Received: 19 March 2023 | Revised: 3 May 2023 | Accepted: 17 May 2023

DOI: 10.1096/fba.2023-00029

FASEB BioAdvances WILEY

REVIEW ARTICLE

Combinatorial islet protective therapeutic approaches in β-cell transplantation: Rationally designed solutions using a target product profile

Katie Lu[1,2] | **Timothy Brauns**[1] | **Ann E. Sluder**[1] | **Mark C. Poznansky**[1] | **Fatma Dogan**[1]

[1]Vaccine and Immunotherapy Center, Massachusetts General Hospital, Boston, Massachusetts, USA

[2]Department of Biology, Stanford University, Stanford, California, USA

Correspondence
Fatma Dogan, Vaccine and Immunotherapy Center, Massachusetts General Hospital, Boston, Massachusetts, USA.
Email: fdogan@mgh.harvard.edu

Funding information
Juvanile Diabetes Research Foundation United States of America, Grant/Award Number: 2-SRA-2021-1075-S-B; VIC Innovation Fund; VIC Education Fund

Abstract

While progress has been made in the development of islet cell transplantation (ICT) as a viable alternative to the use of exogenous insulin therapy in the treatment of type 1 diabetes, it has not yet achieved its full potential in clinical studies. Ideally, ICT would enable lifelong maintenance of euglycemia without the need for exogenous insulin, blood glucose monitoring or systemic immune suppression. To achieve such an optimal result, therapeutic approaches should simultaneously promote long-term islet viability, functionality, and localized immune protection. In practice, however, these factors are typically tackled individually. Furthermore, while the requirements of optimal ICT are implicitly acknowledged across numerous publications, the literature contains few comprehensive articulations of the target product profile (TPP) for an optimal ICT product, including key characteristics of safety and efficacy. This review aims to provide a novel TPP for ICT and presents promising tried and untried combinatorial approaches that could be used to achieve the target product profile. We also highlight regulatory barriers to the development and adoption of ICT, particularly in the United States, where ICT is only approved for use in academic clinical trials and is not reimbursed by insurance carriers. Overall, this review argues that the clear definition of a TPP in addition to the use of combinatorial approaches could help to overcome the clinical barriers to the widespread adoption of ICT for the treatment of type 1 diabetes.

KEYWORDS

bench to bedside development, combinatorial approaches, islet cell transplantation, target product profile, type 1 diabetes

1 | INTRODUCTION

Type 1 diabetes (T1D) is a complex autoimmune disease characterized by the selective destruction of pancreatic beta cells, which leads to severe insulin deficiency and subsequent hyperglycemia. Conventional treatment of T1D is lifelong exogenous insulin administration that requires high compliance with regular subcutaneous injections of insulin, by syringe or insulin pumps, along with assiduous blood glucose monitoring.[1] However, this highly burdensome treatment is inefficient at managing the complex condition of T1D as it does not fully recapitulate the dynamics of native pancreatic islet responses to insulin requirements.[2,3] As a result, up to 41.8%, of people living with T1D experience severe hypoglycemic reactions despite optimal insulin therapy.[4] These patients with severe, intractable, recurring hypoglycemic reactions are candidates for alternatives to T1D management such as islet cell transplantation (ICT).

ICT is a promising, and in many ways, less complex for the patient, alternative to exogenous insulin injections that restores the insulin-producing β-cell mass.[5,6] The first successful ICT method was established in 2000, in which 800,000 pancreatic islets were injected into the hepatic portal vein under an immunosuppressive regimen. While this protocol, known as the "Edmonton protocol", was successful at establishing insulin independence, only eight percent of the patients were able to maintain insulin independence at 1 year post-transplant.[7] Even with subsequent advances in immunosuppression treatments that improved islet survival, less than twenty percent of patients were able to maintain insulin independence for 5 years.[8] The inherent limitations of ICT—low islet survival rates, the loss of function of the transplanted cells due to poor vascularization at the implantation site, development of antibodies against the donor cells, graft rejection and post-surgical complications that come with the requirements of lifelong immunosuppression.[9–11]—are the main reasons why islet transplantation is still considered an experimental procedure by the US Food and Drug Administration (FDA).

Many clinical studies have sought to overcome these challenges by testing new strategies to protect transplanted β-cells from the recipient's immune system, increase availability of oxygen and nutrients to the islets, and promote long-term cell survival, all of which are needed for successful long-term ICT.[12–14] This review will focus on microscale and macroscale islet cell encapsulation approaches due to their prevalence and clinical promise at achieving these goals. These encapsulation approaches can be further classified into four main categories: mechanical modification to the biomaterial such as size or stiffness, chemical modification to the biomaterial, biological co-encapsulation, and chemical co-encapsulation.

We posit that one of the reasons that novel ICT approaches have not fared well in clinical testing is due to the focus on a single encapsulation approach that can only target one desired clinical outcome for the patient rather than all of the entire clinically necessary ones.[15] Furthermore, the difficulty of achieving multiple clinical outcomes in clinical trials has been exacerbated because there is no description in the literature of the ideal characteristics for an ICT product that would reliably achieve the clinical outcomes necessary for successful widespread adoption.

Here we consider solutions to the challenges of ICT holistically and in a combinatorial manner. This review aims to remedy a gap in current literature by reviewing and proposing combinatorial approaches to ICT encapsulation using an explicit clinical product profile that covers multiple desired clinical outcomes. First, we review current clinical trials and academic approaches to islet transplantation. Next, we identify the most clinically relevant criteria for inclusion in a TPP. Then, we review current combinatorial methods that have come closest to achieving this TPP. Finally, we propose novel, combinatorial, next-generation T1D ICT products with the potential for fully achieving our TPP.

2 | BUILDING A TARGET PRODUCT PROFILE FOR ICT

2.1 | Current state of clinical trials: identifying metrics that define ICT success

Since Shapiro et al. revolutionized ICT, advances in transplant techniques, immunosuppression regimes, and alternative islet sourcing have added to the long-term safety of ICT.[16] The three primary clinical outcomes for ICT are graft survival rates, frequency of severe hypoglycemic episodes (SHEs), and insulin dependence status. Current studies show an overall average of 55% 10-year graft survival rate as assessed by.[17] SHEs have been abrogated by an average of 62.5% in the context of ICT versus standard of care use of exogenous insulin while five-year insulin independence rates range from 50% to 80%.[18,19] These three clinical outcome endpoints reflect underlying product characteristics of cell viability, safe insulin release rates, and long-term cell functionality, respectively. Other promising results and metrics include median HbA1c levels (an indicator of insulin resistance) showing at least 1% reduction in 1 year, positive C-peptide status (an indicator of insulin levels), and ongoing protection from SHEs. The most advanced, up-to-date, multicenter

phase 3 clinical trial reported 87.5% of patients achieving an HbA1c level of <7.0% and minimal SHEs for the first 365 days post-transplant.[20]

This degree of T1D management has not yet been achieved through other modern strategies, including intelligent insulin pumps and glucose monitoring technologies. Recent trials that have compared ICT with sensor-augmented pump therapies demonstrated that only ICT could correct the HbA1c levels and reduce the progression of diabetic retinopathy and nephropathy.[21,22] While tremendously promising, even these most current clinical trials fail to take full advantage of all ICT approaches that could help achieve multiple primary and secondary clinical endpoints.

2.2 | Identifying clinical outcomes necessary for the TPP

2.2.1 | Low cell viability post-transplantation hinders long-term success

Islet cell transplantation, compared to other organ transplants, is uniquely challenging. Before they are incorporated into eventual products, islets must go through a complex isolation procedure from syngeneic, allogeneic, or xenogenic pancreata and then survive and function ex vivo prior to transplantation.[23] Even with optimal procedures in these areas, the necessary donor to recipient ratio often ranges from 2–4 in order to promote the engraftment of sufficient islets to achieve insulin independence.[24] At each step of this process, loss of islet viability causes decreased ability to achieve normoglycemia due to the inability of engrafted islets to dynamically respond to glucose levels in the same way that native islets do. Overall, the quality of islets following procurement and isolation drastically affects patient outcomes.[25] Additional restrictions and considerations include feasible device dimensions and implantation procedures for patient approval, which remains a barrier to creating effective treatments.[26] ICT procurement and islet isolation procedures and their effects on patient outcomes remain important topics in ICT development. Pancreatic islets are highly metabolic cells, and the many stress factors and hypoxic episodes experienced during islet isolation or the process of creating new human islets from stem cells, and as a result of transplant procedures are challenges for islet recovery and function.[27–30]

Conventionally, islets have been implanted in the hepatic portal vein with eventual embolization in the liver.[31] Although this method has been well characterized, only 30% of the original islet mass remains viable.[32] Hepatic portal ICT has low graft survival rates and transient insulin independence, with many patients in clinical trials resuming insulin injections post transplantation.[33]

Oxygen availability is one of the major obstacles to islet cell viability due to their high metabolic rate and sensitivity to hypoxia. Oxygenation heavily impacts islet survival through downregulation of hypoxia-inducible factor (HIF)-1, which reduces apoptosis events.[34] Vascularization also remains critical, as the islets rely on diffusion to obtain nutrients and metabolites in their non-native environment.[35] Lastly, the instant blood-mediated inflammatory reaction (IBMIR) activates a complement cascade resulting in leukocyte and macrophage-mediated islet cell death.[36]

Clinical trials have investigated the impact of various transplantation sites with better vascularization including bone marrow, omentum, gastric submucosa, kidney, subcutaneous, intramuscular, and spleen.[37] Compared to the historically preferred site of intraportal liver transplantation, one study showed that kidney and muscle sites yielded superior insulin independence results (100% and 70% normoglycemia rates, respectively) in a rodent model.[38] The kidney site in particular yielded many advantages, including easy graft retrieval and comparatively higher oxygen availability.[39] Another study delivered syngeneic islets to the cremaster muscle of nondiabetic mice and showed functional intraislet blood vessels at 3–5 days after transplantation, but no difference in glucose levels compared to control.[40] Hawthorne et al. demonstrated that a pancreas graft in the renal capsule in a porcine model showed resistance to hypoxic-related injury and a shorter recovery time to graft function.[41] Additionally, further investigations have shown that the required islet mass to achieve euglycemia is lower in omentum sites compared to intrahepatic locations.[42]

In addition to use of optimal transplantation sites, encapsulation methods can also increase cell viability and survival rates.[8] Encapsulation provides a support structure for the islets that mimics the native pancreatic extracellular matrix (ECM) and a physical barrier that prevents graft rejection and innate inflammatory responses.[43] These methods can utilize biomaterials of any size for encapsulation, from nanoscale to the micro-macroscale. In clinical settings, encapsulation methods can promote islet viability and prolong cell survival, prolonging functionality.[8]

Key first-generation islet encapsulation techniques that have been investigated clinically include Novocell's acrylated polyethylene glycol (PEG) nanoencapsulation, alginate microencapsulation described by Soon-Shiong et al. and Calafiore et al. and Beta-O2's alginate macroencapsulation device.[11,44–46] Novocell also initiated a phase I/II clinical trial in two patients utilizing PEG nanoencapsulation without immunosuppression. However, the trial was terminated because neither of the patients achieved

insulin independence in the 6 months after implantation. Similarly, microencapsulation methods such as those of Soon-Shiong et al. and Calafiore et al. achieved modest reduction of exogenous insulin requirements but did not provide full insulin independence. Lastly, Beta-O2 developed the BAir macroscale device that supplies exogenous oxygen to the islets inside an alginate slab.[47] In a case report for the BAir device, the islets were able to retain function for 10 months with a modest reduction in exogenous insulin.[11] However, the BAir device suffered in other areas, such as graft rejection resulting in fibrous tissue deposition and a blunted glucose-stimulated insulin response.

In summary, poor cell viability has remained an obstacle in ICT and two main techniques (adjusting transplant site and encapsulation) are inadequate to fully overcome it. Furthermore, in clinical trials investigating these techniques, other important clinical outcomes such as insulin independence and graft acceptance have not been achieved. As we will discuss, other clinical approaches that target these other outcomes often disregard cell viability and survival as factors in transplant efficacy. This demonstrates the need for a shift in ICT strategy to a holistic evaluation of the clinical target product profile and use of the full toolkit available.

2.2.2 | Systemic, lifelong immunosuppression limits clinical feasibility

The consequences of lifelong, systemic immunosuppression remain the largest barrier to successful ICT therapy. Chronic and systemic immunosuppression is required to prevent foreign body response and graft rejection.[48] Importantly, frequent and sustained delivery of immunosuppressive drugs causes clinically important side effects, such as increased opportunistic infections, nephrotoxicity, systemic organ and islet toxicity, and cancer.[49] Consequently, the main cause of terminated ICT clinical trials is the need for maintenance of immunosuppressive agents and their subsequent complications.[50]

New clinical approaches to protecting transplanted islets from immune damage include corticosteroid-free drugs to avoid renal dysfunction, replacement of systemic drugs with targeted immunomodulatory molecules, and physical barriers to avoid immune detection.[7,51,52] Here, we will focus on key studies and clinical trials in the latter two categories.

Immunological tolerance is defined as the lack of a destructive immune response against specific antigens while retaining the full capacity of the immune system to react against other foreign antigens. In ICT, tolerogenic approaches are used to allow immunological acceptance of the graft. Common tolerogenic approaches aim to suppress autoreactive T cell activation or expand Treg activity.[53,54] Some key clinical trials in this area have aimed to restore Treg function through exogenous mature CD4+ cells and BOX 1 tolerogenic dendritic cells.[55–57] However, these trials had high variability in effectiveness and limited efficacy in some cases, with transient effects and yielding little mechanistic knowledge. Another tolerogenic approach is to deliver cytokines/agents to promote the recruitment of regulatory T cells at the site of reactivity. Immunosuppressant factors can be attached to the surface of the islets and deactivate T cell function.[58] For example, FasL (a type II transmembrane protein) preferentially eliminates effector T cells and supports Tregs.[59] However, tolerogenic treatments often fail to achieve their primary endpoint of 1 year of insulin independence and require improvements to their stability, potency, and localization.[60] The other main approach to avoiding lifelong immunosuppression is encapsulation to physically segregate islets from the host immune system.

Biomaterials are commonly used for the immunoisolation of cellular transplants and controlled drug delivery for T1D immune modulation.[61] These materials allow localized and targeted infusion of immunosuppressive agents, which minimizes adverse side effects and systemic toxicity. In a recently completed phase I/II clinical trial, Viacyte developed a single immunoisolating membrane to protect the transplanted cells from direct interaction with immune cells.[62] However, their first cohort of trial participants experienced severe device malfunctions, precluding any further studies for efficacy. A case study of islets within alginate-poly-l-ornithine microcapsules found up to 30% reduction of exogenous insulin requirements and follow-up trials found reductions of HbA1c to <7% for more than 600 days post transplantation.[63,64] Lastly, a crystallized formulation of GW2580, a colony stimulating factor 1 receptor inhibitor, inhibited fibrosis across subcutaneous, intraperitoneal, and intramuscular implant sites in non-human primates.[65]

Nevertheless, fibrotic tissue formation around transplantation sites remains one of the challenges for micro- and macro-encapsulation of islets. Although biomaterials may sequester the islets away from host immune cells, the materials themselves can cause inflammation and islet death.[66] The consequent need for lifelong immunosuppression thus still presents a significant barrier to ICT adoption and a combinatorial approach is needed for improvements in the long-term efficacy of islet transplantation.

2.3 | Proposing a target product profile for ICT

While the various elements that contribute to optimal ICT outcomes have been described in numerous reviews, our

view is that a comprehensive set of criteria to guide clinical development of ICT has not been articulated. A TPP outlines the desired characteristics of a target product that is aimed at a particular disease. TPPs state intended attributes, including safety and efficacy-related characteristics.[67] In the past, ICT clinical trials focused on a single outcome, such as higher cell viability or elimination of systemic immunosuppression, and struggled to achieve the other, resulting in ineffective therapies. Here, we have expanded on these two goals and highlighted the four clinical outcomes that we believe are necessary for an ICT TPP (Table 1). Novel solutions will not be effective without achieving all these elements. In the following sections, we analyze potential solutions that are capable of addressing all the requirements for optimal ICT.

3 | COMBINATORIAL APPROACHES TO ACHIEVE AN IDEAL TARGET PROFILE

Currently, the strategies to achieve outcomes described in the TPP use islet encapsulation approaches in a variety of ways: (a) mechanical modification, resulting in changing factors such as capsule size, surface charge, mechanical strength, permeability, and material biocompatibility; (b) chemical modification, through the inclusion of immunomodulatory factors including anti-inflammatory agents, targeted immunosuppressant pharmaceuticals, and anticoagulant materials; (c) co-encapsulations with biologicals such as bioengineered cells, chemokines, ECM proteins, and angiogenic factors; and (d) co-encapsulations with chemical agents.[68–73] However, to date, none of these strategies alone have been successful at achieving all criteria outlined in the TPP.

In this section, for each clinical outcome in the TPP, we have highlighted three to five key preclinical studies that combine encapsulation approaches to better achieve ideal clinical outcomes. The studies were chosen based on the availability of the methodology as well as the primary metric used in each category (e.g. survival rates for viability of islets and insulin independence).

3.1 | Mechanical modifications combined with co-encapsulations increase initial cell survival and viability

The main causes of early and high loss of islets after transplantation in preclinical models are immunological responses against the islets, inflammatory reactions, and hypoxic environment.[74] These barriers to achieving a high engraftment survival rate are seen translationally as well, with up to 70% of islets lost upon delivery in clinical trials.[32] The current toolbox of strategies discussed in the previous section consists of mechanical/chemical biomaterial encapsulation modifications, adjustment of the transplantation site, and biological/chemical co-encapsulations. However, a few preclinical studies have gone beyond these discrete methods and combined strategies for improved results. These studies are outlined in Table 2.

Combination approaches have yielded promising results, with some reported increases in cell viability of up to 40% compared to unencapsulated islets. The most common biomaterial used for ICT is alginate, a polymer derived from bacterial or seaweed sources. Alginate is often used in a hydrogel form, which is low-cost and applicable in drug discovery, tissue regeneration, and encapsulation.[75] Microencapsulation of islets for T1D treatment was first reported by Lim and Sun in 1980, where islets were able to survive for 3 weeks compared to 8 days in a rat model for non-encapsulated islets.[76] However, alginate can cause a foreign body response (FBR), therefore

TABLE 1 Target product profile for islet cell encapsulation approaches in ICT.

Product targets	Minimum acceptable result	Ideal results
Cell viability and initial survival	>80% initial cell viability 7 days after implantation	>90% initial cell viability 7 days after implantation
Cell functionality and insulin secretion rates	Sustained normoglycemia >1 year after implantation, significantly reduced insulin requirement	Sustained normoglycemia >5 years after implantation, completely insulin independent
Systemic immunosuppression requirements	Systemic immunosuppression with minimal side effects, minimal inflammation or immune response	Elimination of systemic immunosuppression, minimal inflammation and immune response
Vascularization and long-term survival	Graft survival >1 year after implantation, minimal islet death	Graft survival >5 years after implantation, minimal islet death

TABLE 2 Overview of combinatorial studies in improving cell viability and initial islet survival rates.

Encapsulation approach (Size and material)	Type of modification (Mechanical, chemical, biological, chemical co-encapsulation?)	Transplant location	Results	References
Alginate microcapsules	Mechanical modification: Alginate microcapsules Chemical co-encapsulation: Hyaluronic acid	Epididymal fat pad	Alginate-HA hybrid microcapsules enhance the viability of encapsulated cells, reducing early apoptosis percentage and decreasing membrane damage	78
Macroscale collagen hydrogel	Mechanical modification: Collagen hydrogel Chemical co-encapsulation: Hyaluronic acid	Omentum	HA-COL hydrogel showed significantly improved in vitro viability over unencapsulated islets and retained their morphology	80
Alginate microcapsules	Biological co-encapsulation: Mesenchymal stem cells (MSCs)	Intraperitoneal	Increase of 31.9% in islet viability from the alginate encapsulated islets with MSC's compared to the naked islets	81
Alginate microcapsules	Biological co-encapsulation: Mesenchymal stem cells (MSCs) Biological co-encapsulation: Tripeptide arginine-glycine-aspartate (RGD)	In vitro	Increase of 29.9% in islet viability from composite capsules (RGD-enhanced alginate microcapsules with MSC's and islets) compared to alginate islets	84
Poly(lactic-co-glycolic acid) (PLGA) microspheres	Mechanical modification: microspheres within microcapsules Chemical co-encapsulation: exenatide	In vitro	Exenatide capsule with capsule system exhibited improved survival and glucose-stimulated insulin secretion	86
Macroscale alginate device with external gas chamber	Mechanical modification: macroscale device with immunoisolating alginate slabs and oxygen-permeable membrane	Dorsal skin	βAir device retains up to 95% islet viability over 229 days	87

it has been combined with biological and chemical co-encapsulations to reduce FBR and increase cell viability.[77]

One particularly promising combinatorial study utilizes hyaluronic acid, a major component of the pancreatic extracellular matrix, as a co-encapsulation with islets ex vivo.[78] In addition to providing structural support and protection to embedded cells, hyaluronic acid also reduces immunogenicity by preventing the adsorption of immune-recruiting proteins.[79] Canibano-Hernandez et al. were able to demonstrate a significant viability enhancement for islets encapsulated with hyaluronic acid inside alginate compared to alginate-only encapsulation.[63] Furthermore, there was no significant impairment on the insulin secretion ability of the islets. In a similar study, alginate was replaced with collagen, another ECM component and common encapsulation biomaterial. Harrington et al. reported significant viability enhancement of hyaluronic acid-collagen embedded islets compared to collagen-only encapsulation with less fibrotic growth than occurred with alginate-encapsulated islets.[80] However, neither of these studies the encapsulated islets showed improvement in glucose-stimulated insulin secretion (GSIS) in vivo.

Another promising combinatorial study by Vaithingam et al. utilizes mesenchymal stem cells (MSCs)

co-encapsulated with islet cells in a mouse model.[81] MSCs have a role in tissue repair and angiogenesis by secreting factors such as vascular endothelial growth factor (VEGF).[82,83] This study was the first to examine the direct effects of co-encapsulated MSCs on fibrotic growth and islet survival. The authors reported a 31.9% increase in islet viability from the alginate-encapsulated islets with MSC's compared to the islets encapsulated alone. Additionally, the MSC-co-encapsulated groups had significantly less fibrotic growth compared to the encapsulated islets alone. In a similar vein, Laporte et al. reported in 2020 on supplementation of the alginate microencapsulated MSCs and islets with the tripeptide arginine-glycine-aspartate (RGD).[84] RGD is a component of the ECM and has been shown to improve MSC viability and secretion capabilities.[85] The authors reported a significant 29.9% increase in islet viability using composite capsules (RGD-enhanced alginate microcapsules with MSCs and islets) compared to islets encapsulated in alginate alone. However, this study did not evaluate the fibrotic response to the composite capsules in vivo and fibrotic response due to the islets, and biocompatibility was only measured in vitro.

An alternative approach to direct microscale co-encapsulation is a microsphere-within-microcapsule platform that exhibits sustained release of chemical agents. Lew et al. fabricated exenatide-loaded poly(lactic-co-glycolic acid) (PLGA) microspheres and co-encapsulated them with islet cells within alginate microcapsules.[86] Exenatide, a glucagon-like peptide-1 analogue, has been shown to inhibit beta cell apoptosis and enhance glucose-dependent insulin secretion. The exenatide-loaded poly(lactic-co-glycolic acid) (PLGA) microspheres encapsulated within the alginate microcapsules were slowly released over 21 days. The islets exhibited improved survival rates compared to those in alginate microcapsules alone. This innovative capsule-within-capsule design creates a unique ability to prolong the release of pharmaceuticals alongside islets, which is very useful for long-term successful grafts.

Another unique approach is macroscale devices that mechanically create a favorable environment for islet engraftment. Evron et al. presented the βAir device, a macroencapsulation device that enhances oxygen supply while shielding islets from immune attack.[87] The device contained islets within an alginate slab that is overlaid by immunoisolating barriers. The slab was supplied with exogenous oxygen through an oxygen-permeable membrane and an externalized gas chamber. The authors reported under an average of <5% viability loss over the 229 day monitoring period for all animals, indicating minimal tissue loss.

These studies provide insight into the effect of integrating complementary preclinical methods to achieve multiple outcomes. While cell viability has been improved using these combined methods, a further combinatorial approach utilizing the most efficacious of all modifications may be needed to achieve the full target product profile. However, cell viability is only one of many factors that affect long-term graft functionality and survival, and does not ensure insulin independence alone.

3.2 | Mechanical modifications combined with co-encapsulations allow optimal insulin release rates

Graft functionality is one of the most important outcomes in ICT for the clinical goal of successfully managing T1D. Failure to achieve the primary clinical outcome of insulin independence is a major basis for ICT clinical studies being terminated.[88] Although there is no single common metric for measuring cell functionality, some common options are GSIS, rates of insulin independence ex vivo after recovery, and required islet mass per body mass. The current toolbox of encapsulation strategies most commonly used for preserving cell functionality includes mechanical and chemical modifications, as well as biological and chemical co-encapsulations. These studies are summarized in Table 3.

One modification to the commonly used alginate encapsulation is the inclusion of melanin, which is a near-infrared responsive biological pigment that has been utilized in photothermal treatment of tumors and antibacterial therapy.[89,90] Application of melanin in the treatment of diabetes is based on the use of melanin as a photothermal drug delivery platform for depression therapy. Huang et al. report use of a sodium alginate–polyethyleneimine–melanin (SA–PEI–Melanin) double-helical thread-like hydrogel to improve biocompatibility and increase glucose control.[91] While this system produced ex vivo GSIS results similar to those observed in alginate-only groups, light-controlled glucose regulation and enhanced long-term cell functionality were not observed.

Another biomaterial modification is plasma-supplemented hydroxypropylmethyl cellulose (HPMC-Plasma).[92] HPMC-Plasma contains fibronectin and growth factors (EGF, FGF, etc.), key factors that improve the performance of the islets in vitro.[93] Additionally, the authors used a novel implantation technique named h-Omental Matrix Islet filliNG (hOMING) to reduce contact between the islet and blood, in conjunction with a large surface area to volume ratio for transplantation. The authors reported that the HPMC-Plasma system combined with the hOMING technique had numerous promising results, including a reduction of up to 35% in the required islet transplanted mass and improved vascularization. This study provides a particularly poignant example of efficiency by combining the positive effects of the transplantation site, implantation technique, and encapsulation system.

TABLE 3 Overview of combinatorial studies in improving islet cell functionality.

Encapsulation approach (Size and material)	Type of modification (Mechanical, chemical, biological/chemical co-encapsulation?)	Results	Transplant location	References
Macroscale sodium alginate–polyethyleneimine–melanin (SA–PEI–Melanin) threadlike hydrogel	Mechanical modification: Threadlike hydrogel Biological co-encapsulation: melanin	SA–PEI–Melanin hydrogel stably controlled blood glucose below the diabetic blood glucose criteria	Intraperitoneal	[91]
Macroscale plasma-supplemented HPMC hydrogel	Mechanical modification: HPMC hydrogel Biological co-encapsulation: Plasma-supplemented	Glycemia control was observed when islet mass was decreased by 25% or 35% in the plasma-supplemented hydrogel group	Omentum	[92]
Macroscale silk-based scaffold	Mechanical modification: Silk fibroin Biological co-encapsulation: Mesenchymal stem cells (MSCs) and ECM proteins	3.2-fold synergistic improvement in islet insulin secretion was observed when islets were co-encapsulated with MSCs and ECM proteins	In vitro	[94]
Alginate microbeads	Chemical modification Ca^{2+} and Ba^{2+} grafted microbeads	Inhomogeneous alginate-Ca^{2+}/Ba^{2+} microbead islets show higher insulin secretion	Intraperitoneal	[97]

In a similar approach, alginate was replaced by a silk-based scaffold containing ECM proteins (laminin and collagen IV) and mesenchymal stromal cells (MStCs).[94] Silk fibroin has been shown to support cell adhesion, proliferation, and differentiation, as well as to exhibit desirable material properties such as biocompatibility, slow degradation rate, and strong mechanical integrity.[95] As discussed in the previous section, ECM proteins have been used to restore the native microenvironment and MStCs have been shown to secrete regulatory islet growth factors that are angiogenic and anti-apoptotic.[96] Here, the synergistic combination of islets with ECM proteins and MStCs in a silk-ECM scaffold enhanced insulin secretion by 3.2-fold in the presence of ECM proteins, indicating specific humoral factors secreted by MStCs may be enhanced by laminin and collagen IV.

Qi et al. investigated a stronger and more stable alternative to alginate microencapsulation, inhomogeneous alginate-Ca^{2+}/Ba^{2+} microbeads.[97] Important considerations in long-term capsule stability are permeability, composition, and biocompatibility, which can be tuned by changes in alginate molecular weight and gelling solution. Here, alginate of high molecular weight was combined with Ca^{2+} and a minimal concentration of Ba^{2+} in a mannitol gelling solution. Islets in the alginate-Ca^{2+}/Ba^{2+} microbeads were observed to have a 5-fold increase in insulin secretion, while maintaining viability rates similar to those of un-encapsulated islets. Additionally, the capsules and encapsulated islets were stable for 200 days, indicating potential usage for long-term in vivo islet graft function.

An interesting observation regarding studies of long-term cell functionality outcomes is their tendency to utilize macroscale, rather than microscale, encapsulation approaches. Macroscale encapsulation enables localization and ease of retrieval but needs to be balanced with nutrient needs for large islet clusters and immune response, which tend to be more successful in smaller encapsulation approaches. Generally, all of these findings have important implications for investigating the synergistic effects of

cellular and chemical modifications. These trends toward macroscale approaches are also seen in perhaps the largest clinical barrier to ICT: lifelong immunosuppression and subsequent complications.

3.3 | Mechanical modifications combined with co-encapsulations allow immune system evasion

As discussed in Section 2, the two main approaches employed in ICT clinical trials to combat immune detection and destruction of the graft are immunoisolation and immunomodulation.[61] Immunoisolation involves encapsulation approaches with semi-permeable materials that allow the passage of nutrients, oxygen, and insulin while blocking the entry of immunoglobulins and effector cells.[98] Immunomodulation aims to regulate the host immune response to prevent graft rejection, avoiding systemic immunosuppression through use of targeted and localized immunomodulatory molecules.[99] Recently, immunoisolation and immunomodulation approaches have been combined to improve long-term graft outcomes in preclinical and clinical studies. In addition, given the wide range of mechanisms involved in T1D and our incomplete understanding of FBR and requirements for graft acceptance, these combinatorial approaches have the potential to expand our understanding of associated physiological pathways. These studies are summarized in Table 4.

Immunomodulation consists of delivering immunosuppressants, anti-inflammatory factors, or cytokines that promote the recruitment, proliferation, and expansion of regulatory immune cells at the graft site. In a screen testing 16 anti-inflammatory molecules delivered systemically in rat ICT recipients, curcumin (a Tumor necrosis factor alpha (TNFα) antagonist) had the largest effect in decreasing cathepsin activity and reactive oxygen species, two markers of inflammation secreted by early immune cells.[100] The levels of numerous immune cell markers—CD68 (macrophages), CD8 (cytotoxic T cells), CD74 (dendritic cells), and CD19 (B cells), inflammatory cytokines—TNFα and TGFβ, as well as fibrosis markers—collagen 1A1 (Col1a1) and α smooth muscle actin (α SMact), were decreased by curcumin treatment. Curcumin also reduced fibrotic overgrowth and improved graft function compared to control capsules. As a TNFα antagonist, curcumin has also been investigated with other delivery approaches such as thermally responsive chitosan gels and peptide-functionalized PEG gels.[71,101]

Transforming growth factor-beta1 (TGF-β1) is another highly investigated anti-inflammatory immunomodulatory factor. TGF-β1 has a central role in innate immunity, regulating the recruitment, activation, and function of neutrophils, macrophages, and NK cells.[102] TGF-β1 release could decrease local inflammation in the context of ICT by promoting the differentiation of naïve CD4+ T cells into regulatory T cells.[103] When TGF-β1 was loaded into poly-lactide-co-glycolide (PLG) scaffolds in epididymal fat pads, there was reduced expression of inflammatory cytokines (CXCL10 and MCP-1) within the adipose tissue for 3 days after implant, likely contributing to the reduced leukocyte infiltration observed after 7 days.[104]

Another immunomodulator of interest is IL-33, a novel cytokine that interacts with Treg, macrophages and innate lymphoid group 2 cells (ILC2s).[105] When IL-33 was encapsulated inside a PLG scaffold, a change in the local composition of resident innate immune cells was observed.[106] Specifically, there was an increase in the proportion of Foxp3+ cells within the total CD4+ population from 25% to 45% and a significant decrease in the number of CD3+ CD8+ cells. These results suggest that local delivery of a cytokine such as IL-33 can increase the local Treg population and reduce graft-destructive T cell populations.

Another chemokine of interest as an immunomodulatory factor is CXCL12, which binds to the CXCR4 receptor. While the CXCR4/CXCL12 axis can have opposing effects within specific disease states, it exhibits a protective effect in the context of ICT.[107] When islet-containing alginate microcapsules are coated and co-encapsulated with CXCL12, the graft evades the pericapsular fibrotic response and exhibits enhanced insulin secretion.[108] CXCL12 modulates the infiltrating immune cells toward an anti-inflammatory and immune suppressive phenotype and recruits Tregs.[109] This approach achieved long-term graft survival with no systemic immunosuppression, suggesting a CXCL12-mediated immune protective environment. Opposing effects are hypothesized to be due to levels of secretions determining chemotaxis or fugetaxis. These results also suggest a high potential for using CXCL12 to convert effector T cells to regulatory T cells in the context of graft survival.

Fas ligand (FasL) has been hypothesized to act as an immunomodulator by eliminating alloreactive effector T cells.[51] Islet encapsulation using a streptavidin-bound FasL (SA-FasL) conjugated to biotinylated PEG microgels to produce SA-FasL-PEG microgels resulted in increased death of effector T cells.[110] Shirwan et al. and Lei et al. reported six-month graft survival in non-human primates, with an increased density of FoxP3+ Tregs in the graft site (with usage of transitional rapamycin).[111] The FasL body of work surrounding reducing the effector T cell population and increasing the local Treg population demonstrates the promise of "induced" immune privilege to allografts.

Lastly, a non-biological approach to immunomodulation and immunoisolation is to adjust the mechanical

TABLE 4 Overview of combinatorial studies in avoiding systemic immunosuppression.

Encapsulation approach (Size and Material)	Type of Modification (Mechanical, chemical, biological/chemical co-encapsulation?)	Transplant location	Results	References
Alginate microcapsules	Chemical co-encapsulation: Curcumin and dexamethasone	Intraperitoneal	Alginate microcapsules with curcumin decreased markers of inflammation, reduced fibrotic overgrowth, and improved graft function compared to control capsules	100
Macroscale Poly-lactide-co-glycolide (PLG) scaffolds	Mechanical modification: PLG scaffolds Biological co-encapsulation: TGF-β1	Epididymal fat pads	TGF-β1 loaded PLG scaffolds reduced expression of inflammatory cytokines (CXCL10 and MCP-1)	104
Macroscale Poly-lactide-co-glycolide (PLG) scaffolds	Mechanical modification: PLG scaffolds Biological co-encapsulation: IL-33	Epididymal fat pads	IL-33 loaded PLG scaffolds increased the proportion of Foxp3+ cells	106
Alginate microcapsules	Mechanical modification: Alginate microcapsules Biological co-encapsulation: CXCL12	Intraperitoneal	Alginate microcapsules co-encapsulated with CXCL12 achieved long-term graft survival without systemic immunosuppression	108,109
Polyethylene glycol (PEG) microgels	Mechanical modification: Biotinylated PEG microgels Biological co-encapsulation: streptavidin-Fas ligand(conjugated to biotinylated microgel)	Epididymal fat pads	Streptavidin-bound Fas ligand (SA-FasL) conjugated to biotinylated PEG microgels produced indefinite graft survival in non-human primates, with an increased amount of FoxP3+ Tregs in the graft site	110,111
Alginate microcapsules	Chemical modification: Three triazole alginate analogues	Subcutaneous	Triazole modified alginate creates a unique hydrogel surface that inhibits recognition by macrophages and fibrous deposition	113

and chemical properties of the encapsulation material to reduce the foreign body response.[112] In a combinatorial hydrogel library of covalent modifications to the alginate backbone, Vegas et al. generated 774 alginate analogues and evaluated their biocompatibilities.[113] Top-performing combinations had a common structural factor of triazole functionality, the product of a Huisgen cycloaddition between azides and alkynes. The authors hypothesize that the distribution of the triazole modification creates a unique hydrogel surface that inhibits recognition by macrophages and subsequent fibrous deposition. A further combination of these covalently modified alginate microcapsules with immunomodulatory factors discussed earlier may succeed in providing immune privilege to engrafted islets.

Immunomodulation combined with immunoisolation target a wide range of biological pathways, and the mechanisms of foreign body response and graft rejection are not well understood. Promising results have been obtained from taking advantage of native pathways by using artificially provided anti-inflammatory cytokines as well as use of cytokines to increase the Treg population at the graft site. While these biologically-based approaches are highly promising, mechanical approaches such as covalent modification of encapsulated biomaterials should also be considered.

3.4 | Mechanical modifications combined with co-encapsulations increase long-term cell survival

The last clinical outcome that is important to ICT advancement is promotion of long-term graft survival by improving factors such as vascularization and cell proliferation. While initial islet viability, cell functionality, and immune tolerance are important for long-term graft survival, complementary approaches seek solutions to enhance angiogenesis, improve cell proliferation, and provide a stable longitudinal environment.[9] The most promising approaches in this area focus on growth factors such as VEGF and endothelial growth factor (EGF), in combination with functional modifications of the encapsulation biomaterials.[114] While the growth factors can be injected locally, encapsulation approaches can control release rates and thereby prevent local overdoses. These studies are summarized in Table 5.

The two major processes involved in blood vessel formation are the budding and branching of vessels from pre-existing vessels and the de novo differentiation of endothelial cells from mesoderm.[115] One of the three major families of angiogenic factor receptor tyrosine kinases respond to VEGF, a growth factor that is a major regulator of the revascularization of transplanted islets.[116] Starting with an RGD-enhanced PEG hydrogel system, Weaver et al. further tethered VEGF onto the gel surface.[117] VEGF-enhanced hydrogels containing islets experienced enhanced vascularization fractional area and the lowest degree of inflammatory cell recruitment when implanted in the epididymal fat pad. These findings suggest the ability of sustained VEGF delivery to create stable, mature, and functional blood vessels.

A further investigation immobilized VEGF electrostatically on the surface of an alginate scaffold using heparin-VEGF interactions.[118] The favorable electrostatic interactions allowed a 3.6-fold increase in VEGF loading capacity relative to alginate without heparin, indicating capacity to deliver higher concentrations of VEGF. Furthermore, VEGF delivery resulted in enhanced

TABLE 5 Overview of combinatorial studies in improving long-term graft survival.

Encapsulation approach (Size and Material)	Type of modification (Mechanical, chemical, biological/chemical co-encapsulation?)	Transplant location	Results	References
Macroscale PEG hydrogel	Mechanical modification: RGD-enhanced PEG hydrogel Biological co-encapsulation: VEGF	Subcutaneous, small bowel mesentery, and epididymal fat pad (EFP)	VEGF-enhanced hydrogels experienced enhanced vascularization fractional area and lowest degree of inflammatory cell recruitment in EFP	117
Alginate microcapsules	Mechanical modification: Heparin-coated alginate Biological co-encapsulation: VEGF	In vitro	Heparin immobilization improves the amount of VEGF retained up to 3.6 fold and enhances angiogenesis in close proximity to scaffolds	118
Macroscale polylactic acid (PLA) device	Mechanical modification: 3D-printed PLA device Biological co-encapsulation: VEGF	Subcutaneous	Positive correlation between VEGF concentration and number of vessels surrounding the device	119
Macroscale silk fibroin scaffold	Mechanical modification: Silk fibroin Chemical co-encapsulation: Heparin	Epididymal fat pad	Macroporous heparin-releasing silk fibroin scaffold had a significant increase in islet cell proliferation and sustained elevation of VEGR expression	120

neoangiogenesis in close proximity to and on the surface of the scaffold containing islets. Similarly, a 3D-printed PLA device loaded with VEGF alongside islets found positive correlation between VEGF concentration and number of vessels surrounding the device.[119]

A particularly noteworthy related approach to supporting long-term cell survival is a macroporous heparin-releasing silk fibroin scaffold.[120] The authors reported a significant increase in islet endocrine and endothelial cell proliferation when encapsulated in heparin-releasing silk fibroin compared to non-heparin silk. They also observed sustained elevation of VEGF expression in the surrounding tissue, suggesting heparin-dependent activation of a VEGF pathway in promoting islet revascularisation and proliferation. These investigations provide evidence for pro-angiogenic, pro-survival, and minimal post-transplantation inflammatory activities of VEGF.

4 | DESIGNING NEXT-GENERATION THERAPEUTIC COMBINATIONS HOLISTICALLY

As discussed thus far, the four clinical outcomes necessary for ICT advancement have benefited greatly from combinatorial approaches. Here we will discuss further advancements in ICT rational design and promising target product profiles based on these findings. In order to achieve all clinical criteria outlined in our TPP (Table 1 and Figure 1), we propose novel, untried combinations of different encapsulation approaches. We build this holistic ICT product based on the most promising investigations to date in each category of encapsulation approach (mechanical and chemical modification, and biological and chemical co-encapsulations).

First, many mechanical and chemical modifications to encapsulated biomaterials have improved targeted clinical outcomes in preclinical models. The macroscale modifications discussed in this review often suffer from enhanced immune response due to larger device size, while the microscale approaches are more difficult to localize and retrieve. Safe and fast retrieval is clinically necessary in cases of adverse reactions and localization to non-optimal areas reduces chances for graft acceptance. However, the immune response in microscale approaches has been explored more, and these show higher promise for reduced deleterious immune reactions. In particular, microencapsulation strategies have been able to support a native pancreatic ECM-like environment through the inclusion of RGD peptides, plasma, and hyaluronic acid. These chemical modifications have increased cell viability and survival rates in the initial period following implantation (Section 3.1). Additionally, the combinatorial library by Vegas et al. demonstrates a triazole modification to alginate that inhibits recognition by macrophages that leads to fibrous deposition. Other studies suggest that larger size and higher molecular weight alginate reduces FBR. Combining these results, a holistic product could microencapsulate islets using alginate with triazole modifications in slightly larger capsules (1.5 mm vs. 0.5 mm) and higher molecular weight hyaluronic acid, as a next-generation combination approach that has not been explored.[121,122]

Next, biological co-encapsulations are commonly used to target specific immune mechanisms, especially within graft-infiltrating immune cells. The most promising

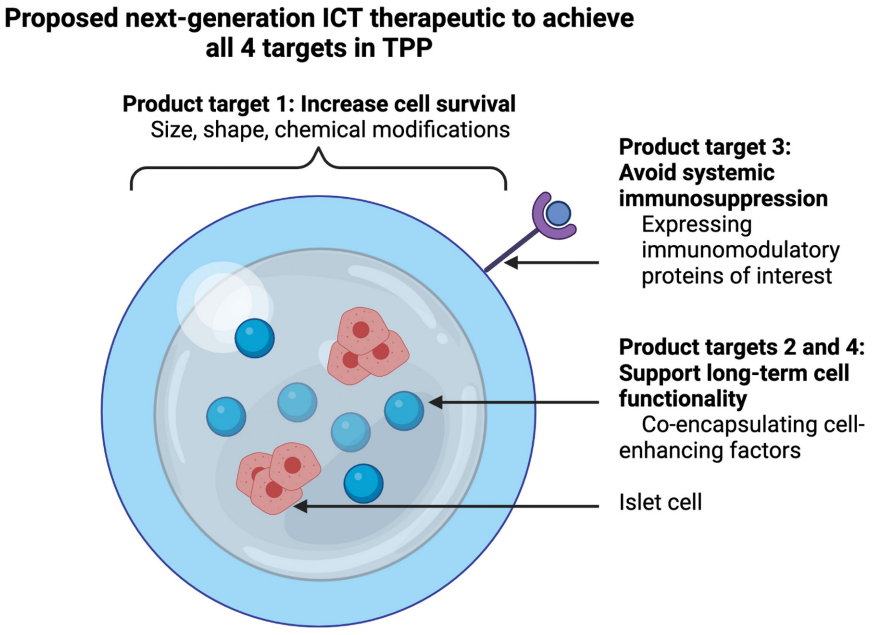

FIGURE 1 Graphical representation of available modifications to achieve TPP.

agents in promoting an anti-inflammatory and immune-privileged environment around the graft are TGF-β1, CXCL12, and FasL. Furthermore, a VEGF and heparin hydrogel combination supports islet revascularisation and proliferation. Since the VEGF-heparin combination tested did not reach full saturation at heparin-binding sites, in future studies, one could use these available sites to bind a second immunomodulatory factor. Untried immunomodulatory agents include JAG-1, a Notch ligand implicated in Treg generation, the CD200-CD200R axis, implicated in the activation/effector functions of T cells, interleukin-2, implicated in upregulation of Foxp3 + Tregs, basic fibroblast growth factor (bFGF), a potent angiogenic factor, and Insulin-like Growth Factor-1 (IGF-1), a survival factor.[123–127] To promote both long-term graft survival and immune evasion, any combination of these immunomodulatory factors, such as IL-2 with bFGF, could be investigated.

Lastly, chemical co-encapsulations allow the delivery of natural products instead of synthetic pharmaceuticals. Exenatide, hyaluronic acid, melanin, and curcumin were highlighted here for their usage in promoting the four clinical outcomes.[78,86,91,100] Specifically, hyaluronic acid provides structural support and protection of embedded cells, reduces graft immunogenicity, and enhances islet viability. It is also a component of the pancreatic ECM, making it a promising chemical to include alongside islets.

Now that we have highlighted promising tried and untried approaches in each category, we propose a few concrete next-generation combinatorial products. These products contain promising components targeting each clinical outcome to help achieve all 4 targeted outcomes together. First, triazole-modified alginate microcapsules with VEGF/heparin and hyaluronic acid contain promising modifications for graft survival and functionality.[78,113,120] Secondly, large alginate microcapsules (1.5 millimeter diameter) with CXCL12 and FasL could provide powerful immunomodulation for long-term graft success.[108,110,121] Lastly, higher molecular weight alginate microcapsules with FasL, and RGD peptides is a promising combination to mimic the native pancreatic environment.[84,110,122] Each of these products, and many other possible combinations, integrate individual approaches that can together potentially achieve all of our target product profile criteria.

5 | REGULATORY AND COMMERCIAL BARRIERS AND CONCLUSIONS

Since the Edmonton protocol was first established more than 20 years ago, ICT has demonstrated clinical promise in managing type 1 diabetes. However, clinical trials are often unsuccessful in achieving the full potential shown in preclinical models. We posit that this is due at least in part to clinical outcomes being considered and targeted separately when all are needed for reliable long-term efficacy and widespread adoption of ICT. In this review, we consider the most clinically relevant barriers to adoption, provide a target product profile, present tried combinatorial methods, and propose untried combinations to achieve our target product profile. The current understanding of ICT should evolve to consider encapsulation approaches as a toolkit, rather than individual tools, with which to generate a holistic, clinically relevant product. This approach is becoming increasingly feasible due to the expanding number of therapeutic tools available, arising from an increased mechanistic understanding and targeting of T1D.

However, it is important to note that not all obstacles to ICT are scientific; in fact, regulatory barriers are a major roadblock in the United States. Indeed, ICT is already fully approved and reimbursable in Canada, Australia, the UK, Switzerland, Italy, and France. In contrast, in the United States, the Food and Drug Administration (FDA) considers pancreatic islets as biological drugs instead of organs.[128] This disallows non-research usage for T1D treatment and requires Biological Licensure Application (BLA) approval before deployment as a standard-of-care clinical treatment. Unfortunately, US academic medical centers are not structured to manufacture biological drugs and are unable to submit a BLA for allogeneic islets. Consequently, ICT is only approved for academic clinical trials and insurance carriers in the US do not reimburse it. The latest FDA advisory panel approved ICT for brittle diabetes but with no official decision yet. Regulatory changes such as shifting ICT to regulation as organ transplants rather than biologic drugs, and oversight by the Organ Procurement and Transplantation Network (OPTN) are necessary for safe and efficacious clinical application.[129] Furthermore, combinatorial medical device products face additional regulatory barriers compared to single-agent therapeutic products.[130] In the United States, regulations require combinatorial therapeutics to provide significant additional benefits compared to their constituent parts. These considerations are important in the bench-to-bedside development pathway for next-generation ICT-based therapies for T1D.

Beyond the regulatory barriers themselves, incorporation of multiple novel technologies into a single product could represent a serious barrier to commercialization as the complexity of the product may make the time and expense required to adequately demonstrate for the regulatory agency that the components and combined product can

be consistently produced and safe for the intended use an unattractive prospect for commercial development. Even if viable, such treatments may command a premium over current ICT approaches, which are already estimated to cost over $100,000.[131] While expensive therapies like ICT can make sense for a limited population with significant medical issues (e.g., for the less than 1% of T1D patients with brittle diabetes), the price of innovation required to achieve an ideal TPP may put such therapies out of the reach of the majority of T1D patients with suboptimal glycemic control due to limitations placed on use by payors or the outsized economic costs to the health care system as a whole.

In conclusion, the combinatorial approaches are not necessarily additive, and the interplay between different modifications may affect the outcomes. However, the encapsulation approaches proposed here hold the promise of developing a rational design strategy for achieving multiple outcomes. There is a clear potential for identification of an efficacious combinatorial, rationally designed methodology for long-term treatment of T1D guided by the desired clinical outcomes and previous literature.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting and revising the manuscript.

ACKNOWLEDGMENTS

Figure 1 made by BioRender.com.

FUNDING INFORMATION

FD and MCP were supported by grant 2-SRA-2021-1075-S-B from JDRF. TB and AES were supported by the VIC Innovation Fund. KL was supported by the VIC Education Fund.

DISCLOSURES

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this review article as no datasets were generated or analyzed for manuscript preparation.

ORCID

Katie Lu https://orcid.org/0000-0002-4546-6942
Fatma Dogan https://orcid.org/0000-0003-0632-3719

REFERENCES

1. Li Y, Chen L, Wang C, Tang D. The experimental and clinical aspects of beta cell function and its underlying mechanism. *J Diabetes Res*. 2014;2014:659149. doi:10.1155/2014/659149
2. Joish VN, Zhou FL, Preblick R, et al. Estimation of annual health care costs for adults with type 1 diabetes in the United States. *J Manag Care Spec Pharm*. 2020;26(3):311-318. doi:10.18553/jmcp.2020.26.3.311
3. Cell based therapeutics in type 1 diabetes mellitus–ScienceDirect. https://www.sciencedirect.com/science/article/abs/pii/S037851731730162X?via%3Dihub
4. Ratzki-Leewing A, Harris SB, Mequanint S, et al. Real-world crude incidence of hypoglycemia in adults with diabetes: results of the InHypo-DM study, Canada. *BMJ Open Diabetes Res Care*. 2018;6:e000503. doi:10.1136/bmjdrc-2017-000503
5. Ricordi C, Tzakis AG, Carroll PB, et al. Human islet isolation and allotransplantation in 22 consecutive cases. *Transplantation*. 1992;53(2):407-414. doi:10.1097/00007890-199202010-00027
6. Nakamura T, Fujikura J, Anazawa T, et al. Long-term outcome of islet transplantation on insulin-dependent diabetes mellitus: an observational cohort study. *J Diabetes Investig*. 2020;11(2):363-372. doi:10.1111/jdi.13128
7. Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*. 2000;343(4):230-238. doi:10.1056/NEJM200007273430401
8. Desai T, Shea LD. Advances in islet encapsulation technologies. *Nat Rev Drug Discov*. 2017;16(5):338-350. doi:10.1038/nrd.2016.232
9. Bowers DT, Song W, Wang LH, Ma M. Engineering the vasculature for islet transplantation. *Acta Biomater*. 2019;95:131-151. doi:10.1016/j.actbio.2019.05.051
10. Huurman VAL, Hilbrands R, Pinkse GGM, et al. Cellular islet autoimmunity associates with clinical outcome of islet cell transplantation. *PLOS One*. 2008;3(6):e2435. doi:10.1371/journal.pone.0002435
11. Ludwig B, Reichel A, Steffen A, et al. Transplantation of human islets without immunosuppression. *Proc Natl Acad Sci*. 2013;110(47):19054-19058. doi:10.1073/pnas.1317561110
12. Correia CR, Ghasemzadeh-Hasankolaei M, Mano JF. Cell encapsulation in liquified compartments: protocol optimization and challenges. *PLoS One*. 2019;14(6):e0218045. doi:10.1371/journal.pone.0218045
13. Vaithilingam V, Tuch BE. Islet transplantation and encapsulation: an update on recent developments. *Rev Diabet Stud*. 2011;8(1):51-67. doi:10.1900/RDS.2011.8.51
14. de Vos P, Spasojevic M, Faas MM. Treatment of diabetes with encapsulated islets. In: Pedraz JL, Orive G, eds. *Therapeutic Applications of Cell Microencapsulation*. Advances in Experimental Medicine and Biology. Springer; 2010:38-53. doi:10.1007/978-1-4419-5786-3_5
15. Skyler JS. Prevention and reversal of type 1 diabetes-past challenges and future opportunities. *Diabetes Care*. 2015;38(6):997-1007. doi:10.2337/dc15-0349
16. Pepper AR, Bruni A, Shapiro AMJ. Clinical islet transplantation: is the future finally now? *Curr Opin Organ Transplant*. 2018;23(4):428-439. doi:10.1097/MOT.0000000000000546
17. final-nhsbt-pancreas-and-islet-transplantation-annual-report-2020-2021.pdf. Accessed September 8, 2022. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/24590/final-nhsbt-pancreas-and-islet-transplantation-annual-report-2020-2021.pdf
18. Markmann JF, Rickels MR, Eggerman TL, et al. Phase 3 trial of human islet-after-kidney transplantation in type 1 diabetes. *Am J Transplant*. 2021;21(4):1477-1492. doi:10.1111/ajt.16174

19. CITR_11AR Scientific Summary_FINAL.pdf. https://citregistry.org/system/files/CITR_11AR%20Scientific%20Summary_FINAL.pdf
20. Foster ED, Bridges ND, Feurer ID, Eggerman TL, Hunsicker LG, Alejandro R. Improved health-related quality of life in a phase 3 islet transplantation trial in type 1 diabetes complicated by severe hypoglycemia. *Diabetes Care*. 2018;41(5):1001-1008. doi:10.2337/dc17-1779
21. Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA*. 2013;310(12):1240-1247. doi:10.1001/jama.2013.277818
22. Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. *Transplantation*. 2011;91(3):373-378. doi:10.1097/TP.0b013e31820437f3
23. Rother KI, Harlan DM. Challenges facing islet transplantation for the treatment of type 1 diabetes mellitus. *J Clin Invest*. 2004;114(7):877-883. doi:10.1172/JCI200423235
24. Shapiro AM, Ricordi C. Unraveling the Secrets of Single Donor Success in Islet Transplantation. *Am J Transplant*. 2004;4(3):295-298. doi:10.1046/j.1600-6143.2003.00375.x
25. Bellin MD, Sutherland DER, Beilman GJ, et al. Similar islet function in islet allotransplant and autotransplant recipients, despite lower islet mass in autotransplants. *Transplantation*. 2011;91(3):367-372. doi:10.1097/TP.0b013e318203fd09
26. Johnson LM, Swarner SL, van der Straten A, Rothrock GD. *Methods for Assessing the Adherence to Medical Devices*. RTI Press; 2016 http://www.ncbi.nlm.nih.gov/books/NBK532362/
27. Cooper TT, Hess DA. The IsletCore program: improving the supply of human islets to satisfy the demand for research see article in endocrinology 2016;157:560–569. *Endocrinology*. 2016;157(3):997-1002. doi:10.1210/en.2016-1061
28. Nano R, Clissi B, Melzi R, et al. Islet isolation for allotransplantation: variables associated with successful islet yield and graft function. *Diabetologia*. 2005;48(5):906-912. doi:10.1007/s00125-005-1725-3
29. Plesner A, Verchere CB. Advances and challenges in islet transplantation: islet procurement rates and lessons learned from suboptimal islet transplantation. *J Transplant*. 2011;2011:979527. doi:10.1155/2011/979527
30. Balamurugan AN, Samaga KK, Narayanan S, Kodipad AA, Mokshagundam SPL, Nathan JD. Chapter 5–Allogeneic islet isolation: methods to improve islet cell transplantation with new technologies in organ transplant retrieval and isolation techniques. In: Hawthorne WJ, ed. *Pancreas and Beta Cell Replacement*. Vol 1. Regenerative and Transplant Medicine. Academic Press; 2022:81-96. doi:10.1016/B978-0-12-824011-3.00008-4
31. Funaki B. Islet Cell Transplantation. *Semin Interv Radiol*. 2006;23(3):295-297. doi:10.1055/s-2006-948762
32. Bennet W, Groth CG, Larsson R, Nilsson B, Korsgren O. Isolated human islets trigger an instant blood mediated inflammatory reaction: implications for intraportal islet transplantation as a treatment for patients with type 1 diabetes. *Ups J Med Sci*. 2000;105(2):125-133. doi:10.1517/03009734000000059
33. Delaune V, Berney T, Lacotte S, Toso C. Intraportal islet transplantation: the impact of the liver microenvironment. *Transpl Int*. 2017;30(3):227-238. doi:10.1111/tri.12919
34. Wang N, Shi XF, Khan SA, et al. Hypoxia-inducible factor-1 mediates pancreatic β-cell dysfunction by intermittent hypoxia. *Am J Physiol Cell Physiol*. 2020;319(5):C922-C932. doi:10.1152/ajpcell.00309.2020
35. Muratore M, Santos C, Rorsman P. The vascular architecture of the pancreatic islets: a homage to august Krogh. *Comp Biochem Physiol A Mol Integr Physiol*. 2021;252:110846. doi:10.1016/j.cbpa.2020.110846
36. Naziruddin B, Iwahashi S, Kanak MA, Takita M, Itoh T, Levy MF. Evidence for instant blood-mediated inflammatory reaction in clinical autologous islet transplantation. *Am J Transplant*. 2014;14(2):428-437. doi:10.1111/ajt.12558
37. Schuetz C, Markmann JF. Islet cell transplant: update on current clinical trials. *Curr Transplant Rep*. 2016;3(3):254-263. doi:10.1007/s40472-016-0103-z
38. Cayabyab F, Nih LR, Yoshihara E. Advances in pancreatic islet transplantation sites for the treatment of diabetes. *Front Endocrinol*. 2021;12:732431. doi:10.3389/fendo.2021.732431
39. Stokes RA, Cheng K, Lalwani A, et al. Transplantation sites for human and murine islets. *Diabetologia*. 2017;60(10):1961-1971. doi:10.1007/s00125-017-4362-8
40. Christoffersson G, Henriksnäs J, Johansson L, et al. Clinical and experimental pancreatic islet transplantation to striated muscle. *Diabetes*. 2010;59(10):2569-2578. doi:10.2337/db10-0205
41. Hawthorne WJ, Simond DM, Stokes R, et al. Pre-clinical model of composite foetal pig pancreas fragment/renal xenotransplantation to treat renal failure and diabetes. *Xenotransplantation*. 2011;18(6):390-399. doi:10.1111/j.1399-3089.2011.00681.x
42. Damyar K, Farahmand V, Whaley D, Alexander M, Lakey JRT. An overview of current advancements in pancreatic islet transplantation into the omentum. *Islets*. 2021;13(5–6):115-120. doi:10.1080/19382014.2021.1954459
43. Espona-Noguera A, Ciriza J, Cañibano-Hernández A, et al. Review of advanced hydrogel-based cell encapsulation systems for insulin delivery in type 1 diabetes mellitus. *Pharmaceutics*. 2019;11(11):597. doi:10.3390/pharmaceutics11110597
44. Soon-Shiong P. Encapsulated islet cell therapy for the treatment of diabetes: intraperitoneal injection of islets. *J Control Release*. 1996;39(2):399-409. doi:10.1016/0168-3659(95)00151-4
45. Calafiore R, Basta G, Luca G, et al. Microencapsulated pancreatic islet allografts into nonimmunosuppressed patients with type 1 diabetes: first two cases. *Diabetes Care*. 2006;29(1):137-138. doi:10.2337/diacare.29.1.137
46. Carlsson PO, Espes D, Sedigh A, et al. Transplantation of macroencapsulated human islets within the bioartificial pancreas βAir to patients with type 1 diabetes mellitus. *Am J Transplant*. 2018;18(7):1735-1744. doi:10.1111/ajt.14642
47. Neufeld T, Ludwig B, Barkai U, et al. The efficacy of an immunoisolating membrane system for islet xenotransplantation in minipigs. *PloS One*. 2013;8(8):e70150. doi:10.1371/journal.pone.0070150
48. Takaki T, Shimoda M. Pancreatic islet transplantation: toward definitive treatment for diabetes mellitus. *Glob Health Med*. 2020;2(4):200-211. doi:10.35772/ghm.2020.01057
49. Hirshberg B, Rother KI, Digon BJ, et al. Benefits and risks of solitary islet transplantation for type 1 diabetes using

steroid-sparing immunosuppression: the National Institutes of Health experience. *Diabetes Care*. 2003;26(12):3288-3295. doi:10.2337/diacare.26.12.3288
50. Shapiro AMJ, Pokrywczynska M, Ricordi C. Clinical pancreatic islet transplantation. *Nat Rev Endocrinol*. 2017;13(5):268-277. doi:10.1038/nrendo.2016.178
51. Askenasy N, Yolcu ES, Yaniv I, Shirwan H. Induction of tolerance using Fas ligand: a double-edged immunomodulator. *Blood*. 2005;105(4):1396-1404. https://pubmed.ncbi.nlm.nih.gov/15486063/
52. King A, Lau J, Nordin A, Sandler S, Andersson A. The effect of capsule composition in the reversal of hyperglycemia in diabetic mice transplanted with microencapsulated allogeneic islets. *Diabetes Technol Ther*. 2003;5(4):653-663. doi:10.1089/152091503322250677
53. Serra P, Santamaria P. Antigen-specific therapeutic approaches for autoimmunity. *Nat Biotechnol*. 2019;37(3):238-251. doi:10.1038/s41587-019-0015-4
54. Smith EL, Peakman M. Peptide immunotherapy for type 1 diabetes—clinical advances. *Front Immunol*. 2018;9:392. doi:10.3389/fimmu.2018.00392
55. Bluestone JA, Buckner JH, Fitch M, et al. Type 1 diabetes immunotherapy using polyclonal regulatory T cells. *Sci Transl Med*. 2015;7(315):315ra189. doi:10.1126/scitranslmed.aad4134
56. Marek-Trzonkowska N, Myśliwiec M, Dobyszuk A, et al. Therapy of type 1 diabetes with CD4(+)CD25(high)CD127-regulatory T cells prolongs survival of pancreatic islets–results of one year follow-up. *Clin Immunol*. 2014;153(1):23-30. doi:10.1016/j.clim.2014.03.016
57. Phillips BE, Garciafigueroa Y, Engman C, Trucco M, Giannoukakis N. Tolerogenic dendritic cells and T-regulatory cells at the clinical trials crossroad for the treatment of autoimmune disease; emphasis on type 1 diabetes therapy. *Front Immunol*. 2019;10:148. doi:10.3389/fimmu.2019.00148
58. Ghasemi A, Akbari E, Imani R. An overview of engineered hydrogel-based biomaterials for improved β-cell survival and insulin secretion. *Front Bioeng Biotechnol*. 2021;9:662084. doi:10.3389/fbioe.2021.662084
59. Headen DM, Woodward KB, Coronel MM, et al. Local immunomodulation with Fas ligand-engineered biomaterials achieves allogeneic islet graft acceptance. *Nat Mater*. 2018;17(8):732-739. doi:10.1038/s41563-018-0099-0
60. Jo S, Fang S. Therapeutic strategies for diabetes: immune modulation in pancreatic β cells. *Front Endocrinol*. 2021;12:716692. doi:10.3389/fendo.2021.716692
61. Omid V, Robert L, Daniel A. Immune modulatory biomaterials for cell-based therapies. *Front Bioeng Biotechnol*. 2016;4:4. doi:10.3389/conf.FBIOE.2016.01.00745
62. A Safety, Tolerability, and Efficacy Study of VC-01™ Combination Product in Subjects With Type I Diabetes Mellitus–Study Results–ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/results/NCT02239354
63. Elliott RB, Escobar L, Tan PLJ, Muzina M, Zwain S, Buchanan C. Live encapsulated porcine islets from a type 1 diabetic patient 9.5 yr after xenotransplantation. *Xenotransplantation*. 2007;14(2):157-161. doi:10.1111/j.1399-3089.2007.00384.x
64. Matsumoto S, Abalovich A, Wechsler C, Wynyard S, Elliott RB. Clinical benefit of islet xenotransplantation for the treatment of type 1 diabetes. *EBioMedicine*. 2016;12:255-262. doi:10.1016/j.ebiom.2016.08.034
65. Farah S, Doloff JC, Müller P, et al. Long-term implant fibrosis prevention in rodents and non-human primates using crystallized drug formulations. *Nat Mater*. 2019;18(8):892-904. doi:10.1038/s41563-019-0377-5
66. Tang L, Eaton JW. Inflammatory responses to biomaterials. *Am J Clin Pathol*. 1995;103(4):466-471. doi:10.1093/ajcp/103.4.466
67. Target product profiles. https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/target-product-profile/who-target-product-profiles
68. Hu S, de Vos P. Polymeric approaches to reduce tissue responses against devices applied for islet-cell encapsulation. *Front Bioeng Biotechnol*. 2019;7:134. doi:10.3389/fbioe.2019.00134
69. Zhang Q, Gonelle-Gispert C, Li Y, et al. Islet encapsulation: new developments for the treatment of type 1 diabetes. *Front Immunol*. 2022;13:869984. doi:10.3389/fimmu.2022.869984
70. Moore SJ, Gala-Lopez BL, Pepper AR, Pawlick RL, Shapiro AJ. Bioengineered stem cells as an alternative for islet cell transplantation. *World J Transplant*. 2015;5(1):1-10. doi:10.5500/wjt.v5.i1.1
71. Shamji MF, Hwang P, Bullock RW, Adams SB, Nettles DL, Setton LA. Release and activity of anti-TNFα therapeutics from injectable chitosan preparations for local drug delivery. *J Biomed Mater Res B Appl Biomater*. 2009;90B(1):319-326. doi:10.1002/jbm.b.31289
72. Pathak S, Regmi S, Gupta B, et al. Single synchronous delivery of FK506-loaded polymeric microspheres with pancreatic islets for the successful treatment of streptozocin-induced diabetes in mice. *Drug Deliv*. 2017;24(1):1350-1359. doi:10.1080/10717544.2017.1377317
73. Andersson J, Larsson R, Richter R, Ekdahl KN, Nilsson B. Binding of a model regulator of complement activation (RCA) to a biomaterial surface: surface-bound factor H inhibits complement activation. *Biomaterials*. 2001;22(17):2435-2443. doi:10.1016/S0142-9612(00)00431-2
74. van der Windt DJ, Bottino R, Casu A, Campanile N, Cooper DKC. Rapid loss of intraportally transplanted islets: an overview of pathophysiology and preventive strategies. *Xenotransplantation*. 2007;14(4):288-297. doi:10.1111/j.1399-3089.2007.00419.x
75. Lee KY, Mooney DJ. Alginate: properties and biomedical applications. *Prog Polym Sci*. 2012;37(1):106-126. doi:10.1016/j.progpolymsci.2011.06.003
76. Lim F, Sun AM. Microencapsulated islets as bioartificial endocrine pancreas. *Science*. 1980;210(4472):908-910. doi:10.1126/science.6776628
77. Scharp DW, Marchetti P. Encapsulated islets for diabetes therapy: history, current progress, and critical issues requiring solution. *Adv Drug Deliv Rev*. 2014;67-68:35-73. doi:10.1016/j.addr.2013.07.018
78. Cañibano-Hernández A, Saenz Del Burgo L, Espona-Noguera A, et al. Hyaluronic acid enhances cell survival of encapsulated insulin-producing cells in alginate-based microcapsules. *Int J Pharm*. 2019;557:192-198. doi:10.1016/j.ijpharm.2018.12.062
79. Tan H, Li H, Rubin JP, Marra KG. Controlled gelation and degradation rates of injectable hyaluronic acid-based hydrogels through a double crosslinking strategy. *J Tissue Eng Regen Med*. 2011;5(10):790-797. doi:10.1002/term.378

80. Harrington S, Williams J, Rawal S, Ramachandran K, Stehno-Bittel L. Hyaluronic acid/collagen hydrogel as an alternative to alginate for long-term immunoprotected islet transplantation. *Tissue Eng Part A*. 2017;23(19–20):1088-1099. doi:10.1089/ten.TEA.2016.0477
81. Vaithilingam V, Evans MDM, Lewy DM, Bean PA, Bal S, Tuch BE. Co-encapsulation and co-transplantation of mesenchymal stem cells reduces pericapsular fibrosis and improves encapsulated islet survival and function when allografted. *Sci Rep*. 2017;7(1):10059. doi:10.1038/s41598-017-10359-1
82. Shi M, Liu ZW, Wang FS. Immunomodulatory properties and therapeutic application of mesenchymal stem cells. *Clin Exp Immunol*. 2011;164(1):1-8. doi:10.1111/j.1365-2249.2011.04327.x
83. Cheng Y, Liu YF, Zhang JL, Li TM, Zhao N. Elevation of vascular endothelial growth factor production and its effect on revascularization and function of graft islets in diabetic rats. *World J Gastroenterol*. 2007;13(20):2862-2866. doi:10.3748/wjg.v13.i20.2862
84. Laporte C, Tubbs E, Pierron M, et al. Improved human islets' viability and functionality with mesenchymal stem cells and arg-gly-asp tripeptides supplementation of alginate microencapsulated islets in vitro. *Biochem Biophys Res Commun*. 2020;528(4):650-657. doi:10.1016/j.bbrc.2020.05.107
85. Ho SS, Murphy KC, Binder BYK, Vissers CB, Leach JK. Increased survival and function of mesenchymal stem cell spheroids entrapped in instructive alginate hydrogels. *Stem Cells Transl Med*. 2016;5(6):773-781. doi:10.5966/sctm.2015-0211
86. Lew B, Kim IY, Choi H, Kim KK. Sustained exenatide delivery via intracapsular microspheres for improved survival and function of microencapsulated porcine islets. *Drug Deliv Transl Res*. 2018;8(3):857-862. doi:10.1007/s13346-018-0484-x
87. Evron Y, Colton CK, Ludwig B, et al. Long-term viability and function of transplanted islets macroencapsulated at high density are achieved by enhanced oxygen supply. *Sci Rep*. 2018;8(1):6508. doi:10.1038/s41598-018-23862-w
88. Welsch CA, Rust WL, Csete M. Concise review: lessons learned from islet transplant clinical trials in developing stem cell therapies for type 1 diabetes. *Stem Cells Transl Med*. 2018;8(3):209-214. doi:10.1002/sctm.18-0156
89. Rong L, Zhang Y, Li WS, Su Z, Fadhil JI, Zhang C. Iron chelated melanin-like nanoparticles for tumor-associated macrophage repolarization and cancer therapy. *Biomaterials*. 2019;225:119515. doi:10.1016/j.biomaterials.2019.119515
90. Wang Z, Tschirhart T, Schultzhaus Z, et al. Melanin produced by the fast-growing marine bacterium vibrio natriegens through heterologous biosynthesis: characterization and application. *Appl Environ Microbiol*. 2020;86(5):e02749-e02719. doi:10.1128/AEM.02749-19
91. Huang L, Xiang J, Cheng Y, et al. Regulation of blood glucose using islets encapsulated in a melanin-modified immune-shielding hydrogel. *ACS Appl Mater Interfaces*. 2021;13(11):12877-12887. doi:10.1021/acsami.0c23010
92. Schaschkow A, Sigrist S, Mura C, et al. Glycaemic control in diabetic rats treated with islet transplantation using plasma combined with hydroxypropylmethyl cellulose hydrogel. *Acta Biomater*. 2020;102:259-272. https://www.sciencedirect.com/science/article/pii/S1742706119307974
93. Daoud J, Petropavlovskaia M, Rosenberg L, Tabrizian M. The effect of extracellular matrix components on the preservation of human islet function in vitro. *Biomaterials*. 2010;31(7):1676-1682. doi:10.1016/j.biomaterials.2009.11.057
94. Davis NE, Beenken-Rothkopf LN, Mirsoian A, et al. Enhanced function of pancreatic islets co-encapsulated with ECM proteins and mesenchymal stromal cells in a silk hydrogel. *Biomaterials*. 2012;33(28):6691-6697. doi:10.1016/j.biomaterials.2012.06.015
95. Wang Y, Kim HJ, Vunjak-Novakovic G, Kaplan DL. Stem cell-based tissue engineering with silk biomaterials. *Biomaterials*. 2006;27(36):6064-6082. doi:10.1016/j.biomaterials.2006.07.008
96. Ding Y, Xu D, Feng G, Bushell A, Muschel RJ, Wood KJ. Mesenchymal stem cells prevent the rejection of fully allogenic islet grafts by the immunosuppressive activity of matrix metalloproteinase-2 and -9. *Diabetes*. 2009;58(8):1797-1806. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2712800/
97. Thu B, Gåserød O, Paus D, et al. Inhomogeneous alginate gel spheres: an assessment of the polymer gradients by synchrotron radiation-induced X-ray emission, magnetic resonance microimaging, and mathematical modeling. *Biopolymers*. 2000;53(1):60-71. doi:10.1002/(SICI)1097-0282(200001)53:1<60::AID-BIP6>3.0.CO;2-F
98. David A, Day J, Shikanov A. Immunoisolation to prevent tissue graft rejection: current knowledge and future use. *Exp Biol Med*. 2016;241(9):955-961. doi:10.1177/1535370216647129
99. Braun LM, Zeiser R. Immunomodulatory therapies for the treatment of graft-versus-host disease. *HemaSphere*. 2021;5(6):e581. doi:10.1097/HS9.0000000000000581
100. Dang TT, Thai AV, Cohen J, et al. Enhanced function of immunoisolated islets in diabetes therapy by co-encapsulation with an anti-inflammatory drug. *Biomaterials*. 2013;34(23):5792-5801. doi:10.1016/j.biomaterials.2013.04.016
101. Lin CC, Metters AT, Anseth KS. Functional PEG-peptide hydrogels to modulate local inflammation induced by the proinflammatory cytokine TNFα. *Biomaterials*. 2009;30(28):4907-4914. doi:10.1016/j.biomaterials.2009.05.083
102. Yang L, Pang Y, Moses HL. TGF-β and immune cells: an important regulatory axis in the tumor microenvironment and progression. *Trends Immunol*. 2010;31(6):220-227. doi:10.1016/j.it.2010.04.002
103. Fu S, Zhang N, Yopp AC, et al. TGF-beta induces Foxp3 + T-regulatory cells from CD4 + CD25 - precursors. *Am J Transplant*. 2004;4(10):1614-1627. doi:10.1111/j.1600-6143.2004.00566.x
104. Liu J, Zhang J, Zhang X, et al. Biomaterials transforming growth factor-beta 1 delivery from microporous scaffolds decreases inflammation post-implant and enhances function of transplanted islets. *Biomaterials*. 2016;80:11-19. doi:10.1016/j.biomaterials.2015.11.065
105. Miller AM, Asquith DL, Hueber AJ, et al. IL-33 induces protective effects in adipose tissue inflammation during obesity in mice. *Circ Res*. 2010;107(5):650-658. doi:10.1161/CIRCRESAHA.110.218867
106. Liu JMH, Zhang X, Joe S, Luo X, Shea LD. Evaluation of biomaterial scaffold delivery of IL-33 as a localized immunomodulatory agent to support cell transplantation in adipose tissue. *J Immunol Regen Med*. 2018;1:1-12. doi:10.1016/j.regen.2018.01.003
107. Britton C, Poznansky MC, Reeves P. Polyfunctionality of the CXCR4/CXCL12 axis in health and disease: implications for therapeutic interventions in cancer and immune-mediated diseases. *FASEB J*. 2021;35(4):e21260. doi:10.1096/fj.202001273R

108. Alagpulinsa DA, Cao JJL, Driscoll RK, et al. Alginate-microencapsulation of human stem cell–derived β cells with CXCL12 prolongs their survival and function in immunocompetent mice without systemic immunosuppression. *Am J Transplant*. 2019;19(7):1930-1940. doi:10.1111/ajt.15308
109. Chen T, Yuan J, Duncanson S, et al. Alginate encapsulant incorporating CXCL12 supports long-term Allo- and xenoislet transplantation without systemic immune suppression. *Am J Transplant*. 2015;15(3):618-627. doi:10.1111/ajt.13049
110. Shirwan H, Woodward KB, Headen DM, et al. SA-FasL-engineered PEG microgels as a novel means of modulating immune response to allogeneic islet grafts. *J Immunol*. 2018;200(1 Supplement):55.36.
111. Lei J, Coronel MM, Yolcu ES, et al. FasL microgels induce immune acceptance of islet allografts in nonhuman primates. *Sci Adv*. 2022;8(19):eabm9881. doi:10.1126/sciadv.abm9881
112. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. *Semin Immunol*. 2008;20(2):86-100. doi:10.1016/j.smim.2007.11.004
113. Vegas AJ, Veiseh O, Doloff JC, et al. Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. *Nat Biotechnol*. 2016;34(3):345-352. doi:10.1038/nbt.3462
114. Xiong Y, Scerbo MJ, Seelig A, et al. Islet vascularization is regulated by primary endothelial cilia via VEGF-A-dependent signaling. *eLife*. 2020;9:e56914 https://elifesciences.org/articles/56914
115. Carmeliet P. Angiogenesis in health and disease. *Nat Med*. 2003;9(6):653-660. doi:10.1038/nm0603-653
116. Brissova M, Shostak A, Shiota M, et al. Pancreatic islet production of vascular endothelial growth factor–a is essential for islet vascularization, revascularization, and function. *Diabetes*. 2006;55(11):2974-2985. doi:10.2337/db06-0690
117. Weaver JD, Headen DM, Aquart J, et al. Vasculogenic hydrogel enhances islet survival, engraftment, and function in leading extrahepatic sites. *Sci Adv*. 2017;3(6):e1700184. doi:10.1126/sciadv.1700184
118. Marchioli G, Luca AD, de Koning E, et al. Hybrid Polycaprolactone/Alginate Scaffolds Functionalized with VEGF to Promote de Novo Vessel Formation for the Transplantation of Islets of Langerhans. *Adv Healthc Mater*. 2016;5(13):1606-1616. doi:10.1002/adhm.201600058
119. Farina M, Ballerini A, Fraga DW, et al. 3D printed vascularized device for subcutaneous transplantation of human islets. *Biotechnol J*. 2017;12(9):1700169. doi:10.1002/biot.201700169
120. Mao D, Zhu M, Zhang X, et al. A macroporous heparin-releasing silk fibroin scaffold improves islet transplantation outcome by promoting islet revascularisation and survival. *Acta Biomater*. 2017;59:210-220. https://www.sciencedirect.com/science/article/abs/pii/S174270611730421X?via%3Dihub
121. Veiseh O, Doloff JC, Ma M, et al. Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates. *Nat Mater*. 2015;14(6):643-651. https://www.nature.com/articles/nmat4290
122. Cowman MK, Lee HG, Schwertfeger KL, McCarthy JB, Turley EA. The content and size of hyaluronan in biological fluids and tissues. *Front Immunol*. 2015;6:261. doi:10.3389/fimmu.2015.00261
123. Izadi Z, Hajizadeh-Saffar E, Hadjati J, et al. Tolerance induction by surface immobilization of Jagged-1 for immunoprotection of pancreatic islets. *Biomaterials*. 2018;182:191-201. doi:10.1016/j.biomaterials.2018.08.017
124. Liu JQ, Hu A, Zhu J, Yu J, Talebian F, Bai XF. CD200-CD200R pathway in the regulation of tumor immune microenvironment and immunotherapy. *Adv Exp Med Biol*. 2020;1223:155-165. doi:10.1007/978-3-030-35582-1_8
125. Johnson MC, Garland AL, Nicolson SC, et al. β-Cell–specific IL-2 therapy increases islet Foxp3+Treg and suppresses type 1 diabetes in NOD mice. *Diabetes*. 2013;62(11):3775-3784. doi:10.2337/db13-0669
126. Li G, Huang LS, Jiang MH, et al. Implantation of bFGF-treated islet progenitor cells ameliorates streptozotocin-induced diabetes in rats. *Acta Pharmacol Sin*. 2010;31(11):1454-1463. doi:10.1038/aps.2010.130
127. Hughes A, Rojas-Canales D, Drogemuller C, Voelcker NH, Grey ST, Coates PTH. IGF2: an endocrine hormone to improve islet transplant survival. *J Endocrinol*. 2014;221(2):R41-R48. doi:10.1530/JOE-13-0557
128. Witkowski P, Philipson LH, Buse JB, et al. Islets transplantation at a crossroads–need for urgent regulatory update in the United States: perspective presented during the scientific sessions 2021 at the American Diabetes Association congress. *Front Endocrinol*. 2022;12:789526. doi:10.3389/fendo.2021.789526
129. Pullen LC. Islet cell transplantation hits a milestone. *Am J Transplant*. 2021;21(8):2625-2626. doi:10.1111/ajt.16039
130. Tian J, Song X, Wang Y, et al. Regulatory perspectives of combination products. *Bioact Mater*. 2021;10:492-503. doi:10.1016/j.bioactmat.2021.09.002
131. Bandeiras C, Hwa AJ, Cabral JMS, Ferreira FC, Finkelstein SN, Gabbay RA. Economics of beta-cell replacement therapy. *Curr Diab Rep*. 2019;19:75. doi:10.1007/s11892-019-1203-9

How to cite this article: Lu K, Brauns T, Sluder AE, Poznansky MC, Dogan F. Combinatorial islet protective therapeutic approaches in β-cell transplantation: Rationally designed solutions using a target product profile. *FASEB BioAdvances*. 2023;5:287-304. doi:10.1096/fba.2023-00029