https://doi.org/10.2337/db25-0037



CGM, continuous glucose monitoring; CRTs, cell replacement therapies; DTs, diabetes technologies; ESC, embryonic stem cell; iPSC, induced pluripotent stem cell; SC, stem cell.

Advances in Cell Replacement Therapies for Diabetes

Bernhard J. Hering,[1] Michael R. Rickels,[2] Melena D. Bellin,[3] Jeffrey R. Millman,[4] Alice A. Tomei,[5] Andrés J. García,[6] Haval Shirwan,[7] Cherie L. Stabler,[8] Minglin Ma,[9] Peng Yi,[10] Xunrong Luo,[11] Qizhi Tang,[12] Sabarinathan Ramachandran,[1] Jose Oberholzer,[13] Camillo Ricordi,[5] Timothy J. Kieffer,[14] and A.M. James Shapiro[15]

Diabetes 2025;74:1068–1077 | https://doi.org/10.2337/db25-0037

Islet cell replacement therapies have evolved as a viable treatment option for type 1 diabetes complicated by problematic hypoglycemia and glycemic lability. Refinements of islet manufacturing, islet transplantation procedures, peritransplant recipient management, and immunosuppressive protocols allowed most recipients to achieve favorable outcomes. Subsequent phase 3 trials of transplantation of deceased donor islets documented the effectiveness of transplanted islets in restoring near-normoglycemia, glycemic stability, and protection from severe hypoglycemia, with an acceptable safety profile for the enrolled high-risk population. Health authorities in several countries have approved deceased donor islet transplantation for treating patients with type 1 diabetes and recurrent severe hypoglycemia. These achievements amplified academic and industry efforts to generate pluripotent stem cell–derived β-cells through directed differentiation for β-cell replacement. Preliminary results of ongoing clinical trials suggest that the transplantation of stem cell–derived β-cells can consistently restore insulin independence in immunosuppressed recipients with type 1 diabetes, thus signaling the profound progress made in generating an unlimited and a uniform supply of cells for transplant. Avoiding the risks of chronic immunosuppression represents the next frontier. Several strategies have entered or are approaching clinical investigation, including immune-isolating islets, engineering immune-privileged islet implantation sites, rendering islets immune evasive, and inducing immune tolerance in transplanted islets. Capitalizing on high-dimensional, multiomic technologies for deep profiling of graft-directed immunity and the fate of the graft will provide new insights that promise to translate into sustaining functional graft survival long-term. Leveraging these parallel progression paths will facilitate the wider clinical adoption of cell replacement therapies in diabetes care.

ARTICLE HIGHLIGHTS

- Transplantation of deceased donor–derived primary human islets has restored near-normoglycemia and protection from severe hypoglycemia in immunosuppressed recipients with type 1 diabetes.
- Transplantation of embryonic stem cell–derived β-cells has restored insulin independence in immunosuppressed recipients with type 1 diabetes.
- Clinical trials are underway and planned to evaluate the safety and efficacy of transplantation of mature stem cell–derived β-cells with transient, local, minimal, and/or no-maintenance immunosuppression in recipients with type 1 diabetes.
- The high-dimensional, multiomic monitoring of immunity to transplanted islets and of the fate of the islet graft will faciliate the identification of determinants of sustained islet graft function and of patients most likely to benefit from cell replacement therapies.

[1]Department of Surgery, Schulze Diabetes Institute, University of Minnesota Medical School, Minneapolis, MN
[2]Division of Endocrinology, Diabetes & Metabolism, Department of Medicine, and Institute for Diabetes, Obesity & Metabolism, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
[3]Division of Endocrinology, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, MN
[4]Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine, St. Louis, MO
[5]Diabetes Research Institute, Miller School of Medicine, University of Miami, Miami, FL
[6]George W. Woodruff School of Mechanical Engineering and Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, GA
[7]Department of Pediatrics, Ellis Fischel Cancer Center, University of Missouri School of Medicine, Columbia, MO
[8]J. Crayton Pruitt Family Department of Biomedical Engineering, Herbert Wertheim College of Engineering, University of Florida, Gainesville, FL
[9]Department of Biological and Environmental Engineering, Cornell University, Ithaca, NY
[10]Section for Islet Cell and Regenerative Biology, Joslin Diabetes Center, Boston, MA
[11]Duke Transplant Center, Duke University School of Medicine, Durham, NC
[12]Diabetes Center, University of California, San Francisco, San Francisco, CA

Islet β-cell replacement therapies are evolving as an alternative treatment option for people with type 1 diabetes (T1D), with more than 2,000 individuals treated with allogeneic islet transplants (1,2). As a part of a series of publications celebrating the 75th anniversary of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), here we offer a perspective of the field of cell replacement for diabetes.

Advancing research on islet transplantation has been an objective of NIDDK over its history as part of its mission to conduct and support research to improve people's health and quality of life. The progress achieved in developing islet transplantation into a viable treatment for T1D is, in large part, the result of decades of research supported by NIDDK. Notably, the Clinical Islet Transplantation Consortium, cofunded by NIDDK and the National Institute of Allergy and Infectious Diseases (NIAID), conducted the first phase 3 trials of a cell therapy for diabetes and established pathways to islet product licensure. Discoveries made by the NIDDK-funded Beta Cell Biology Consortium and Human Islet Research Network led to the generation of a potentially unlimited supply of stem cell (SC)-derived islets (SC-islets) for transplantation.

In the following sections, we review the lessons learned from key clinical trials of transplantation of primary human islets, present progress made in generating a virtually unlimited supply of SC-derived β-cells (SC-β-cells), point out the advances in avoiding chronic immunosuppression, and discuss the remaining challenges and future directions in the implementation of β-cell replacement therapies in diabetes care.

LESSONS FROM CLINICAL TRIALS OF PRIMARY HUMAN ISLETS

Key Trials of Allogeneic Islets and Efficacy Outcomes

Early single-center trials revealed that the transplantation of a high islet mass from one or more donors and the use of steroid-free immunosuppression promoted the attainment of insulin independence after transplantation of allogeneic human islets (3–5). Incorporating these insights, the Edmonton group achieved insulin independence in seven of seven recipients with T1D by using freshly isolated islets from two or more donors and a glucocorticoid-free immunosuppressive regimen (6). The International Trial of the Edmonton Protocol for Islet Transplantation demonstrated in 36 individuals with T1D and severe hypoglycemia that the intraportal infusion of islets from median two donor pancreases led to insulin independence at 1 year after the final transplantation in only 44% recipients (7). Nevertheless, persistent islet graft function in those insulin dependent still provided protection from severe hypoglycemia and improved glycemic control.

These findings led to the adoption of changes in both islet manufacturing (8) and peritransplant management of the recipient for improvement of the transplanted islet mass surviving intrahepatic engraftment (9), and to a shift in emphasis from insulin independence to glycemic control as the primary outcome (10). The resulting Phase 3 Trial of Transplantation of Human Islets in T1D Complicated by Severe Hypoglycemia demonstrated among 48 individuals the achievement of glycated hemoglobin (HbA_{1c}) <7.0% (53 mmol/mol) in the absence of severe hypoglycemia in 87.5% at 1 year with 52% insulin independent despite more often receiving islets isolated from a single donor pancreas (10). These outcomes were further confirmed in the Phase 3 Trial of Human Islet-After-Kidney Transplantation in Type 1 Diabetes in 24 individuals with T1D achieving HbA_{1c} <7.0% (53 mmol/mol) in the absence of severe hypoglycemia in 62.5% at 1 year with 37.5% insulin independent and with significantly improved health-related quality of life (11). Islet recipients from these islet transplant alone (ITA) and islet-after-kidney (IAK) phase 3 trials were followed for median 5.5 and >3.0 years, respectively, with 84% and 69% maintaining islet graft function and 77% and 57% HbA_{1c} <7% (53 mmol/mol) and >90% freed from severe hypoglycemia in both cohorts, with more than one-half of those achieving insulin independence maintaining freedom from exogenous insulin therapy during long-term follow-up (12). A randomized trial of islet transplantation versus intensive insulin therapy has also confirmed the metabolic control and quality-of-life benefits of islet transplantation over a 6-month period, after which those assigned to the control group underwent islet transplantation (13).

Thus, islet transplantation can result in durable islet graft survival and achievement of glycemic control targets in the absence of severe hypoglycemia for most recipients.

Determinants of Long-term Efficacy Outcomes

Balancing risk-benefit for any patient is far from an exact science. To date, regulatory agencies and clinicians have chosen only those at highest risk for hypoglycemia and complications to receive human islet transplantation. While

[13]Department of Visceral Surgery and Transplantation, University Hospital Zurich, Zurich, Switzerland
[14]Department of Cellular and Physiological Sciences and Department of Surgery, Life Sciences Institute, and School of Biomedical Engineering, University of British Columbia, Vancouver, British Columbia, Canada
[15]Clinical Islet Transplant Program, Department of Surgery, University of Alberta, Edmonton, Alberta, Canada
Corresponding author: Bernhard J. Hering, bhering@umn.edu

Received 14 January 2025 and accepted 27 February 2025
This article is part of a special article collection available at https://diabetesjournals.org/collection/2745/NIDDK-75th-Anniversary-Collection.

randomized long-term data are lacking due to cost, complexity, and limited numbers of transplanted patients, published 20-year outcome data provide robust ongoing justification for the safety and success of cell-based therapy. Patient survival, rates of insulin independence, risk of severe hypoglycemic episodes (SHEs), corrected HbA_{1c}, rates of procedural and immunosuppression-related complications, and impact on quality of life form the basis of determinants of long-term outcome success.

The Edmonton team followed 255 patients who underwent islet transplantation for up to 20 years and reported that 201 (79%) achieved insulin independence, and 178 (70%) had sustained graft function over a median follow-up of 7.4 years. Two anti-inflammatory medications (anakinra plus etanercept) increased the odds ratio by 7.5 times for sustained graft survival (14). The Miami group reported a 90% 20-year patient survival in 49 patients, with marked reduction in diabetes-related mortality in comparison with diabetes registry data (15). Chetboun et al. (16) analyzed 1,210 islet recipients from 39 centers registered in the Collaborative Islet Transplant Registry (CITR) and found a highly significant linear inverse relationship between primary graft function at 1 month after the last infusion and 5-year incidence of graft failure, meaning that successful early engraftment is critical for long-term graft functional success. Furthermore, Flatt et al. (17) measured β-cell insulin secretory capacity annually over 6 years by glucose-potentiated arginine testing in islet recipients and found that a functional β-cell mass of ≥40% of normal was a strong predictor of sustained insulin independence and long-term outcome, again highlighting the need to optimize initial islet engraftment mass. Long-term outcomes demonstrated in the National Institutes of Health (NIH)-supported Clinical Islet Transplantation (CIT) Consortium ITA trials, with follow-up for 8.3 years, included 56% of patients with graft survival and 49% with HbA_{1c} <7.0%, and no patients with ongoing function had SHEs (12).

Safety of Islet Transplantation and Immunosuppression

Key sources of safety information include reports from the CITR (18,19), the CIT Consortium (12), and large single centers (14,15). The CITR 11th Annual Report includes the serious adverse events (SAEs) experienced by 1,373 alloislet recipients followed for a mean of 5.8 years. There was a sharp decline in the number of patients who experienced SAEs post-2010, largely explained by the decrease in procedural complications. In a CITR analysis of 126 ITA recipients with a history of SHEs who met four criteria associated with favorable efficacy outcomes, the incidence of procedural- and immunosuppression-related SAEs per recipient that resulted in sequelae, disability, or death was 0.056 per person. In the CIT-08 study long-term outcomes were examined for up to 8 years in the participants of the CIT-07 ITA and CIT-06 IAK licensure trials (12). There were five nonskin cancers in four patients and no deaths during posttransplant follow-up. While an initial decline in estimated glomerular filtration rate was observed in the ITA cohort, this is expected following the initiation of calcineurin inhibitor–based immunosuppression and may also reflect reduced glomerular hyperfiltration with normalization of glycemia. Importantly, renal function remained stable during long-term follow-up.

The available information suggests an acceptable safety profile for the high-risk subgroup of patients with T1D and recurrent SHEs. A more comprehensive analysis is needed and underway at CITR.

Insights From Total Pancreatectomy With Islet Autotransplantation

For patients with clinically disabling recurrent acute or chronic pancreatitis, total pancreatectomy may be performed to relieve pain along with an autologous islet transplantation (TPIAT) to reduce the risk for and severity of postpancreatectomy diabetes. TPIAT has been performed since 1977 in the U.S., with most procedures performed in the most recent two decades. The procedure of islet isolation/infusion is similar to that for allogeneic islet transplant, with the difference that recipients of autologous islets are receiving their own islets and so are not at risk for alloimmune rejection, nor is their risk of autoimmunity to β-cells in these patients with surgical diabetes but without T1D. Thus, no immunosuppression is required, so these patients are also not subject to the adverse/toxic effects on β-cells of these medications. This makes autologous islet transplant also an appealing model for understanding the potential and limitations of islet transplantation (20).

Among patients with pancreatitis undergoing TPIAT, the autologous islet transplant restores some endogenous islet function (C-peptide positivity) in 80%–90% and allows for insulin independence in 20%–30%, despite a significantly lower islet mass (often <5,000 islet equivalents [IEQ]/kg) than seen in allotransplant. Notably, when TPIAT is performed in young children, insulin independence rates are particularly high with sustained islet function, potentially highlighting the advantages of "younger" β-cells (21,22).

From a research perspective, TPIAT has allowed for randomized controlled trials of a number of adjuvant therapies aimed at improving islet transplantation (23).

PROGRESS IN GENERATING SC-ISLETS

SC-Derived Pancreatic Progenitors and Their Maturation In Vivo

The in vitro differentiation of pluripotent SCs into functional insulin-producing cells represents a significant breakthrough for diabetes treatment, offering a renewable source of SC-β-cells (24,25). Decades of effort with model species like zebrafish and mice unraveled key signaling pathways by which developing embryos form an endocrine pancreas. This body of work has been leveraged to drive pluripotent SCs down a pancreatic lineage through the stepwise

manipulation of these pathways, to orchestrate the timed expression of transcriptional machinery guiding cell fate. Robust induction of definitive endoderm cells was achieved by activation of TGF-β and Wnt signaling in human embryonic SCs (26), and this was then guided through primitive gut tube and posterior foregut and then to pancreatic endoderm marked by the two key transcription factors PDX1 and NKX6.1 (27). Cells with these markers were previously characterized in 6- to 9-week human fetal pancreas, a stage at which the cells are competent to complete differentiation into functional β-cells following transplant into immunodeficient mice (28). Kroon et al. (27) found that the SC-derived pancreatic progenitors (SC-PPs) can generate functional islet endocrine cells, including glucose-responsive SC-β-cells, several months after implant into mice. Moreover, the cells can protect mice from diabetes when endogenous β-cells are depleted with the β-cell toxin streptozotocin. ViaCyte developed scalable methods to produce large quantities of SC-PPs and began clinical testing in 2014, ultimately demonstrating improved glycemic control and reduced exogenous insulin requirements in humans following the cell implants (29). SC-PPs can be relatively quickly and consistently manufactured, thus representing a promising implantable cell source for diabetes.

Functional Human SC-β-Cells From Embryonic Stem and Induced Pluripotent SCs In Vitro

Recent advancements in differentiation protocols have increased the efficiency of generating SC-β-cells capable of glucose-stimulated insulin secretion. These improvements have been achieved through identification of novel pathways and optimizing differentiation with existing growth factors and small molecules (30,31). As a result, in vitro–generated cells have shown enhanced glucose-stimulated insulin secretion, exhibiting both first- and second-phase insulin secretion kinetics, and demonstrated improved function upon transplantation into diabetic mice.

Despite this progress, challenges remain regarding SC-β-cell functionality and maturation, including insulin secretory capacity compared with that of primary β-cells, as replicating the complex signaling and mechanical cues of the in vivo environment remains a significant challenge for in vitro culture (24,25,32). Thus, further refinements in differentiation protocols are essential to yield fully mature, functional SC-β-cells and bring them closer to clinical application.

Single-Cell Multiomic–Guided Differentiation of SC–Islet Cell Products

Single-cell multiomic technologies have revolutionized our understanding of SC differentiation and islet cell maturation. Use of these approaches has provided insights into cellular heterogeneity and dynamic regulatory changes during differentiation, and critical pathways and biomarkers associated with each stage of β-cell development have been identified. Single-cell RNA sequencing has been used to investigate the SC-β-cell differentiation process (33,34), revealing the presence of off target cell types, such as pancreatic exocrine and intestinal-like enterochromaffin cells, that can arise from these differentiation methods. A recent meta-analysis of single-cell RNA-sequencing data from SC-β-cells produced by multiple groups with multiple cell lines and protocols revealed that SC-β-cells exhibit a core transcriptional identity characterized by markers such as IAPP, HADH, DLK1, INS, PCSK1, and PDX1 across a wide range of differentiation protocols and human developmental states (35).

Recent studies with use of single-cell assay for transposase-accessible chromatin sequencing (scATAC-seq) have provided significant insights into cellular identity through analysis of chromatin accessibility at both promoter and *cis* regulatory regions (32,36). These analyses enhanced our understanding of the acquisition of on and off target cellular identities during in vitro differentiation, pinpointing stages at which cells may deviate from the desired β-cell fate, and enabling real-time adjustments for more efficient and precise differentiation. Multiomic data are also invaluable for establishing quality control benchmarks, ensuring that SC–islet cell products meet standards of identity, purity, and functionality before clinical application. Predictive models built from multiomic profiles can flag cells with off target differentiation or insufficient maturity, supporting the production of homogeneous, high-quality β-cell populations.

Recent Clinical Trials of SC-PPs and SC-Islets

ViaCyte initiated clinical trials with SC-PPs in 2014 after extensive testing in mice confirmed safety and diabetes reversal, with functional maturation of SC-β-cells over time when transplanted within a semipermeable immunoprotective polymer device. Initial clinical testing with subcutaneous implantation of encapsulated SC-PPs confirmed safety but with minimal cell survival and only low levels of detectable graft-derived human C-peptide (37,38). In another trial with use of microperforated devices, results of one case study with 10 devices showed marked improvement in time with glucose in target range (29). Using more mature SC-β-cells, Vertex Pharmaceuticals initiated a phase 1/2 clinical trial (VX-880) in 2021, with cells transplanted intraportally into the liver under full-dose immunosuppression. By June 2024, 12 patients had been dosed; 11 of 12 had marked reduction or complete insulin independence, and all had HbA_{1c} $<7.0\%$ and percentage of time spent with glucose in target range $>70\%$ on continuous glucose monitoring (39). Based on these promising data, VX-880 has progressed to a phase 1/2/3 pivotal trial with goals of enrolling 50 patients and seeking early regulatory approval.

Preliminary clinical data with autologous induced pluripotent stem cell–derived islets have been reported from two additional trials in China. The autologous concept theoretically allows for successful transplantation without need for immunosuppression in patients without autoimmunity, substantially altering the risk-benefit for patients with diabetes in favor of transplantation. For both trials insulin independence and substantial HbA_{1c} reduction

were reported in their respective case report. However, both individuals were under immunosuppression for existing kidney or liver transplants. Nevertheless, these reports provide indication of preliminary success with autologous SC-β-cells production and initial clinical safety and efficacy (40,41). Personalized autologous induced pluripotent stem cell–derived β-cells are clearly more complex to manufacture, release, and regulate, and further data are needed to confirm their efficacy.

PROGRESS IN AVOIDING CHRONIC IMMUNOSUPPRESSION

Protecting Islets/Cells With Encapsulation

The aim of encapsulation of glucose-responsive, insulin-secreting islet β-cells in a selectively permeable biomaterial device is to shield transplanted islets from immune attack, thus minimizing the need for immunosuppression. Primary engineering challenges for this approach include balancing immunoprotection with nutrient and therapeutic molecule transport (e.g., oxygen, glucose, insulin) while ensuring scalability for clinical use.

Macrodevices facilitate graft retrievability but limit oxygen supply. Microcapsules offer better nutrient support due to higher surface-to-volume ratios (42). Immunologically, encapsulation reduces immune responses by preventing direct activation and cytotoxicity of graft-reactive T cells, masking MHC molecules, and blocking antibody-mediated complement destruction. However, small antigens and damage-associated molecules can diffuse through capsules, indirectly activating graft-reactive T cells and causing graft dysfunction and loss. This issue may be particularly pronounced in confined, vascularized transplantation sites such as the subcutaneous or intramuscular spaces.

Despite demonstrated safety in clinical trials, the efficacy of encapsulation devices remains uncertain, necessitating further optimization and testing in animal models. Emerging advancements in macrodevice design include improved biocompatibility (43), vascularization, and cell density, and microcapsule innovations to optimize transport and minimize transplant volumes include conformal coating (44). These developments enable the use of extrahepatic sites for encapsulated islet transplantation and allow for the investigation of immune mechanisms to refine future therapies. Combining encapsulation with localized delivery of immunomodulatory drugs and/or cells could further enhance islet graft protection and therapeutic efficacy, paving the way for more effective clinical applications.

Engineering Immune-Privileged Implantation Sites

New approaches in engineering immune-privileged implantation sites present exciting strategies for eliminating the need for systemic immunosuppressive regimens. These innovative approaches include seeking to deliver two key advantages: *1*) an immune-privileged niche with immune acceptance of the graft, and *2*) direct integration of the graft with the host, including vascularization and innervation, for improved response kinetics and improved metabolic control.

Macroporous ("open"), vessel-permissive polymeric scaffolds create a local niche that provides graft cell support, including the presentation of appropriate biophysical and biochemical cues. These constructs can also locally deliver survival factors (e.g., oxygen) and immunomodulatory agents to improve engraftment and mitigate immune attack. Various formats, from injectable, degradable hydrogels to open nondegradable scaffolds, demonstrate improved engraftment features (e.g., revascularization) with robust survival and metabolic control (45).

Biomaterials can be engineered to present potent immunomodulatory signals (FasL, PD-L1, anti-CD40L) or drugs (rapamycin) that can alter immune responses toward graft acceptance (46–50), thereby reducing reliance on systemic immunosuppression. Integrating agents within or onto biomaterials provides an off-the-shelf approach for their subsequent codelivery with therapeutic cells.

Immunomodulatory accessory cells, isolated or genetically engineered, can be cotransplanted with islets to induce local immunomodulation. For example, mesenchymal stromal cells engineered to express high levels of programmed death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 immunoglobulin fusion proteins (CTLA-4Ig) protected allogeneic islets transplanted under kidney capsules and reversed diabetes in mice (49).

Many of these strategies are progressing toward pivotal studies in large animals and first-in-human studies. These engineered immune-privileged implantation sites are expected to accelerate the development of an effective and broadly applicable cell-based treatment modality for T1D.

Engineering Cytoprotective, Hypoimmune, and Immunomodulatory Islets

Engineering β-cells to resist immune destruction represents the next significant hurdle for advancing cell replacement therapy in T1D. Immune evasion is critical to ensuring the survival and functionality of transplanted β-cells, which face threats from both autoimmunity and alloimmunity, depending on their source. Addressing these challenges is key to developing effective and durable therapies.

Emerging research suggests that β-cell stress may play a pivotal role in making β-cells targets for autoimmune destruction (51). For instance, Cai et al. (52) demonstrated that targeting *RNLS*, a T1D genome-wide association studies–identified gene in humans, can alleviate cellular stress and render β-cells more resilient to autoimmune attack. This approach could enhance the survival of transplanted cells in reducing stress-induced immune recognition and subsequent destruction.

Additionally, allogeneic or xenogeneic cells could be genetically modified to evade general immune recognition, primarily through editing immune recognition or immune checkpoint genes such as *HLA-E/G*, *PDL1*, *FasL*, or *IDO*. A

recent demonstration of such strategies included deleting β2-microglobulin (*B2M*) and *CIITA* to eliminate MHC class I and II expression, along with overexpressing *CD47* to prevent innate immune attack (53). Significant safety concerns remain, however, as hypoimmune cells may evade all immune detection, posing risks of unchecked growth or infection. An additional strategy is to retain a few selected HLA molecules to preserve immune surveillance while allowing HLA matching of the grafts to recipients (54,55). Further, balancing immune evasion with robust safety measures, e.g., integrating a safety switch, may be critical for the successful implementation of these transformative therapies.

Inducing Immune Tolerance of Transplanted Islets

Inducing immune tolerance will ultimately ensure long-lasting function of the transplanted islets. Central immune tolerance refers to a process of negative selection, eliminating clonalities with specific allo-, xeno-, and autoimmunity. This has been attempted with grafting of bone marrow and/or thymus prior to islet transplantation, albeit in most cases attempts are still at the stage of preclinical models (56). To make this approach more acceptable, nonmyeloablative cytoreduction and minimization or possibly elimination of irradiation are being actively investigated.

Peripheral immune tolerance refers to the process of immune regulation, controlling the pathogenicity of immune cells with specificities to allo-, xeno-, and autoantigens. This strategy depends on the induction of various immunoregulatory cell populations in the host, is likely less stable than central tolerance, and can possibly be subverted by extreme immune stimulations. One such approach is through exposing the recipient to donor antigens (and/or relevant autoantigens) in a tolerogenic fashion. An example of success is use of ethylene carbodiimide to cross-link donor antigens and/or autoantigens as a form of "tolerogenic" delivery to induce immune tolerance (57), which has laid the foundation for effective and feasible translation to human transplantation (58). An alternative approach is to significantly augment one such immunoregulatory cell population, such as regulatory T cells (Tregs). Much effort has been invested in expanding large numbers of antigen-specific Tregs ex vivo for adoptive transfers in vivo (59). An engineering feat in this approach is to engineer antigen specificities to chimeric antigen receptors (CARs) on Tregs, with a goal of optimizing their in vivo stability and potency of suppression (60). Overall, overcoming alloimmune and autoimmune barriers to β-cell replacement therapy will likely require multipronged approaches to reduce graft immunogenicity, inactivate pathogenic T cells, and promote immune regulation.

REMAINING CHALLENGES AND FUTURE DIRECTIONS

Sustaining Metabolic Benefits Long-term

The durability of metabolic function correlates strongly with β-cell engraftment mass. In a direct comparison of outcomes of whole pancreas versus islet transplantation from the Edmonton group, whole pancreas transplantation resulted in 52% insulin-independent graft survival with HbA_{1c} <6.5% by 20 years, which was 8.65-fold higher than after islet transplantation over the same period (14). Many donor, recipient, and immunological factors have direct impact on the quality and engraftment of an intraportal islet mass. An analysis by CITR clearly identified four factors (recipient age ≥35 years, islet mass ≥325,000 IEQ, induction with T-cell depletion and/or TNF-α inhibition, and maintenance of immune suppression with rapamycin and calcineurin inhibitors) to be strongly associated with the best long-term metabolic benefit after deceased donor islet allotransplantation (19). As the field now progresses from the major surgical intervention of whole pancreas to cellular infusion of deceased donor islets and now SC-islets, it has become feasible to use a prescribed engraftment mass that can provide a far more robust insulin secretory reserve.

Incorporating Novel Surveillance Methodologies

Refining our approaches to monitoring the graft and graft-directed immunity will help fill critical gaps in our understanding of the roles of alloimmunity, recurrent autoimmunity, and unresolved endoplasmic reticulum stress in determining the long-term acceptance of transplanted islets.

Single-cell multiomic technologies (61) present opportunities for deep profiling of donor alloantigen– and islet autoantigen–specific T cell clusters, including the monitoring of the T-cell receptor (TCR) use and the functional state of donor alloantigen–specific and islet autoantigen–specific T cells (62). Machine learning algorithms can predict the epitopes that could bind to differentially expressed TCR clonotypes identified by unbiased TCR assembly, thereby facilitating the identification of epitopes involved in allo- and autoreactivity. Tracking the kinetics of TCR repertoire turnover and the enrichment of allo- and autospecific clonotypes in effector and exhausted and Treg phenotypes will provide new insights into the interactions between the graft and the host immune system that drive acceptance and rejection. Analyses of circulating demethylated insulin DNA (63), miRNAs (64), and prohormone processing products (65) as well as multiomic profiling of circulating extracellular vesicles derived from transplanted islet β-cells and their cargo present noninvasive opportunities for interrogating the fate of transplanted islet β-cells (66), thereby improving our understanding of the impact of islet β-cell endoplasmic reticulum stress and immunosuppressive drug cytotoxicity on islet graft survival.

Identifying Recipients With Favorable Risk-Benefit Profiles

Because islet allotransplantation for T1D currently requires immunosuppression for successful islet engraftment and sustained islet graft function, it is performed

only in a selected subset of patients with T1D, where the benefits of restoring islet function outweigh the risk of immunosuppression. For most clinical islet transplants and research protocols focus has been on two selected groups: *1*) individuals with SHEs, glycemic lability, and/or hypoglycemia unawareness despite efforts including use of all other T1D treatment approaches, who may be considered for ITA, and or *2*) individuals who have received or are receiving a kidney transplant who are candidates for IAK or, less often, simultaneous islet-kidney transplantation (18). The rationale for ITA is that restoring endogenous islet graft function can effectively prevent SHEs in >90% of recipients. Thus, the risk of immunosuppression is justified because severe and life-threatening hypoglycemic episodes are essentially eliminated in islet transplant recipients (19).

For individuals who undergo IAK, the risk is justified because these individuals already require immunosuppression and will experience the benefit of improved glycemic control from having a functioning islet graft that appears protective against recurrent diabetic nephropathy (67). Both life expectancy with a functioning kidney graft and the overall life expectancy are also more favorable among IAK recipients, mainly driven by a ~60% reduction in risk of death (67), which is an argument for wider access to IAK transplantation. In the largest multicenter trials of ITA and IAK in the U.S., insulin independence was additionally achieved in 74% of islet transplant recipients overall (12).

Clinical results suggest slowed progression and even reversal of microvascular diabetes lesions following pancreas and islet transplantation (68,69). With progress toward generating SC-islets for transplant and reducing immunosuppression for rejection prophylaxis, islet replacement might be considered for intervention in selected patients with progressive microvascular diabetes complications.

Implementing Islet Cell Therapies in Routine Diabetes Care

An important step toward the implementation of islet transplantation in diabetes care came with the U.S. Food and Drug Administration approval of donislecel-jujn (Lantidra; CellTrans Inc.) in 2023. Donislecel-jujn consists of purified human pancreatic islets isolated from a deceased donor pancreas. Transplantation of deceased donor–derived islets has been available in clinical practice throughout much of Canada, Europe, and Australia, where national health authorities regulate deceased donor islets similarly to regulation of whole organs used for transplantation. In contrast, the U.S. regulation of deceased donor islets as a drug requiring biologic licensure rather than an organ has delayed islet transplantation becoming a standard of care treatment and restricted the use of islet transplantation in diabetes care (70).

The impact of other developments on the implementation of islet transplantation could be far-reaching. SC-islets may soon provide an unlimited and uniform supply of islet cells for transplantation. Technologies that will reduce the reliance on systemic immunosuppression for graft protection in ongoing and planned clinical trials will boost the benefit-risk profile of cell replacement in diabetes, with long-term safety evaluations of novel technologies playing a critical role. The lessons learned from the refined monitoring of transplanted islets and islet-directed immunity will ultimately support their long-term survival. Together, these developments will promote the availability, acceptance, therapeutic outcomes, and reimbursement of cell replacement therapies and thereby their wider adoption in routine diabetes care.

CONCLUSIONS

Continuous glucose monitoring and automated insulin delivery continue to improve. Despite increased adoption of advanced diabetes technologies, a high proportion of people with T1D do not achieve glycemic targets and continue to experience SHEs and impaired awareness of hypoglycemia (71), suggesting a continued need for more effective treatment strategies.

Advances in islet replacement strategies have significantly improved the lives of people with T1D. Islet cell therapy can markedly improve glycemic control and reduce both SHEs and impaired awareness of hypoglycemia, with these benefits being achievable in islet transplant recipients while reducing the burden of hypoglycemia avoidance and the challenges associated with the management of the increasingly complex systems for exogenous insulin delivery. Individuals unsatisfied with present insulin management options can make informed decisions about the potential risks and benefits in considering islet transplantation.

Today's translational impact of islet transplantation research would not have been possible without the sustained funding from NIDDK. Going forward, the increasing options of islet cell sources available from human pluripotent SCs make consideration of expanding β-cell replacement therapy eligibility criteria possible, especially should the level of required immunosuppression be reduced. With cell replacement therapies remaining a NIDDK priority and with the increasing commitment of nongovernmental organizations and industry, real opportunities now exist to close these remaining gaps.

Acknowledgments. The authors thank Camillo Ricordi, University of Miami Miller School of Medicine, for providing the photograph of isolated human primary islets used in the graphical abstract and Matthew Ishahak, Washington University School of Medicine, for providing the photograph of human SC-islets for use in the graphical abstract.

Funding. A.A.T. has received funding support from the NIH (grants R01 DK141150 and R01 DK109929 A1), Breakthrough T1D (3-SRA-2024-1477-S-B), and the Diabetes Research Institute Foundation. A.J.G. has received funding support from the NIH (R01 DK128840 and DK133702) and Breakthrough T1D. B.J.H. has received funding support from the NIH (U19 AI174966, U01 DK133709, R01 DK131209, and R21 AI166163). C.L.S. has received funding support from the NIH

(R01 DK126413 and UH3 DK122638). C.R. has received funding support from the NIH (R01 DK133610-01 and R01 DK129343-01A1), Breakthrough T1D, the Diabetes Research Institute Foundation, and The Cure Alliance. H.S. has received funding support from the NIH (R01 AI121281, R01 DK128840, and R01 DK133702) and the Department of Defense (DOD; W81XWH-21). J.R.M. has received funding support from the NIH (R01 DK114233, R01 DK127497, R01 DK138469, and UG3 DK142188), Breakthrough T1D (3-SRA-2023-1295-S-B, 3-SRA-2024-1555-S-B, and 2-SRA-2023-1314-S-B), the Edward Mallinckrodt, Jr. Foundation, and the Anita Palmer Corbin Trust. M.D.B. has received funding support from the NIH (R01 DK138809, DK133709, and DK126728). M.M. has received funding support from the NIH (R01 DK105967-01A1). M.R.R. has received funding support from the NIH (R01 DK091331) and Breakthrough T1D (1-SRA-2019-728-A-N). Q.T. has received funding support from the NIH (R01 DK133645 and U01 DK137140) and Breakthrough T1D. P.Y. has received funding support from the NIH (R01 R01DK120445) and Breakthrough T1D. S.R. has received funding support from the NIH (U19 AI174966 and R21 AI166163). T.J.K. has received funding support from Breakthrough T1D, Diabetes Canada, and the Stem Cell Network. X.L. has received funding support from the NIH (U01 AI090956, R01 DK141374, R01 DK132889, and U19 AI131471).

The authors are solely responsible for the contents of this article, which do not necessarily represent the official views of the NIH.

Duality of Interest. B.J.H. holds equity in and serves as a paid executive officer and director of Diabetes Free, Inc., a company that may commercially benefit from the results of research in islet transplantation. This interest has been reviewed and managed by the University of Minnesota in accordance with its conflict of interest policies. M.R.R. received research support from Dompé farmaceutici and from Tandem Diabetes Care and serves on the Type 1 Diabetes Clinical Development Program Steering Committee for Vertex Pharmaceuticals and the independent data and safety monitoring board for Sernova. M.D.B. received research support from ViaCyte and serves on the independent data and monitoring committee for Vertex Pharmaceuticals. J.R.M. is an inventor on patents and patent applications related to SC-islets. J.R.M. was recently employed at and has stock in Sana Biotechnology. A.A.T. is an inventor of the conformal coating intellectual property, which has been licensed to Sernova. A.A.T. has received payment from Sernova related to IP and stands to gain royalties from commercialization of the IP. Additionally, A.A.T. is an equity holder in Sernova. A.J.G. and H.S. are scientific cofounders of iTolerance, Inc., pursuing microgel presenting FasL technology as an immunomodulatory strategy for β-cell transplantation. M.M. is a cofounder of Persista Bio, a company formed to commercialize oxygenated islet encapsulation technologies. S.R. received research support from Diabetes Free, Inc. J.O. is the founder and president of CellTrans Inc. and was the principal investigator of the pivotal phase 1, 2 and 3 trials at the University of Illinois that led to the U.S. Food and Drug Administration approval of Lantidra. His conflicts of interest have been reviewed and managed by the University of Illinois according to its conflict of interest policies. J.O. has been a consultant to Vertex Pharmaceuticals. C.R is a cofounder and equity holder of AION Healthspan and Lipogems International and consultant of Vertex Pharmaceuticals, Novo Nordisk, Seraxis, and iTolerance, Inc. C.R. has received funding support from Humacyte (SA00002358) and Vertex Pharmaceuticals (VX-880 and VX-264 clinical trials). T.J.K. received research support from ViaCyte, served as chief scientific officer (CSO) at ViaCyte, and at the time of writing serves as CSO at Fractyl Health, developing gene therapy for diabetes and obesity. A.M.J.S. previously served as a consultant for ViaCyte and has ongoing consultancies with Vertex Pharmaceuticals, Betalin Therapeutics, and Aspect Biosystems. No other potential conflicts of interest relevant to this article were reported.

References

1. Kieffer TJ, Hoesli CA, Shapiro AMJ. Advances in islet transplantation and the future of stem cell-derived islets to treat diabetes. Cold Spring Harb Perspect Med 2025;15:a041624
2. Berney T, Andres A, Bellin MD, et al.; International Islet Transplant Centers. A worldwide survey of activities and practices in clinical islet of Langerhans transplantation. Transpl Int 2022;35:10507
3. Scharp DW, Lacy PE, Santiago JV, et al. Insulin independence after islet transplantation into type I diabetic patient. Diabetes 1990;39:515–518
4. Tzakis AG, Ricordi C, Alejandro R, et al. Pancreatic islet transplantation after upper abdominal exenteration and liver replacement. Lancet 1990;336:402–405
5. Warnock GL, Kneteman NM, Ryan E, Seelis RE, Rabinovitch A, Rajotte RV. Normoglycaemia after transplantation of freshly isolated and cryopreserved pancreatic islets in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1991;34:55–58
6. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230–238
7. Shapiro AMJ, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. N Engl J Med 2006;355:1318–1330
8. Ricordi C, Goldstein JS, Balamurugan AN, et al. National Institutes of Health–Sponsored Clinical Islet Transplantation Consortium Phase 3 Trial: Manufacture of a Complex Cellular Product at Eight Processing Facilities [published correction appears in Diabetes 2017;66:2531]. Diabetes 2016;65:3418–3428
9. Hering BJ, Kandaswamy R, Ansite JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. JAMA 2005;293:830–835
10. Hering BJ, Clarke WR, Bridges ND, et al.; Clinical Islet Transplantation Consortium. Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care 2016;39:1230–1240
11. Markmann JF, Rickels MR, Eggerman TL, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. Am J Transplant 2021;21:1477–1492
12. Rickels MR, Eggerman TL, Bayman L, et al.; Clinical Islet Transplantation Consortium. 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;45:2967–2975
13. Lablanche S, Vantyghem M-C, Kessler L, et al.; TRIMECO trial investigators. 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;6:527–537
14. Marfil-Garza BA, Imes S, Verhoeff K, et al. Pancreatic islet transplantation in type 1 diabetes: 20-year experience from a single-centre cohort in Canada. Lancet Diabetes Endocrinol 2022;10:519–532
15. Lemos JRN, Baidal DA, Ricordi C, Fuenmayor V, Alvarez A, Alejandro R. Survival after islet transplantation in subjects with type 1 diabetes: twenty-year follow-up (Letter). Diabetes Care 2021;44:e67–e68
16. Chetboun M, Drumez E, Ballou C, et al.; Collaborative Islet Transplant Registry (CITR) Investigators Study Group. Association between primary graft function and 5-year outcomes of islet allogeneic transplantation in type 1 diabetes: a retrospective, multicentre, observational cohort study in 1210 patients from the Collaborative Islet Transplant Registry. Lancet Diabetes Endocrinol 2023;11:391–401
17. Flatt AJ, Matus AM, Gallop RJ, et al. β-Cell secretory capacity predicts metabolic outcomes over 6 years following human islet transplantation. Diabetes 2025;74:749–759
18. CITR Coordinating Center Collaborative Islet Transplant Registry. Eleventh annual report, 2022. Accessed 20 March 2025. Available from https://citregistry.org/system/files/11th_CITR_Network_Report_Allograft_2022_0.pdf
19. Hering BJ, Ballou CM, Bellin MD, et al. Factors associated with favourable 5 year outcomes in islet transplant alone recipients with type 1 diabetes complicated by severe hypoglycaemia in the Collaborative Islet Transplant Registry. Diabetologia 2023;66:163–173
20. Sutherland DER, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg 2012;214:409–424

21. Bellin MD, Schwarzenberg SJ, Cook M, Sutherland DER, Chinnakotla S. Pediatric autologous islet transplantation. Curr Diab Rep 2015;15:67
22. Bellin MD, Beilman GJ, Sutherland DE, et al. How durable is total pancreatectomy and intraportal islet cell transplantation for treatment of chronic pancreatitis? J Am Coll Surg 2019;228:329–339
23. Abdel-Karim TR, Hodges JS, Herold KC, et al. Peri-transplant inflammation and long-term diabetes outcomes were not impacted by either etanercept or alpha-1-antitrypsin treatment in islet autotransplant recipients. Transpl Int 2024; 37:12320
24. Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells in vitro. Cell 2014;159:428–439
25. Rezania A, Bruin JE, Arora P, et al. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol 2014;32:1121–1133
26. D'Amour KA, Agulnick AD, Eliazer S, Kelly OG, Kroon E, Baetge EE. Efficient differentiation of human embryonic stem cells to definitive endoderm. Nat Biotechnol 2005;23:1534–1541
27. Kroon E, Martinson LA, Kadoya K, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol 2008;26:443–452
28. Castaing M, Péault B, Basmaciogullari A, Casal I, Czernichow P, Scharfmann R. Blood glucose normalization upon transplantation of human embryonic pancreas into beta-cell-deficient SCID mice. Diabetologia 2001;44:2066–2076
29. Keymeulen B, De Groot K, Jacobs-Tulleneers-Thevissen D, et al. Encapsulated stem cell-derived β cells exert glucose control in patients with type 1 diabetes. Nat Biotechnol 2024;42:1507–1514
30. Hogrebe NJ, Augsornworawat P, Maxwell KG, Velazco-Cruz L, Millman JR. Targeting the cytoskeleton to direct pancreatic differentiation of human pluripotent stem cells. Nat Biotechnol 2020;38:460–470
31. Velazco-Cruz L, Song J, Maxwell KG, et al. Acquisition of dynamic function in human stem cell-derived β cells. Stem Cell Reports 2019;12:351–365
32. Augsornworawat P, Hogrebe NJ, Ishahak M, et al. Single-nucleus multi-omics of human stem cell-derived islets identifies deficiencies in lineage specification. Nat Cell Biol 2023;25:904–916
33. Veres A, Faust AL, Bushnell HL, et al. Charting cellular identity during human in vitro β-cell differentiation. Nature 2019;569:368–373
34. Weng C, Xi J, Li H, et al. Single-cell lineage analysis reveals extensive multimodal transcriptional control during directed beta-cell differentiation. Nat Metab 2020;2:1443–1458
35. Schmidt MD, Ishahak M, Augsornworawat P, Millman JR. Comparative and integrative single cell analysis reveals new insights into the transcriptional immaturity of stem cell-derived β cells. BMC Genomics 2024;25:105
36. Zhu H, Wang G, Nguyen-Ngoc K-V, et al. Understanding cell fate acquisition in stem-cell-derived pancreatic islets using single-cell multiome-inferred regulomes. Dev Cell 2023;58:727–743.e11
37. Ramzy A, Thompson DM, Ward-Hartstonge KA, et al. Implanted pluripotent stem-cell-derived pancreatic endoderm cells secrete glucose-responsive C-peptide in patients with type 1 diabetes. Cell Stem Cell 2021;28:2047–2061.e5
38. Shapiro AMJ, Thompson D, Donner TW, 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;2:100466
39. Reichman TW, Ricordi C, Naji A, 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 (Abstract). Diabetes 2023;72(Suppl. 2):826-P
40. Wu J, Li T, Guo M, et al.; Clinical Group. Treating a type 2 diabetic patient with impaired pancreatic islet function by personalized endoderm stem cell-derived islet tissue. Cell Discov 2024;10:45
41. Wang S, Du Y, Zhang B, et al. Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient. Cell 2024;187:6152–6164.e18
42. De Toni T, Stock AA, Devaux F, et al. Parallel evaluation of polyethylene glycol conformal coating and alginate microencapsulation as immunoisolation strategies for pancreatic islet transplantation. Front Bioeng Biotechnol 2022;10:886483
43. Bochenek MA, Veiseh O, Vegas AJ, 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;2:810–821
44. Stock AA, Gonzalez GC, Pete SI, 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:eabm3145
45. Weaver JD, Headen DM, Aquart J, et al. Vasculogenic hydrogel enhances islet survival, engraftment, and function in leading extrahepatic sites. Sci Adv 2017;3:e1700184
46. Coronel MM, Martin KE, Hunckler MD, et al. Immunotherapy via PD-L1-presenting biomaterials leads to long-term islet graft survival. Sci Adv 2020;6:eaba5573
47. Headen DM, Woodward KB, Coronel MM, et al. Local immunomodulation Fas ligand-engineered biomaterials achieves allogeneic islet graft acceptance. Nat Mater 2018;17:732–739
48. Lei J, Coronel MM, Yolcu ES, et al. FasL microgels induce immune acceptance of islet allografts in nonhuman primates. Sci Adv 2022;8:eabm9881
49. Burke JA, Zhang X, Bobbala S, et al. Subcutaneous nanotherapy repurposes the immunosuppressive mechanism of rapamycin to enhance allogeneic islet graft viability. Nat Nanotechnol 2022;17:319–330
50. Anwar IJ, Berman DM, DeLaura I, 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:eadf6376
51. Roep BO, Thomaidou S, van Tienhoven R, Zaldumbide A. Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?). Nat Rev Endocrinol 2021;17:150–161
52. Cai EP, Ishikawa Y, Zhang W, et al. Genome-scale in vivo CRISPR screen identifies RNLS as a target for beta cell protection in type 1 diabetes. Nat Metab 2020;2:934–945
53. Hu X, Gattis C, Olroyd AG, et al. Human hypoimmune primary pancreatic islets avoid rejection and autoimmunity and alleviate diabetes in allogeneic humanized mice. Sci Transl Med 2023;15:eadg5794
54. Xu H, Wang B, Ono M, et al. Targeted disruption of HLA genes via CRISPR-Cas9 generates iPSCs with enhanced immune compatibility. Cell Stem Cell 2019;24:566–578.e7
55. Parent AV, Faleo G, Chavez J, et al. Selective deletion of human leukocyte antigens protects stem cell-derived islets from immune rejection. Cell Rep 2021;36:109538
56. Chang CA, Bhagchandani P, Poyser J, et al. Curative islet and hematopoietic cell transplantation in diabetic mice without toxic bone marrow conditioning. Cell Rep 2022;41:111615
57. Luo X, Pothoven KL, McCarthy D, et al. ECDI-fixed allogeneic splenocytes induce donor-specific tolerance for long-term survival of islet transplants via two distinct mechanisms. Proc Natl Acad Sci U S A 2008;105:14527–14532
58. Singh A, Ramachandran S, Graham ML, et al. Long-term tolerance of islet allografts in nonhuman primates induced by apoptotic donor leukocytes. Nat Commun 2019;10:3495
59. Lee LM, Zhang H, Lee K, et al. A comparison of ex vivo expanded human regulatory T cells using allogeneic stimulated B cells or monocyte-derived dendritic cells. Front Immunol 2021;12:679675
60. MacDonald KG, Hoeppli RE, Huang Q, et al. Alloantigen-specific regulatory T cells generated with a chimeric antigen receptor. J Clin Invest 2016;126:1413–1424
61. Irac SE, Soon MSF, Borcherding N, Tuong ZK. Single-cell immune repertoire analysis. Nat Methods 2024;21:777–792
62. Lledó-Delgado A, Preston-Hurlburt P, Currie S, et al. Teplizumab induces persistent changes in the antigen-specific repertoire in individuals at risk for type 1 diabetes. J Clin Invest 2024;134:e177492
63. Akirav EM, Lebastchi J, Galvan EM, et al. Detection of β cell death in diabetes using differentially methylated circulating DNA. Proc Natl Acad Sci U S A 2011;108:19018–19023

64. Aljani B, Lindner A, Weigelt M, et al. Small RNA-Seq and real time rt-qPCR reveal islet miRNA released under stress conditions. Islets 2024;16:2392343
65. Rodriguez-Calvo T, Chen Y-C, Verchere CB, et al. Altered β-cell prohormone processing and secretion in type 1 diabetes. Diabetes 2021;70:1038–1050
66. Vallabhajosyula P, Korutla L, Habertheuer A, et al. Tissue-specific exosome biomarkers for noninvasively monitoring immunologic rejection of transplanted tissue. J Clin Invest 2017;127:1375–1391
67. Maanaoui M, Lenain R, Foucher Y, et al.; TREPID-ABM Study Group. Islet-after-kidney transplantation versus kidney alone in kidney transplant recipients with type 1 diabetes (KAIAK): a population-based target trial emulation in France. Lancet Diabetes Endocrinol 2024;12:716–724
68. Fioretto P, Steffes MW, Sutherland DE, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 1998;339:69–75
69. Warnock GL, Thompson DM, Meloche RM, et al. A multi-year analysis of islet transplantation compared with intensive medical therapy on progression of complications in type 1 diabetes. Transplantation 2008;86:1762–1766
70. Witkowski P, Anteby R, Olaitan OK, et al.; Islets for US Collaborative; Cell Transplantation Committee of the American Society of Transplant Surgeons (ASTS). Pancreatic islets quality and potency cannot be verified as required for drugs: reflection on the FDA review of a biological license application for human islets. Transplantation 2021;105:e409–e410
71. Sherr JL, Laffel LM, Liu J, et al. Severe hypoglycemia and impaired awareness of hypoglycemia persist in people with type 1 diabetes despite use of diabetes technology: results from a cross-sectional survey. Diabetes Care 2024;47:941–947