Diabetes Ther (2025) 16:1125–1138
https://doi.org/10.1007/s13300-025-01732-9

REVIEW

# Cell Therapy for T1D Beyond BLA: Gearing Up Toward Clinical Practice

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Received: February 4, 2025 / Accepted: March 18, 2025 / Published online: April 11, 2025


## ABSTRACT

Type 1 diabetes (T1D) remains a significant global health challenge and patients with T1D need lifelong insulin therapy. Islet transplantation holds transformative potential by replacing autoimmune-mediated destruction of insulin-producing beta cells. This review examines the trajectory of islet transplantation for T1D, focusing on the process and benefits of obtaining biologics license application (BLA) approval for cell-based therapies. Following US Food and Drug Administration (FDA) approval, the authors identify key steps urgently needed to foster islet transplantation as a viable treatment for a broader population of patients with T1D. Furthermore, the authors highlight recent advances in encapsulation technologies, stem cell-derived islets, xenogeneic islets, and gene editing as strategies to overcome challenges such as immune rejection and limited islet sources. These innovations are pivotal in enhancing the safety and efficacy of islet transplantation. Ultimately, this review emphasizes that while BLA approval represents a critical milestone, realizing the full potential of cell therapy for T1D requires addressing the scientific, clinical, and logistical challenges of its real-world implementation. By fostering innovation, collaboration, and strategic partnerships, the field can transform T1D care, offering patients a durable, life-changing alternative to traditional insulin therapy.

**Keywords:** Diabetes; Type 1 diabetes (T1D); Islet transplant; Biologics license application (BLA); Food and Drug Administration (FDA); LANTIDRA; Islet encapsulation; Stem cells

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| Key Summary Points |
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| Islet transplantation offers a life-changing alternative for T1D patients. |
| LANTIDRA, an FDA-approved cellular product, is a critical step toward advancing cell-based therapies for T1D treatment. |
| Real-world application of LANTIDRA requires addressing scientific, clinical, and logistical barriers to expand access and ensure safety and efficacy. |
| Strategic partnerships and continued innovation are vital for integrating islet transplantation into standard T1D care and improving patient outcomes. |
| Advances in encapsulation, stem cell-derived islets, xenogeneic islets, and gene editing aim to overcome immune rejection and limited islet supply. |

## BRIEF HISTORY OF ISLET TRANSPLANTATION

Islet transplantation for type 1 diabetes (T1D) began in the 1960s, focusing on islet isolation techniques and a few clinical trials that were largely experimental and faced significant challenges [1]. Between the 1970s and 1980s, further improvements in islet isolation were achieved, but clinical success in achieving insulin independence was very low [2–6].

A breakthrough occurred in the late 1990s with the Edmonton Protocol [7], which combined improved islet isolation methods, advanced immunosuppressive therapies, and the portal vein as a transplant site. This protocol led to successful cases of insulin independence in unstable patients with T1D, especially for those who had severe hypoglycemia and glycemic instability despite insulin therapy. Since then, worldwide clinical studies have demonstrated that islet transplantation can significantly improve glycemic control and insulin independence in patients with T1D, as well as prevent complications [8–16]. Additional evidence demonstrates that islet transplantation after kidney transplant can notably improve the quality of life for individuals with unstable T1D diabetes and help protect against long-term complications such as neuropathy, retinopathy, and kidney disease [17, 18]. However, despite these clinical successes, islet transplantation has remained a niche therapy owing to limited donor supply, immune rejection, and the need for lifelong immunosuppressants.

## BIOLOGICS LICENSE APPLICATION (BLA)

To apply islet transplantation as standard therapy for patients with T1D in the USA, allogeneic islet biologics from deceased donors must obtain biologics license application (BLA) approval from the US Food and Drug Administration (FDA). FDA issued two important documents guiding the process: The FDA's "Considerations for Allogeneic Pancreatic Islet Cell Products" in 2008 (Docket Number: FDA-2008-D-0293) and "Guidance for Human Somatic Cell Therapy and Gene Therapy" in 2009 (Docket Number: FDA-2009-D-0132-0016) to ensure islet transplant safety, efficacy, and consistent manufacturing quality while assessing immune responses and long-term outcomes (Fig. 1).

Key areas in the guidance include product characterization (source, isolation, and quality control), manufacturing controls (consistency, storage, and contamination prevention), and preclinical studies (animal testing for safety and efficacy) (Fig. 2).

It also addresses immunogenicity (immune response and rejection risk), clinical studies (design, endpoints, and adverse events), post-approval monitoring (long-term outcomes and patient registry), and regulatory pathways (submission of trial and manufacturing data).

On 28 June 2023, the FDA approved LANTIDRA from CellTrans, Inc. as the first islet cell therapy for T1D (https://www.fda.gov/news-events/press-announcements/fda-approves-first-cellular-therapy-treat-patients-type-1-diabetes),

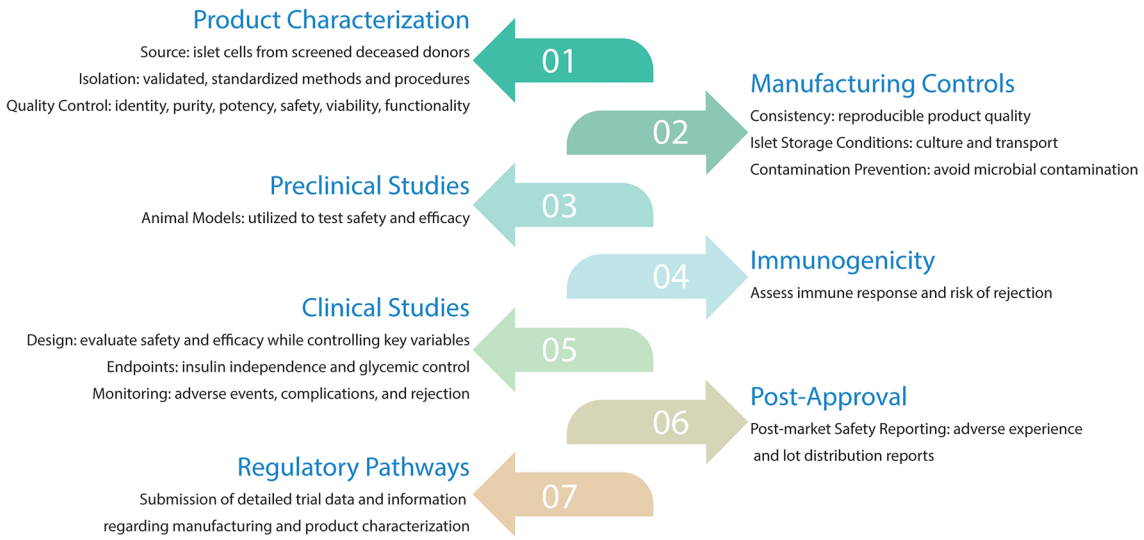


**Fig. 1** FDA guidance on islet biologics for a biologics license application (BLA)


**Fig. 2** Comprehensive guidance of key evaluation areas in the biologics license application (BLA) process

which is a significant milestone in the field of islet transplantation.

In the FDA's new release, Peter Marks, MD, PhD, the Director of the FDA's Center for Biologics Evaluation and Research, commented, "Severe hypoglycemia is a dangerous condition that can lead to injuries resulting from loss of consciousness or seizures. The approval, the first-ever cell therapy to treat patients with type 1 diabetes, provides individuals living with type 1 diabetes and recurrent severe hypoglycemia an additional treatment option to help achieve target blood glucose levels." The FDA approval ensured islet transplantation follows established safety and quality guidelines in the USA.

The FDA's decision to regulate islet transplants as a biologic drug requiring a BLA has generated debate among medical and research professionals. Key concerns include increased regulatory burdens, potential limitations on patient access, and the impact on islet classification, research, and innovation [19–21]. However, this classification underscores the FDA's dedication to ensuring patient safety through stringent oversight.

## NEXT STEPS FOR ISLET TRANSPLANTATION POST BIOLOGICS LICENSE APPROVAL

Addressing the challenges related to islet supply, long-term efficacy, and cost are essential to making islet transplantation a viable treatment option for a larger population of patients with T1D after FDA approval (Fig. 3), in which each component is equally important.

### Scaling Production to Meet Demand

Scaling up requires the establishment of regional and nationwide Current Good Manufacturing Practice (cGMP) facilities for islet production, with strict adherence to regulatory and safety standards. Such practices ensure that the biological products are manufactured with consistent quality, potency, and purity, while minimizing the risk of contamination and batch-to-batch variability. Importantly, incorporating automation of isolation process efficiencies will help lower costs while maintaining high-quality islet products.

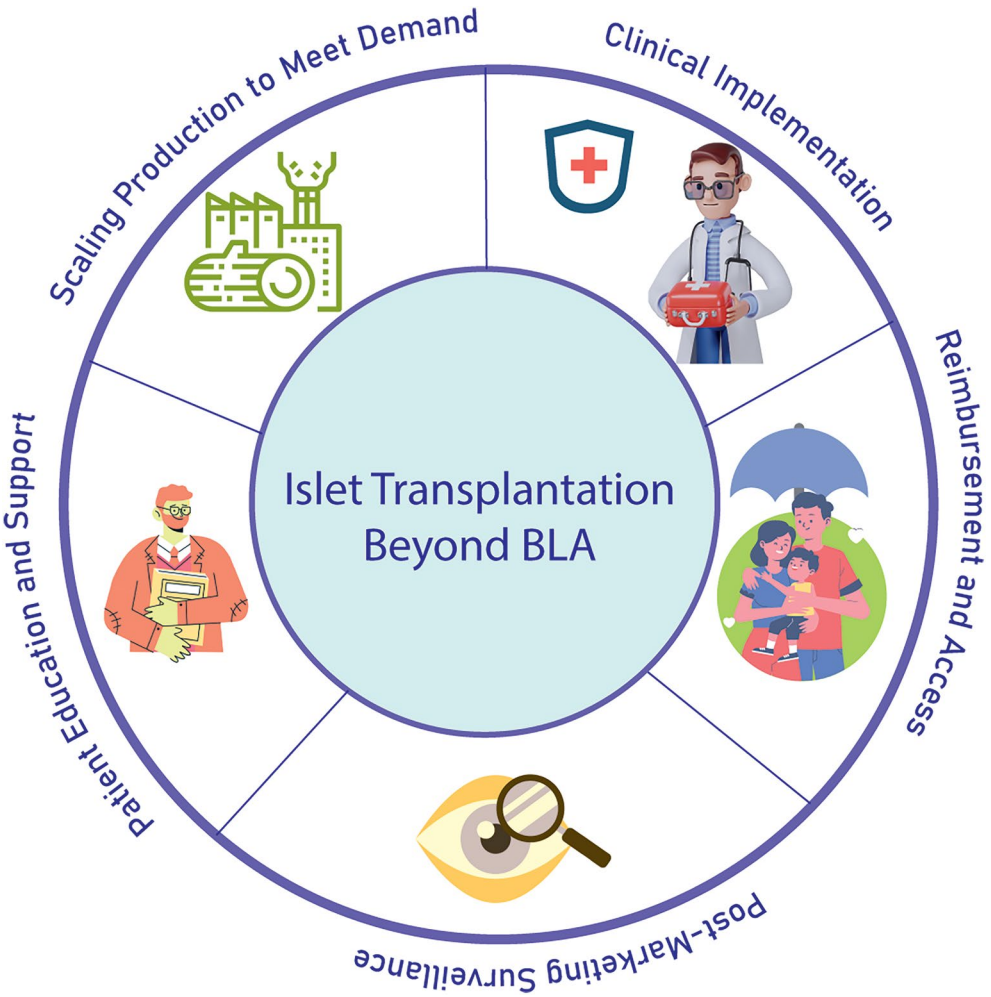


**Fig. 3** Next steps for islet transplantation following biologics license application (BLA) approval

The evaluation process for LANTIDRA, particularly within the context of the BLA process, focuses on ensuring the highest standards of safety, efficacy, and consistency, as required by the FDA. Unlike most islet isolation centers with unverified protocols and equipment, LANTIDRA's approval allows its use without the need for receiving centers to have their islet isolation capabilities. This could increase access to islet transplantation in clinical settings that previously lacked the resources or expertise to perform these procedures.

### Clinical Implementation

Collaborating with qualified transplant centers is crucial for successfully implementing LANTIDRA, including training transplant surgeons and medical staff on established protocols and procedures. Adherence to screening processes and clearly defined selection criteria is essential. Eligible candidates must be 18 years or older, have had T1D for at least 5 years, and maintain a body mass index (BMI) below 27. They should have experienced at least one severe hypoglycemic episode within the past year and exhibit impaired awareness of hypoglycemia despite ongoing insulin therapy, intensive diabetes management, and education. Furthermore, candidates must be free from significant cardiovascular, respiratory, liver, or neurological conditions and should not have any active infections [13, 22]. These criteria ensure that islet transplantation is provided to individuals who are most likely to benefit from the procedure.

### Reimbursement and Access

Negotiating reimbursement with health insurers is important to improve patient access to LANTIDRA. Given the substantial costs of the procedure and post-transplant care, collaboration with payors to secure coverage both from government programs, such as the Centers for Medicare and Medicaid Services (CMS), and private insurers, is critical for the broader adoption of islet transplantation. Currently, many private insurers in the USA include LANTIDRA in their coverage for unstable T1D. However, coverage policies vary across insurers, with some imposing specific criteria or limitations. To address these disparities, healthcare providers and stakeholders must continue ongoing discussions with insurers to ensure comprehensive and equitable coverage for islet transplantation.

### Post-Marketing Surveillance

The FDA requires LANTIDRA to comply with specific post-marketing surveillance regulations to ensure patient safety. Under 21 CFR 600.80 (Code of Federal Regulations, Title 21, Part 600.80, the Reporting of Adverse Events for biological products), CellTrans is obligated to monitor and report adverse events, complications, and issues related to immunosuppressive therapies associated with LANTIDRA. Furthermore, as mandated by 21 CFR 600.81, manufacturers must submit lot distribution reports every 6 months. These reports detail the quantity of the product distributed, including the amounts provided to distributors. This information is vital for tracking product distribution and ensuring its appropriate use.

### Patient Education and Support

Comprehensive patient education programs must be developed for recipients to understand the risks, benefits, and the need for lifelong follow-up and medication adherence. Support networks and programs also play a vital role in helping recipients manage their health, offering guidance on immunosuppression management and monitoring for signs of rejection or complications. For example, the University of Illinois Hospital & Health Sciences System emphasizes the significance of thorough pre-transplant evaluations to determine if patients are medically suitable for the procedure. In addition, the National Institute of Diabetes and Digestive and Kidney

Diseases (NIDDK) provides valuable resources on pancreatic islet transplantation, emphasizing its potential benefits and the critical role of patient adherence to post-transplant care.

In summary, the clinical implementation of LANTIDRA presents significant challenges, and CellTrans has been working diligently to establish a clear pathway for its adoption. Efforts to collaborate with transplant centers across the US are ongoing to expand access to LANTIDRA. Additional measures are needed to ensure the readiness of transplant centers. This includes expanding training programs for transplant surgeons, but equally important is engaging diabetologists and diabetes educators to support patient identification, referral pathways, and post-transplant care. Further studies are needed to optimize integration into clinical practice and ensure broader accessibility. Equally important, future considerations should refine the patient selection criteria on the basis of additional evidence, with insulin requirements being a key determinant in patient selection for islet transplantation.

## CHALLENGES AND OPPORTUNITIES BEYOND THE BLA

While the BLA approval represents a major regulatory milestone, it does not address critical challenges that impede the widespread adoption of islet transplantation.

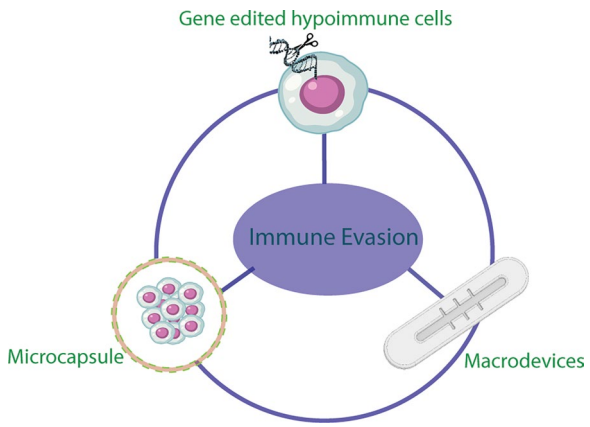


**Fig. 4** Solutions to solve islet cell source availability beyond the biologics license application (BLA)

### Limited Islet Cell Sources

The shortage of viable donor pancreata has led to a significant gap between the number of patients that can benefit from the therapy and the availability of islets. Since this subject has been extensively reviewed, here, we only outline key progress related to the current practice of human islet transplantation (Fig. 4).

#### *Xenogeneic Islets*

Porcine islets are a promising option for human transplantation owing to their physiological similarity to human islets. They can address the critical shortage of human donor organs by providing a more abundant and scalable source, potentially reducing wait times through consistent availability. Genetic modifications in pigs are advancing to minimize immune rejection [23–26], including expressing human leukocyte antigen (HLA) molecules to decrease immune recognition, deleting the alpha-galactosidase gene to prevent immune responses to alpha-gal epitopes, and introducing genes that encode immunomodulatory proteins such as cytotoxic T-lymphocyte antigen 4 immunoglobulin (CTLA4-Ig) or programmed death-ligand 1 (PD-L1). In addition, pigs can be engineered to express human complement regulators, such as cluster of differentiation 46 (CD46) or cluster of differentiation 55 (CD55), to protect islet cells from complement-mediated damage. Advanced gene-editing tools, such as CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9), are also being used to knock out pro-inflammatory genes or introduce genes promoting immune tolerance [27].

Preclinical studies using naïve and genetically modified pig islets have shown encouraging results, particularly in non-human primates [28–30]. These studies demonstrated that pig islets could survive and function in primates for extended periods, especially

when combined with immunosuppressive therapy or encapsulation. Clinical trials using pig islets in humans began in 2009 in New Zealand, led by Living Cell Technology. These trials yielded promising outcomes, such as improved blood sugar control and reduced insulin requirements, though they did not achieve long-term graft function or complete insulin independence [31, 32]. Recently, an Investigational New Drug (IND) application for encapsulated pig islets has been approved for clinical trials (ClinicalTrials.gov NCT06575426), with results expected in 2025.

Despite its potential, xenotransplantation faces significant regulatory challenges, particularly regarding biosafety concerns. A primary issue is the risk of transmitting porcine endogenous retroviruses (PERVs). The FDA mandates stringent safety protocols and continuous monitoring for xenotransplantation trials. The future of xenotransplantation will depend on advancements in genetic engineering, enhanced immune protection strategies, and addressing ethical and safety concerns.

### *Stem Cell-Derived Islet Biologics*

In the 1990s, research focused primarily on differentiating embryonic stem cells (ESCs) into insulin-producing beta-cells [33]. Progress accelerated with the advent of induced pluripotent stem cells (iPSCs), enabling the generation of beta cells from adult cells in 2006 [34]. Throughout the 2010s, advancements in differentiation protocols significantly improved the functionality of these cells, allowing them to more closely resemble natural insulin-producing beta cells and effectively normalize blood sugar levels in diabetic mice [35–39].

Successful studies have demonstrated that human pluripotent stem cell (hPSC)-derived islets can improve glycemic control and alleviate diabetes symptoms in non-human primates (NHPs) [40], underscoring their potential as a promising therapy for diabetes.

ViaCyte is testing PEC-Direct (Pancreatic Endocrine Cells Direct), which involves implanting stem cell-derived pancreatic progenitors in a semi-permeable device under the skin. These progenitors mature into insulin-producing beta cells, potentially reducing or eliminating the need for external insulin [41, 42]. In February 2022, ViaCyte and CRISPR Therapeutics announced Phase I clinical trials for VCTX210, a hESC-based therapy for T1D that does not require immunosuppression. The CyT49 human embryonic stem cell (hESC) line has been genetically engineered to lack the beta-2 microglobulin (*B2M*) gene, preventing expression of major histocompatibility complex (MHC) class I molecules, and to express a transgene encoding programmed death-ligand 1 (PD-L1) to protect against CD8+ cytotoxic T-cell attack. These modifications enhance immune evasion, potentially reducing the need for long-term immunosuppression and improving graft survival [43, 44].

In 2021, Vertex Pharmaceuticals initiated a clinical trial (VX-880) using beta cells differentiated from human pluripotent stem cells with immunosuppression. These cells are engineered to function like natural beta cells. At the American Diabetes Association's 84th Scientific Session in 2024, Vertex reported that all twelve patients receiving a single VX-880 infusion exhibited islet engraftment and glucose-responsive insulin production by day 90. All patients showed improved glycemic control, with reduced or eliminated insulin use. The three patients with over a year of follow-up met the primary endpoint of eliminating severe hypoglycemic episodes (SHE) with HbA1c < 7.0% and the secondary endpoint of insulin independence. VX-880 was generally well tolerated, with mostly mild-to-moderate adverse events and no serious treatment-related complications. Two deaths were reported, but they were unrelated to VX-880. In addition, the VX-264 clinical trial from Vertex was designed to combine allogeneic human stem cell-derived islets with encapsulation technology to shield the cells from the recipient's immune system.

On the basis of the chemically induced pluripotent stem cell (CiPSC) technology [40, 45–47], a recent study reported the 1-year outcomes of a patient with T1D who underwent autologous transplantation of chemically induced pluripotent stem cell-derived islets (CiPSC islets) beneath the abdominal

anterior rectus sheath, using standard immunosuppression. The patient achieved sustained insulin independence within 75 days, with time-in-target glycemic range increasing from 43.18% at baseline to 96.21%, stabilizing at over 98% with an HbA1c of approximately 5% [45]. Two additional patients have been implanted, with results expected in 2025. This marks significant progress toward personalized cell therapy for T1D using CiPSCs. The study employed standard immunosuppression, despite implanting autologous CiPSC-derived islets, owing to potential risks, including residual allogeneic antigens, autoimmune recurrence, and inflammatory responses that could compromise graft survival. It is worth noting that different immunosuppression strategies may be required for stem cell-derived islet transplants compared with traditional islet transplants, considering factors such as alloimmune rejection, autoimmune recurrence, and potential off-target immune responses.

Several ongoing national and international clinical trials are listed on ClinicalTrials.gov, though no transplant outcomes have been reported to date. Some research efforts combine stem cell-derived islet transplantation with novel immunotherapies aimed at retraining the immune system to tolerate beta cells, an approach that has been well-reviewed elsewhere [48]. While stem cell-based therapies have demonstrated considerable benefits for glycemic control, challenges remain, including immune rejection, long-term graft function, in vivo cell maturation, efficacy and safety concerns, and high manufacturing costs.

Stem cell-based therapies for diabetes will face stricter regulatory scrutiny than human islet transplants owing to safety concerns, such as the risk of tumor formation and genetic instability (https://www.isscr.org). Genetic modifications, long-term outcomes, and potential immunogenicity will require rigorous testing. Manufacturing processes for stem cells and their derivatives must meet high standards for quality control and consistency. Ethical concerns, particularly regarding the sourcing of stem cells, will also influence regulations. Regulatory agencies will demand extensive preclinical and clinical data to ensure the safety, efficacy, and ethical compliance of these therapies before they are approved for widespread use.

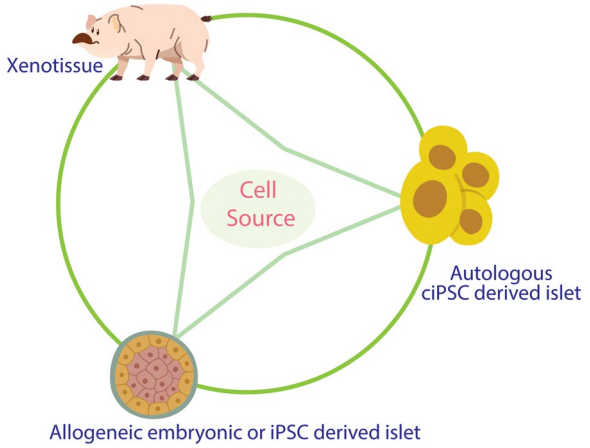


**Fig. 5** Immuno-evasive strategies in islet transplantation. iPSC-derived islet, induced pluripotent stem cell-derived islet-like cell; ciPSC, chemically induced pluripotent stem cell

## Immune Evasion Strategies in Islet Transplant

In human islet transplantation, immune rejection occurs because the recipient's immune system recognizes the transplanted allogeneic islet grafts as foreign and attacks them. Without immunosuppression, islet grafts will be rejected, and function will be lost. Recently, it has shown that recurrent autoimmunity is a critical factor in islet graft loss, as seen in pancreas transplantation, where it may also trigger alloimmune responses [49]. Notably, a retrospective study suggests that HLA-DQ8 positivity may be associated with improved C-peptide levels, possibly indicating a role in immune tolerance [50]. Further investigation is needed to clarify the mechanisms and optimize patient selection. In the last three decades, various immune-evasive strategies have been applied for preventing islet graft loss (Fig. 5).

### *Islet Encapsulation*

The concept of islet microencapsulation originated in the 1970s, with early research focusing on alginate, a biocompatible polymer, to form a semi-permeable membrane that allows insulin and nutrients to pass through while blocking immune cells and antibodies [51]. In the 1980s and 1990s, advancements in alginate-based encapsulation techniques demonstrated promise. However, fibrosis (formation of tissue overgrowth around the capsules) remained a significant challenge, limiting long-term islet function [52–54]. Clinical trials demonstrated short-term protection, but often failed due to capsule surface fibrotic overgrowth on the capsule surface [55]. From the 2010s onward, new encapsulation strategies have emerged, focusing on reducing fibrosis and improving islet survival. These include advanced biocompatible materials, nanotechnologies such as ultra-thin coatings designed to be more biocompatible or durable, and new transplant sites [56–62].

Macrodevices are another approach to implantable devices that house clusters of islets. Macrodevices have shown promise in preclinical studies as a strategy to shield transplanted islets or stem cell-derived islets from immune-mediated attack, potentially reducing or eliminating the need for systemic immunosuppression. One notable example is the TheraCyte device, which uses a semi-permeable membrane to encase the islets. It has shown some success in both preclinical and clinical trials, particularly in improving long-term islet survival and function [63–65]. Another promising macrodevice is the Beta-O2 device, which features an oxygen reservoir that sustains islet function by providing a steady oxygen supply. This method has demonstrated superior outcomes in maintaining islet viability and function [66–68]. Implantable scaffolds, made from biocompatible materials, encourage vascularization around the islets, enhancing their survival and insulin production [69]. Using alginate fibers for islet encapsulation is an innovative approach that utilizes modified alginate formulations and combination materials to improve biocompatibility and reduce immune responses [70–72]. These advancements have shown promising preclinical results for islet transplant outcomes but have not been demonstrated in human clinical trials.

Ongoing clinical trials are investigating advanced polymers, oxygen-releasing agents, bioengineered scaffolds, and xenogeneic tissues to enhance islet transplantation availability and effectiveness, potentially eliminating the need for lifelong immunosuppression.

### *Gene Editing*

Gene editing tools, such as CRISPR-Cas9, are transforming islet biologics and stem cell-derived islets by enabling precise genetic modifications to enhance safety, efficacy, and immune evasion. CRISPR-Cas9 targets specific DNA sequences, creating double-strand breaks to allow targeted changes. This technique's precision, efficiency, and versatility make it a revolutionary tool for genetic research and medical treatments. The application of these genetic modifications is to reduce islet immune responses, improve islet functionality, and increase the efficiency of differentiating stem cells into insulin-producing cells.

Traditional immune-evasive strategies, such as immunoisolation devices, immunosuppressive drugs, and tolerance induction techniques, have been used to improve graft survival and function. However, gene editing introduces new possibilities by directly altering the islet cells' genetic makeup. For example, deleting genes responsible for expressing MHC class I molecules and co-stimulatory signals can reduce the immune system's ability to recognize and attack the islets. One study showed that deleting polymorphic human leukocyte antigens (HLAs) in human pluripotent stem cells (hPSCs) significantly reduced natural killer (NK) cell activity and T-cell-mediated immune responses in humanized mouse models, enhancing the survival of stem cell-derived islet cells [73].

In addition, other studies have successfully engineered hypoimmune islets (e.g., B2M–/–, CIITA–/–, CD47+) in rhesus macaques, demonstrating long-term survival and insulin independence without immunosuppression [74]. Furthermore, researchers have enhanced protection against rejection by genetically engineering

stem cell-derived islets to secrete immunomodulatory cytokines such as interleukin (IL)-10, transforming growth factor (TGF)-β, and IL-2, which promote a tolerogenic microenvironment and recruit regulatory T cells to the graft site [75]. These gene-edited islets demonstrated resistance to rejection and successfully reversed diabetes in animal models.

## CONCLUSIONS

The future of islet transplantation beyond the BLA presents significant challenges and promising opportunities. The path toward the widespread clinical adoption of LANTIDRA remains complex and lengthy. As of this writing, LANTIDRA has been covered by many private insurers in the USA for patients with unstable T1D. In addition, the FDA recently approved LANTIDRA's shipping protocols to extend the shelf life of LANTIDRA up to 48 h, facilitating a broader distribution scheme. On 25 November 2024, the University of Illinois Health in Chicago initiated LANTIDRA therapy in partnership with CellTrans. Throughout 2024, CellTrans engaged in extensive discussions with regional and national islet transplant programs, aiming to launch multicenter implementation by 2025.

The need for islet transplantation, including LANTIDRA, may extend beyond those with severe hypoglycemia and glycemic variability. While insulin therapy improves glucose control, it does not eliminate disease burden, insulin dependency, or long-term complications. Expanding islet transplantation eligibility could benefit a broader population, particularly those struggling despite advanced technologies. However, with fewer than 3000 donor pancreata suitable for islet isolation annually in the USA, supply remains a major constraint. This underscores the urgent need for alternative sources, such as stem cell-derived islets, and advancements in immunomodulatory strategies to expand accessibility. Clearly outlining these potential expansions will help define a long-term vision for improving access to cell-based therapies for T1D.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

***Author Contributions.*** Yong Wang: writing—review and editing, and writing—original draft. YingYing Chen: writing—review and editing, and writing—original draft. James McGarrigle: writing—review and editing. Jenny Cook: writing—review and editing. Peter D. Rios: writing—review and editing. Giovanna La Monica: writing—review and editing. Wei Wei: writing—review and editing. Jose Oberholzer: writing—original draft, and writing—review and editing.

***Funding.*** The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

### *Declarations*

***Conflicts of Interest.*** Authors (Yong Wang, James McGarrigle, Jenny Cook, Peter D. Rios, Giovanna La Monica, and Jose Oberholzer) are employed by CellTrans, Inc. YingYing Chen and Wei Wei have nothing to disclose.

***Ethical Approval.*** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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