

REVIEW

Strategies for durable β cell replacement in type 1 diabetes

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Technological advancements in blood glucose monitoring and therapeutic insulin administration have improved the quality of life for people with type 1 diabetes. However, these efforts fall short of replicating the exquisite metabolic control provided by native islets. We examine the integrated advancements in islet cell replacement and immunomodulatory therapies that are coalescing to enable the restoration of endogenous glucose regulation. We highlight advances in stem cell biology and graft site design, which offer innovative sources of cellular material and improved engraftment. We also cover cutting-edge approaches for preventing allograft rejection and recurrent autoimmunity. These insights reflect a growing understanding of type 1 diabetes etiology, β cell biology, and biomaterial design, together highlighting therapeutic opportunities to durably replace the β cells destroyed in type 1 diabetes.

Type 1 diabetes (T1D) results from the autoimmune destruction of pancreatic β cells, leading to insulin deficiency. Although the disease features common genetic risk factors and autoantibody biomarkers, extensive variability in clinical presentation and management results in challenges in meeting glycemic targets, which elevates risk of complications and comorbidities (1).

In the past decade, enhancements in glucose sensors, insulin pumps, and their communication have drastically improved diabetes care and management (2); however, delays in glucose sensing and insulin absorption hinder physiological glycemic control. Device use also imparts a considerable mental and financial burden on people living with T1D.

Cellular therapy for T1D has the potential to provide an autonomous, curative therapy, as the implanted cells can inherently sense, respond, and manage blood glucose concentrations. Recipients of clinical islet transplantation (CIT), where allogenic, cadaveric pancreatic islets are infused into the portal vein and reside in the liver microvasculature, exhibit physiological glycemic control in the absence of exogenous insulin (3). Nevertheless, the promise of cell therapy for diabetes resolution is currently impaired by several factors. First, a paucity of cadaveric human organ donors creates an imbalance in supply versus clinical demand. Second, CIT recipients require lifelong immunosuppressive therapy to prevent immune-mediated graft loss—an untenable risk for most people, especially children. Finally, graft mass typically declines after transplantation, par-

tially due to the hostile implantation site. To leverage cellular replacement as a regenerative approach, a multipronged research strategy is needed, whereby an unlimited β cell source is generated, an optimal implant site is engineered, and targeted immunomodulatory approaches are implemented for durable graft protection.

Procuring abundant β cell sources for T1D cell therapy

The positive results from CIT have triggered extensive research in the development of more broadly accessible and safe sources of insulin-producing cells (Fig. 1A). Several therapeutic opportunities have progressed, spurred by enhanced understanding of β cell biology and new biological tools.

Porcine islets are a readily available source of mature β cells, but their clinical translation is limited in practice and success, with only modest and brief reductions in exogenous insulin requirements (4). Key challenges associated with this cell source include hyperacute xenograft rejection and potential zoonosis risk (4). Rapid progress in genetic engineering of pigs, however, is dampening xenoreactivity and improving safety, although the reduced insulin secretory response of porcine islets to glucose stimulation remains a concern (4, 5).

Human pluripotent stem cells (PSCs)—both embryonic (ESCs) and induced (iPSCs)—have taken center stage in regenerative medicine approaches owing to their ability to rapidly self-renew and theoretically differentiate into any human cell type. ESCs are the gold standard for pluripotency, but ethical and human leukocyte antigen (HLA) matching concerns remain. iPSCs alleviate these concerns, as they are derived from consenting donors and can provide an autologous cell source; however, reproducible differentiation is challenged by clonal variability.

There are two main approaches for effectively creating stem cell-derived β -like cells (sBCs), each with its own set of challenges and opportunities. The more developed approach

implants pancreatic progenitor (PP) cells, which subsequently differentiate into sBCs via largely unknown in vivo-derived cues. This in vivo maturation process requires months to reach a therapeutic functional mass, and grafts exhibit considerable cellular heterogeneity, with variable contributions of other pancreatic and PP cells (6). These findings, however, provided sufficient impetus for a first-in-human clinical trial (NCT03162926). An alternative approach is the in vitro generation of sBCs, which has the advantage of more immediate graft function, reduced total transplant volume, and a defined cell product at the time of transplantation (7–9).

Despite glucose responsiveness in static stimulation in vitro, sBC cultures display a suboptimal phenotype, akin to an immature fetal stage. Recent reports indicate that β cell maturation could be partially triggered by manipulation of circadian entrainment or nutritional supply (10, 11). β purification and reaggregation of propagated cell clusters during sBC differentiation also promote maturation, while concurrently removing unwanted cell contamination (12, 13). Because cell enrichment of large-scale cultures poses substantial translational challenges, improving current differentiation protocols would be preferred.

Multiple cell sources have created insulin-producing pancreatic β cells via transdifferentiation (the conversion of one differentiated cell type into another). Numerous murine pancreatic sources, such as acinar and other islet-resident hormonal cells, have been converted to functional, insulin-positive cells (14), although this approach has yet to be tested in a human setting. Recent advances in refining the tropism of clinically approved adeno-associated viruses for human endocrine cells might provide an opportunity to induce *in situ* pancreatic β cell conversion (15).

Another emerging β cell procurement method involves growing whole organs using patient-specific iPSCs by blastocyst complementation. By disabling native pancreas genesis in a host blastocyte, complementation with xenogeneic pluripotent cells results in the subsequent formation of a pancreas within the vacant developmental niche. Early successful rodent approaches are translating to larger porcine models that could host the development of a functional organ from exogenous pluripotent cells (16), although the capacity to grow a human pancreas has yet to be reported. While this is an intriguing concept, the prospect of growing chimeric human organs raises ethical questions, including theoretical concerns related to the potential for human cells to differentiate into neurons or germ cells within a disparate species.

Advances in β cell engineering approaches have catalyzed efforts to overcome critical requirements for clinical translation, including the establishment of master cell banks with

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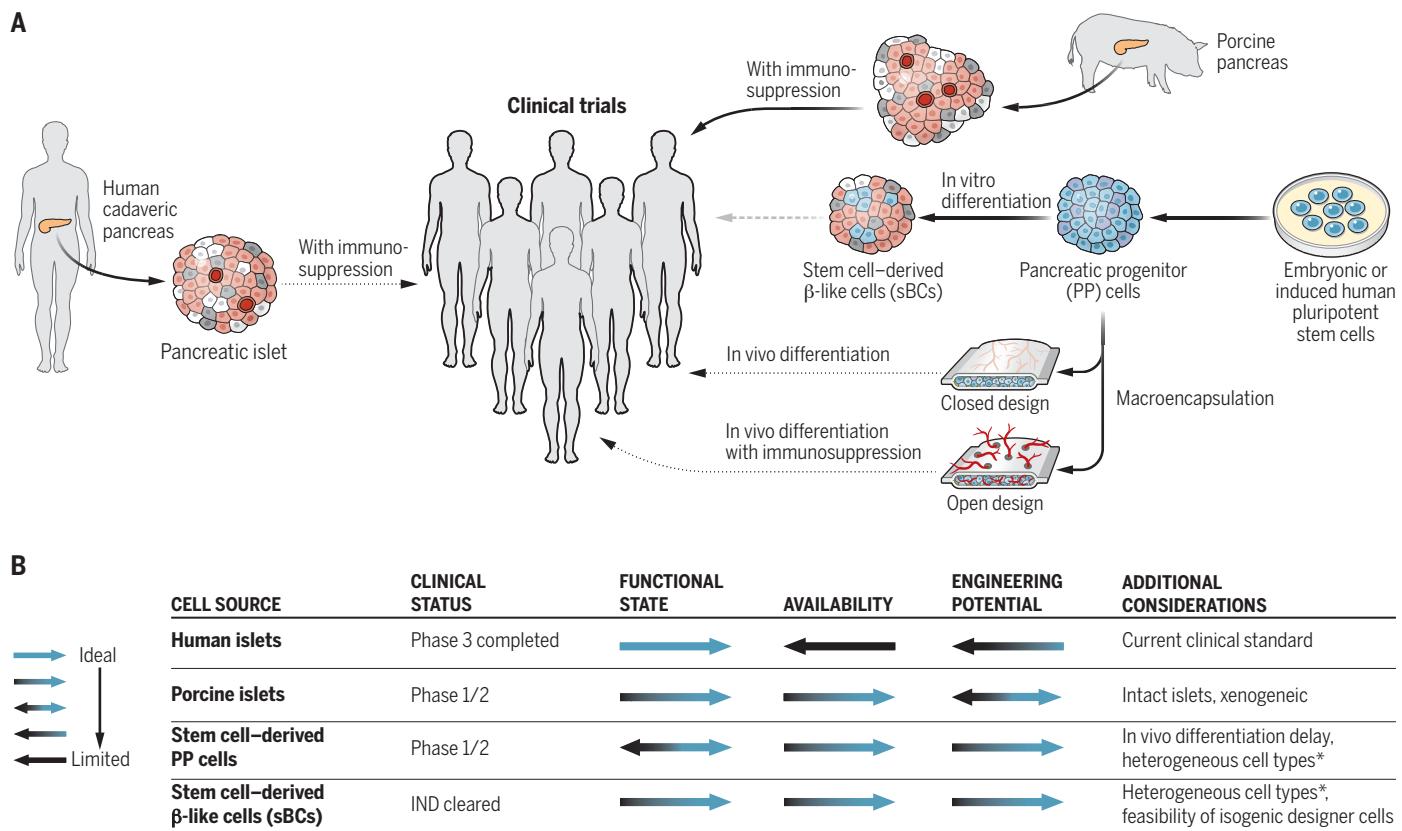


Fig. 1. Functional β cell sources for use in cell therapy for people with type 1 diabetes. (A) Schematic highlighting current islet and stem cell–derived β cell sources and their translation to clinical use. (B) Global summary of key cell sources for cell therapy; their status in the clinical research pipeline; and respective pros and cons in terms of function, availability, and potential for customization through engineering. Note that the heterogeneous populations within the PP and sBC stem cell sources may not be equivalent. IND, investigational new drug.

reproducible quality-control measurements, scalable culture conditions, and the development of cryopreservation and recovery methods (6). The clinical landscape indicates that sBC sources are at the forefront of T1D cellular replacement, with some approaches recently receiving Food and Drug Administration approval for clinical translation (Fig. 1B). However, further work is needed to address key limitations of sBCs, including functional immaturity, immunogenicity, and in vivo survival.

Engineering an optimal cellular transplant microenvironment

A critical obstacle hindering cell-based restorative therapies in T1D is poor islet survival in vivo. CIT trials observed acute damage to more than half of the infused organoids after transplantation (7). Intrahepatic islet infusion is implicated in this severe cellular decline, as islets experience aggressive inflammatory responses and exposure to high concentrations of immunosuppressive drugs. Further, this site exhibits insufficient islet revascularization, resulting in central islet necrosis. Studies indicate a similar acute impact on sBC sources, albeit the severity appears to correlate with cell differentiation state, with progenitors sur-

viving at higher rates than more-differentiated sBCs (18). Paradoxically, sBCs that persist through cell engraftment exhibit improved β cell maturation when compared with their in vitro counterparts (19). Substantial β cell loss after infusion not only increases the required therapeutic dose, it also serves as a stimulatory signal for immune attack, as dying cells release antigenic debris and immunogenic factors that accelerate immune cell recruitment.

Unlike whole-organ transplantation, β cell implantation has the appeal of flexible site choices and implant design parameters. That said, β cell-containing spheroids require specific features for optimal engraftment. Primary pancreatic islets are distinct multicellular clusters distributed throughout the pancreas. Despite constituting only ~2% of the pancreatic organ mass, islets contain a rich vascular network and receive more than fivefold higher blood flow than the surrounding exocrine tissue. Copious perfusion of the islets serves to provide optimal glucose sensing, prompt insulin delivery via portal vein drainage, and optimal nutritional support to the metabolically demanding β cells. Another distinct feature of the islet niche is its peri-islet extracellular matrix (ECM) (20).

These critical features are perturbed during islet isolation. The loss of tonic signaling leads to apoptosis via anoikis, while the culture of isolated islets results in the loss and/or compression of the intra-islet vascular network. For sBCs, nonendocrine supporting cell types are absent, which may contribute to their immature phenotype and suboptimal function. Thus, examining the impact of integrating endothelial cells, pericytes, and/or ECM niches on improving downstream sBC insulin responses and overall cellular engraftment would be of interest (21).

Preclinical and clinical studies have screened numerous extrahepatic engraftment locations with the aim of improving β cell survival (Fig. 2A). As potential teratoma formation is a concern, locations that allow for monitoring and complete retrieval are of particular interest for sBC implants. While sites tested to date have shown specific advantages, most are not ideal for these demanding organoids. For example, the subcutaneous site provides ease of implantation, monitoring, and retrieval but exhibits poor vascular access and is immunologically reactive. Other more vascular-rich sites, such as the omentum, present the challenge of a more invasive surgical procedure.

Material-based approaches, such as devices, hydrogels, and scaffolding, can integrate desirable attributes within the local site (Fig. 2B). The selection of materials and design parameters can alleviate the deficiencies of the selected implant location, delivering features such as mechanical support, vascularization, safety, and even immunoprotection. For example, temporary catheters can be used to create neovascularized subcutaneous channels for improving nourishment of the cellular implant (22, 23). Islets can also be coinfused with discrete extracellular components to promote cell survival and engraftment (24, 25). Alternatively, three-dimensional (3D) biomaterials can support cellular distribution and protection from mechanical stress, while also sup-

porting healthy host cell remodeling and islet revascularization (26). Alternatively, injectable polymeric hydrogels can deliver similar features, using a less invasive surgical procedure, although these materials tend to be weaker and less amenable to complete retrieval (26).

PSC-sourced implants pose additional safety concerns because of their potential for non-terminal differentiation, thus biomaterials can deliver the security features of site retention and graft retrieval. In a popular approach, PP cells are loaded in a single closed encapsulation device coated with semipermeable membranes (6). The porous membranes support nutrient delivery but prevent the exchange of implanted and host cells, which can also impart immuno-

protective features. Early reports from phase 1 clinical trials indicated differentiation of PP cells into insulin- and glucagon-positive cells with no noted teratoma formation (27). Although these reports are exciting, subsequent analyses observed detrimental responses, including graft hypoxia and a foreign body response (FBR) to the implant (27). A phase 2 trial is underway to evaluate an improved closed encapsulation device (NCT04678557), while a separate trial is using a modified prototype with larger macroscale pores that support host infiltration and vascularization (NCT03163511) (Fig. 1B). Although the latter approach favors improved nutrient delivery and glycemic control, it requires long-term systemic immunosuppression.

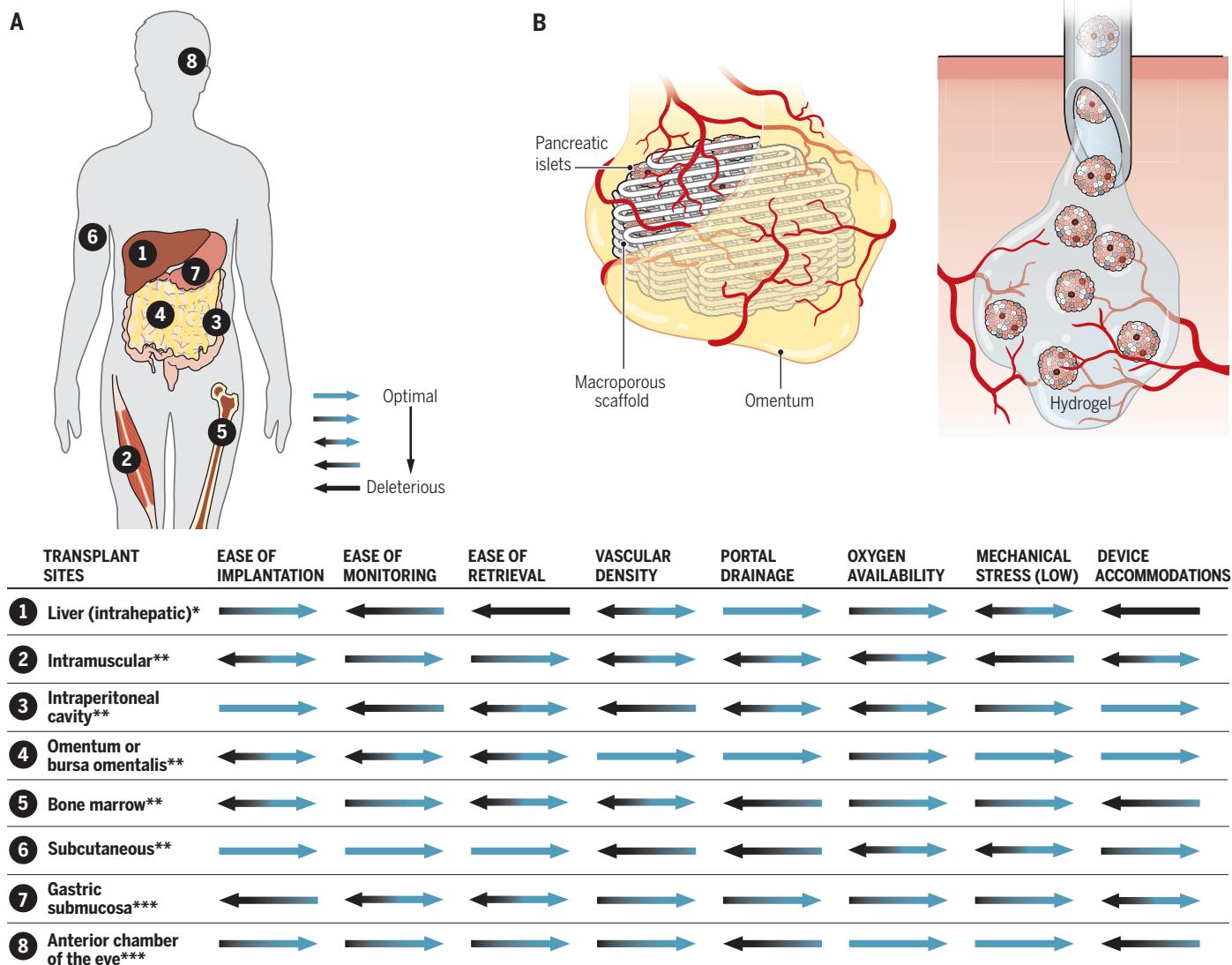


Fig. 2. Clinically relevant transplant sites and biomaterial engineering approaches explored for islet transplantation. (A) Transplant sites, with a global summary of the general pros and cons of key implantation parameters, such as surgical ease, microenvironment, and device accommodation. (B) Material approaches serving to enhance the implant site and promote 3D cellular distribution, vascularization, and local

drug delivery. Examples include (left) open 3D macroporous scaffolds implanted within the omentum and (right) injectable and degradable hydrogels within the subcutaneous site. Single asterisk denotes primary implantation site clinically approved in several countries. Double asterisk denotes completed clinical trials. Triple asterisk denotes active or recruiting clinical trials.

Beyond serving as a supportive platform, materials could be functionalized to direct favorable host and/or implant responses. One approach is the integration of extracellular motifs or β cell supportive agents into inert materials to improve cell survival, function, and even sBC differentiation (28–30). Alternatively, β cell supportive matrices can be linked to proangiogenic factors, which direct the generation of vascular networks (31). The integration of oxygen-generating materials can further impart an immediate nutritional benefit to islet survival (32).

Immunological challenges associated with β cell restorative therapies for T1D

The immune system is exquisitely sensitive to stress signals and can generate persistent immunological memory, which poses major challenges for cell replacement. Transplanted islets are subjected to (i) instant blood-mediated inflammatory reaction (IBMIR), (ii) allogeneic immune recognition and rejection, and (iii) recurrent autoimmune responses from pre-existing adaptive immune memory.

Intrahepatic implantation of islets activates coagulation and complement systems (17). Local inflammatory responses stress islets and induce host leukocyte chemotaxis. Although IBMIRs are more conspicuous in xenotransplantation, clinical islet autografts experience

similar inflammatory reactions. These early stress events impair β cell function and induce substantial cell loss within the first few hours to days after transplantation.

Allograft recognition, the immunological detection of genetic polymorphisms between the recipient and graft donor(s) of the same species, plays a central role in the rejection of transplanted donor islets. Strategies for protecting transplanted β cells from immune-mediated rejection depend on cell origin and quality, genetic polymorphisms between host and donor(s), the immune profile of the recipient, and the immunosuppression regimen used to condition the recipient.

For pancreatic islet transplants, multiple islet donor preparations are needed to yield a therapeutic β cell mass. Hence, HLA matching for islets is often minimal, except for the avoidance of preformed anti-HLA antibodies. Direct alloantigen recognition of transplanted islets occurs via direct contact of host CD8 $^{+}$ and CD4 $^{+}$ T cells with islets and resident antigen-presenting cells (APCs). Indirect recognition occurs when host APCs collect and present alloantigens released from the foreign graft to the host adaptive immune system (33). After host priming of alloreactivity, the transplanted graft is destroyed by the infiltration of alloreactive CD8 $^{+}$ T cells and host innate cells

clearing foreign cells via recognition of non-host HLA class I or alloantibodies (33).

The autoimmune pathogenesis of T1D results in lymphocytic islet infiltration in the pancreas that can persist for decades (34). HLA class I hyperexpression in insulin-containing islets and the presence of autoreactive CD8 $^{+}$ T cells are prominent histopathological features of the disease. After T1D diagnosis, islet autoantibody titers wane over time (35), presumably reflecting loss of antigen. However, T1D recipients of islet or pancreas transplants exhibit autoimmune T and B cell-mediated β cell destruction despite treatment with immunosuppressive therapies.

CIT recipients currently require both broad and targeted immunosuppressive agents in a two-stage manner involving pretransplant induction followed by a maintenance phase (36). Current induction protocols typically target lymphocyte depletion, whereas maintenance regimens include various combinations of broad immunosuppressive inhibitors, antiproliferative agents, and biologics that block inflammatory cytokines or T cell cytokine signaling or costimulation (37). An armament of other biological drugs is emerging, with a focus on agents that promote regulatory T cell (T_{reg}) preservation while depleting or modulating effector populations (38) (Fig. 3A).

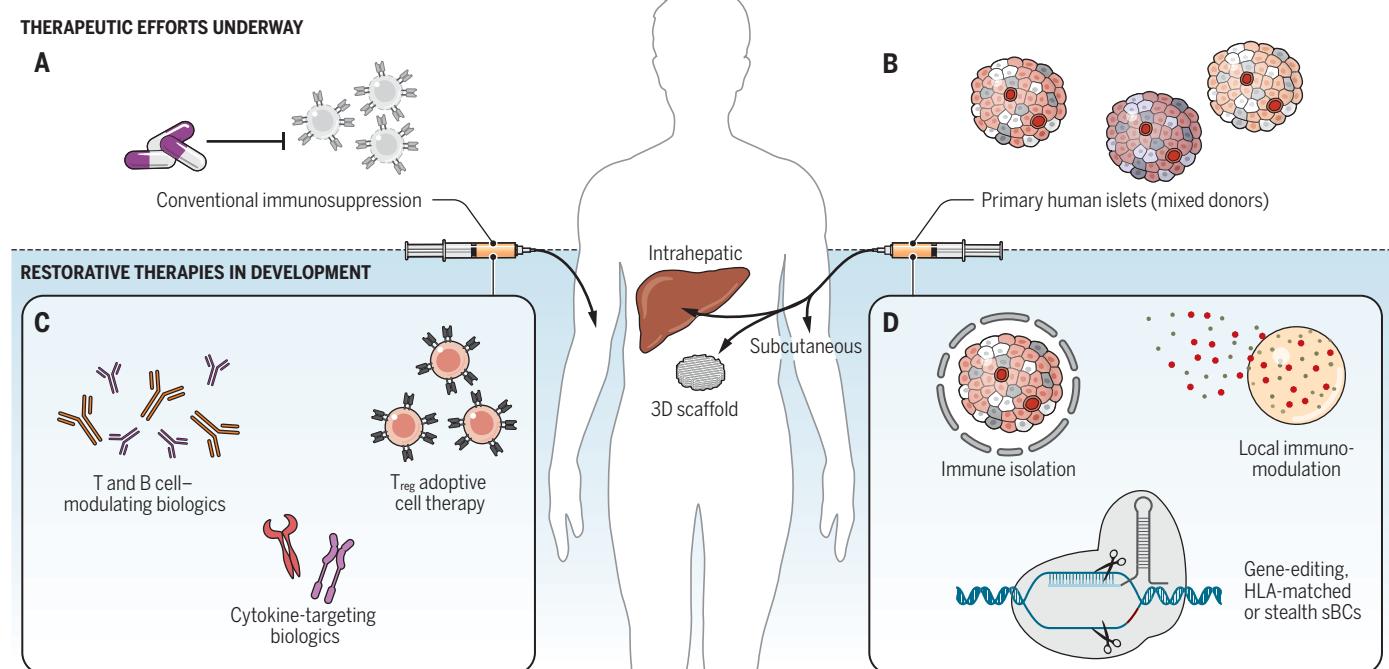


Fig. 3. Strategies for protecting transplanted β cells from immune-mediated rejection. The long-term restoration of β cells or islets in patients with established T1D requires two phases of immunomodulatory treatments involving initial host preconditioning, followed by long-term immunotherapy capable of protecting grafts from allo- and recurrent autoimmune-mediated rejection. Islet transplantation regimens currently use (A) antirejection drugs and preconditioning biologics before (B) mixed donor islet allografts (depicted above the horizontal line). The next generation of restorative therapies (below the horizontal line) will incorporate (C) new experimental biologics and T_{reg} -based adoptive cell therapies to combat recurrent autoimmunity and induce persistent graft tolerance. (D) After host conditioning, gene editing can be used to escape immune-mediated killing of sBCs, while biomaterial-based strategies can facilitate physical protection and localized immunosuppression to condition the microenvironment and further optimize graft survival.

horizontal line). The next generation of restorative therapies (below the horizontal line) will incorporate (C) new experimental biologics and T_{reg} -based adoptive cell therapies to combat recurrent autoimmunity and induce persistent graft tolerance. (D) After host conditioning, gene editing can be used to escape immune-mediated killing of sBCs, while biomaterial-based strategies can facilitate physical protection and localized immunosuppression to condition the microenvironment and further optimize graft survival.

Although current immunosuppressive regimens suppress prompt islet rejection, clinical markers indicate incomplete suppression of adaptive immune responses, particularly for autoimmune activation pathways. Hence, islet function commonly declines over time, such that by 5 years after transplantation, less than 10% of patients remain insulin independent.

With the emergence of approaches to derive β cells from renewable PSC sources, HLA-matching concerns can be mitigated by creating master cell banks of PSC-derived β cells matching the major histocompatibility complex (MHC) class I and II alleles common in people with T1D. PSCs have been difficult to genetically modify, in part because of defense mechanisms safeguarding early development stages. The advent of CRISPR-Cas9 technology

has transformed the field in this regard and established the possibility of engineering a “hypoimmunogenic” PSC. CRISPR-Cas9 gene editing to knock out endogenous HLA molecules can create “stealth” β cells that avoid immune-mediated recognition (Fig. 3B) (39). These cell systems can be further induced to express HLA-G or HLA-E molecules to escape natural killer cell-mediated killing (40). This approach of eliminating source MHC expression, in combination with α -1,3-galactosyltransferase knockout (GTKO) pigs to eliminate hyperacute rejection, is also under development for creating stealth xenogeneic porcine islets (5). Beyond the capacity for reducing immunogenicity, the ability to gene edit PSCs offers potential to knock in negative regulators capable of facilitating localized immune regulation in derived

β cells (Fig. 3B) (41). Translating these conceptually attractive gene editing concepts into pre-clinical and clinical trials is a critical next step (39). Finally, with the potential for autoimmune reemergence, an effective strategy may require “debulking” of autoreactive memory before cell engraftment with repopulating lymphocytes conditioned to favor durable immune tolerance.

Current immunosuppression regimens elevate a patient’s risk for infections and cancer. Therefore, reducing the duration and/or dosage of broad immunosuppression should be a top priority in β cell regenerative therapies. A promising means for inducing durable long-term tolerance involves harnessing the potential of T_{reg} s to establish a class of “living drugs.” T_{reg} s suppress immune reactivity via negative regulators, immunoregulatory cytokines, and biochemical pathways through mechanisms involving bystander suppression and infectious tolerance (42). A clinical trial currently underway is testing the capacity of ex vivo expanded polyclonal T_{reg} s in the context of islet transplantation and conditioning (NCT03444064).

Animal data support the notion that late-stage autoimmune diabetes can be treated with antigen-specific T_{reg} s. This suggests that such T_{reg} s may also serve a critical role in the transplant setting, where preexisting immunity is a barrier to restorative therapies. Translating studies from animal models to humans presents several challenges, including the need to generate sufficient antigen-specific T_{reg} s. The procurement of human T_{reg} s expressing native T cell receptors (TCRs) recognizing T1D autoantigens, such as insulin, is impractical, because they are extraordinarily rare in circulation. This challenge can be overcome by redirecting polyclonal T_{reg} s to recognize β cell antigens in MHCII via TCR gene transfer or through the use of chimeric antigen receptors (CARs) encoding single-chain variable fragments that target β cell surface antigens linked to downstream signaling elements (43). CAR- T_{reg} s capable of recognizing HLA-A*02-01 prevented the development of xenograft-versus-host disease after HLA-A2 T cell implantation (44). However, T_{reg} -based therapies still present challenges, including the need to optimize their specificity and affinity of receptors, stability, and function.

A goal of immunomodulation for cell therapy is to establish durable immune tolerance. Inducing this nuanced response likely requires complex interventions, including lymphocyte depletion, the induction of autoreactive cell exhaustion or anergy, and the expansion of T_{reg} s and regulatory B cells (42). With enhanced flexibility in the timing of the β cell transplant, a potential tolerogenic approach is the use of antigen preconditioning. The delivery of antigen under tolerogenic conditions has been tested in T1D prevention studies. While early trials demonstrated limited broad clinical efficacy

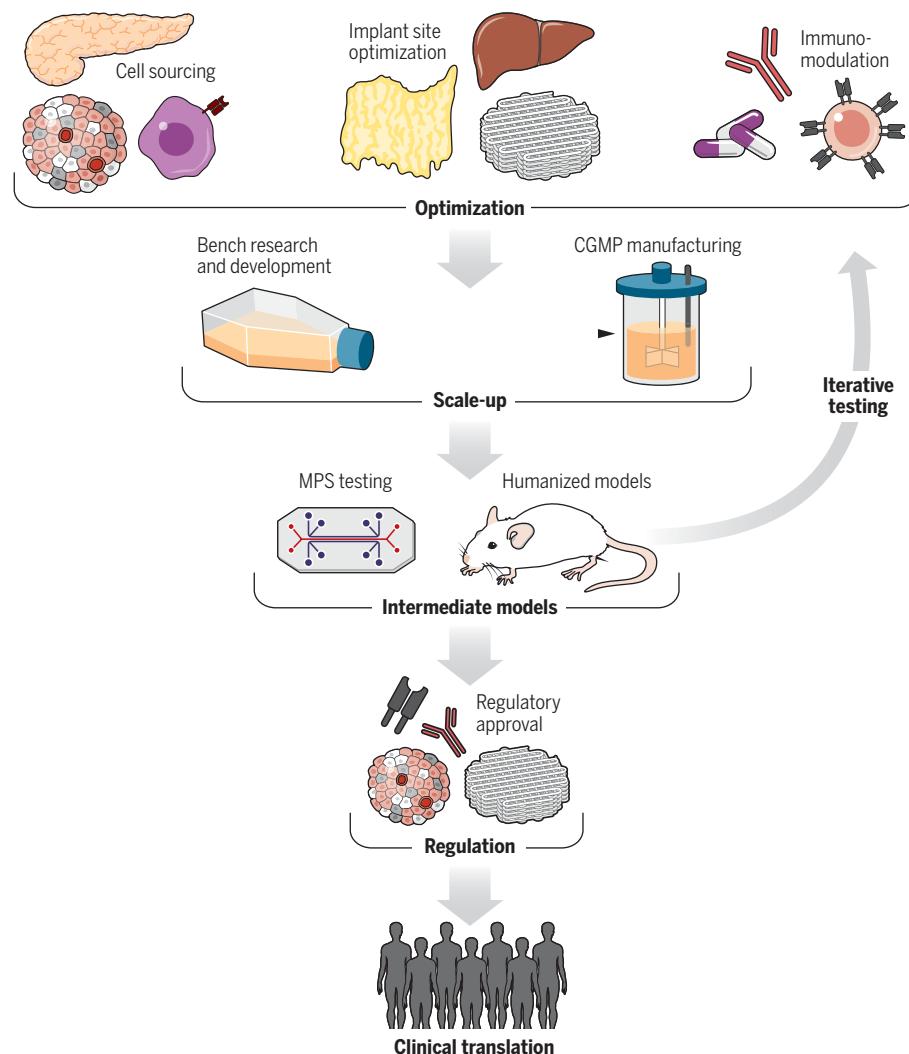


Fig. 4. The research and development pipeline for β cell replacement therapy in T1D. Advances in cell sources, implantation site and biomaterial devices, and immunomodulatory therapies to protect engrafted β cells from immune-mediated rejection will converge to improve long-term outcomes. As these strategies progress from research and development at the bench to Current Good Manufacturing Practice (CGMP)-compliant protocols, they can be iteratively tested to refine design features during preclinical testing in microphysiological systems (MPS) and humanized mouse models. This process will involve the integrated and collaborative efforts of stakeholders, academia, industry, and regulators to move combinatorial approaches forward.

(45, 46), distinct response endotypes related to specific MHCII genotypes support a precision medicine-based approach to autoantigen-specific tolerance induction (47).

The polymeric encapsulation of β cells within a semipermeable material is a popular approach to block host immune cell infiltration. A variety of polymers and geometric configurations have imparted durable protection of both islets and sBCs in rodent models but have failed to exhibit these robust benefits in large-scale animal models and clinical trials (27, 48, 49). The postulated failure points for these studies are numerous, including nontherapeutic cell dosage, aggressive FBR to the materials, insufficient nutritional support, immune cell attack, and immature sBC phenotype. Thus, scalable engineering designs, comprehensive FBR material screening in preclinical models, and the careful selection of the implant site are needed to strengthen translational efficacy (27, 49).

Despite continuous improvements in encapsulation designs, encapsulated cells still induce immunorecognition. Antigen released by the implant can lead to antibody generation, T cell activation and expansion, and the instigation of innate immune responses that contribute to graft failure (50). This immunorecognition is further exacerbated when cells are stressed or dying. Hence, current encapsulation should not be used as a monotherapy but should instead be paired with additional immunomodulatory agents. Several studies have reported enhanced protection of cellular grafts when encapsulation was combined with low-dose, systemic immunosuppression (51, 52).

The development of a distinct site for cellular implantation creates the possibility of providing local immunomodulation and/or tolerance induction. The integration of immunosuppressive or immune-instructive materials and/or cells into the local site creates a more nuanced, local, and targeted approach. For example, the translation of classic immunosuppressive agents from systemic to local delivery via biomaterials can mitigate the drug burden and decrease side effects (53). Alternatively, the local delivery of agents that target early activation events, such as antigen recognition and presentation and/or T cell activation and egress, may hinder the initiating effects of immune attack (54, 55). The co-delivery of T_{reg} or other regulatory cells represent adjunct cellular therapeutic approaches that can be incorporated into the graft site to deliver multifaceted modulatory signals, albeit with challenges related to antigen specificity. Alternatively, the local delivery of agents that mimic selected T_{reg} signals may also enhance graft acceptance. Proof-of-concept data supporting a biomaterials-based approach have been demonstrated for allogenic islets in rodent models when combined with short-course, systemic rapamycin (56, 57).

Conclusions and future outlook

Our increased understanding of T1D pathogenesis has driven immunotherapeutic interventions, which are gaining momentum in preserving endogenous β cell mass and function in both preclinical and recent-onset stages of the disease (58, 59). Although these efforts offer optimism for establishing effective prevention strategies, there remains an urgent need for treatment options to restore functional β cell mass in people with established T1D. Engineered closed-loop systems offer an effective stopgap but still fail to replicate the dynamic responses of native islets.

Recent advances in cell sourcing for β cell replacement, implant design, and immuno-regulatory therapies present the opportunity to restore endogenous β cell function while limiting long-term immunosuppression in subjects with established T1D (Fig. 4). Moving these complex treatments from concept to clinical translation in populations at-scale will present its own set of challenges. Coordinated multidisciplinary treatments will require contributions by stem cell and β cell biologists, engineers, and immunologists working with clinicians. Thus, the success of these efforts will depend on research infrastructure, focused network support, and academic and industry partnerships.

Finally, the success of β cell therapies for the treatment of T1D will ultimately rely on demonstrating clinical efficacy and durability to justify the considerable manufacturing and regulatory costs associated with any cell-based product. To that end, the risks associated with clinical trials should be mitigated through the development of informative model systems for preclinical iterative testing; these may involve organs-on-a-chip microphysiological systems that can model complex cellular interactions or animal models capable of supporting the engraftment of human cellular materials. Finally, regulatory bodies must continue to assist in navigating investigators through the regulatory hurdles associated with translating a combinatorial product. Notwithstanding these many challenges, progress is being made toward establishing the strategic pillars needed to generate an effective restorative therapy, albeit at a slower pace than desired. One hundred years after the discovery of therapeutic insulin, there remains great hope for advancing strategies aimed at restoring metabolic control in T1D through β cell replacement therapies.

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Strategies for durable β cell replacement in type 1 diabetes

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