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Engineering immune-evasive islet replacement: cell-intrinsic and peri-graft strategies

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Islet transplantation offers a physiological approach for restoring endogenous insulin secretion in type 1 diabetes, yet its broad clinical application remains constrained by donor scarcity, immune-mediated rejection, and limited graft durability. Stem cell-derived islets have emerged as a scalable alternative, supported by recent clinical progress, but long-term therapeutic efficacy remains challenged by incomplete maturation, immune incompatibility, and persistent immune-mediated injury after transplantation. Early efforts to mitigate immune rejection relied on physical immunoisolation strategies, including micro- and macroencapsulation, to limit immune cell access to transplanted grafts. However, incomplete protection from soluble inflammatory mediators and diffusion-related constraints highlighted the need for more direct immune modulation. In response, substantial efforts have focused on engineering immune-evasive islets through a spectrum of cell-intrinsic strategies, ranging from permanent genome engineering to transient gene silencing and immune signal programming. Among them, clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9-based genome editing has emerged as a central platform, enabling precise modification of immune-related pathways that reduce immune recognition and inflammatory signaling. In parallel, advances in biomaterials and biofabrication have enabled regulation of the peri-graft physicochemical milieu, referring to the local graft microenvironment that governs immune exposure, mass transport, and mechanical constraints while supporting scalable manufacturing. Increasing evidence indicates that neither genetic immune modulation nor extrinsic microenvironmental control alone is sufficient to ensure durable graft function. This review highlights convergent design principles that integrate immune evasion, peri-graft milieu regulation, and manufacturability to advance clinically deployable islet replacement therapies.

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1. Introduction

Type 1 diabetes (T1D) is an autoimmune disorder characterized by the destruction of insulin-producing pancreatic β cells, affecting approximately 5–10% of all diabetes cases worldwide.[1] Patients with T1D rely on lifelong exogenous insulin delivery through multiple daily injections or continuous pump-based systems.[2] Despite substantial advances in glucose monitoring technologies and insulin formulations, current insulin-based therapies cannot fully replicate the spatiotemporal patterns of endogenous insulin release.[3] As a consequence, glycemic variability, hypoglycemia risk, and long-term complications continue to impose a significant burden on individuals with T1D.[4,5]

Islet transplantation has emerged as a compelling strategy to restore physiological glucose regulation by reintroducing functional insulin-producing cells.[6] Following approval by the U.S. Food and Drug Administration in 2023, clinical transplantation of donor-derived human islets has demonstrated clear metabolic benefits, including improved glycemic control and reduced hypoglycemia unawareness.[7–9] However, the widespread application of this approach remains limited by fundamental constraints, most notably the scarcity of suitable donor islets, variability in graft quality, and the requirement for chronic systemic immunosuppression.[10–13] Collectively, these limitations have motivated a paradigm shift toward islet replacement strategies that are both scalable and resilient to immune-mediated rejection.

Stem cell-derived islets (SC-islets) represent a promising and unlimited source of insulin-producing cells for islet trans-

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plantation.[14] Advances in directed differentiation protocols have enabled the generation of SC-islets that exhibit glucose-responsive insulin secretion and key features of endocrine lineage specification *in vitro*.[15–17] Early clinical studies of SC-islet transplantation have suggested the feasibility and short-term safety of this approach in patients with T1D.[18] In phase I/II trials using pancreatic endoderm-derived grafts, transplanted cells survived and underwent functional maturation for up to one year, with meal-stimulated C-peptide secretion detectable at 26 and 52 weeks after transplantation.[19] No teratoma formation or uncontrolled graft proliferation was observed, and reported adverse events were largely attributable to systemic immunosuppressive regimens rather than the islet transplants themselves.[19,20] However, the magnitude and durability of metabolic benefit achieved with early SC-islet therapies remained limited, with meal-stimulated C-peptide levels generally low and insufficient to support sustained reductions in exogenous insulin use or long-term glycemic normalization. These clinical outcomes underscore that SC-islets can engraft and acquire insulin-secretory capacity in humans. However, their therapeutic durability is constrained by multiple factors, including allogeneic immune responses, persistence of autoreactive immune memory in T1D, and inflammatory stress within the transplantation microenvironment.

To address immune-mediated barriers, early efforts in islet transplantation focused on physical immunoisolation strategies that limit immune cell access to transplanted grafts.[21,22] Encapsulation-based approaches, including microencapsulation using alginate and macroencapsulation devices such as Encaptra, were developed to establish semi-permeable barriers that permit the diffusion of glucose, oxygen, nutrients, and insulin while preventing direct contact with host immune cells.[23] These strategies provided a conceptually straightforward means of mitigating immune rejection without systemic immunosuppression and demonstrated proof-of-principle efficacy in preclinical and early clinical settings.[20,24–26] However, progressive fibrotic overgrowth and diffusion limitations revealed the fundamental constraints of purely physical immunoisolation, including incomplete protection from soluble inflammatory mediators and antigen-specific immune signaling, which underscored the need for cell-intrinsic immune evasion strategies.

More recently, biomaterial and biofabrication approaches have been developed to regulate the peri-graft physicochemical milieu, including mass transport, mechanical confinement, and immune exposure at the graft–host boundary.[27–29] Alongside conventional encapsulation architectures, these emerging strategies represent a shift from passive immunoisolation toward more sophisticated designs that actively modulate inflammatory signaling through localized delivery of immunomodulatory chemokines or incorporation of immune checkpoint signaling into encapsulated islet grafts. Furthermore, advanced strategies, such as integration of auxiliary oxygen-supply modules, have been developed to enable continuous oxygen delivery to transplanted islets without direct immune contact, thereby preserving functional viability under diffusion-limited conditions. These developments underscore that immune rejection can be addressed not only by regulating the host–graft interfaces through physical barrier strategies, but also by engineering the graft materials and device architectures themselves. However, because immune rejection is ultimately driven by cell-intrinsic antigen presentation and inflammatory signaling pathways within the graft, these extrinsic engineering approaches alone may not be sufficient, thereby underscoring the need for complementary cell-intrinsic immune-evasive strategies.

Building on this foundation, a broad spectrum of cell-intrinsic immune-evasive strategies have been explored to reduce immune recognition and inflammatory destruction of transplanted islets. These approaches encompass permanent genome engineering, transient gene silencing, and immunomodulatory signal programming, which collectively aim to attenuate both adaptive and innate immune responses.[30–34] Earlier programmable nuclease systems such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) established the feasibility of targeted genome editing in pluripotent stem cells and related lineages.[35,36] However, their limited multiplex capacity and minimal application to immune-evasive islet transplantation models constrained broader therapeutic development. The advent of CRISPR-Cas9 substantially expanded these possibilities, enabling efficient and permanent multiplex modification of genes governing antigen presentation, immune checkpoint signaling, and inflammatory chemokine pathways. Targeted disruption of human leukocyte antigen (HLA) class I and II pathways, combined with knock-in of immune-inhibitory ligands such as programmed death-ligand 1 (PD-L1), CD47, and nonclassical HLA molecules, has enabled the generation of islets with robust resistance to T cell-, natural killer (NK) cell-, and antibody-mediated immune attacks. Furthermore, gene silencing approaches, including RNA interference, CRISPR interference (CRISPRi), and epigenetic repression strategies, have been investigated as complementary or intermediate solutions. These methods allow reversible suppression of pro-inflammatory mediators or immune-recruiting signals, such as CXCL10, without permanent genomic alteration, offering tunable immune modulation at the expense of long-term stability. Together, these advances establish genome editing as the cornerstone of immune-evasive islet engineering, while highlighting the growing recognition that cell-intrinsic immune evasion can be achieved through multiple, hierarchically integrated genetic and regulatory modalities.[37–39]

Although biomaterial- and biofabrication-based physical immunoisolation and cell-intrinsic immune engineering have been pursued as largely independent solutions, it is increasingly evident that durable islet transplantation cannot be achieved by addressing either axis in isolation. Genetic immune modulation alone cannot resolve extrinsic constraints imposed by hypoxia, inflammatory signaling, and mechanical stress, while peri-graft milieu control strategies remain insufficient to prevent immune-mediated graft loss in the absence of intrinsic immune protection. Looking forward, emerging strat-

egies aim to couple multiplex genome editing with reinforcement of the intrinsic peri-islet niche, enabling SC-islets to achieve enhanced functional maturation while simultaneously evading immune recognition. Such integrative designs foreshadow next-generation islet replacement therapies, including immune-evasive strategies and scalable production of islet-like aggregates with engineered niche support, thereby challenging conventional distinctions between immune evasion and islet niche engineering.

In this review, we examine recent advances in immune engineering and peri-graft milieu regulation for islet replacement, with a particular focus on how cell-intrinsic immune modulation and engineered peri-graft contexts can be jointly leveraged to overcome key barriers to durable graft function. By synthesizing insights across cell source considerations, immune modulation strategies, microenvironmental regulation, and scalable manufacturing principles, we propose a unified framework for the rational design of next-generation islet replacement therapies with clinical durability and translational feasibility (Fig. 1).

2. The current landscape of islet sources for transplantation

Islet transplantation has evolved as a therapeutic strategy aimed at restoring endogenous insulin secretion in diabetes. Clinical experience with donor-derived human islets has provided essential insights into the functional requirements for successful engraftment and metabolic benefit, while also revealing practical and biological constraints associated with donor dependence. More recently, progress in stem cell

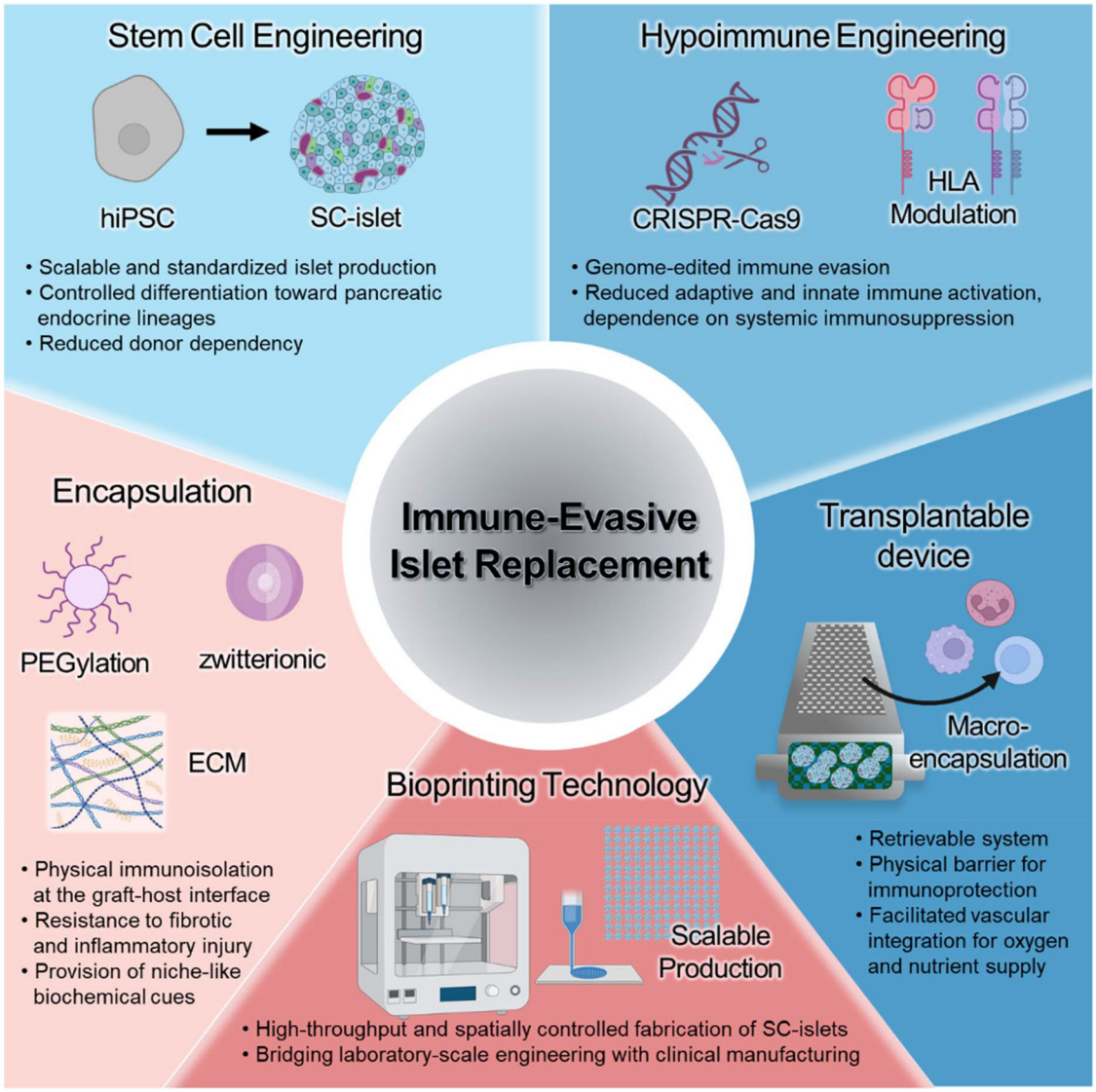

Fig. 1 Convergent bioengineering strategies for immune-evasive islet replacement.

technologies has enabled the generation of SC-islets, broadening the spectrum of candidate cell sources by introducing opportunities for scalable production and controlled manufacturing. Despite differences in origin and production, both primary and SC-islets encounter shared challenges following transplantation, including susceptibility to inflammatory stress and immune-mediated injury within the host environment. Consequently, the comparative evaluation of islet sources has shifted beyond considerations of availability alone to encompass functional competence and immune interactions *in vivo*. In this section, we outline the defining features, advantages, and limitations of currently available islet sources, with a focus on how these factors shape translational potential in islet transplantation.

2.1. Primary human islets as a reference cell source

Primary human pancreatic islets have long served as the clinical reference standard for islet transplantation.[40,41] The modern era of clinical islet transplantation was established by the Edmonton Protocol, which standardized key parameters such as transplantation of a sufficient cumulative islet mass, typically at least 10 000 islet equivalents per kilogram (IEQs per kg) of recipient body weight, and the use of glucocorticoid-free immunosuppressive regimens.[13] Building on this foundation, accumulated clinical experience with donor-derived islets has led to the commonly applied cumulative target range of approximately 5000–11 000 IEQs per kg and has further defined the benchmarks for evaluating engraftment efficiency and long-term endocrine function following transplantation. These outcomes are commonly assessed by sustained fasting C-peptide levels above ~0.1 nmol L^{-1} and maintenance of near-normoglycemic control (*i.e.*, hemoglobin A1c < 7.0%).[42]

Despite these advances, the clinical performance of islet transplantation remains constrained by limitations inherent to donor-dependent islet procurement and isolation process.[43] Under current isolation protocols, only approximately 30–50% of islets can be successfully recovered from donor pancreas, reflecting the sensitivity of islets to enzymatic digestion, mechanical dissociation, purification, and *ex vivo* handling.[44,45] As a result, transplantation outcomes are strongly influenced by donor characteristics and isolation efficiency.[46] Standardized clinical guidelines involve enzymatic dissociation using collagenase and neutral protease, followed by density gradient purification and short-term culture prior to transplantation, commonly not exceeding 72 hours.[47,48] However, even under these standardized steps, islet damage and functional decline during the isolation workflow remain difficult to fully prevent, directly affecting graft quality and transplantation success.

Beyond its impact on graft quality, islet isolation from donor pancreas is also a technically demanding and resource-intensive procedure that is not widely available across medical centers.[19] These technical constraints are compounded by the limited supply of suitable donor organs relative to the growing prevalence of diabetes. Together, they highlight fundamental challenges in scalability and long-term sustainability for transplantation strategies that rely exclusively on donor-derived islets. Consequently, while primary human islets remain indispensable to the clinical foundation of islet transplantation, their inherent supply and logistical limitations motivate the exploration of renewable cell sources capable of meeting these established criteria.

2.2. SC-derived islets as a scalable alternative source

Advances in human pluripotent stem cell (hPSC) biology have enabled the *in vitro* generation of insulin-producing endocrine cells, positioning SC-islets as a uniquely scalable cell capable of supporting islet transplantation at the clinically relevant scale. Contemporary differentiation protocols recapitulate key stages of pancreatic development through sequential modulation of developmental signaling pathways, yielding endocrine-enriched clusters composed of β-, α-, and δ-like cells.[15,17,49–52] Following transplantation and a period of *in vivo* maturation, SC-islets acquire glucose responsiveness and are capable of glucose-stimulated insulin secretion (GSIS) in multiple preclinical models of diabetes.[53–56] Importantly, pre-manufactured SC-islets enables standardized production and batch-to-batch consistency. This represents a fundamental advantage over donor-derived primary islets and supports their feasibility as a broadly deployable transplantation therapy.

Early clinical studies have clarified how differentiation state and functional maturity of SC-islets influence transplantation outcomes. In an initial phase 1/2 study initiated in 2017, hPSC-derived pancreatic endoderm cells were transplanted within a protective macroencapsulation format (NCT03163511).[20,57] While graft survival was achieved, metabolic efficacy was limited, highlighting the functional constraints of transplanting pancreatic progenitors rather than fully differentiated β cells. In contrast, a subsequent phase 1/2 clinical trial initiated in 2021 delivered fully differentiated SC-islets *via* intraportal infusion under systemic immunosuppression (NCT04786262). In this study, treated individuals with T1D exhibited robust engraftment, endogenous insulin production, and marked improvements in glycemic control, with the first recipient achieving insulin independence. Recent clinical updates report partial to complete insulin independence in treated patients, supporting continued advancement toward late-stage trials.

While recent clinical studies demonstrate functional insulin independence, experimental studies have demonstrated that SC-derived β-like cells may exhibit incomplete metabolic maturation and altered glucose-responsive dynamics compared to primary human islets, raising important questions regarding long-term physiological durability. *In vitro*-generated β cells often exhibit reduced insulin secretory dynamics, immature mitochondrial metabolism, aberrant calcium signaling, and heterogeneous cellular composition, including off-target endocrine populations.[57,58] Although prolonged *in vivo* engraftment promotes progressive maturation, the molecular and microenvironmental cues governing this process remain incompletely understood, limiting the ability to reproducibly generate adult-like islet function during

Table 1 Comparative gene editing strategies for engineering immune-evasive SC-islet grafts

Immune target/strategy	Genetic modification	Immune mechanism	Key outcomes	Ref.
Antigen presentation (HLA class I)	B2M knockout	Eliminates surface HLA-I expression, reducing $CD8^+$ T cell recognition	Reduced T cell-mediated rejection and prolonged graft survival in SC-islet grafts	64
Peptide loading to HLA-I	TAP1/TAP2 disruption	Impairs antigen processing and peptide loading onto HLA-I	Identified as key modulators of immune rejection in genetic screens of SC-islets	62
HLA class II induction	CIITA knockout	Prevents IFN-γ-induced HLA-II expression, limiting $CD4^+$ T cell activation	Reduced helper T cell-mediated immune responses in hypoimmune iPSC-derived grafts	31 and 38
Immune checkpoint signaling	PD-L1 overexpression	Engages PD-1 on T cells to suppress effector activation	Delayed rejection and improved functional persistence of SC-islet grafts	30 and 34
Innate immune recognition	CD47 overexpression	Activates SIRPα signaling to inhibit macrophage phagocytosis	Reduced innate immune clearance in hypoimmune iPSC-derived grafts	31 and 38
NK cell activation	HLA-E or HLA-G expression	Engages inhibitory NK receptors to counteract NK activation after HLA-I loss	Mitigated NK-mediated cytotoxicity in hypoimmune PSC derivatives	64 and 68
Combinatorial hypoimmune designs	$B2M^{-/-}$ + $CIITA^{-/-}$ + $CD47^+$	Simultaneous suppression of adaptive and innate immune recognition	Long-term survival of SC-islet grafts in fully immunocompetent models	31 and 38

in vitro manufacturing.[53] Consequently, while SC-islets have emerged as a clinically actionable and scalable cell source, the durability of transplantation outcomes remains governed by both intrinsic graft maturity and extrinsic host responses encountered *in vivo*, underscoring immune modulation as a key requirement for long-term therapeutic success.

2.3. Immune incompatibility across islet sources

Immune incompatibility remains a central obstacle to the clinical translation of islet transplantation. Both primary human islets and SC-islets inherently express polymorphic HLAs, rendering them readily distinguishable from host tissues and vulnerable to immune recognition following transplantation. As a result, transplanted islets are subjected to both direct and indirect T cell-mediated immune attacks.[34] Host $CD8^+$ cytotoxic T lymphocytes recognize allogeneic HLA class I molecules on grafted cells and induce apoptosis through perforin- and granzyme-dependent mechanisms, whereas $CD4^+$ helper T cells respond to HLA-derived peptides presented by antigen-presenting cells, thereby amplifying inflammatory cascades and recruiting additional immune effectors. Beyond direct T cell mediated recognition, immune rejection of transplanted islets is governed by coordinated innate and adaptive immune mechanisms that unfold sequentially after transplantation.[59] In the early post-transplantation phase, non-specific innate immune responses predominate and contribute to inflammatory graft injury. This is followed by antigen-specific adaptive immune activation mediated by antigen presenting cells and dendritic cells, which process donor-derived antigens and prime host T cell responses. Together, these processes drive both acute and chronic graft rejection.

To address these challenges, CRISPR-Cas9-based genome engineering strategies have been widely pursued to reduce graft immunogenicity by simultaneously targeting alloantigen presentation, modulating innate immune checkpoints, and attenuating pro-inflammatory signaling pathways.[60] In practice, such immune-evasive strategies operate either by increasing the expression of immune suppressive proteins, including immune checkpoint regulators, or by removing cell surface molecules that are essential for immune cell recognition. These strategies typically involve combinatorial knock-out and knock-in designs intended to mitigate both adaptive and innate immune responses.

Nevertheless, in clinical settings where grafts are transplanted without intrinsic immune protection, long-term systemic immunosuppression remains the primary method to preserve graft survival. Chronic exposure to immunosuppressive agents is associated with substantial risks, including increased susceptibility to opportunistic infections, impaired immune surveillance with elevated malignancy risk, and adverse metabolic consequences such as insulin resistance. Collectively, the convergence of adaptive and innate immune mechanisms imposes profound limitations on the survival, functional stability, and therapeutic durability of islet grafts *in vivo*. In this context, increasing attention has been directed toward transplantation strategies that incorporate targeted genome editing to confer immune-evasive properties to islet grafts.

3. Engineering cell-intrinsic immune properties of transplanted islets

Immune incompatibility remains a primary determinant of graft failure following islet transplantation. Although systemic immunosuppression can partially mitigate rejection, its long-term toxicity and inability to fully prevent immune-mediated

graft loss have motivated strategies that directly reduce the immunogenicity of transplanted islets themselves. Building on advances in SC-islet differentiation, recent efforts have increasingly focused on engineering cell-intrinsic immune-evasive properties through genetic and transcriptional modulation (Table 1). These approaches aim to interfere with antigen presentation, restrain innate immune surveillance, and locally suppress immune activation within the graft, thereby enabling prolonged survival without reliance on chronic immunosuppression.

3.1. Disruption of antigen presentation pathways

A central strategy to reduce immune recognition of islets involves direct interference with antigen presentation pathways, which represents an early and proximal trigger for allogeneic T cell activation. In particular, host T cell responses to transplanted islets are strongly driven by HLA class I-restricted antigen presentation. Accordingly, multiple studies have focused on genetic disruption of key components required for HLA class I surface expression, most commonly β2-microglobulin (B2M).[61] B2M deletion reduces $CD8^+$ T cell recognition and establishes a foundational decrease in adaptive immune activation. In SC-islets, this approach consistently attenuates T cell-mediated cytotoxicity *in vitro* and extends graft survival in preclinical transplantation models. Complementary strategies have also targeted antigen-processing factors such as transporters associated with antigen processing (TAP1/2), which further limit peptide loading onto HLA class I complexes and reinforce suppression of $CD8^+$ T cell activation.[62,63]

In parallel, modulation of HLA class II has been considered in inflammatory contexts, where cytokine exposure may induce aberrant class II programmes and enhance $CD4^+$ T cell help. Targeting class II major histocompatibility complex transactivator (CIITA), a master regulator of HLA class II transcription, provides a rational means to suppress inducible class II expression and helper T cell activation. Although class I-restricted $CD8^+$ responses remain the dominant axis in most transplantation settings, integrating class II control can further strengthen multiplex immune-evasion designs.[64] Disruption of antigen presentation provides a direct and highly effective means to attenuate T cell-mediated graft rejection at its proximal trigger. However, permanent elimination of HLA expression establishes a fixed immunological configuration and, given its coupling to interferon signaling, may limit adaptive cellular responses under inflammatory stress, necessitating complementary strategies beyond antigen-specific T cell modulation.[65,66]

3.2. Modulation of innate immune surveillance and immune checkpoint signaling

While disruption of antigen presentation effectively attenuates adaptive immune recognition, it simultaneously exposes islet grafts to innate immune surveillance, particularly NK cell-mediated missing-self recognition. To counterbalance this vulnerability, immune-evasive designs incorporate expression of inhibitory ligands that restrain innate immune activation. Among these, CD47 has emerged as a prominent signal that suppresses macrophage-mediated phagocytosis through interaction with signal regulatory protein alpha (SIRPα). Overexpression of CD47 on SC-islets reduces innate immune clearance and prolongs graft persistence *in vivo*.[37] However, sustained CD47 upregulation may interfere with physiological phagocytic surveillance and promote immune escape mechanisms in malignant contexts, underscoring the importance of controlled expression in therapeutic applications.[67] In parallel, immune checkpoint ligands such as PD-L1 have been widely employed to attenuate adaptive immune activation by engaging PD-1 receptors on activated T cells, thereby suppressing T cell proliferation, cytokine secretion, and cytotoxic function within the graft microenvironment.

Additional strategies have leveraged nonclassical HLA molecules such as HLA-E or HLA-G, which preferentially engage inhibitory receptors on NK cells.[68] Expression of these ligands provides surrogate signals that restrain NK cell activation without restoring conventional antigen presentation. Collectively, these approaches underscore that effective immune evasion in islet transplantation requires coordinated modulation of both adaptive and innate immune pathways.

3.3. Combinatorial genome engineering for multilayered immune evasion

Increasingly, studies have converged on the view that a single genetic modification is insufficient to fully protect SC-islet grafts from immune attack. Therefore, combinatorial genome engineering integrates complementary mechanisms to broaden resistance across adaptive and innate immune axes. Typical designs combine knockout of antigen presentation components, such as B2M or CIITA, with knock-in of immunoregulatory ligands, including CD47 and PD-L1. This integrated strategy establishes multilayered resistance to T cell-, NK cell-, and macrophage-mediated cytotoxicity. In SC-islets, such composite designs demonstrate substantially improved resistance compared with single-modification counterparts. They more closely approximate an immune-evasive phenotype and support prolonged survival in immunocompetent hosts without systemic immunosuppression. However, increasing genetic complexity raises safety considerations, including unintended effects on cell identity, stress responses, and long-term immune surveillance. In addition, CRISPR-Cas9-mediated multiplex editing introduces further methodological risks, including potential off-target mutations, large genomic rearrangements, and unintended alterations in genomic integrity.[69,70] Such events may not be immediately phenotypically apparent but could influence long-term graft stability and safety, necessitating comprehensive genome-wide validation and clonal screening strategies.[71] At the same time, escalating editing layers intensify validation and regulatory demands during translational development. These combined biological and operational constraints have driven interest in strategies that complement permanent genome engineering with more tunable regulatory layers.[72,73]

3.4. Gene silencing as a regulatory layer for immune modulation

In addition to permanent genome editing, gene silencing approaches have been reported as complementary strategies for modulating inflammatory activation in transplanted islets. Methods based on RNA interference (RNAi), CRISPRi, and epigenetic repression enable reversible suppression of immune-recruiting signals without permanent alteration of the genomic sequence. In islet transplantation studies, such approaches have primarily been used to downregulate pro-inflammatory chemokines and interferon-responsive pathways, with CXCL10 frequently highlighted as a mechanistically relevant mediator of islet–immune crosstalk.[74–77]

Rather than serving as substitutes for genome editing, gene silencing strategies are increasingly viewed as regulatory layers that mitigate immune activation during critical post-transplantation windows. Early inflammatory responses following transplantation can amplify immune priming even in genetically engineered grafts. Transient suppression of inflammatory signaling during this phase may reduce immune recruitment and complement permanent immune-evasive modifications. Nevertheless, limitations in durability, delivery efficiency, and scalability currently constrain broader clinical adoption of silencing-based approaches. Furthermore, the extent and stability of transcriptional repression achieved by RNAi or CRISPRi can be context-dependent and incomplete, with residual gene expression or compensatory pathway activation potentially attenuating the intended immunomodulatory effect.[78] Moreover, prolonged suppression of interferon-responsive signaling may perturb endogenous stress-adaptation programs, warranting careful functional validation prior to transplantation.[79]

3.5. Translational constraints

Despite substantial progress in cell-intrinsic immune engineering, immune evasion alone is insufficient to overcome the full spectrum of post-transplantation challenges encountered by islet grafts. Even extensively engineered islets remain vulnerable to non–cell-autonomous stressors, including hypoxia, inflammatory cytokines, mechanical strain, and early innate immune activation, which collectively destabilize graft survival and functional performance. These limitations become particularly pronounced as islet grafts approach clinically relevant scales, where architectural organization and mass transport constraints emerge as dominant determinants of engraftments. Therefore, addressing extrinsic barriers requires strategies that extend beyond genetic modification to regulate the local transplantation microenvironment, including oxygen and nutrient availability, inflammatory signaling, and early host–graft interactions. Together, these considerations underscore that durable islet replacement requires coordinated design across two interdependent dimensions: reduction of intrinsic graft immunogenicity and regulation of the host–graft interface. Accordingly, immune-evasive cell engineering and peri-graft physicochemical milieu regulation should be viewed not as independent strategies, but as complementary and mutually reinforcing components of a unified therapeutic framework. This conceptual transition motivates the peri-graft bioengineering approaches discussed in the following section.

4. Convergent bioengineering approaches for peri-graft regulation

Following transplantation, islet grafts are immediately exposed to blood-mediated inflammatory and immune stressors, leading to early graft injury and loss that are not fully addressed by cell-intrinsic immune modulation alone. Therefore, translating this integrative framework into practice requires deliberate engineering of the host–graft interface. Peri-graft bioengineering focuses on shaping the physicochemical and immunological conditions surrounding transplanted islets, with the goal of stabilizing immune-evasive grafts and preserving long-term function. This goal has long been pursued through biomaterial- and biofabrication-based engineering strategies that have increasingly converged to regulate both the physicochemical and immunological interfaces encountered by transplanted islets. Encapsulation technologies across nano-, micro-, and macro-scales enable controlled modulation of mass transport, mechanical confinement, and vascular integration, thereby mitigating exposure to hypoxic and inflammatory microenvironments. Beyond passive isolation, these strategies actively shape the peri-graft physicochemical milieu by integrating immunomodulatory cues and regulating immune exposure at the host–graft boundary that reprogram local immune responses and reduce alloimmune rejection and recurrent autoimmunity. In parallel, scalable biofabrication technologies provide the architectural and manufacturing control necessary to reproducibly implement these physicochemical and immune-regulatory features at a clinically relevant scale, supporting the generation of structurally and functionally mature islet constructs. This section synthesizes convergent bioengineering strategies that collectively regulate the peri-graft niche through immunoprotection, immune modulation, and manufacturability, thereby complementing genetic immune-evasion approaches discussed above.

4.1. Encapsulation for immunoisolation and physicochemical regulation

Islet encapsulation represents a foundational bioengineering strategy that provides physical immunoprotection while preserving the molecular exchange required for endocrine function.[80] By enclosing islets within semi-permeable biomaterials, encapsulation establishes a controlled peri-graft interface that permits diffusion of glucose, oxygen, nutrients, and insulin while restricting direct immune cell contact. Distinct encapsulation architectures spanning nano-, micro-, and macro-scales reflect different design priorities in regulating mass transport, transplant volume, immunoisolation, and retrievability, each associated with specific immunological trade-offs.

4.1.1. Nanoencapsulation. Nanoencapsulation indicates conformal coating of ultrathin polymer layers (generally <200 nm) directly onto the islet surface, generating immune barriers with minimal diffusion distance. By preserving rapid oxygen and nutrient transport, this strategy minimizes hypoxia-associated metabolic stress and supports intraportal delivery without increasing vascular occlusion risk.[81]

Among various nanoencapsulation approaches, surface modification strategies such as PEGylation (*i.e.*, the covalent attachment of polyethylene glycol) have been widely used to reduce non-specific adsorption of plasma and complement proteins and attenuate early innate immune activation at the graft interface.[82] PEG-based coatings have been shown to preserve islet architecture while reducing pericapsular accumulation of macrophage and mononuclear cells following transplantation.[83] However, because passive shielding alone is insufficient to fully prevent progressive immune-mediated graft loss, nanoencapsulation has been combined with localized immunosuppressive delivery, such as rapamycin, to reinforce graft persistence and insulin production over extended periods.[84] Islets co-delivered with rapamycin-loaded microspheres (RMs), corresponding to rapamycin dose equivalents of 0.1–10 mg kg^{-1} (RM0.1–10), demonstrated dose-dependent prolongation of graft survival. Notably, PEGylated islets combined with RMs exhibited markedly delayed immune-mediated rejection and significantly improved graft survival compared to non-PEGylated controls. This combinatorial approach further suppressed sustained macrophage and lymphocyte recruitment at the graft–host interface, resulting in preserved insulin-positive grafts retrieved 120 days post-transplantation (Fig. 2A). Together, these studies illustrate how surface engineering can synergize with local immune suppression to enhance long-term engraftment.

Despite these advantages, the small physical footprint of nanoencapsulated islets limits spatial confinement, raising concerns regarding redistribution or vascular clearance from the transplantation site over time. These constraints highlight the trade-off between minimal diffusion distance and long-term graft stability inherent to nano-scale encapsulation.

4.1.2. Microencapsulation. Microencapsulation encloses individual islets or small clusters within semi-permeable spherical capsules, typically ranging from 300 to 1000 μm in diameter, providing discrete immunoisolation units with favorable surface-area-to-volume ratios.[27,85] This format enables minimally invasive intraperitoneal transplantation and has historically served as a primary strategy for immunoprotective islet delivery. More recent microencapsulation strategies have evolved beyond passive isolation to integrate immune-evasive signaling and microenvironmental support within the capsule. For example, incorporation of immune checkpoint signaling into encapsulated islet grafts, such as PD-L1 expression, has been shown to locally attenuate immune recognition at the graft interface while achieving sustained insulin secretion and durable glycemic control.[86] Notably, these microspheres exhibited reduced infiltration of both T cells and macrophages, accompanied by reduced local inflammatory signaling and fibrotic overgrowth, highlighting how immune-evasive cues embedded within microencapsulation can enhance functional graft persistence. This was further complemented by auxiliary oxygen-supporting components such as *Chlorella*, to alleviate intracapsular hypoxia under diffusion-limited conditions, thereby supporting islet survival and function by mitigating metabolic stress (Fig. 2B).

However, because long-term graft stability is crucially influenced by immune cell recruitment and fibrotic remodeling at the capsule–host interface, localized delivery of immunomodulatory chemokines, such as CXCL12, has emerged as a complementary approach to regulate pericapsular immune infiltration and matrix deposition. This strategy has demonstrated the ability to suppress pericapsular fibrotic overgrowth and extend functional graft survival in the absence of systemic immunosuppression.[87] Notably, incorporation of CXCL12 markedly mitigated fibrotic overgrowth and enabled sustained glycemic control with 100% graft survival for more than 150 days, whereas CXCL12-free microcapsules exhibited rapid graft rejection, with survival declining to approximately 20% by 90 days post-transplantation (Fig. 2C).

Advances in materials chemistry have also enabled mitigation of foreign body responses through antifouling capsule designs. In particular, zwitterionic and chemically modified alginate formulations, such as carboxybetaine (CB) and sulfobetaine (SB), strongly bind water molecules *via* ionic solvation, forming a stable hydration layer that markedly resists non-specific protein adsorption, cellular adhesion, and fibrotic encapsulation, thereby preserving mass transport and long-term graft viability.[88] These modifications have been associated with prolonged maintenance of normoglycemia (>200 days) and improved retrievability of functional grafts, compared with unmodified alginate capsules, which developed pronounced fibrosis and functional failure within 100 days *in vivo* (Fig. 2D).

Nevertheless, conventional alginate remains largely bioinert and lacks instructive microenvironmental cues required to support islet identity and resilience.[89] These limitations have driven increasing interest in incorporating extracellular matrix (ECM)-derived cues into microencapsulation systems. Beyond recreating native niche cues, supplementation of microcapsules with defined ECM components has been shown to attenuate cytokine-induced inflammatory signaling and enhance resistance to inflammatory stress.[90] Specifically, incorporation of the pancreatic islet basement membrane-abundant proteins, such as laminin, markedly reduced the expression of proinflammatory genes, including IL-33, IL-8, and MCP-1, under cytokine exposure. Notably, secretion of inflammatory chemokine MCP-1 was further reduced by approximately 42% relative to laminin-free controls (Fig. 3A).[91] More recently, decellularized pancreatic tissue-derived ECM has emerged as a tissue-specific alternative that restores key basement membrane components lost during isolation, such as collagen IV and fibronectin. In addition, pdECM enhances resistance to proinflammatory injury, exhibiting only a moderate increase in necrotic cell numbers following cytokine treat-

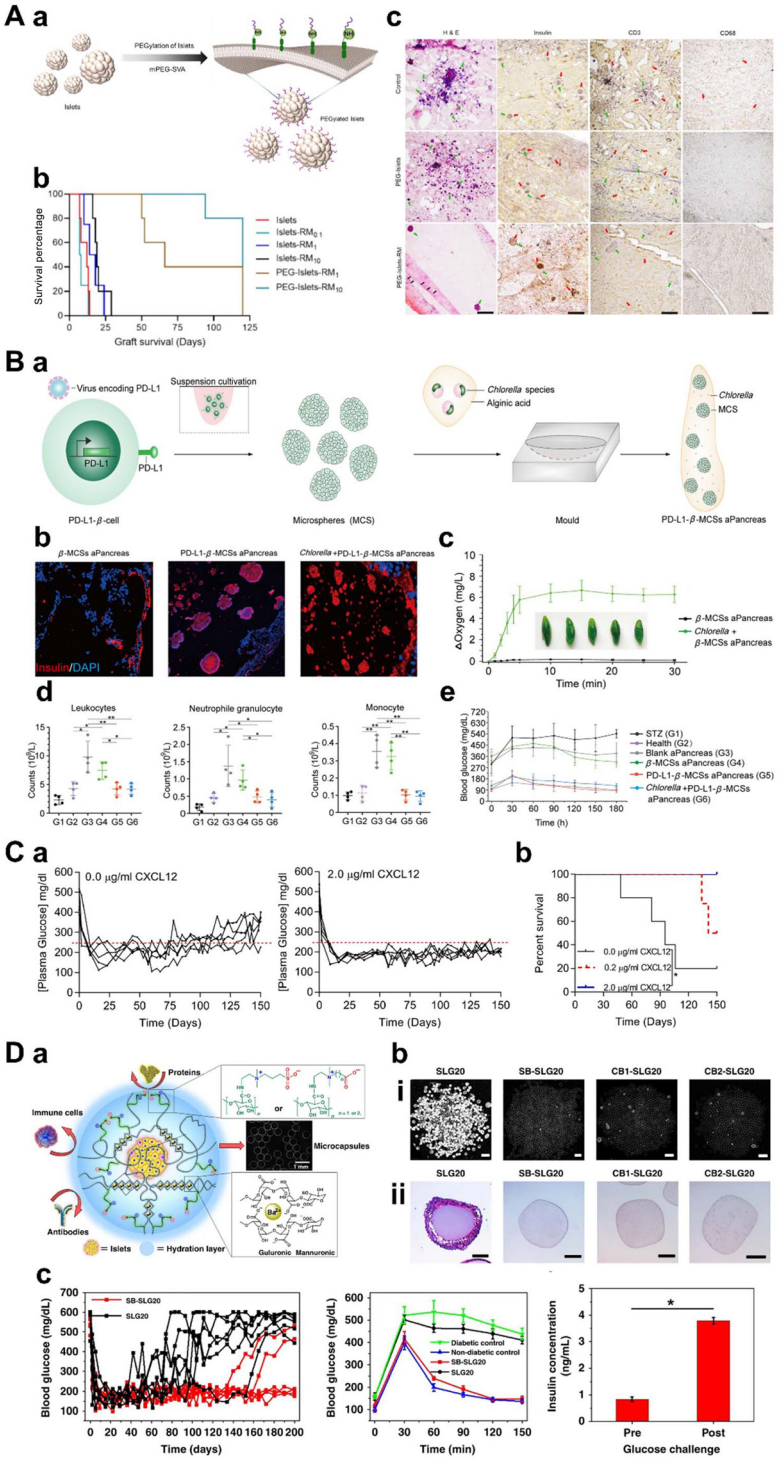

Fig. 2 Biomaterial-assisted strategies for islet immunoisolation and immune evasion. (A) (a) PEGylated nanoencapsulation of islet delivery combined with localized immunosuppressive delivery. (b) RM dose-dependent prolongation of graft survival. (c) Reduced immune cell infiltration in PEGylated islets with 10 mg kg^{-1} of equivalent RMs (scale bar: 100 μm) (reproduced with permission.[84] Copyright 2025, Elsevier). (B) (a) PD-L1 overexpressing β-cell microspheres combined with auxiliary oxygen-supporting components. (b) Preserved graft function confirmed by insulin immunofluorescence staining. (c) Oxygen production *via* incorporation with *Chlorella*. (d) Reduced immune cell numbers in peripheral blood 1 month after transplantation. (e) Monitored blood glucose levels showing stable glycemic control in PD-L1 modified MSCs (reproduced with permission.[86] Copyright 2025, Elsevier). (C) (a) Incorporation of the immunomodulatory chemokine CXCL12 enabling sustained glycemic control. (b) CXCL12 dose-dependent prolonged graft survival (reproduced with permission.[87] Copyright 2019, Elsevier). (D) (a) Zwitterionic-modified alginate microcapsules. (b) H&E staining histological analysis confirming reduced fibrotic encapsulation in SB and CB modified alginates (scale bar; i: 2000 μm, ii: 200 μm). (c) Improved diabetes correction in mice in a 90-day study using SB-SLG20 microcapsules, maintaining long-term graft viability and retrievable graft functionality (reproduced with permission.[88] Copyright 2019, Springer Nature).

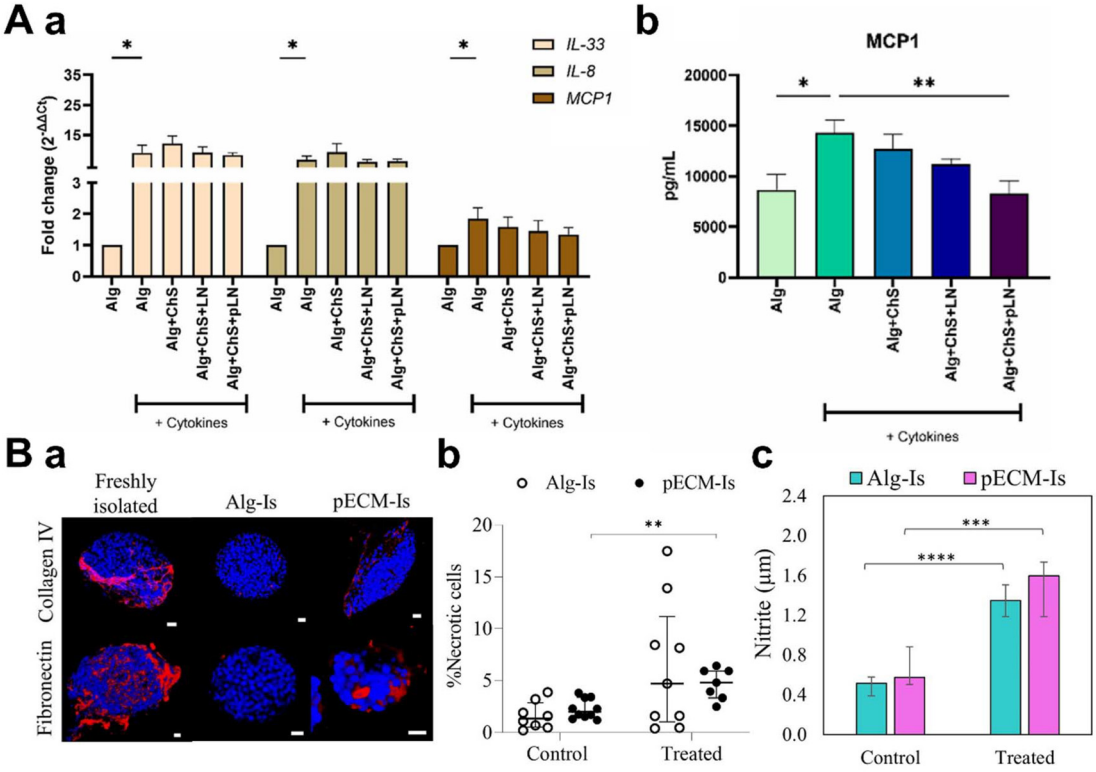

Fig. 3 ECM-based biomaterials for regulating the peri-graft microenvironment and inflammatory resistance. (A) Laminin-supplemented microcapsules for attenuation of cytokine-induced inflammatory signaling. (a) Downregulation of proinflammatory gene expression in islets encapsulated with laminin (LN)- and polymerized laminin(pLN)-modified microcapsules under cytokine-induced stress. (b) Reduced MCP-1 secretion following the addition of LN and pLN to the capsule composition (reproduced with permission.[91] Copyright 2025, Elsevier). (B) (a) Restoration of key basement membrane components by pdECM (scale bar: 20 μm). (b) Reduced percentage of necrotic cells in pECM-encapsulated islets (pECM-Is) 72 h after proinflammatory cytokine treatment. (c) Increased nitrite levels in pECM-Is 72 h after cytokine treatment, indicating enhanced resistance to proinflammatory injury (reproduced with permission.[92] Copyright 2023, Elsevier).

ment, whereas islets encapsulated in alginate display a markedly increased percentage of necrosis. This protective effect is further supported by reduced nitrite accumulation, a marker of cytokine-induced oxidative damage, following inflammatory cytokine treatment (Fig. 3B).[92] Notably, these biological advantages of dECM increasingly align with its clinical translational potential. Importantly, ongoing optimization of decellularized ECM toward low-xenogeneic and standardized formulations supports its translational feasibility as a clinically relevant encapsulation material.[93–95]

Despite these advances, microencapsulation remains constrained by transplant volume requirements. Increasing capsule size improves islet loading but exacerbates diffusion limitations and restricts feasible transplantation sites, particularly when capsule thickness exceeds approximately 100 μm.[96] These competing factors underscore an inherent trade-off between immunoprotection, mass transport efficiency, and clinical deployability.

4.1.3. Macroencapsulation. Macroencapsulation encloses large islet masses within transplantable devices composed of semi-permeable membranes, most commonly deployed in subcutaneous sites to enable surgical accessibility and retrieval. However, the subcutaneous environment imposes significant metabolic constraints due to limited vascularization and low oxygen tension, particularly at high cell densities. This leads to a central design challenge in macroencapsulation of balancing sufficient vascular access to the graft with effective immunoisolation. Fully isolating membranes with sub-micron pore sizes can effectively block immune cell ingress but preclude vascular coupling, often leading to hypoxia-driven graft dysfunction. In contrast, more permissive membrane designs allow closer apposition of host microvasculature and improved oxygen diffusion, albeit at the expense of increased inflammatory cell accumulation and fibrotic overgrowth at the device interface.

Clinical experience with early-generation TheraCyte devices has demonstrated that adequate resolution of this trade-off can be achieved through the use of multilayered polytetrafluoroethylene (PTFE) membranes.[97] The outer layer, featuring micrometer-scale pores (~5 μm), supported host neovascularization, while the inner layer with much smaller pores (~0.4 μm) physically excluded immune cells such as T cells and macrophages (typically 8–30 μm in diameter). This hierarchical pore architecture enabled effective peridevice vascular

coupling and improved mass transport to the graft in rodent and non-human primate models. Building on this concept, ViaCyte developed the Encaptra device (PEC-Encap; VC-01) to achieve complete immunoisolation of stem cell-derived pancreatic endoderm cells and conducted a clinical trial in patients with T1D (NCT02239354).[98] However, full immunoisolation was not achieved, as host fibrotic overgrowth led to hypoxia within the device and limited survival of transplanted cells in most explants. Subsequently, ViaCyte shifted toward a vascularization-permissive strategy (PEC-Direct; VC-02), in which membrane porosity was optimized to promote direct host–graft vascular integration. In a clinical trial (NCT03163511) involving transplantation in 55 patients with T1D, the safety, tolerability, and efficacy of the VC-02TM product were evaluated. A one-year follow-up study demonstrated that the device was safe and well tolerated in patients, with detectable C-peptide responses following meal stimulation. Furthermore, retrieved encapsulated pancreatic endoderm cells within the device survived and continuously produced insulin, exhibiting features of a mature phenotype.[24,99,100]

Beyond promoting vascular integration, oxygenated macroencapsulation strategies have been developed that integrate auxiliary oxygen delivery modules into device architectures. In contrast to biomaterial-mediated oxygen carriers, electrochemical oxygen generation systems actively supply oxygen *in situ* through electrolysis of surrounding tissue moisture, producing molecular oxygen that is continuously delivered to the densely packed islet grafts (60 000 IEQ mL^{-1}) to maintain high viability and insulin secretion in subcutaneous sites. Furthermore, continuous oxygenation resulted in maintained normoglycemia for up to 88 days, along with sustained insulin secretion in retrieved islets and preserved ability to respond to changes in glucose levels (Fig. 4A).[101] More recently, convective delivery of an oxygen- and nutrient-rich ultrafiltrate (UF) has been introduced as an alternative immunoisolation paradigm. A device has been designed to sustain long-term islet viability and function by enabling convective exchange of UF. In this system, an accumulation disc is transplanted subcutaneously to generate a localized void space. Driven by pressure gradients, interstitial fluid from surrounding tissue accumulates within this disc, while UF from the vascular compartment continuously enters the device. The collected UF is actively delivered into a downstream cell house *via* a piezoelectric pump, where transplanted islets are embedded within a 3D hydrogel matrix. This configuration enables continuous delivery of oxygen and nutrients to the encapsulated islets without direct blood contact, providing sustained metabolic support for graft survival exceeding 180 days with ongoing insulin production while limiting exposure to circulating immune cells (Fig. 4B).[102]

Despite these innovations, fibrotic overgrowth at the device–host interface remains a dominant barrier to durable macroencapsulation. Sustained foreign body responses promote macrophage-dominated inflammation and collagen-rich fibrotic overgrowth, which progressively lengthen diffusion paths and elevate metabolic demand at the device interface, resulting in impaired oxygen and nutrient transport and consequent deterioration of graft performance. Accordingly, rational material selection and interface engineering have emerged as critical determinants of long-term success. Appropriately designed biomaterials can not only mitigate fibrosis but also provide instructive biochemical and mechanical cues that support endocrine function and graft maturation.[103]

Collectively, nano-, micro-, and microencapsulation strategies represent distinct design principles rather than merely different size scales. Nanoencapsulation prioritizes minimal diffusion barriers but may compromise long-term spatial stability, whereas microencapsulation enhances discrete immunoisolation units at the cost of increased transplant volume and diffusion distance. In contrast, macroencapsulation offers retrievability and architectural control but introduces vascularization constraints, particularly when large graft volumes are required. Thus, selection of an appropriate encapsulation scale requires careful consideration of transplantation site, degree of immune exclusion, mass transport efficiency, and clinical deployability.

4.2. Biomaterial-assisted immune reprogramming

Beyond physical immunoprotection, biomaterial-assisted immune reprogramming aims to directly modulate immune cell fate at the graft site through localized immunomodulatory cues. Given that T1D is mediated by antigen-specific $CD4^+$ T cells, localized strategies that selectively eliminate pathogenic T cells have attracted increasing attention.[104] In this context, biomaterials functionalized with Fas ligands can induce apoptosis of activated effector T cells, which upregulate Fas death receptors upon activation, thereby prolonging graft survival. When combined with short-term systemic immunosuppression, these localized interventions can sustain long-term graft function for over 200 days without the need for continuous systemic immunosuppression.[105]

Macrophage polarization constitutes a complementary axis of biomaterial-assisted immune reprogramming. Proinflammatory M1 macrophages amplify oxidative stress and cytokine-mediated islet dysfunction through the production of reactive oxygen species (ROS) and proinflammatory cytokines (*e.g.*, IL-6 and TNF-α), whereas M2 macrophages support tissue repair, angiogenesis, and immune tolerance.[106–108] Leveraging this immunological balance, biomaterial-assisted strategies that bias macrophage polarization toward M2 phenotypes have been shown to reduce inflammatory cytokine production and improve metabolic outcomes following transplantation. For example, incorporation of antioxidants such as bilirubin for scavenging excessive ROS promotes a polarization toward an anti-inflammatory M2 macrophage phenotype. Therefore, islets encapsulated in the ε-polylysine–bilirubin conjugate (PLL-BR) exhibit anti-inflammatory effects by suppressing proinflammatory cytokine secretion while enhancing anti-inflammatory signaling, thereby preserving graft function (Fig. 5).[109]

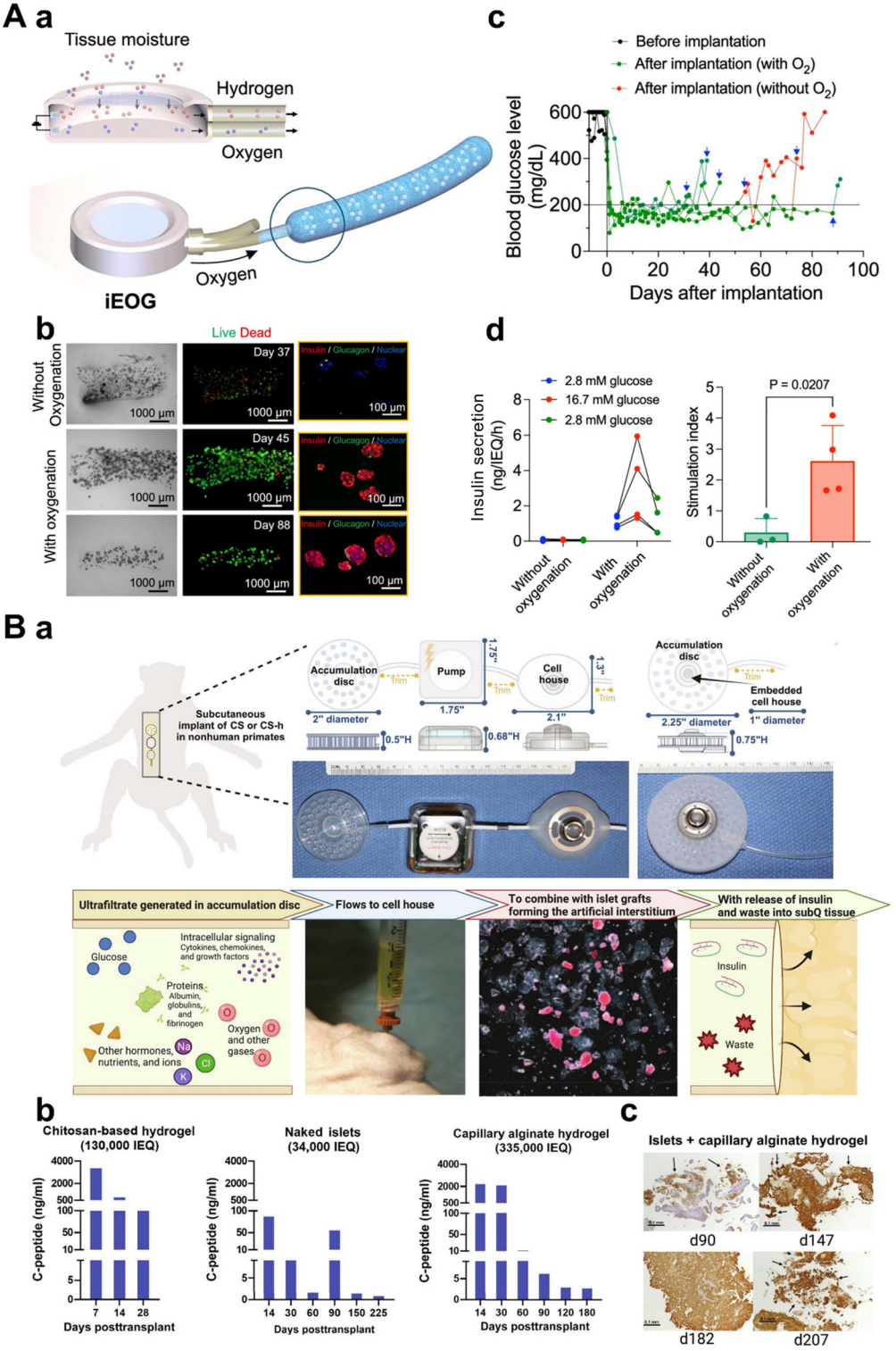

Fig. 4 Device-based strategies for immunoprotection and mass transport. (A) (a) Incorporation of an electrochemical oxygen generation module into the microencapsulation system. (b) Sustained high-density islet viability and insulin secretion *via* continuous oxygen supply. (c) Maintenance of normoglycemia for up to 88 days *via* continuous oxygenation. (d) Substantial insulin secretion in retrieved islets and preserved ability to respond to changes in glucose levels under continuous oxygenation (reproduced with permission.[101] Copyright 2025, Springer Nature). (B) (a) Device-based ultrafiltrate delivery system providing continuous metabolic support to encapsulated islets. (b) Prolonged survival of transplanted islets encapsulated in capillary alginate hydrogel, as measured using C-peptide levels. (c) Positive insulin staining in capillary alginate hydrogel-encapsulated islets, indicating improved graft survival under diffusion-limited environments (reproduced with permission.[102] Copyright 2024, The American Association for the Advancement of Science).

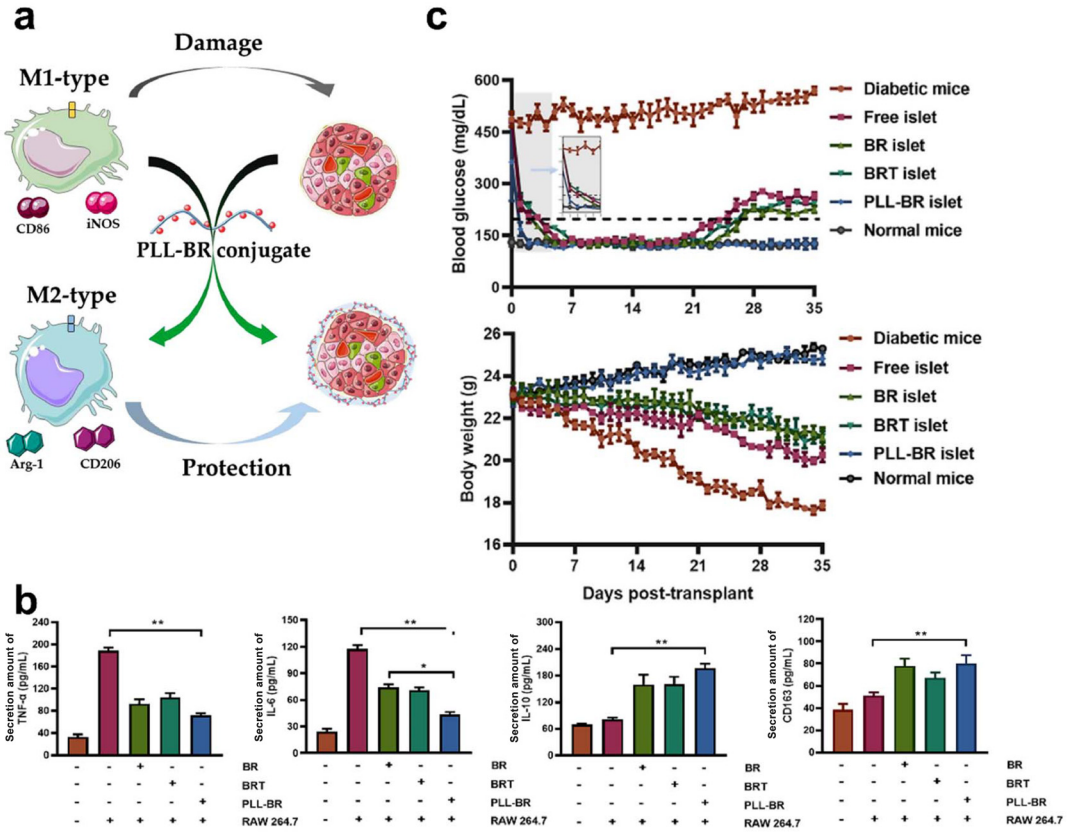

Fig. 5 Biomaterial-assisted immune reprogramming. (A) (a) Antioxidant delivery promoting anti-inflammatory M2 macrophage polarization. (b) Anti-inflammatory effects of bilirubin derivative treatment *via* reduction of local inflammatory cytokine production. (c) Sustained euglycemia in the PLL-BR islet group with maintained healthy body weight (reproduced with permission.[109] Copyright 2021, Elsevier).

In addition to immune modulation, some approaches simultaneously remodel the local stromal environment to create a supportive niche for islet engraftment. Biomaterials functionalized with mannose receptor-targeting moieties, such as konjac glucomannan, activate resident fibroblasts and stimulate deposition of basement membrane components, including collagen type I and IV. This stromal remodeling facilitates structural stabilization of transplanted islets and improves resistance to inflammatory stress, particularly in transplantation sites with limited endogenous matrix, such as spleen.[110] Together, these strategies highlight that effective immune reprogramming often depends on concurrent regulation of the peri-graft physicochemical milieu.

4.3. Scalable biofabrication for clinically translatable islet therapeutics

As islet replacement advances toward widespread clinical deployment, strategies focused solely on graft protection do not fully address the translational demands associated with therapeutic implementation. Therapeutic implementation requires scalable, reproducible, and standardized manufacturing of functional islet units. Therefore, biofabrication strategies have emerged as essential tools for translating lab-scale physicochemical and immune-regulatory engineering into clinically manufacturable islet therapeutics.

Early scalable approaches focused on size-controlled islet aggregation using micropatterned platforms, such as V-shaped microwell arrays, which enable improved functional consistency relative to randomly formed clusters.[111] Building on advances in biofabrication strategies, bioassembly approaches have recently emerged as powerful tools for scalable cell aggregate manufacturing.[112,113] In particular, acoustic assembly systems leverage standing bulk acoustic waves through the use of three orthogonally arranged piezoelectric transducers, which generate a 3D dot array (25 × 25 × 22) of levitated acoustic nodes. This configuration enables rapid organization of suspended cells into approximately 7500 uniformly sized aggregates (~100 μm in diameter) in a single operation, with tunable layered aggregate numbers controlled by the solution height (Fig. 6A).[114]

Three-dimensional bioprinting technologies have further expanded scalable islet fabrication by enabling precise spatial control over cellular composition, material distribution, and construct geometry while maintaining high throughput and reproducibility.[115–122] Among diverse bioprinting modalities, multi-nozzle and array-based bioprinting have demonstrated the capacity to rapidly deposit 576 spheroids with defined

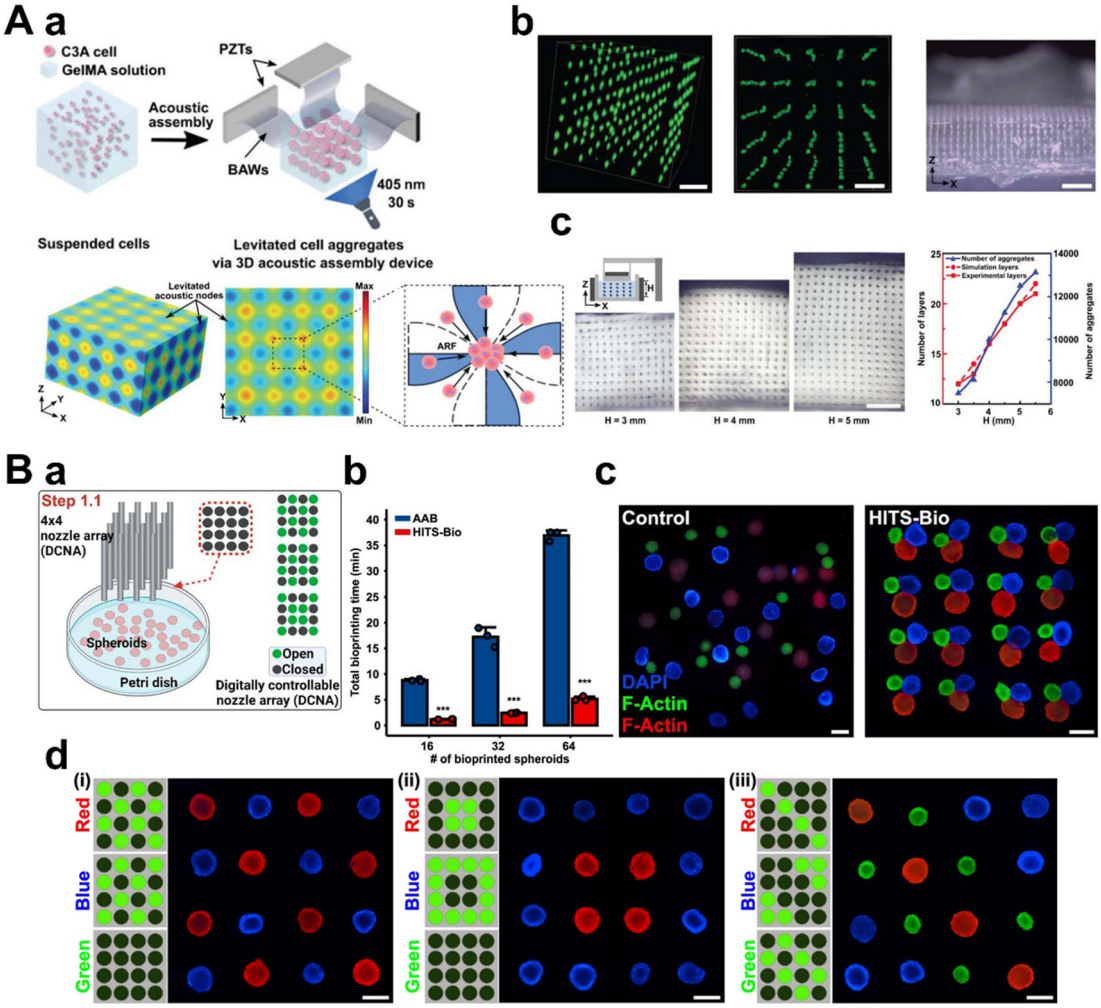

Fig. 6 3D bioprinting-enabled scalable manufacturing of islets. (A) (a) High-throughput acoustic assembly system generating thousands of uniformly sized cell aggregates from suspended cells in a single operation. (b) Images of the acoustically assembled cell aggregates (scale bar: 1 mm). (c) Tunable layered aggregate numbers depending on solution height (scale bar: 1 mm) (reproduced with permission.[114] Copyright 2023, AccScience Publishing). (B) (a) Multi-nozzle-based bioprinting enabling rapid positioning of large numbers of spheroids. (b) High efficiency of multi-nozzle-array bioprinting for producing a large number of spheroids. (c) Triple arrangements patterned with different sizes and colors (scale bar: 500 μm). (d) Selectively patterned spheroids (scale bar: 500 μm) (reproduced with permission.[123] Copyright 2024, Springer Nature).

sizes and spatial relationships into a centimeter-scale tissue construct (~1 × 1 × 1 cm^3), highlighting their suitability for high-throughput manufacturing. This approach exhibits high efficiency in printing a large number of spheroids compared to conventional aspiration-assisted bioprinting, while enabling easy patterning of spheroids of varying sizes and compositions (Fig. 6B).[123]

Moreover, scalable bioprinting technology facilitates downstream integration with encapsulation systems and transplantable devices by producing islet units with predefined sizes, shapes, and spatial interfaces. Such geometric consistency simplifies subsequent encapsulation, improves packing efficiency within devices, and supports more predictable mass transport properties. In this regard, bioprinting does not function in isolation but rather serves as a foundational manufacturing layer that enables seamless coupling between cell engineering, biomaterial-based protection, and device-level implementation. Collectively, biofabrication technologies provide a critical bridge between advanced islet engineering and clinically manufacturable cell therapies, complementing both genetic immune evasion and biomaterial-assisted perigraft physicochemical milieu regulation.

Despite these technological advances, several challenges remain in ensuring reproducibility and consistency in large-scale manufacturing. Biofabrication processes require precise control over bioink formulation, cell sourcing, and fabrication parameters, all of which can significantly influence transplant uniformity and functional performance, thereby introducing batch-to-batch heterogeneity. While these technologies demonstrate promising scalability under controlled laboratory conditions, translation to clinically compliant production requires not only automation but also integrated real-time

monitoring, closed-loop process control, and standardized quality metrics aligned with good manufacturing practice (GMP) frameworks.[124–126]

5. Conclusions and outlook

In summary, next-generation islet replacement is rapidly transitioning from a proof-of-concept cell therapy to a clinically deployable modality that must satisfy three interdependent requirements: durable immune compatibility, robust post-transplant function, and manufacturability at scale. Across the studies discussed in this review, a consistent message emerges that cell-intrinsic immune-evasive engineering can reduce immune recognition. However, durable therapeutic efficacy ultimately depends on the engineered peri-graft physicochemical milieu and delivery context, which govern early engraftment stress, mass transport, and host–graft interface biology. Accordingly, the field is converging toward integrated immune-evasive islet therapeutics that combine multiplex genome editing with biomaterial- and biofabrication-enabled control of inflammatory and fibrotic responses, while preserving retrievability and safety. Critically, convergent designs are increasingly expected to co-optimize immune evasion with functional maturation by reinforcing the intrinsic peri-islet niche, rather than treating immunoprotection and endocrine performance as separable objectives. Looking forward, future research should prioritize integrated evaluation platforms that simultaneously assess immune compatibility, functional maturation, and peri-graft interface dynamics within unified preclinical models, rather than optimizing each parameter in isolation. Establishing standardized comparative frameworks for these multidimensional outcomes will be essential to guide rational design and accelerate translational decision-making.

A principal translational inflection point will be scalable biomanufacturing. Clinical dosing for adult recipients is expected to require very large quantities of functional endocrine cells, often approaching the 10^9-cell range per treatment. This requirement places stringent demands on production throughput, cost efficiency, and reproducibility. While suspension-based differentiation systems and three-dimensional culture approaches offer theoretical scalability, hydrodynamic stress, oxygen and nutrient gradients, and aggregate heterogeneity can compromise differentiation fidelity and cell viability. Conversely, adherent differentiation strategies followed by aggregation improve process control but impose intrinsic constraints on manufacturing scale. To reconcile these trade-offs, the next phase of clinical translation will require industrialized manufacturing paradigms that incorporate automation, closed and modular processing, and in-line quality control frameworks. These systems must be centered on product-defining critical quality attributes such as endocrine composition, functional potency, genomic stability, and long-term safety. In this context, scalable biofabrication and bioassembly approaches provide a practical route to encode construct geometry, cellular composition, and peri-graft milieu features with high reproducibility, thereby enabling standardized implementation of immune- and niche-engineering principles at clinically relevant throughput. Future efforts should also focus on defining quantitative critical quality attributes (CQAs) that link genome editing burden, immune modulation strength, and endocrine function to long-term *in vivo* durability. The development of predictive release criteria and real-time process analytics will be central to de-risking large-scale production and satisfying regulatory expectations.

Additional priorities involve the incorporation of built-in safety architectures appropriate for long-lived immune-evasive grafts, such as retrievable devices and fail-safe control mechanisms. Interface engineering strategies that actively mitigate foreign body responses while supporting rapid vascular coupling without compromising immunoisolation will also be essential. Beyond structural safeguards, future progress will rely on engineered host–graft interfaces that simultaneously restrict immune cell infiltration, dampen local inflammatory signaling, and maintain oxygen and nutrient transport during early engraftment, thereby transforming the peri-graft boundary from a passive barrier into an active regulator of graft survival. In parallel, manufacturing innovations that digitally encode construct geometry and composition through bioassembly and bioprinting technology will be critical to minimizing operator dependence and batch-to-batch variability. Regulatory readiness will increasingly depend on the demonstration of reproducible manufacturing, traceable process analytics, and clinically meaningful durability. These factors are now regarded as equally important as biological efficacy in enabling SC-islet therapies to achieve broad clinical adoption. Finally, advancing the field will require coordinated collaboration among genome engineers, biomaterial scientists, manufacturing specialists, and regulatory experts to align biological innovation with scalable and compliant production infrastructures. Such cross-disciplinary integration represents a practical roadmap for translating immune-evasive islet units from experimental constructs into standardized therapeutic products.

Taken together, the most credible path to widespread clinical deployment lies not in a single technological breakthrough but in the coordinated integration of immune-evasive cell design, peri-graft physicochemical milieu regulation, and scalable manufacturing strategies. As these components mature in concert, the field is now transitioning from strategies centered on shielding transplanted islets from host immunity toward the deliberate engineering of host compatibility. This shift is driven by the convergence of immune-evasive cell design with bioengineered peri-graft milieus that promote vascular integration, stabilize endocrine function, and support post-transplantation maturation. In this context, emerging platforms increasingly resemble manufacturable immune-evasive islet units endowed with encoded niche logic, enabling standardized production, quality control, and deployment across transplantation settings. Such convergence positions immune-evasive islet units with engineered niche properties as a credible blueprint for the next generation of islet replacement,

transforming the therapy from a donor constrained intervention into a scalable and durable modality, with functional performance specified by design rather than sustained immunosuppression.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review.

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