

Vascularized Immunoprotective Biomaterials as a Platform for β -Cell and Islet Replacement Therapy in Diabetes: Mechanisms and Translational Potential

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Abstract

Islet and β -cell replacement can restore physiological insulin secretion in type 1 diabetes, but donor scarcity, chronic immunosuppression, and the fragility of avascular grafts have kept the approach from becoming routine therapy. Biomaterial engineering has approached these problems from two directions historically treated as separate traditions: immunoisolation, which shields transplanted cells behind a permselective barrier, and vascularization, which restores the oxygen and nutrient supply lost when islets are stripped of their native microvasculature. This review argues that the two goals are mechanistically coupled, because the same barrier properties that exclude immune effectors also constrain the oxygen diffusion on which β -cell survival depends. We examine the biological barriers to graft survival, the determinants of islet revascularization, and the principal classes of immunoprotective biomaterials (macroencapsulation devices, microcapsules, nanothin conformal coatings, hydrogels, and decellularized matrices) with attention to the trade-offs each imposes between permeability, mechanical durability, and immune exclusion. We then synthesize emerging platforms that engineer vascularization and immunoprotection together: pro-angiogenic and oxygen-generating materials, prevascularized and device-less sites, and local immunomodulatory strategies designed to substitute for systemic immunosuppression. Evidence is graded from mechanistic and rodent studies through non-human primate and clinical data, and we discuss why encouraging preclinical results have translated unevenly into durable clinical benefit. We conclude that no single material property solves this problem in isolation; durable, immunosuppression-free β -cell replacement will likely require materials engineered simultaneously for vascular integration, immune modulation, and manufacturable reproducibility, alongside renewable stem-cell-derived cell sources.

Keywords: Islets of Langerhans; Diabetes Mellitus, Type 1; Tissue Engineering; Biocompatible Materials; Neovascularization, Physiologic; Immunomodulation; Cell- and Tissue-Based Therapy; Hydrogels

1. Introduction

Type 1 diabetes results from autoimmune destruction of pancreatic β cells, leaving affected individuals dependent on exogenous insulin for survival. Global diabetes prevalence has continued to climb, with estimates placing the worldwide burden at roughly 537 million adults in 2021 and projecting continued growth over the following two decades (1). Even with rapid-acting insulin analogues, insulin pumps, and hybrid

closed-loop systems, exogenous insulin therapy is an imperfect substitute for an endocrine organ: it cannot reproduce first-pass hepatic insulin extraction, cannot adjust secretion on a minute-to-minute basis in response to portal glucose, and leaves a meaningful fraction of patients exposed to recurrent severe hypoglycemia, particularly once hypoglycemia awareness is lost.

Allogeneic islet transplantation, refined through the Edmonton protocol and subsequent multicenter trials, demonstrated that

restoring endogenous insulin secretion can eliminate severe hypoglycemic events and achieve durable, though not universal, insulin independence (2,3). This clinical proof of concept has not translated into a broadly available therapy. Islets are transplanted as a free cellular suspension into the hepatic portal vein, where they are exposed immediately to the recipient's blood, complement, and coagulation systems, and to any circulating antibodies directed against alloantigens; a large fraction of the infused islet mass is destroyed within hours to days of infusion, well before adaptive rejection has time to develop (4). Surviving islets must then be maintained for years under systemic immunosuppression, which carries its own burden of nephrotoxicity, infection risk, and malignancy risk, and which is itself toxic to β cells. Donor pancreas scarcity compounds these problems, since clinically meaningful engraftment often requires islets pooled from more than one donor per recipient.

These limitations have motivated three decades of biomaterial engineering aimed at replacing the transplanted-suspension paradigm with an engineered graft. Two design objectives have dominated this literature, largely as separate traditions. The first is immunoprotection: enclosing islets, β cells, or their stem-cell-derived surrogates within a selectively permeable material that excludes immune effectors while permitting glucose, oxygen, and insulin to cross. The second is vascularization: restoring a blood supply to tissue that, once enzymatically isolated from the pancreas, has lost the dense intra-islet capillary network on which it physiologically depends. Pursued separately, each strategy has been only partially successful. Immunoisolation without adequate vascular integration protects islets from immune destruction only to lose them to hypoxia, because the encapsulating material that excludes antibodies and immune cells inevitably also lengthens the diffusion path for oxygen. Vascularization without immunoprotection restores nutrient supply but leaves the graft exposed to the same alloimmune and, where relevant, xenoimmune or autoimmune mechanisms that limit free islet transplantation.

The central argument of this review is that vascularization and immunoprotection are not independent design axes to be optimized in sequence but are mechanistically coupled requirements that must be engineered together. A material that achieves immune exclusion by minimizing porosity will, by the same physical mechanism, restrict the vascular ingrowth and oxygen diffusion that graft survival requires; a material engineered purely to recruit blood vessels will, by recruiting the very inflammatory and angiogenic cascades that promote vascular ingrowth, often compromise immune privilege. We review the biological barriers that motivate

biomaterial engineering, the determinants of islet vascularization and revascularization, the major classes of immunoprotective biomaterials and the trade-offs intrinsic to each, and the emerging platforms that attempt to reconcile vascular integration with immune protection. We close by asking what evidence gaps and manufacturing constraints stand between the current state of the field and a biomaterial platform suitable for routine clinical use.

2. Biological and Engineering Barriers to β -Cell and Islet Replacement

2.1 Islet survival and oxygen demand

Pancreatic islets are metabolically demanding tissue. β cells couple glucose sensing to insulin secretion through oxidative metabolism, so their oxygen consumption rate per unit volume is high relative to most transplantable tissues; direct measurement of islet oxygen consumption rate has been shown to predict clinical outcome after autotransplantation, with lower per-islet oxygen consumption associated with failure to achieve insulin independence (5). In the intact pancreas this demand is met by a dense, fenestrated intra-islet capillary network fed by a disproportionate share of pancreatic blood flow relative to islet mass (6). Isolation strips islets of this network entirely: enzymatic digestion and purification remove the native vasculature along with the surrounding exocrine tissue, leaving spherical islet aggregates that must survive on diffusion alone until, and unless, a new vascular supply is established.

2.2 Diffusion limitations and hypoxia

Because oxygen has limited solubility in aqueous tissue and is consumed continuously along its diffusion path, avascular tissue larger than a few hundred micrometers in radius develops a hypoxic core; this constraint is intrinsic to diffusion-reaction kinetics and cannot be engineered away by material choice alone, only managed by minimizing diffusion distance or supplementing oxygen delivery (7). Direct microelectrode measurements confirm the consequence experimentally: transplanted islets equilibrate to markedly lower tissue oxygen tension than native pancreatic islets, regardless of which extrahepatic site is used for implantation (8). This period of hypoxia is most severe in the days immediately following transplantation, before any revascularization has occurred, and is a major contributor to the substantial early loss of islet mass observed even in syngeneic and autologous transplants where immune rejection is not a factor (9). Encapsulating an islet inside an immunoisolating material adds a further diffusion barrier on top of this intrinsic limitation, which is the first point at which

the objectives of immunoprotection and viability come into direct tension.

2.3 Innate and adaptive immune-mediated graft injury

When islets are infused as a free suspension into the portal vein, as in the clinical standard-of-care protocol, they are exposed directly to circulating blood and can trigger an instant blood-mediated inflammatory reaction: tissue factor expressed on the islet surface activates the coagulation cascade, complement is fixed, platelets aggregate around the islets, and neutrophils and monocytes infiltrate within minutes to hours (4). This innate reaction destroys a substantial fraction of transplanted islet mass before adaptive, T-cell- and antibody-mediated rejection has time to develop, and is a principal reason why more than one donor pancreas is often required to achieve insulin independence in a single recipient. Islets that survive this acute phase remain targets for cellular and humoral alloimmunity for as long as they persist, and, in the case of porcine or stem-cell-derived grafts, may additionally confront xenogeneic or context-dependent autoimmune recognition (figure 1).

2.4 Foreign body reaction and fibrotic encapsulation

Any biomaterial implanted in vivo, regardless of its chemical composition, elicits a foreign body reaction: protein adsorption is followed by neutrophil and macrophage recruitment, macrophage fusion into foreign body giant cells at the material surface, and, if the reaction does not resolve, deposition of a dense fibrotic capsule (10). For an immunoisolating device or microcapsule, this fibrotic response is doubly damaging: it does not merely wall off an inert object but progressively occludes the same diffusion pathways the material was designed to preserve, so a device that begins its implanted life with adequate permeability can become hypoxic and non-functional over subsequent weeks purely as a consequence of host fibrosis (10). Pericapsular fibrotic overgrowth of this kind, rather than acute immune rejection, is the failure mode most consistently reported across microencapsulated and macroencapsulated islet studies once the acute peritransplant period has passed (figure 1).

2.5 Loss of β -cell phenotype and function

Islet isolation, culture, and the local inflammatory and hypoxic microenvironment of transplantation together place stress on

β -cell identity: transplanted and cultured islets can show reduced expression of maturity markers, blunted first-phase insulin secretion, and increased apoptosis relative to islets in situ. Because β -cell dedifferentiation and death are difficult to distinguish from graft loss by non-invasive means, functional decline is often detected only once glycemic control has already begun to deteriorate, which complicates the design and interpretation of preclinical and clinical endpoints alike (discussed further in Section 8).

2.6 Limitations of systemic immunosuppression

Chronic immunosuppression, the standard companion to allogeneic islet transplantation, is itself a barrier to wider adoption rather than merely a cost of doing business. Calcineurin inhibitors and mTOR inhibitors used in maintenance regimens are directly toxic to β cells and impair insulin secretion, glucocorticoids induce insulin resistance, and long-term immunosuppression carries cumulative risks of nephrotoxicity, opportunistic infection, and malignancy that are difficult to justify in patients who are not already immunosuppressed for another indication. This is the central rationale for immunoisolation: a material barrier that excludes immune effectors at the graft site, without suppressing immunity systemically, would in principle allow islet or β -cell replacement to be offered to patients for whom the risk-benefit balance of lifelong systemic immunosuppression is currently unfavorable.

2.7 Limitations of current transplantation approaches

Taken together, these barriers explain why allogeneic islet transplantation, despite an established evidence base sufficient to support regulatory approval for a defined patient population (3), has remained a niche therapy rather than a broadly available one. Donor organ scarcity limits supply; intraportal infusion exposes islets to instant blood-mediated injury and provides no protection against fibrotic or immune-mediated attrition; and systemic immunosuppression restricts eligibility to patients with recurrent severe hypoglycemia or already-impaired hypoglycemia awareness. Each of these limitations has a plausible biomaterial-based mitigation in isolation, which is precisely why the field has generated so many partially successful platforms; the difficulty, developed throughout the remainder of this review, is that mitigating any one barrier tends to reintroduce or worsen another.

Table 1. Major biological and engineering barriers to β -cell/islet replacement and biomaterial-based solutions.

Barrier	Biological mechanism	Consequence for graft survival	Biomaterial strategy	Representative evidence	Translational limitation
Hypoxia/diffusion limitation	Loss of intra-islet capillary network on isolation; high islet oxygen demand (5)	Core necrosis of avascular islet aggregates within days of transplantation (8,7)	Oxygen-generating scaffolds; thin/conformal geometries; prevascularized sites	Coronel et al. (11); Razavi et al. (12); Pepper et al. (13)	Finite oxygen-generation lifetime; added device complexity; unproven at clinical islet mass
Instant blood-mediated inflammatory reaction	Tissue factor, complement and platelet activation on contact with portal blood (4)	Rapid loss of a large fraction of infused islet mass before adaptive rejection begins	Extrahepatic/extravascular transplant sites; surface modification	Weaver et al. (14); device-based approaches reviewed in Section 4.1	Extrahepatic sites are less well vascularized than the liver, reintroducing hypoxia risk
Foreign body reaction/fibrosis	Macrophage fusion and fibrotic capsule formation around any implanted material (10)	Progressive occlusion of diffusion pathways over weeks to months	Chemically modified alginates; anti-inflammatory/anti-fibrotic co-delivery; capsule geometry control	Veisheh et al. (15); Vegas et al. (16); Jiang et al. (17)	Reduced fibrosis often measured only over months, not years; NHP and rodent FBR do not fully predict human response (18)
Alloimmune/xenoimmune/autoimmune rejection	Cellular and humoral recognition of graft antigens	Chronic, cumulative loss of functional β -cell mass	Immunoisolating membranes/capsules; local immunomodulation; gene-edited hypoimmune cells	Bochenek et al. (18); Headen et al. (19); Carlsson et al. (20)	Complete immune exclusion is difficult to reconcile with adequate nutrient/oxygen transport (Section 5.1)
Toxicity and burden of systemic immunosuppression	Calcineurin/mTOR inhibitor toxicity to β cells; nephrotoxicity, infection and malignancy risk	Restricts eligible patient population; contributes to graft attrition independent of rejection	Local, device-confined immunomodulation intended to avoid systemic drug exposure	Ramzy et al. (21); Headen et al. (19)	Local immunomodulation has so far achieved partial, not complete, substitution for systemic regimens in humans

3. Vascularization as a Determinant of Graft Survival

3.1 Native pancreatic islet vascular architecture

Islets occupy only one to two percent of pancreatic volume yet receive a disproportionate share, on the order of ten to fifteen percent, of total pancreatic blood flow, reflecting a dense, fenestrated capillary network arranged to support rapid glucose sensing and hormone delivery into the portal circulation (6). This architecture is not incidental to islet function: fenestrated intra-islet capillaries allow secreted insulin to enter the bloodstream with minimal diffusion delay, and blood flow within the islet is itself dynamically regulated by glucose. None of this architecture survives enzymatic isolation, which is the starting condition every subsequent engineering strategy must contend with.

3.2 Revascularization after transplantation

Several terms are used, often loosely, to describe what happens to islet vasculature after transplantation, and the distinctions matter for interpreting the literature. Angiogenesis refers to the sprouting of new capillaries from existing host vessels. Inosculation refers specifically to the anastomotic joining of pre-existing or newly formed vessels within a graft to the host circulation, a process well described in skin and islet grafts alike. Vascularization is the broader, purely structural outcome (the presence of a blood vessel network within tissue) without specifying its origin or whether it is perfused. Vascular integration describes the establishment of continuity between graft and host vasculature specifically. Functional perfusion is a physiological, not structural, endpoint: the demonstration that blood actually flows through graft vessels and delivers oxygen at a rate sufficient to

support tissue metabolism. A graft can be histologically vascularized, in the sense of containing vessel-like structures, without being functionally perfused, and this distinction accounts for a share of the discrepancy between structural vascularization endpoints reported in the encapsulation literature and the persistent hypoxia measured functionally in the same models (8).

Lineage-tracing and ultrastructural studies established that revascularization of transplanted islets proceeds through ingrowth of new vessels from the host, with host-derived endothelial cells eventually predominating in the mature graft vasculature, even though islet-resident endothelial cells present at the time of transplantation contribute transiently to the earliest phase of new vessel formation (22,23). This process is not instantaneous: functional graft perfusion in rodent models typically requires one to two weeks to become established, during which the graft depends entirely on diffusion, which is the mechanistic link between Sections 2 and 3, delayed revascularization is not simply an inconvenience but the direct cause of the early hypoxic islet loss described above (figure 1).

3.3 Oxygen and nutrient transport, angiogenic signaling, and VEGF pathways

Vascular endothelial growth factor-A, produced constitutively by β cells, is the dominant signal driving both developmental islet vascularization and post-transplant revascularization; genetic deletion of islet VEGF-A markedly impairs graft vascular density and function (24). The relationship between VEGF signaling and islet mass is not simply linear, however: conditional inactivation of VEGF-A specifically in mature adult β cells reduces islet vascular density without a correspondingly large loss of islet mass or glycemic function over several months, indicating that adult β cells tolerate a degree of vascular rarefaction that developing islets cannot, a distinction relevant to interpreting how much vascularization an engineered graft actually needs to achieve, rather than how much native tissue happens to have (25).

3.4 Prevascularization strategies and biomaterial-mediated vascular integration

Two general strategies have been used to shorten or bypass the vulnerable pre-perfusion window. The first is

prevascularization of the implantation site before islets are introduced: a device or scaffold is implanted first, allowed to become vascularized and encapsulated by host tissue over several weeks, and then islets are delivered into the resulting vascularized, device-free tissue pocket. This "device-less" approach converts the subcutaneous space (a site that is otherwise poorly vascularized and has historically given inferior results relative to the liver) into a viable, retrievable transplant site, and has restored normoglycemia in diabetic rodent models using a substantially lower islet mass than intraportal transplantation requires (13). The second strategy is to deliver a pro-angiogenic biomaterial together with the islets themselves, most often a hydrogel that presents VEGF in a controlled, matrix-bound fashion rather than as a bolus; this approach has improved islet engraftment and reversed hyperglycemia in extrahepatic sites including the small bowel mesentery, epididymal fat pad, and subcutaneous space, in some cases matching or exceeding outcomes from intraportal infusion while using fewer islets (26,14).

3.5 Risks and limitations of excessive or uncontrolled angiogenesis

Pro-angiogenic strategies are not without cost. VEGF delivered at supraphysiological concentrations or without spatial control can produce disorganized, leaky, and hemorrhagic vasculature rather than the stable, well-organized capillary networks associated with functional graft perfusion, and sustained high VEGF exposure has been linked to vascular malformation in other tissue-engineering contexts. There is, in addition, a more fundamental tension for this review's central question: recruiting new blood vessels to a graft site necessarily recruits the inflammatory and immune cell traffic that travels with active angiogenesis, since many of the same signals and cell types (macrophages prominent among them) participate in both processes. A biomaterial engineered to maximize vascular ingrowth by whatever means available will tend to work against the separate objective of minimizing immune cell infiltration, which is the specific conflict examined mechanistically in Section 5.

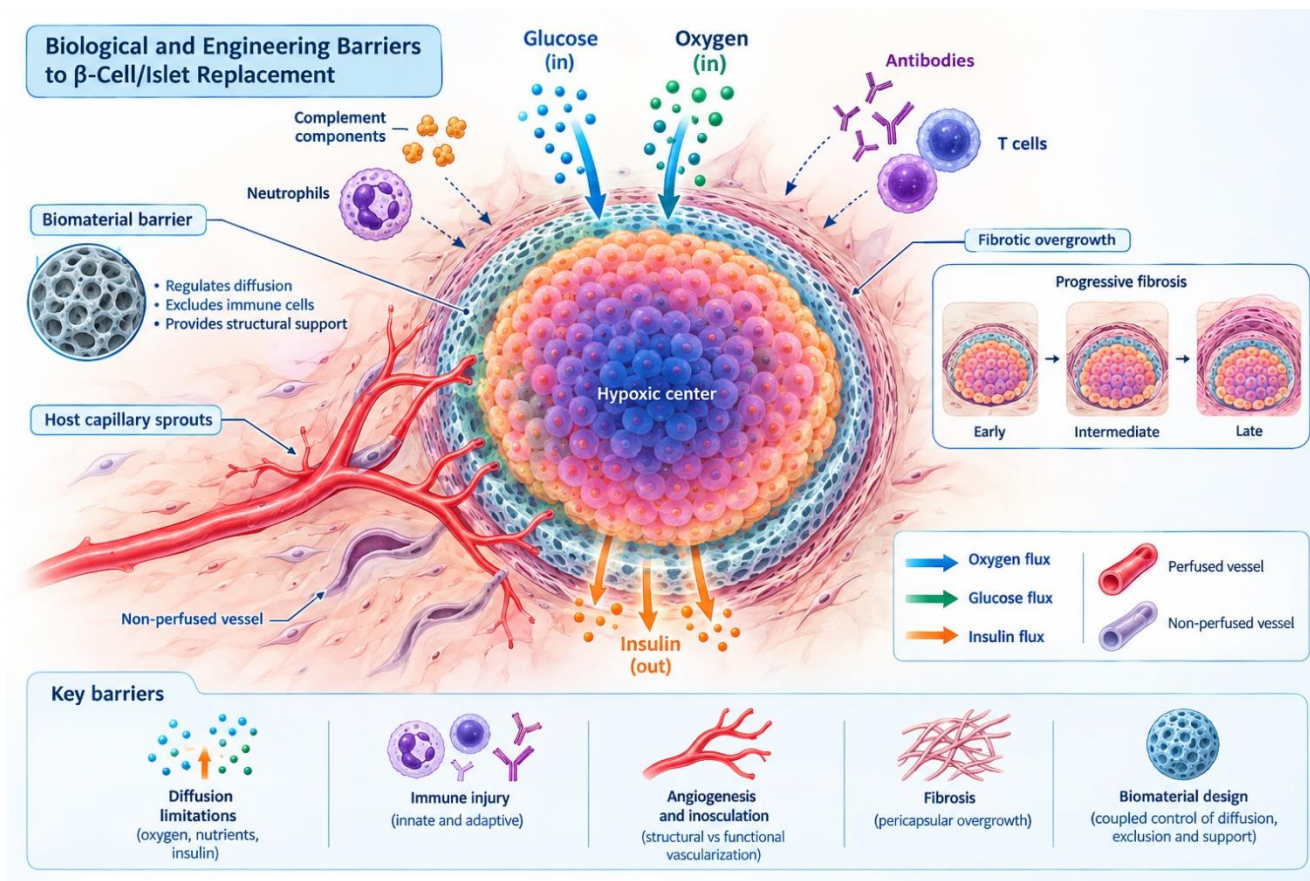


Figure 1. Conceptual framework of the biological and engineering barriers to β -cell/islet replacement. Schematic cross-section of a transplanted islet or β -cell cluster at a generic extrahepatic site, integrating the barriers described in Sections 2 and 3. The islet core is shown with a gradient shading from normoxic periphery to hypoxic center, reflecting the diffusion-limited oxygen gradient described by Colton (7) and measured directly by Carlsson et al. (8). Arrows indicate diffusive fluxes of oxygen and glucose inward and insulin outward across the graft–host interface. Host-derived capillary sprouts are shown approaching the graft from the surrounding tissue, illustrating the angiogenesis and inosculation processes described in Section 3.2 (22,23); a subset of vessels is drawn as non-perfused (vascularized but not functionally perfused) to visualize the structural/functional distinction discussed in the same section. Innate immune elements (complement components, neutrophils) and adaptive immune elements (antibody, T cells) are depicted converging on the graft surface, representing the instant blood-mediated inflammatory reaction and downstream alloimmune or autoimmune injury described in Sections 2.3 and 2.4 (4,10). A thin fibrotic band is drawn at the host–material interface, thickening in a time-series inset to represent progressive pericapsular fibrotic overgrowth. Where a biomaterial barrier is present, it is drawn as a discrete interfacial layer whose pore architecture simultaneously determines oxygen/nutrient influx, insulin efflux, and immune-cell exclusion, visually anchoring the review's argument that these are coupled, not independent, design outputs of a single material property.

4. Immunoprotective Biomaterials for β -Cell and Islet Replacement

Biomaterial-based immunoprotection strategies are conventionally organized by the length scale at which encapsulation is applied, from devices that hold many thousands of islet equivalents in a single retrievable chamber to conformal coatings only tens of nanometers thick. Each scale carries a characteristic profile of advantages and limitations that follows directly from its geometry.

4.1 Macroencapsulation

Macroencapsulation devices enclose a bulk islet or cell mass, typically hundreds of thousands of islet equivalents, within a single retrievable chamber bounded by a permselective

membrane. The defining trade-off is between membrane pore size, which must be small enough to exclude immunoglobulins and immune cells, and diffusion path length, which must be short enough to sustain the enclosed tissue at physiological oxygen and glucose flux. The TheraCyte device addressed this trade-off with an asymmetric architecture: an inner membrane with pores small enough for immunoisolation, paired with an outer membrane with larger pores intended to promote host vascular ingrowth up to, but not across, the immunoisolating layer, an explicit early attempt at the vascularized-immunoprotective design logic developed further in Section 5 (27). Clinical testing of devices built on this logic has shown a consistent pattern: encapsulated stem-cell-derived pancreatic endoderm cells in

a closed, fully immunoisolating device produced detectable but modest, variable insulin secretion, with retrieved devices showing an unfavorable foreign body response and insufficient vascularization reaching the cell compartment (21). A modified device with larger, cell-permissive perforations achieved substantially higher graft cell survival and glucose-responsive C-peptide secretion, but only by abandoning immunoisolation, so recipients required conventional immunosuppression (21,28), a direct clinical illustration of this review's central trade-off. The β -Air bioartificial pancreas took a different route, supplying oxygen to encapsulated islets from a refillable external gas reservoir rather than relying on host vascularization; it was safe and reduced exogenous insulin requirement without immunosuppression in a first-in-human trial, but function remained partial and the device required ongoing gas-refill maintenance unlikely to suit a permanent implant (29). Most recently, a fully closed device carrying allogeneic, gene-edited "hypoimmune" stem-cell-derived islets achieved biochemical evidence of graft survival without any pharmacological immunosuppression, illustrating that macroencapsulation and cell-intrinsic immune evasion are complementary rather than competing strategies (20).

4.2 Microencapsulation

Microencapsulation, enclosing one or a few islets in an individual spherical capsule several hundred micrometers in diameter, was the original islet immunoisolation strategy and remains the most extensively studied at the preclinical and early clinical stage (30). Alginate, an anionic polysaccharide gelled by divalent cations, dominates as a capsule material because it gels under conditions compatible with cell viability and can be tuned chemically to modulate permeability and mechanical stability. Small compositional differences have large biological consequences, however: capsules made with a higher guluronic acid content elicit more severe fibrosis than those with an intermediate content, an effect attributable to cross-linking with the polycation coatings used to reinforce capsule mechanics rather than to the alginate itself (31). Early clinical experience in nonimmunosuppressed patients demonstrated feasibility and safety, with measurable, if transient and incomplete, reduction in exogenous insulin requirement (32). Microencapsulation's central limitation is scale rather than chemistry: reversing hyperglycemia requires an implant volume far larger than the islet mass itself, since each capsule is mostly inert polymer, and this volume is difficult to place anywhere except the peritoneal cavity, a site with comparatively poor and heterogeneous vascular access. Even chemically modified alginates that markedly reduce fibrotic overgrowth in rodents show attenuated, though still

meaningful, benefit on advancement to non-human primates (15,18).

4.3 Nanostructured and nanocomposite systems

Conformal, "nano-thin" coatings, from a few nanometers to tens of micrometers thick, address microencapsulation's principal weakness by minimizing diffusion distance and total implant volume: a coating applied directly to the islet surface adds negligible bulk, so the cell-to-device volume ratio is far more favorable than in conventional microcapsules, and the reduced volume permits intraportal or other minimally invasive delivery. PEG-based conformal coatings, applied by interfacial photopolymerization or covalent surface grafting, and layer-by-layer assembly of alternately charged polymers are the two principal chemistries used. The trade-off is durability: an ultrathin single layer offers a correspondingly thin margin of mechanical and biochemical protection and is easily breached by membrane turnover or shear stress, so nanoencapsulation is, at present, generally paired with a co-delivered immunomodulatory agent (Section 5) rather than relied upon as a standalone barrier.

4.4 Hydrogels

Hydrogels (cross-linked hydrophilic polymer networks with high water content) serve both as freestanding microcapsule or macrodevice matrices and as injectable, in-situ-forming carriers for islets delivered to an extrahepatic site. Natural hydrogels (alginate, collagen, fibrin) offer favorable cell compatibility and, for collagen and fibrin, bioactive integrin-binding motifs that support cell attachment, but batch-to-batch compositional variability complicates regulatory characterization. Synthetic, predominantly PEG-based, hydrogels offer the reverse profile: precise, reproducible control over mesh size, degradation, and any conjugated growth factor's density, at the cost of a bio-inertness that must be engineered back in through peptide functionalization. Photocrosslinked PEG systems allow in-situ encapsulation after injection, while proteolytically degradable PEG hydrogels can be designed to remodel and permit vascular ingrowth as the material erodes, directly linking degradation kinetics to the vascularization strategies discussed in Section 5 (26,14).

4.5 Decellularized extracellular matrix-based biomaterials

Decellularized pancreatic or other tissue matrices retain native extracellular matrix composition, including tissue-specific structural proteins and matrix-bound growth factors, while removing the cellular and antigenic content responsible for most immune recognition of allogeneic or xenogeneic

tissue. Decellularized pancreas scaffolds recellularized with islets have been shown to support islet attachment, survival, and preserved matrix ultrastructure in vitro, motivating interest in decellularized matrix as a biomimetic alternative to purely synthetic encapsulation chemistries (33). The approach's principal translational limitation is reproducibility: decellularization protocols must remove cellular and antigenic material completely enough to prevent immune recognition of residual donor components while preserving the matrix architecture and growth-factor content that make the material attractive in the first place, and batch-to-batch consistency of a decellularized biological scaffold is inherently harder to specify and quality-control than that of a defined synthetic polymer, a tension that recurs in Section 9.

4.6 Synthetic and hybrid biomaterials

Beyond PEG and alginate, a range of synthetic and semisynthetic polymers (polytetrafluoroethylene and expanded PTFE membranes, cellulose acetate, poly(ether sulfone)/poly(N-vinylpyrrolidone) blends, and poly(lactide-co-glycolide)-based scaffolds) have been used chiefly as mechanically robust permselective membranes or as depots for local drug delivery rather than as the primary cell-contacting matrix. Hybrid designs that combine a mechanically reinforcing synthetic mesh, membrane, or fiber scaffold with a cell-compatible hydrogel core are increasingly the norm in macroencapsulation device design, precisely because no single material class simultaneously offers adequate mechanical durability, tunable permselectivity, and favorable cell biocompatibility; this convergence toward multi-material, hybrid device architectures is itself indirect evidence for the review's central thesis that the design problem cannot be solved by optimizing any one material property in isolation.

5. Vascularized Immunoprotective Biomaterial Platforms

5.1 Why vascularization and immunoprotection are traditionally conflicting objectives

This tension is not incidental; it follows from diffusion physics and foreign-body biology together. Immune exclusion requires restricting a material's pore size and tortuosity so that immunoglobulins (roughly 10 nanometers) and immune cells (several micrometers) cannot cross it; the same restriction, applied to a barrier that oxygen and glucose must also cross, increases diffusive resistance for those smaller molecules too, only less severely. Reducing thickness or increasing porosity to relieve this constraint reopens the barrier to immune cell traffic. A biological trade-off compounds the physical one: the host responses that recruit blood vessels and that recruit immune cells to an implant are not run by

separate cell populations. Macrophages are central to both productive angiogenesis, where pro-angiogenic ("M2-like") polarization supports vessel ingrowth, and to the foreign body reaction, where macrophage fusion into giant cells drives fibrotic encapsulation (10). A material that successfully recruits vascularizing macrophage activity is, by the same signal, at risk of recruiting the fibrotic and antigen-presenting activity immunoprotection is meant to prevent, the mechanistic core of why these two objectives cannot be optimized as independent, sequential design problems.

5.2 Strategies for reconciling vascularization with immune protection

Three broad design logics have been used to escape this conflict rather than resolve it at the level of a single membrane. The first is spatial separation: place the vascularizing signal or vascularized tissue outside the immunoisolating barrier, so that the barrier's diffusion distance to the nearest perfused vessel is minimized without the barrier itself needing to admit blood vessels across it. The second is temporal separation: vascularize the implantation site first, in the absence of cells, and introduce the immunoprotected or immune-evasive cell product only once a vascular bed already exists nearby. The third is to abandon a purely physical barrier altogether and instead achieve immune privilege by modulating the local immune response pharmacologically or by engineering immune evasion into the cells themselves, which removes the need for a diffusion-restricting membrane in the first place. Essentially every platform reviewed below is a variant, or a combination, of one of these three logics (figure 2).

5.3 Pro-angiogenic biomaterial design and controlled VEGF delivery

Spatial separation is exemplified by macroencapsulation devices with an asymmetric membrane: a coarse, larger-pore outer membrane interfaces with host tissue and promotes vascular ingrowth to the device surface, while a separate, fine-pore inner membrane maintains immune exclusion, so diffusion distance from perfused host vessel to encapsulated cell is minimized without any vessel crossing the immunoisolating layer itself (27). A related approach couples this membrane strategy to controlled, matrix-bound VEGF delivery rather than the host's basal angiogenic response: a vascularized synthetic PEG macrodevice with a VEGF-releasing outer hydrogel layer around an immunoisolating inner compartment achieved substantially higher local vascular density and improved glycemic correction in diabetic mice than an equivalent device without VEGF, demonstrating that pro-angiogenic signaling can be spatially confined to a

device's outer, non-isolating compartment (34). The advantage of matrix-bound over bolus delivery is control over dose and duration; the corresponding limitation is that this control is itself a manufacturing variable, and batch-to-batch consistency of growth-factor loading and release kinetics is a nontrivial quality-control burden for a combination biologic-device product (Section 9).

5.4 Oxygen-generating biomaterials

A different way to relieve the diffusion constraint is to stop depending on host vascularization, at least early on, and generate oxygen within the device itself. Solid-state materials based on slow hydrolysis of an embedded inorganic peroxide can supply oxygen for weeks without external gas exchange; embedding calcium peroxide within a polymer matrix surrounding an islet-laden hydrogel measurably improved encapsulated cell survival under hypoxic conditions in vitro and in vivo (11), and a collagen-based cryogel scaffold using similar chemistry showed comparable benefit, indicating the principle generalizes across matrix chemistries rather than depending on one polymer system (12). The advantage is that this approach is agnostic to host vascularization and buys time during the period when hypoxic loss is most severe; the limitation is that peroxide-based generation is inherently finite, byproduct management adds complexity, and none of these systems has sustained adequate oxygenation over a clinically relevant multi-year timescale, so oxygen-generating materials are best understood, on current evidence, as a bridging technology rather than a permanent vascular substitute.

5.5 Prevascularized scaffolds and vascularized implantation sites

Temporal separation is exemplified by the device-less, prevascularized subcutaneous site described in Section 3.6, in which a temporary device is implanted, allowed to become encapsulated by a vascularized fibrous tissue pocket over several weeks, and then removed and replaced with islets alone (13). Because no permanent foreign material remains once the islets are introduced, this strategy sidesteps the chronic foreign-body-driven fibrosis that limits long-lived encapsulation devices, at the cost of the islets themselves no longer receiving any physical immunoprotection, prevascularization solves the vascularization side of the coupled problem but reintroduces the need for pharmacological or cell-intrinsic immune protection to solve the other side, illustrating again that no single strategy addresses both requirements simultaneously.

5.6 Local immunomodulatory biomaterials, macrophage modulation, and anti-fibrotic strategies

The third design logic, replacing a physical barrier with local immunomodulation, has converged on strategies that specifically target macrophage behavior at the graft–host interface, consistent with the mechanistic centrality of macrophages described in Section 5.1. Biomaterial-tethered presentation of Fas ligand (FasL) to infiltrating T cells, delivered from a microgel co-transplanted with allogeneic islets, achieved localized immune tolerance and reversed hyperglycemia in immunocompetent diabetic mice without any systemic immunosuppressive drug, and has since been evaluated in non-human primates as a step toward this immunosuppression-free objective (19). Controlled local release of the glucocorticoid dexamethasone from a macroporous scaffold, at carefully titrated low doses, accelerated islet engraftment by shifting local macrophages toward an anti-inflammatory, pro-resolving phenotype during the first week after implantation; the same study found that higher doses impaired the macrophage-mediated remodeling engraftment needs, illustrating that local immunomodulation has an optimal dose window rather than a simple more-is-better relationship (17). Chemically modified alginates selected for their capacity to blunt macrophage-driven fibrosis, rather than for any change in porosity, have achieved multi-month immunoprotection of allogeneic islets in a vascularized non-human primate site without systemic immunosuppression, combining anti-fibrotic chemistry with a favorable site in one translational package (15,18).

5.7 Integrated vascularized immunoprotective platforms: a critical comparison

No platform reviewed above achieves vascularization and immunoprotection through a single, unified mechanism; each instead manages the trade-off by confining one objective spatially, temporally, or biologically so that it does not directly interfere with the other. Membrane-based spatial separation (Section 5.3) is mechanically simple and has the longest track record but has not, in a fully closed clinical device, achieved vascularization adequate to support clinically meaningful graft mass without also sacrificing complete immune exclusion (21,28). Oxygen-generating materials (Section 5.5) address the specific early hypoxic window well but are not a durable long-term solution and add manufacturing complexity. Prevascularization (Section 5.6) solves vascularization convincingly but transfers the entire immunoprotection burden elsewhere. Local immunomodulation (Sections 5.6) is the strategy most directly compatible with genuine vascular integration, since it does not require a diffusion-restricting membrane at all, but has so far demonstrated only partial,

dose-sensitive, and materially variable substitution for systemic immunosuppression in animal models, with human evidence still limited to devices that retained at least a physical permselective barrier (21) or to genetically rather than materially achieved immune evasion (20). On present evidence, the platforms that have advanced furthest clinically

are hybrids that combine two of these logics explicitly, a permselective membrane engineered for vascular proximity plus local anti-inflammatory chemistry, or a vascularized site plus a genetically hypoimmune cell product, rather than any platform relying on a single mechanism to satisfy both requirements at once.

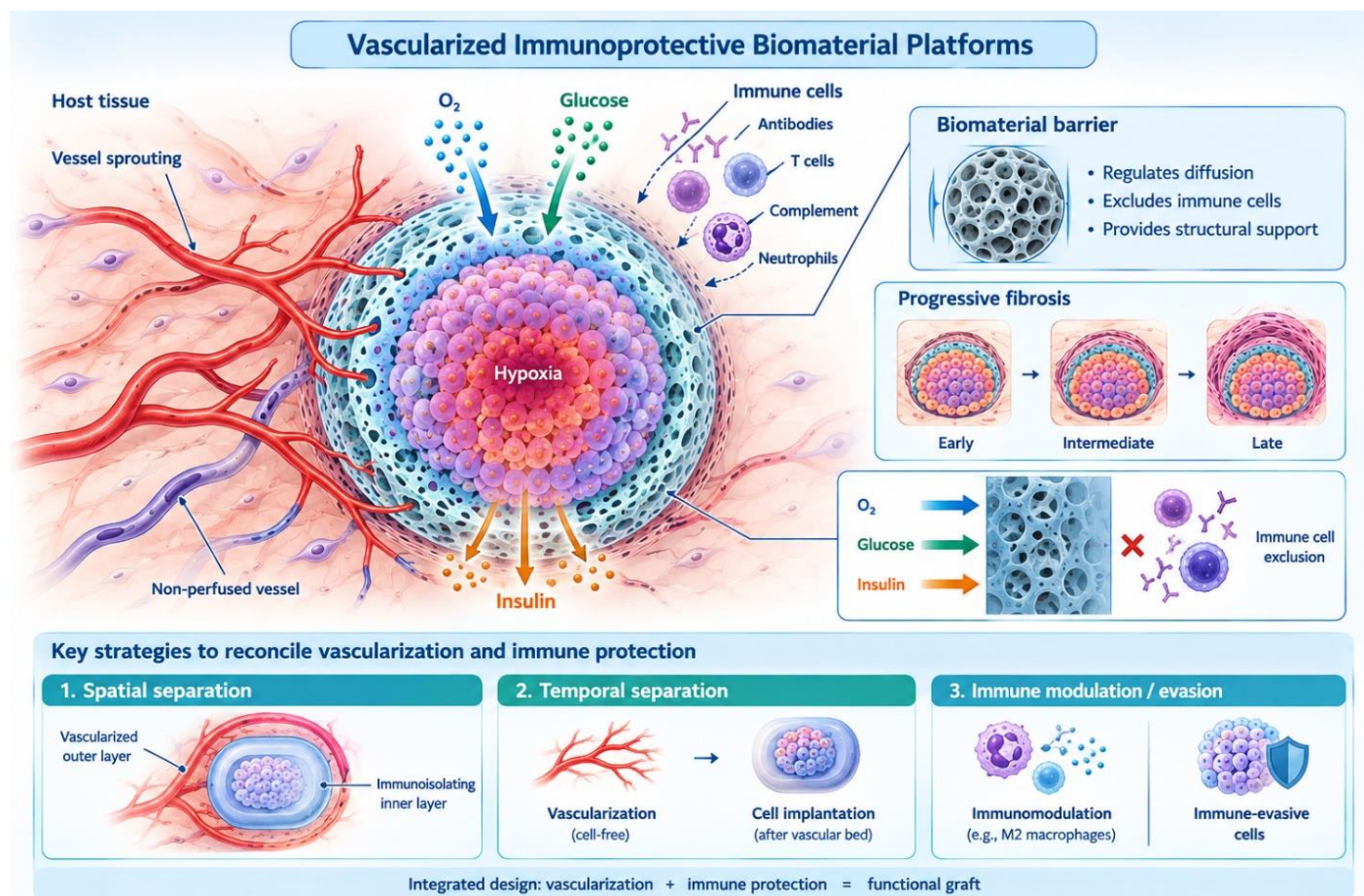


Figure 2. Mechanistic framework of vascularized immunoprotective biomaterials. Central schematic contrasting three design logics described in Section 5.2. Panel A (spatial separation) depicts an asymmetric-membrane macroencapsulation device with an outer, large-pore, VEGF-releasing layer supporting host vessel ingrowth up to the device surface and an inner, fine-pore immunoisolating layer around the cell compartment, following the design logic of the TheraCyte device and of VEGF-releasing PEG macrodevices (27,34). Panel B (temporal separation) depicts the two-stage device-less prevascularization sequence, empty scaffold implantation and vascularized-pocket formation, followed by scaffold removal and islet delivery into the pre-formed vascular bed (13). Panel C (biological/pharmacological separation) depicts an islet graft co-localized with a local immunomodulatory depot (schematically representing FasL-presenting or dexamethasone-releasing biomaterials) acting directly on infiltrating macrophages and T cells at the graft interface, without any enclosing membrane (19,17). Arrows and icons common to all three panels (oxygen and glucose influx, insulin efflux, macrophage and T-cell icons, and a fibrosis-thickness indicator) allow direct visual comparison of how each design logic manages the same set of coupled requirements through different physical or biological means.

Table 2. Comparison of vascularized and immunoprotective biomaterial strategies.

Biomaterial platform	Composition	Immunoprotective mechanism	Vascularization mechanism	Advantages	Limitations	Evidence level	Representative references
Asymmetric dual-membrane macrodevice (TheraCyte-type)	Inner fine-pore + outer coarse-pore ePTFE membranes	Physical exclusion of immunoglobulins/immune cells by inner membrane pore size	Outer membrane pore architecture promotes host vessel ingrowth to device surface	Retrievable; long track record across rodent, NHP and clinical testing	Vascular ingrowth reaches device surface, not cell compartment; historically insufficient in closed clinical configuration	Rodent, NHP, clinical (first-in-human)	Brauker et al. (27); Ramzy et al. (21)
VEGF-releasing vascularized PEG macrodevice	PEG hydrogel with immunoisulating inner compartment and VEGF-loaded outer layer	Fine-pore inner PEG compartment	Localized, matrix-bound VEGF delivery confined to outer, non-isolating layer	Spatially decouples pro-angiogenic signaling from immune-exclusion layer	Growth-factor loading/release is an added manufacturing and quality-control variable	Rodent	Weaver et al. (34)
Device-less prevascularized subcutaneous site	Temporary scaffold, later removed	None intrinsic (relies on separate cell-based or pharmacological protection)	Full host vascularization of a pre-formed tissue pocket prior to islet delivery	Converts a poorly vascularized site (subcutaneous) into a favorable one; avoids chronic foreign-body burden of a permanent device	No physical immunoprotection once islets are delivered; two-stage procedure	Rodent	Pepper et al. (13)
Oxygen-generating composite scaffold (peroxide-based)	Polymer matrix embedding solid inorganic peroxide, surrounding an islet-laden hydrogel	Depends on co-formulated encapsulation layer, if present	Not vascularization; substitutes chemical oxygen generation for the pre-vascularization window	Vascularization-independent protection during the most hypoxia-vulnerable early period	Finite oxygen-generation lifetime; unproven over clinically relevant timescales	In vitro, rodent	Coronel et al. (11); Razavi et al. (12)
Chemically modified (anti-fibrotic) alginate microcapsule	Triazole-thiomorpholine-dioxide-modified alginate	Standard alginate permselectivity, with chemistry selected to additionally blunt macrophage-driven fibrosis	None intrinsic; benefits from vascularized implantation site (e.g., omental bursa)	Reduced fibrotic encapsulation relative to unmodified alginate; multi-month function without immunosuppression in NHP	Benefit attenuated relative to rodent data when advanced to NHP; not all modified formulations translate equally	Rodent, NHP	Vegas et al. (16); Veisheh et al. (15); Bochenek et al. (18)
FasL-presenting immunomodulatory microgel (co-transplanted, unencapsulated)	Biotin-streptavidin-tethered FasL on PEG microgel	Local T-cell apoptosis induction at graft site; no physical membrane	Not addressed by the material; compatible with any vascularized or vascularizing site because no membrane restricts perfusion	No membrane-imposed diffusion barrier at all; durable rodent tolerance without systemic drugs	Efficacy in fully outbred, non-tolerized human immune systems not yet established	Rodent; early NHP evaluation	Headen et al. (19)
Local dexamethasone-releasing scaffold	PDMS-based macroporous construct loaded with dexamethasone	Dose-dependent shift of infiltrating macrophages toward an anti-inflammatory phenotype	Facilitates, rather than replaces, host vascular ingrowth by permitting favorable early remodeling	Accelerates engraftment at optimized low dose	Narrow therapeutic window; higher doses impair engraftment	Rodent	Jiang et al. (17)

Biomaterial platform	Composition	Immunoprotective mechanism	Vascularization mechanism	Advantages	Limitations	Evidence level	Representative references
Genetically hypimmune (HIP) stem-cell-derived islets in closed device	Gene-edited allogeneic SC-islets (reduced HLA expression, checkpoint ligand overexpression) in an encapsulating device	Cell-intrinsic evasion of immune recognition, independent of any membrane pore size	Standard device-level vascularization constraints apply; cell-intrinsic strategy does not by itself solve vascularization	Removes systemic immunosuppression requirement even for a closed device	Long-term durability of immune evasion in humans, and risk of immune escape variants, remain open questions	Early clinical	Carlsson et al. (20)

6. Biomaterial Design Parameters Governing β -Cell Function

The properties discussed qualitatively in Sections 4 and 5 reduce, at the design level, to a small number of measurable material parameters that jointly determine graft outcome. Pore size and mesh size set the upper size limit for molecules and cells that can cross a membrane or hydrogel network; alginate hydrogels typically present mesh sizes in the tens-of-nanometers range, sufficient to exclude immunoglobulin M and cells while remaining permeable to insulin, glucose, and oxygen, whereas the dual-membrane architecture of devices such as TheraCyte uses a submicron inner pore size for immune exclusion paired with a substantially larger outer pore size, on the order of several micrometers, specifically to permit vascular and cellular ingrowth up to that layer (27). Diffusion distance (the path length from the nearest oxygen source to the most distal cell) is arguably the single parameter most directly linked to viability, since oxygen delivery falls off steeply with distance under diffusion-reaction kinetics; this is the parameter that conformal and nanothin coatings (Section 4.3) minimize directly and that macroencapsulation devices must instead manage through device thickness and internal cell density (7). Capsule or device thickness and geometry interact with this constraint: planar or fiber-based geometries with a high surface-area-to-volume ratio shorten the average diffusion path relative to a bulk spherical or cylindrical geometry containing the same total cell mass, which is part of the rationale behind tubular and thin-planar macroencapsulation device designs.

Mechanical stiffness and degradation kinetics govern a separate set of outcomes. Very stiff, non-degradable capsule shells resist membrane turnover-related failure but cannot remodel to accommodate vascular ingrowth or islet swelling; degradable hydrogels can be engineered to open diffusion pathways or permit vascular integration as they erode, but degradation rate must be matched to the timescale of host tissue integration, since premature loss of barrier integrity reintroduces immune exposure before adequate

vascularization or immunomodulatory cover has been established (26,14). Surface chemistry and capsule size independently affect the foreign body response: capsules in the 1.5-millimeter diameter range provoke substantially less fibrotic overgrowth than capsules a few hundred micrometers in diameter across multiple base polymer chemistries in rodent and non-human primate testing, indicating that geometry, not only chemical composition, is an independent lever for controlling fibrosis, though this benefit again illustrates a direct trade-off, since larger capsules simultaneously increase diffusion distance to their core (15). No single parameter set is optimal in the abstract; each represents a specific point on a continuum between oxygen/nutrient transport, immune-cell exclusion, mechanical durability, and vascular accessibility, and the platforms reviewed in Section 5 are best understood as different, explicit choices along these continua rather than as categorically different technologies.

7. Stem-Cell-Derived β -Cells and Islet-Like Clusters

A biomaterial platform is only as useful as the cell source it protects, and donor islet scarcity is itself a barrier this review has treated as fixed up to this point. Directed differentiation of human pluripotent stem cells into insulin-secreting, glucose-responsive β -like cells offers, in principle, an unlimited and standardizable alternative to cadaveric islets. The original demonstration that human pluripotent stem cells could be differentiated in vitro into functional, glucose-responsive insulin-producing cells established feasibility (35), but first-generation stem-cell-derived β cells showed weak, non-dynamic insulin secretion relative to primary islets, lacking the rapid first-phase secretory response characteristic of native β cells. Subsequent refinements targeting transforming growth factor- β signaling during endocrine induction and maturation restored dynamic, first- and second-phase glucose-stimulated insulin secretion in vitro and improved glucose tolerance on transplantation into diabetic mice (36), and later work showed that direct manipulation of cytoskeletal tension during differentiation further increased the yield of mature, polyhormonal-free β -like cells (37), together indicating that

functional maturation, not merely lineage specification, has been the central engineering problem in this field and one that has seen substantial, measurable progress over the past decade.

Connecting this cell-source literature back to the biomaterial platform concept, stem-cell-derived β cells face the identical vascularization and immunoprotection requirements described throughout this review, and in some respects face them more acutely: allogeneic stem-cell products require the same immune protection as cadaveric allogeneic islets unless they are genetically modified for hypoinmunogenicity, and clusters of stem-cell-derived cells, like primary islets, are avascular immediately after differentiation and equally dependent on host revascularization or oxygen-generating support once transplanted (20,35). Two further considerations are specific to this cell source rather than to islets generally. First, tumorigenicity: because differentiation from a self-renewing pluripotent starting population can leave a residual population of undifferentiated cells capable of forming teratomas, any clinical stem-cell-derived cell product requires rigorous, sensitive assays to confirm the absence of residual pluripotent cells before use, a safety requirement with no analogue in cadaveric islet transplantation (38). Second, differentiation heterogeneity and batch consistency: differentiation protocols run over multiple weeks through several intermediate cell states, and incomplete or off-target differentiation at any stage can yield a final cell product with variable hormone content and purity between batches, which is as much a manufacturing and quality-control problem (Section 9) as a developmental-biology one. Scalability is, on current evidence, the strongest argument for this cell source and immune protection and manufacturing consistency the weakest links; a biomaterial platform capable of solving vascularization and immunoprotection together would derive proportionally greater benefit from a stem-cell source than from cadaveric islets, since it would remove the donor-scarcity constraint that otherwise limits how broadly any encapsulation platform could be deployed even if the material science were fully solved.

8. Preclinical and Clinical Translation

Evidence in this field spans a wide range of model systems, and the strength of evidence at each stage does not transfer automatically to the next. In vitro and rodent data (diabetic mouse models in particular) have generated the great majority of the mechanistic findings reviewed in Sections 4 through 6, including essentially all of the vascularized immunoprotective platform data in Section 5 (26,14). Rodent models are useful for isolating mechanism because genetic

tools allow precise manipulation of single variables (for example, conditional VEGF-A deletion (25) or macrophage-lineage tracing), but murine skin and subcutaneous tissue is thinner and more richly vascularized than the corresponding human tissue, and mouse islets differ from human islets in size and cellular composition, so rodent graft survival and vascularization endpoints tend to overstate what the same material will achieve in a larger, bipedal host.

Large-animal and non-human primate studies are the appropriate next check on this optimism and have, in several instances reviewed above, revealed exactly the attenuation one would predict: chemically modified alginate formulations that essentially eliminated fibrotic overgrowth in rodents showed a reduced, though still real, benefit when advanced to NHPs, and only the most effective formulation, combined with a favorably vascularized implantation site, achieved multi-month immunoprotection without immunosuppression (15,18). Endpoints available in large-animal and clinical studies also differ qualitatively from rodent endpoints: glycemic control and insulin dose reduction are measurable in any species, but vascularization is typically assessed only histologically at retrieval in animal studies, whereas immunological and fibrotic endpoints in clinical trials must rely on retrieved-device histology, circulating C-peptide, and indirect markers, since serial biopsy of an implanted human device is rarely feasible.

First-in-human and early-phase clinical trials are where the vascularization-immunoprotection trade-off has been most starkly demonstrated. A fully closed, immunoisolating encapsulation device carrying stem-cell-derived pancreatic progenitor cells produced detectable but limited insulin secretion, with retrieved devices showing an unfavorable foreign body response and inadequate vascular ingrowth to the cell compartment (21). A modified, cell-permissive version of the same underlying device, with larger perforations allowing direct vascular and cellular access to the graft, achieved substantially higher cell survival and glucose-responsive C-peptide secretion, but only under conventional systemic immunosuppression, since the same perforations that admitted vasculature also admitted immune cells (21,28). The β -Air externally oxygenated device was safe and reduced exogenous insulin requirement in a first-in-human trial without immunosuppression, but function was partial and the device required ongoing external maintenance (29). Most recently, allogeneic stem-cell-derived islet cell infusion has achieved insulin independence in a clinical trial cohort under conventional immunosuppression (39), and, in a separate, complementary trial, gene-edited hypoinnate allogeneic β cells implanted without any immunosuppressive drug

produced biochemical evidence of graft survival and insulin secretion (20), together indicating that at least two of the field's central objectives (a scalable, high-quality cell source, and immunosuppression-free graft protection) have each been demonstrated separately in humans within the past two years, even though no single trial has yet combined a fully immunoprotected, vascularized, immunosuppression-free device with this quality of cell product.

It is important, in reading this literature, not to conflate categories of evidence. Reversal of hyperglycemia in a diabetic mouse is proof of mechanism, not proof of clinical

efficacy. A device that is safe and biochemically active in a small first-in-human cohort has cleared an important translational hurdle but has not thereby been shown to be superior, or even equivalent, to the existing standard of allogeneic islet infusion under immunosuppression, for which multicenter, controlled clinical trial evidence and regulatory approval already exist (3). The distinction matters practically as well as rhetorically, because it is precisely the gap between mechanistic promise and controlled clinical evidence that has repeatedly narrowed more slowly than early results suggested it would.

Table 3. *Translational comparison of biomaterial platforms.*

Platform	Cell source	Vascularization	Immune protection	Fibrosis	Scalability	Manufacturing complexity	Preclinical evidence	Clinical evidence	Major translational barrier
Closed macroencapsulation device (dual-membrane)	Cadaveric islets or SC-derived progenitors	Outer-membrane ingrowth only; not to cell compartment	Physical, membrane-based	Moderate–high over time	Device-limited (fixed cell mass per implant)	Moderate	Rodent, NHP	First-in-human (21)	Inadequate vascularization of enclosed cell mass
Open/cell-permissive macrodevice	SC-derived progenitors	Direct vascular/cellular ingrowth	None (requires systemic immunosuppression)	Lower than closed device	Device-limited	Moderate	Rodent, NHP	Phase 1/2 (21,28)	Loss of immune privilege; still requires immunosuppression
Externally oxygenated macrodevice (β -Air)	Xenogenic (porcine) islets	Not required for oxygenation; independent of vascularization	Physical, membrane-based	Moderate	Limited by device size and gas-refill logistics	High (gas delivery hardware)	Rodent, NHP	First-in-human (29)	Partial function; ongoing external maintenance burden
Chemically modified alginate microcapsules	Allogeneic islets	Dependent on implantation site vascularity	Physical + reduced-fibrosis chemistry	Substantially reduced vs. unmodified alginate	High (injectable, scalable production)	Low–moderate	Rodent, NHP	Early-phase (unmodified alginate) (32)	Attenuated benefit and site-dependence on scale-up to NHP/human
Local immunomodulatory biomaterial (no membrane)	Allogeneic islets	Unrestricted (no membrane)	Pharmacological/biological, local	Variable, agent-dependent	Moderate–high	Moderate (drug/ligand loading and release control)	Rodent; early NHP	Not yet reported at scale	Efficacy in outbred human immune systems unconfirmed
Gene-edited hypoinnate SC-islets in device	Allogeneic SC-derived islets	Standard device-level constraints apply	Cell-intrinsic (genetic)	Device-dependent	High (renewable cell source)	High (cell engineering + device manufacturing)	Rodent, NHP	Early clinical (20)	Durability of immune evasion; risk of immune-escape variants
Non-encapsulated SC-derived islet infusion + immunosuppression	Allogeneic SC-derived islets	Not applicable (intraportal)	Systemic immunosuppression	Not applicable	High (renewable cell source)	High (cell manufacturing)	Rodent, NHP	Phase 1/2, insulin independence reported (39)	Retains full systemic immunosuppression burden

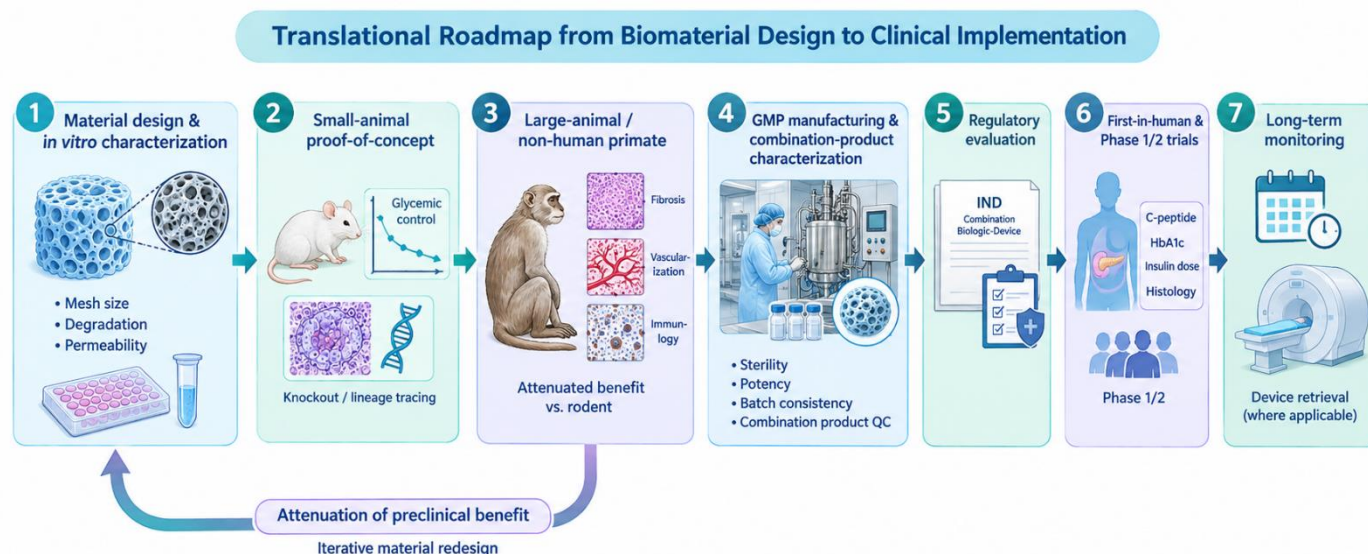


Figure 3. Translational roadmap from biomaterial design to clinical implementation. Linear flow diagram from left to right: (i) material design and in vitro characterization (mesh size, degradation, permeability testing); (ii) small-animal (rodent) proof-of-concept, including diabetic-mouse glycemic correction and mechanistic knockout/lineage-tracing studies (25,35); (iii) large-animal/non-human primate testing, where fibrosis, vascularization and immunological endpoints are assessed histologically at device retrieval and benefit is typically attenuated relative to rodent data (15,18); (iv) GMP manufacturing and combination-product characterization, flagged with the specific quality-control burdens discussed in Section 9; (v) regulatory evaluation as a combination biologic-device product; (vi) first-in-human and phase 1/2 clinical trials, with C-peptide, HbA1c, exogenous insulin dose, and retrieved-device histology as principal endpoints (21,28,29); and (vii) long-term monitoring, including device retrieval planning where applicable. A downward branch at stage (iii) explicitly labeled "attenuation of preclinical benefit" feeds back visually to stage (i), representing the iterative material redesign that non-human primate and clinical data have repeatedly triggered in this field, rather than depicting translation as a one-directional pipeline.

9. Manufacturing, Regulatory, and Commercialization Considerations

Every platform reviewed above must eventually be manufactured reproducibly, characterized to a regulator's satisfaction, and made available at a cost and complexity compatible with routine clinical use, and this section's omission from much of the preclinical literature is itself telling about how far several platforms remain from clinical readiness. A device or capsule combining a biological cell product with a synthetic material, and in several cases with an additionally released drug or growth factor, is regulated as a combination product, for which the biologic, device, and (where present) drug constituents are each subject to the regulatory framework that would apply to that constituent alone, with the sponsor and regulator jointly determining which framework governs the combination as a whole. This classification question is not merely bureaucratic: it determines which quality systems, stability data, and clinical evidence standards apply, and combination-product status has been a recurring source of regulatory complexity for cell-device platforms in this field.

Manufacturing consistency is a distinct challenge for each major component. Batch-to-batch variability in alginate purity and composition has been directly linked to variability in

fibrotic response, meaning that alginate intended for clinical encapsulation requires purification and compositional specification well beyond what is typical for industrial or food-grade alginate (31). Decellularized matrix scaffolds face an analogous, arguably harder problem, since biological source material is inherently more variable than a defined synthetic polymer and the decellularization process itself must be validated to consistently remove antigenic and cellular content without degrading the matrix properties that motivate using it in the first place (33). Stem-cell-derived cell products carry their own manufacturing burden: differentiation protocols run over multiple weeks and must be validated for lot-to-lot consistency of hormone-cell purity, and, distinct from any other quality attribute, every lot must be tested with a sufficiently sensitive assay to exclude residual undifferentiated pluripotent cells capable of forming teratomas before release (38). Device sterilization and shelf-life present a further set of constraints specific to the physical device: sterilization methods compatible with a hydrogel-encapsulated living cell product are far more limited than for an inert device, and any combination product's storage and transport logistics must preserve cell viability, a constraint drug-only or device-only products do not share.

Long-term safety monitoring, biodegradation of any non-retrievable component, the possibility of immune escape in gene-edited hypimmune cell products, and the practical logistics of implant retrieval where a device is not intended to remain permanently, all bear on cost and commercialization feasibility as much as on science. The regulatory landscape for this field is not static background; it has itself been an active site of translational activity. The 2023 approval of an allogeneic, cadaveric-donor islet cell product as a licensed biologic for a defined population of patients with severe hypoglycemia, the first such approval in the United States, established a regulatory precedent for cellular islet products and has simultaneously prompted debate within the transplantation community about whether donor-derived islets are better regulated as a biologic drug or as a form of organ tissue, a distinction with direct consequences for reimbursement, manufacturing standards, and equitable patient access (40). How future encapsulated, stem-cell-derived, or gene-edited platforms will be classified relative to this precedent remains an open and consequential question, since each variation (adding a device, changing the cell source, adding genetic modification) potentially shifts which regulatory framework, and which evidentiary bar, applies.

10. Critical Discussion

What has this field actually demonstrated, as distinct from what it has made plausible? At the mechanistic level, the evidence is strong and largely convergent: islet hypoxia after isolation is a real, measured, and diffusion-limited phenomenon (8,7); revascularization after transplantation is slow, host-vessel-dependent, and VEGF-driven (22,24); foreign body-driven fibrosis, not acute rejection, is the dominant chronic failure mode for encapsulated grafts (10); and macrophage behavior is mechanistically central to both the vascularizing and the fibrosing arms of the host response, which is why interventions targeting macrophage polarization specifically (dexamethasone dosing, FasL presentation) have shown some of the most consistent, mechanistically interpretable benefit in the recent literature (19,17). These are not preliminary observations; they are reproduced across multiple independent laboratories and model systems and constitute a solid mechanistic foundation for the field.

Where the evidence is comparatively preliminary is in the durability and generalizability of any single integrated solution. Every vascularized immunoprotective platform reviewed in Section 5 has demonstrated its central claim in rodents; only a subset have been tested in non-human primates, and in every such case, benefit measured in rodents was attenuated, though not eliminated, on translation

(15,18). No platform has yet demonstrated, in a single human study, simultaneous achievement of adequate vascular integration, complete immune exclusion or its pharmacological/genetic equivalent, preserved β -cell function, and multi-year durability; the closest approaches to date have achieved two or three of these properties while explicitly sacrificing another; a fully closed device with genuine immunoisolation but inadequate vascularization (21), an open device with excellent vascularization but no immune privilege (21,28), or a genetically hypimmune cell product whose device-level vascularization still faces the same unresolved constraints as any other encapsulated graft (20).

This pattern answers, at least provisionally, several of the field's most consequential open questions. Complete immunoisolation by physical barrier alone does not currently appear realistic as a durable, standalone solution, because the physical properties needed for complete immune exclusion and for adequate long-term nutrient/oxygen transport are set by the same diffusion-governing material parameters and cannot both be maximized simultaneously (Section 6). Vascularization and durable immune protection are not inherently incompatible, but achieving both together has so far required abandoning a single-mechanism solution in favor of explicitly hybrid designs that separate the two objectives spatially, temporally, or biologically (Section 5.7), rather than reconciling them within one material property. Local immunomodulation has shown the most promise as a substitute for systemic immunosuppression specifically because it does not impose a membrane-driven diffusion penalty, but the human evidence base for this approach remains thinner than for membrane-based encapsulation, and dose-dependent effects observed for at least one agent (17) indicate that local immunomodulation is not a simple, permissive substitute for systemic drugs but a separate pharmacology requiring its own careful titration.

The most important evidence gap is arguably not in any single material property but in the standardization of translational benchmarks across studies: vascularization is reported inconsistently as vessel density, perfusion, or oxygen tension; fibrosis is graded on non-uniform histological scales; and few studies report all of oxygen tension, immune cell infiltration, and glycemic function together in the same animals at matched time points, which makes it difficult to compare platforms on a common footing or to determine which specific design change caused an observed improvement. Future studies should prioritize head-to-head comparisons using shared, quantitative, and ideally non-invasive vascularization and oxygenation endpoints, and should report large-animal data whenever available rather than resting conclusions on

rodent evidence alone. On present evidence, the strategies closest to clinical translation are those that pair an already-clinically-tested element (a membrane-based device, or systemic immunosuppression) with one incremental, mechanistically targeted improvement, rather than platforms attempting to introduce several novel elements simultaneously.

11. Future Perspectives

Several directions extend logically from the evidence synthesized above, though they should be read as plausible next steps rather than established findings. Multifunctional and stimulus-responsive biomaterials that couple oxygen-generating chemistry, VEGF or other angiogenic signaling, and local immunomodulatory drug or ligand release within a single, spatially organized device represent the most direct extrapolation of the hybrid design logic already emerging in Section 5, though no such fully integrated system has yet been tested beyond isolated components. Oxygen-responsive materials that release their protective cargo (an angiogenic factor, an anti-inflammatory agent) specifically in response to local hypoxia, rather than at a fixed rate, would in principle better match therapeutic delivery to the actual, time-varying severity of the diffusion problem described in Section 2, but this remains a materials-engineering aspiration rather than a demonstrated capability in this specific application. Spatially patterned presentation of angiogenic and immunomodulatory cues (for instance, confining pro-angiogenic signal to a device's outer surface while confining anti-inflammatory or tolerogenic signal to the graft-facing surface) extends the spatial-separation logic already used in asymmetric-membrane devices (Section 5.3) to a finer and potentially more effective spatial resolution.

Engineered implantation sites, building on the device-less prevascularization concept (Section 5.6), could in principle be extended with additional local cues (matrix stiffness gradients, patterned vasculogenic factors) to accelerate and better control the resulting vascular architecture, though this remains to be demonstrated beyond the single-cue VEGF and device-less approaches reviewed here. Continued improvement in stem-cell-derived β -cell maturation protocols (Section 7) will likely remain a parallel and largely independent research track from the biomaterial engineering reviewed in this article, but the two tracks are complementary rather than competing, since a fully solved biomaterial platform is of limited clinical value without a scalable cell source, and a perfectly mature cell product still requires vascularization and immune protection once transplanted. Computational modeling of coupled oxygen-diffusion,

angiogenesis, and immune-cell-infiltration dynamics could help prioritize which combinations of the design parameters in Section 6 are worth testing experimentally, reducing the current reliance on empirical, one-variable-at-a-time optimization; automated, closed-system GMP manufacturing and non-invasive imaging methods capable of monitoring graft vascularization and viability longitudinally in patients would address, respectively, the manufacturing and evidence-standardization gaps identified in Sections 9 and 10. None of these directions should be read as imminent; they are extrapolations from an evidence base that, as emphasized throughout, has repeatedly shown smaller effect sizes on translation from rodent to larger animal and human testing than initial reports suggested.

12. Conclusion

Three decades of biomaterial engineering have established, with considerable mechanistic rigor, why avascular, unprotected islet or β -cell grafts fail: hypoxia sets in before revascularization can occur, foreign body-driven fibrosis progressively closes off whatever diffusion pathway a material initially provides, and immune recognition, whether allogeneic, xenogeneic, or context-dependent autoimmune, persists for as long as the graft survives long enough to be recognized. The field has also established, through repeated and independent demonstration, that no single material property resolves all of these problems together: membrane pore size that excludes immune cells also constrains oxygen and nutrient flux; angiogenic signaling that recruits vasculature also recruits the macrophage-driven inflammatory activity that drives fibrosis; and physical immunoisolation adequate to remove the need for systemic immunosuppression has not yet been reconciled, within a single device, with vascular access sufficient to support a clinically meaningful cell mass.

This is why vascularization and immunoprotection must be engineered together rather than in sequence: they are not separable subsystems of a graft but two outputs of the same underlying material and biological parameters, and optimizing one without regard for the other has, across the studies reviewed here, reliably produced a platform that fails on the dimension left unaddressed. The most credible translational direction, on current evidence, is not a single unifying material breakthrough but the deliberate combination of complementary, already-partially-validated elements: a permselective architecture engineered for vascular proximity, paired with a local, mechanistically targeted immunomodulatory strategy or a genetically hypoimmune cell source, applied to a renewable, well-characterized stem-cell-

derived β -cell product, and developed alongside the manufacturing and regulatory frameworks needed to make such a combination product reproducible and evaluable at scale. Before this can move from a promising research direction to a routine clinical option, the field needs standardized, quantitative, and preferably non-invasive measures of vascularization and immune status that allow platforms to be compared on common ground; large-animal validation as a required, not optional, step before first-in-human testing; and regulatory clarity on how increasingly hybrid biologic-device-drug combination products will be classified and evaluated. The biological and materials-science pieces of this problem are, individually, substantially better understood than they were even five years ago; what remains is the harder task of integrating them into a single, manufacturable, and durable platform.

Authors' Contributions

All authors contributed to the conception, literature review, drafting, and critical revision of this manuscript and approved the final version for submission.

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Abbreviations

Abbreviation	Full term
VEGF	Vascular endothelial growth factor
FBR	Foreign body reaction/response
PEG	Poly(ethylene glycol)
PDMS	Poly(dimethylsiloxane)
GMP	Good Manufacturing Practice
NHP	Non-human primate
HIP	Hypoimmune (gene-edited to evade immune recognition)

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Availability of Data and Materials

The literature synthesized in this review is publicly available through the cited peer-reviewed sources. No new datasets were generated for this article.

Ethics Approval and Consent to Participate

Not applicable. This article does not report any new studies with human participants or animals performed by any of the authors.

Consent for Publication

Not applicable.

Conflicts of Interest

The authors declare that they have no competing interests.

Declaration to the Journal Editor

For the sake of full transparency, the authors declare that artificial intelligence (AI) tools were used during the preparation of this article. Specifically, the Claude model (developed by Anthropic) was employed for grammatical corrections and language polishing of the draft text. In addition, ChatGPT (developed by OpenAI) was used to assist with the preparation and design of the figures and graphical illustrations presented in the manuscript. The authors remain fully responsible for the scientific content, accuracy, interpretation, originality, and final approval of all text and figures included in the article.

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