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REVIEW ARTICLE

Enhancing Clinical Islet Transplantation through Tissue Engineeering Strategies

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Abstract

Clinical islet transplantation (CIT), the infusion of allogeneic islets within the liver, has the potential to provide precise and sustainable control of blood glucose levels for the treatment of type 1 diabetes. The success and long-term outcomes of CIT, however, are limited by obstacles such as a nonoptimal transplantation site and severe inflammatory and immunological responses to the transplant. Tissue engineering strategies are poised to combat these challenges. In this review, emerging methods for engineering an optimal islet transplantation site, as well as novel approaches for improving islet cell encapsulation, are discussed.

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Introduction

Type 1 diabetes mellitus (T1DM) is a disorder characterized by targeted autoimmune-directed destruction of a patient's β cells within the pancreatic islets of Langerhans.[1] Approximately 15,000 patients are diagnosed with T1DM annually in the United States, adding to the approximately three million existing insulin-dependent diabetes patients.[2] Exogenous insulin replacement is the most common treatment, where manual insulin delivery is dictated by periodic monitoring of blood glucose levels. Mimicking the complex and nonlinear dynamics of natural insulin release from native β cells through insulin shots or even implantable pumps is a difficult task, although engineering advancements have moved the concept of a "closed-loop" glucose sensor/insulin secretion system closer to reality.[3] Given this lack of precise control, T1DM patients currently face earlier mortality and a higher risk of angiopathic lesions, often resulting in neuropathy, nephropathy, and retinopathy.[4]

Beta cell replacement via cellular transplantation has the promise of providing a long-term cure for T1DM. At the forefront of cellular replacement therapy is clinical islet transplantation (CIT), which currently involves the intraportal infusion of allogeneic islets.[4–6] To date, these trials found strong improvements in metabolic control, with 57% of patients insulin independent and ~70% with measureable C-peptide levels at five years.[6–12]

While CIT is promising, it has become evident that inflammatory and immunological host responses to the implant, as well as the suboptimal location of the liver, lead to significant islet dysfunction and destruction. The early loss of transplanted islets has been partially attributed to the hepatic engraftment site, where as much as 60% of the islets may be lost during engraftment.[13–15] As islet emboli lodge in the hepatic microvasculature, capillary bed occlusion results in hypoxia and subsequent

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Abbreviations: (APC) antigen-presenting cell, (CIT) clinical islet transplantation, (ECM) extracellular matrix, (IBMIR) instant blood-mediated inflammatory reaction, (IL) interleukin, (PEG) polyethylene glycol, (PLL) poly-lysine, (T1DM) type 1 diabetes mellitus, (TNF) tumor necrosis factor

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inflammatory cytokine release by surrounding tissue.[16] Of greater significance, islets in direct contact with blood instigate a potent inflammatory response, termed instant blood-mediated inflammatory reaction (IBMIR).[16,18] Additionally, islets experience non-native mechanical stress and exposure to toxins filtering through the liver.[19] Finally, allograft rejection and recurrent autoimmunity persists in spite of glucocorticoid-free immunosuppression regimens.[20-25]

Tissue engineering approaches, which combine biomaterials and cells to fabricate three-dimensional implants, have the potential to improve CIT outcomes by providing novel platforms for improving islet survival and engraftment. In particular, there is a strong need to investigate alternative transplant sites, supporting devices and/or scaffolds, and to develop means to minimize the powerful inflammatory and immunological responses to an allogeneic, and possibly xenogeneic, transplant. This article outlines several of these promising strategies.

Engineering an Alternate Transplantation Site

Significance of the Site

The transplantation site microenvironment plays a major role in engraftment. An ideal site would be one that provides an intimate vascular supply for adequate oxygenation and real-time access to blood glucose levels, mechanical protection to the implant, minimal inflammation, and ease in access and retrievability. With IBMIR-mediated islet death now well-documented for CIT, as well as the loss of islet retrievability, intravascular intraorgan sites such as the liver, spleen, and pancreas are not ideal. The kidney capsule, the most widely used site in rodents, has been shown to be a hospitable environment to islets, with an islet equivalent load similar to the intraportal site; however, the clinical feasibility of this site is limited.[26] The peritoneal site is common for the implantation of microcapsules and devices; however, low oxygen tension and reduced vascularization result in delayed glucose responsiveness and the need for higher islet loadings.[27–30]

Sites that are emerging as promising alternatives to the liver, with clinical relevance, are the subcutaneous, intramuscular, and omental sites (**Figure 1**). The subcutaneous site is particularly appealing given its ease of access; however, low vascular access and high mechanical stress commonly results in poor engraftment of free islets.[31,32] In spite of inevitable mechanical stress, the intramuscular site has the advantages of ease in monitoring, loading, and retrievability, as well as higher vascular access compared to the subcutaneous site. Intramuscular islet transplantations in the forearm of diabetic patients have shown promise.[31,33,34] Nevertheless, limited publications on this site warrant additional studies to fully evaluate the potential of this location. The fabrication of a surgically engineered pouch from the omentum has the advantage of a rich vascular supply, ease of access, and the accommodation of larger volumes for the implantation of devices or encapsulated cells.[35–39] It has been postulated that this site may also promote islet engraftment, given its demonstrated ability to facilitate healing and positive remodeling in clinical settings.[40–43] This site has clinical relevance and is feasible in larger animal models, further justifying the need for additional investigations as to its potential.[25,44]

Bioengineering Approaches to Enhance Islet Microenvironment

While the inherent environment of the transplantation site is strongly correlated to islet engraftment outcomes, bioengineering methods can be applied to further enhance the supporting environment or to convert an inhospitable environment to a suitable site. Given the high nutrient demand of islets, a common challenge with most sites is adequate vascular access. In order to overcome nutrient mismatch, investigators have examined the feasibility of using devices and biomaterials to accelerate angiogenesis and islet engraftment.

One strategy that has shown promise is the use of devices to promote the development of a vascular bed prior to islet transplantation. For instance, Pileggi and colleagues[45] have demonstrated that prevascularization of a subcutaneous site using a cylindrical stainless steel

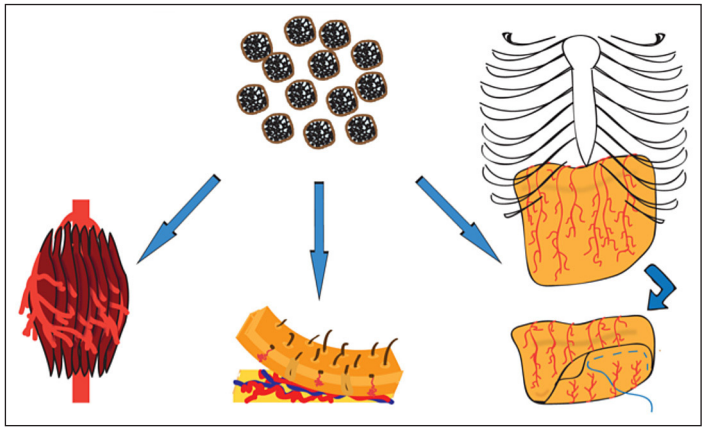

Figure 1. Schematic of selected sites for islet transplantation: Intramuscular (left), subcutaneous (center), and omental pouch (right).

mesh device can enhance islet function, with efficacy shown in rodent syngeneic models.[45] Similar methods have been utilized by other groups, where vascularization techniques have resulted in improved islet function.[46–49] In these cases, the use of hollow devices provides a means to reengineer a highly undesirable site to one that is comparable to both the liver and renal sites.

The use of highly porous, three-dimensional, macroporous scaffolds may also provide a means to reengineer the transplant site. These scaffolds have been studied extensively for bone regeneration, where they provide a mechanically stable, three-dimensional platform for uniform cell loading.[50,51] The large void spaces within these scaffolds, generally greater than 70%, permit full integration into the host and infiltration of nascent blood vessels. In addition, the surface can be modified with extracellular matrix (ECM) ligands, thus promoting infiltration of vascular precursor cells and/or enhancing islet–ECM interactions, an essential factor in maintaining islet function.[52] Scaffolds can be made from biodegradable materials, which can result in complete integration of the implant, or nondegradable biocompatible materials, which allow for retrieval of the implant. Studies in syngeneic murine models found the implantation of macroporous poly(lactide-co-glycolide) scaffolds within the epididymal fat pad site resulted in maintenance of the native islet architecture, more efficient conversion to euglycemia, greater weight gain, and comparable function to transplants lacking the scaffold.[53] Furthermore, an ECM protein coating led to a reduction in the time required to achieve diabetes reversal in mice, postulated to be due to the promotion of endothelial cell infiltration.[54] Berman and associates[43] have also reported using scaffolds for implantation of islets in their evaluation of the omentum as an alternative transplantation site using a nonhuman primate model.[44] Although these scaffolds do not provide immunoisolation from the host, they provide a vehicle for islet transplantation that promotes engraftment, revascularization, and integration of the implant with the host.

Additional strategies to promote islet revascularization have explored the incorporation of growth factors, vascular precursor cells, or even microvessel fragments into biomaterials.[55–58] One example is the prevascularized pancreatic encapsulating device, an islet-loaded collagen disk sandwiched between two disks containing isolated microvessel fragments, where subcutaneous implants exhibited enhanced islet function and viability compared to free-islet controls.[59] Alternatively, other groups have attempted to provide oxygen to the graft through oxygen generators in a transient fashion. Although not tested *in vivo*, co-encapsulation of islets with algae, which produce oxygen when exposed to light, and devices using electrochemical generators to decompose water into oxygen and hydrogen enhanced islet function *in vitro*.[60,61] Newer approaches entail the development of oxygen-releasing biomaterials that could be included in specialized devices. These generate oxygen via water degradation of peroxide, which decomposes into water and oxygen under basic conditions.[62]

Immunoisolation through Polymer Encapsulation

While optimization of transplant sites through bio-engineering can dramatically decrease the functional islet mass for syngeneic animal models, immunological response to the transplant will still necessitate potent immunosuppressive drugs. To alleviate this issue, strategies that can significantly reduce, or even eliminate, immune attack of the transplanted islets would prove highly beneficial. Following allogeneic transplantation, the immune system relies on two pathways for the recognition of foreign antigens: direct and indirect antigen presentation (**Figure 2**). In the direct presentation pathway, donor antigen-presenting cells (APCs), in this case the transplanted graft itself or passenger APCs, activate T cells through the major histocompatibility complex via direct cell-to-cell contact. In the indirect presentation pathway, host APCs pick up donor cell

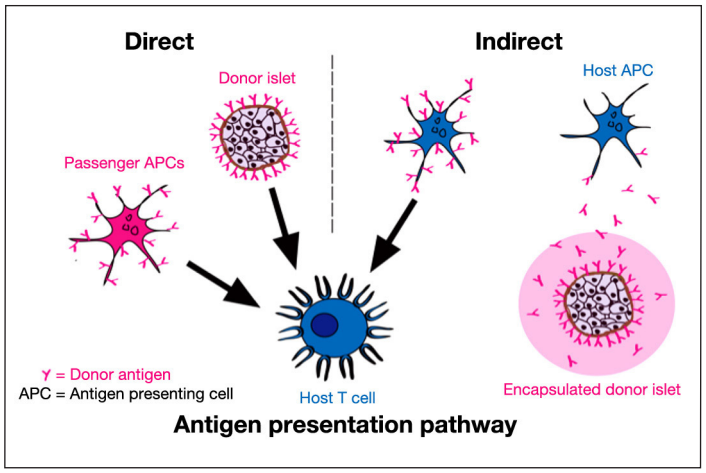

Figure 2. Examples of activation routes for both direct and indirect antigen presentation pathways. Direct antigen pathway activation (left schematic) is mediated by antigens presented directly by the transplanted tissue, e.g. by islets or inadvertently transplanted passenger antigen presenting cells (APCs). Indirect antigen pathway activation (right schematic) is mediated by host APC presentation of donor antigens, which are shed by the donor tissue, e.g. shed antigens diffusing through an encapsulation barrier.

antigen fragments and present them to T cells, inducing activation.[63]

Since the 1980s, researchers have tested a variety of designs for a bioartificial pancreas capable of replacing the endocrine function of the pancreas while preventing graft rejection due to immune response (**Figure 3**). In principle, a stable biocompatible semipermeable barrier made from a variety of natural and/or synthetic materials should separate the tissue graft from the host's immune effectors, both cellular and humoral, while allowing for proper diffusion of nutrients such as oxygen and glucose, as well as metabolic waste and therapeutic cell products, such as insulin.[4,64]

Macroscale Encapsulation

Bioartificial pancreas devices are generally classified in two categories according to their implantation strategies: intravascular or extravascular. Several groups investigated arteriovenous shunts anastomosed directly into the circulatory system. These early intravascular devices generally consist of a synthetic hollow fiber semipermeable membrane that passes through a compartment seeded with pancreatic islets.[65–68] It was reasoned that close proximity to circulation would facilitate proper insulin secretion kinetics in response to blood glucose levels; however, *in vivo* studies were plagued with problems of membrane collapse, thrombosis, and limitations in transport properties.[65,69]

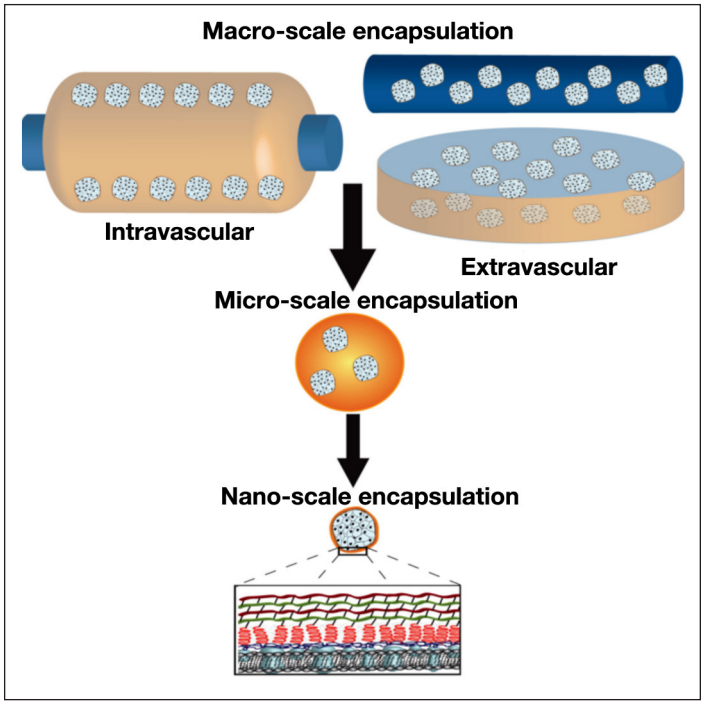

Figure 3. Summary of encapsulation devices from the macro- to nano-scale. Macro-scale encapsulation devices include intravascular, which are perfused with blood, or extravascular devices. Micro-scale devices are typically microcapsules (as illustrated). Nano-scale encapsulation commonly employs the coating of the islet spheroid with polymeric layers, as illustrated in expanded view.

Extravascular devices refer to macroencapsulated cells that are implanted outside of the vasculature, e.g., subcutaneously, intraperitoneally, or in the omentum. Although these devices, such as hollow fibers, diffusion chambers, and polymeric sheets, yielded encouraging results in rodents[70–77] and canines,[78–80] their large size and exclusive reliance on diffusive transport resulted in islet dysfunction and device failure in the long term. Mathematical modeling predicts inadequate transport profiles, indicating scalability of these devices to larger animal models will be problematic after islet density optimization, thereby rendering such implants bulky or requiring multiple devices.[71,78,81–84] More recently, Gimi and coworkers[85] reported on a microcontainer made from an epoxy-based polymer with 50 μm thick walls and a nanoporous lid assembled through adhesion layering techniques. Advantages of these microcontainers include reproducibility and precision due to the automated nature of the manufacturing process, increased mechanical strength, small size resulting in proper transport properties, and the ability to monitor *in vivo* islet function noninvasively through functional magnetic resonance imaging. While encapsulation of mouse islets in these microcontainers did not hamper their function, further studies need to be performed to optimize automation of islet loading and lid placement and evaluate *in vivo* function.

Microscale Encapsulation and Conformal Coating

Encapsulation of small groups or individual islets within micron scale capsules evolved as an alternative strategy to macroscale devices, where the increased surface-area-to-volume ratio results in enhanced transport properties. Traditional islet microencapsulation involves enclosing islets in a semipermeable alginate/poly-lysine (PLL) capsule held together by ionic interactions where porosity, and thus diffusive properties, is commonly controlled by altering the quantity and molecular weight of PLL used during processing.[86–88] Agarose has also been extensively studied as an encapsulation material, where beads are generated by cooling cell/agarose-oil emulsions to induce gelation.[89,90]

Although the surface-to-volume ratio is improved, these capsules have drawbacks. Despite their reduced size, a large void space remains between the islet and its surrounding environment, imposing significant increases

in implant size and longer diffusion distances for nutrients and insulin.[91] Depending on the implant site and state of vascularization, this large void space could lead to graft dysfunction and apoptosis due to hypoxia[92] and a lag in glucose-stimulated insulin release into the bloodstream.[93,94] In addition, the instability of the ionic interactions lead to decomposition of the capsule under physiologic conditions over time.[95]

While reduction of the alginate capsule size has been achieved via air-driven droplet generators[96,97] or high voltage pulses,[98–100] these methods resulted in an increased incidence of inadequate or incomplete coating of the islets and thus graft rejection by immune attack.[87] To avoid these issues and precisely control membrane properties, several groups developed methods to conformally coat islets in polymeric layers in the range of 10–100 μm thick. Approaches include entrainment through traversing liquid–liquid interfaces via a variety of methods such as centrifugation,[101,102] selective withdrawal,[103] emulsions,[104] and interfacial photopolymerization.[105,106] All of these methods establish the feasibility of conformal coating for islet encapsulation, but further *in vivo* studies need to be performed to evaluate the potential of these coatings to prevent rejection.

Nanoscale Encapsulation

While research in conformal coating was progressing, researchers in the field of blood transfusion were developing alternative cell-coating strategies for a universal blood substitute. Sparked by the findings that covalent attachment of methoxy-polyethylene glycol (PEG) to exogenous proteins increased half-life and reduced immunogenicity without affecting function,[107,108] researchers attempted to immune-camouflage red blood cells with a biocompatible steric barrier by cross linking the cell surface proteins with methoxy- PEG. Indeed, PEGylation of red blood cells via a cyanuric chloride cross linker resulted in reduced antigenicity *in vitro* and *in vivo* and maintained normal cell function. This opened the doors for PEGylation of a wide variety of tissues used for transplantation, including pancreatic islets, and gave rise to the concept of nanoscale encapsulation.[109]

Several groups have carried out PEGylation on the surface of islets through varying approaches, which include linking islet surface amine groups with isocyanate and *N*-hydroxysuccinimide functionalized PEG polymers[110–114] or inserting lipid moieties linked to a PEG chain within islet cell membranes.[115] Not only did PEGylation have no adverse effects on islet viability or function,[110,111] but it was also found to reduce islet recognition and activation of immune cells *in vitro*,[112,113] prolong survival of the allograft in the absence of immunosuppression,[116] and reverse diabetes when combined with mild immunosuppression in rodent models.[117]

Covalent modification of amine groups on islet surface proteins presents a problem due to periodic turnover of membrane components[110] and possible interference with cell surface protein activity.[118] To avoid these issues, Wilson and colleagues[119] have used a noncovalent approach of coating islets via electrostatic interactions with modified PLL. Exposure to PLL alone, as with other polycations, results in high levels of cytotoxicity; however, if modified to the appropriate degree with PEG, the PLL, referred to as PP-OCH_3, can interact with the islet surface without inducing apoptosis. In addition, the chemoselective reactive groups hydrazide, azide, and biotin were introduced by functionalization of the PEG macromers prior to PLL modification.[119–121]

PEGylation and noncovalent coating of islet surfaces have also opened the door to the fabrication of complex coatings though layer-by-layer assembly. These layers are stabilized by ionic interactions between oppositely charged polymers[122] or by complimentary chemoselective reactive groups tethered to adjacent layers.[118] While still in the preliminary stages, nanoscale encapsulation has the potential to allow for the reengineering of the islet surface with polymers in a manner that is precisely controlled.

"Bioactive" Polymers to Optimize Microenvironment

There has been growing interest in modifying encapsulation materials to confer biological functionality, thus controlling the *in vivo* microenvironment to enhance islet function and modulate immune response. For example, after isolation, islets exhibit a progressive decline in function as measured by insulin expression, insulin content, and glucose-stimulated secretion.[119] This can be circumvented by reestablishing islet–ECM interactions using ECM protein coatings or adhesive peptide sequences.[123] Weber and associates[124] exploited this and demonstrated enhanced glucose-stimulated insulin secretion of murine islets for up to a month *in vitro* following encapsulation in PEG hydrogels containing collagen IV, laminin, and the adhesive peptide RGD (arginine-glycine-aspartic acid). Lin and Anseth[125] described a PEG-diacrylate-derived hydrogel cofunctionalized with the laminin adhesive sequence IKVAV and a glucagon-like peptide-1 analog modified with a carboxyl terminal cysteine group to allow for

covalent thiol-acrylate photo cross linking. Glucagon-like peptide-1 has been previously described to protect islets from cytokine-induced apoptosis and enhance insulin secretion. Murine islets encapsulated in these gels exhibited enhanced viability and function compared to controls, although overall viability was low due to free radical generation during the polymerization process.[125]

Surface modifications of the polymeric coatings with anti-inflammatory agents can serve to mask IBMIR-associated responses and generalized inflammatory processes. For example, reactive groups on functionalized encapsulating polymers can be used for ligation of different bioactive effectors such as thrombomodulin, with the idea of generating a localized anti-inflammatory microenvironment.[120,121] Other examples include tethering of urokinase and heparinization.[116,126,127]

While encapsulation has the capacity to prevent immune activation via the direct antigen presentation pathway, antigen shedding from the transplanted cells and subsequent indirect pathway activation is difficult to prevent due to permeability requirements that must be satisfied to allow nutrient influx and insulin outflux (see **Figure 2**). Furthermore, proinflammatory cytokines freely diffuse through the polymers, instigating graft cellular apoptosis.[88] To combat these responses, another avenue for polymer functionalization seeks to confer additional immune-protective effects *in vivo* via immuno-modulation of the host environment. Su and coworkers[128] described a four-arm PEG-derived hydrogel network generated through amine-thioester native chemical ligation cofunctionalized with an interleukin (IL)-1β antagonist peptide sequence and an adhesive peptide sequence via maleimide-thiol cross linking. The scheme allows for efficient control of gelation and functionalization due to the chemoselectivity of the reactions. Despite debatable results of cytotoxic T cell coculture experiments and the preliminary nature of the publication, this study showed enhanced viability and function as measured by glucose-stimulated insulin secretion in MIN6 cell clusters as a result of IL-1 receptor inhibition after exposure to multiple cytokines. Lin and collegues[129] described the cofunctionalization of PEG-diacrylate hydrogels with an RGD adhesive peptide and a tumor necrosis factor (TNF)-α-sequestering peptide sequence, resulting in inhibition of TNF receptor 1 activation. Upon encapsulation within these gels, TNF-α challenged murine islets exhibited decreased caspase 3/7 activity, indicative of inhibition of apoptotic pathways, along with metabolic activity and insulin secretion comparable to that of encapsulated, unchallenged islets. Modifications to encapsulation materials such as these show promise in enhancing islet function and prolonging graft survival once implanted in the recipient.

Conclusions

The potential of CIT to provide a life-long cure for T1DM is a lure too powerful to ignore. While current results from CIT trials do not quite fulfill the promise of this therapy, lessons learned from these studies have proven invaluable. By identifying key challenges in maintaining the survival and function of transplanted islets, both in the short and long term, new strategies are evolving in the research pipeline. As outlined in this article, researchers are working to engineer an optimal islet transplantation site. In addition, novel platforms are being developed that seek to combat the significant inflammatory and immunological responses facing allogeneic islet transplantation. For example, the fabrication of novel biomaterials capable of harnessing nature's own agents for combating inflammation could generate a localized anti-inflammatory environment potent enough to mask the transplant from inflammatory-mediated damage. Undoubtedly, the future of diabetes therapies will entail agents emerging from these bioengineering platforms.

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