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# Oxygenation strategies for encapsulated islet and beta cell transplants

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ABSTRACT

Human allogeneic islet transplantation (ITx) is emerging as a promising treatment option for qualified patients with type 1 diabetes. However, widespread clinical application of allogeneic ITx is hindered by two critical barriers: the need for systemic immunosuppression and the limited supply of human islet tissue. Biocompatible, retrievable immunoisolation devices containing glucose-responsive insulin-secreting tissue may address both critical barriers by enabling the more effective and efficient use of allogeneic islets without immunosuppression in the near-term, and ultimately the use of a cell source with a virtually unlimited supply, such as human stem cell-derived β-cells or xenogeneic (porcine) islets with minimal or no immunosuppression. However, even though encapsulation methods have been developed and immunoprotection has been successfully tested in small and large animal models and to a limited extent in proof-of-concept clinical studies, the effective use of encapsulation approaches to convincingly and consistently treat diabetes in humans has yet to be demonstrated. There is increasing consensus that inadequate oxygen supply is a major factor limiting their clinical translation and routine implementation. Poor oxygenation negatively affects cell viability and β-cell function, and the problem is exacerbated with the high-density seeding required for reasonably-sized clinical encapsulation devices. Approaches for enhanced oxygen delivery to encapsulated tissues in implantable devices are therefore being actively developed and tested. This review summarizes fundamental aspects of islet microarchitecture and β-cell physiology as well as encapsulation approaches highlighting the need for adequate oxygenation; it also evaluates existing and emerging approaches for enhanced oxygen delivery to encapsulation devices, particularly with the advent of β-cell sources from stem cells that may enable the large-scale application of this approach.



**Contents**



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## 1. Introduction

Progressive autoimmune destruction of insulin-producing β-cells in the endocrine pancreas leads to type 1 diabetes (T1D) and its associated chronic microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (ischemic heart disease, cerebrovascular disease, peripheral vascular disease) complications. T1D patients are currently treated with insulin therapy, and in severe cases with whole pancreas transplantation. Insulin can be delivered via multiple daily injections or a subcutaneous infusion through an insulin pump [1,2]. Continuous glucose monitoring sensors, in some cases integrated with insulin pumps are increasingly adopted [3]. However, issues affecting accuracy, glycemic variability, cost, and development of standards for optimal use, remain as challenges for manufacturers, health care providers and patients [3]. Human pancreas transplantation is an option for the treatment of qualified patients with severe T1D. It represents a procedure that may attain normoglycemia without the need for exogenous insulin and in a way that better resembles the host's physiological glucose control mechanisms prior to β-cell destruction. Pancreas transplants can be conducted as single procedures or in conjunction with kidney transplants [4]. Graft survival rates have improved for all transplant categories one year after transplantation (79-90%) [4]. However, the need for major surgery, immunosuppression regimens in all subjects for the life of the transplant, and anticoagulation therapy in a subset of patients, are limiting the use of pancreas transplantation as a therapeutic option for more T1D patients [4–6]. Since the success of intrahepatic allogeneic islet transplantation (ITx) — using islets obtained from deceased donor pancreata and a steroid-free immunosuppressive drug regimen (the Edmonton Protocol) — this procedure has gained attention and is currently implemented for a selected number of qualified T1D patients in a variety of countries around the world [7] and on a clinical research basis in the US [8]. ITx has the advantage of being a minimally-invasive procedure with intra-portal islet infusion conducted under radiological guidance and is the procedure of choice in qualified patients with high surgical risk, where available [9]. Follow up studies evaluating long-term outcomes of ITx using the Edmonton protocol indicated that only about 10% of patients were insulin-independent after five years, with a median duration of insulin independence of 15 months, which are significantly worse than those of a single vascularized whole pancreas transplant [10]. Over the past decade, ITx has continued to evolve with substantial improvements in terms of outcomes [7,11]. Despite the improvements, ITx still requires immunosuppression, and islets from more than one pancreas donor are often needed to achieve the same short and long-term (5 year) outcomes achieved with a single whole pancreas transplant [8,10–16].

Major factors that contribute to the need for multiple pancreas donors in islet transplantation include stressors associated with pancreas procurement and preservation [8,17–24], as well as pancreas digestion for islet isolation, purification and culture [23,25–28]. Other stressors encountered during islet infusion and engraftment into the liver may also affect their viability and function [17–35]. Ischemia and in particular hypoxia have been identified as major underlying factors contributing to the loss of islet mass, viability and function before, during and after islet transplantation [12]. Using *in silico* diffusion-reaction models, it has been shown that hypoxia and hypoxia-related events are at the center of islet loss of viability and function after transplantation [20]. Multiple experimental studies have demonstrated that islet size and oxygen microenvironment are key determinants of islet survival, function and clinical outcomes lending further support to the hypotheses put forth based on mathematical models [20,36,37].

## 2. Critical barriers limiting the large-scale, clinical implementation of islet transplantation (ITx) and potential solutions

The widespread clinical application of ITx is currently hindered by two critical barriers: the finite and low supply of human islets and the need for life-long systemic immunosuppression (Fig. 1). The risks associated with immunosuppression include increased incidence of infections, nephrotoxicity, islet β-cell toxicity, and malignancies, which exclude the implementation of ITx in cases where immunosuppression may be contraindicated (i.e. pediatrics). Biocompatible, retrievable immunoisolation devices (e.g. macrocapsules) containing glucose-responsive-insulin secreting tissue (Fig. 2) may address both critical barriers by enabling the more effective and efficient use of allogeneic islets without immunosuppression in the near-term, and ultimately the use of a cell source with a virtually unlimited supply such as human stem cell-derived β-cells/islets or xenogeneic (porcine) β-cells/islets (Fig. 1, Table 1) with minimal or no immunosuppression [38–42].

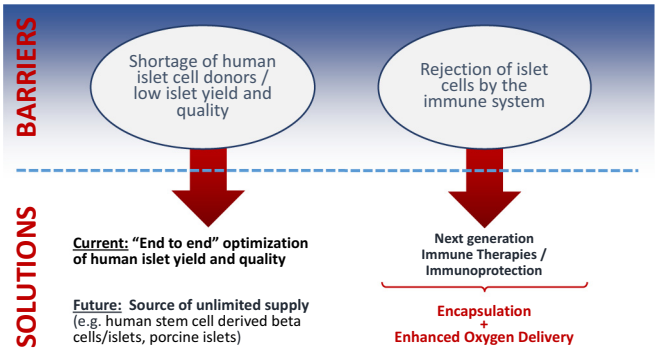


**Fig. 1.** Current barriers to large-scale application for cell-based therapies for the treatment of diabetes and potential solutions.

### 2.1. Cell supply

The future use of alternative β-cell sources such as human stem cell-derived β-cells and porcine islets is becoming increasingly likely based on the number of publications demonstrating significant progress (Table 1), and a substantial industry investment (in the hundreds of millions of dollars) for scale-up and GMP manufacturing of "clinical grade" cells [40,43–54]. The recent development of genetically-modified pigs and use of novel gene editing tools to make porcine islets look more like human to the immune system, and to eliminate retroviruses further reduces the barrier of using xenogeneic porcine donors and enhances the likelihood of success [55–63]. Alternative sources of insulin-producing cells that have been investigated for transplantation

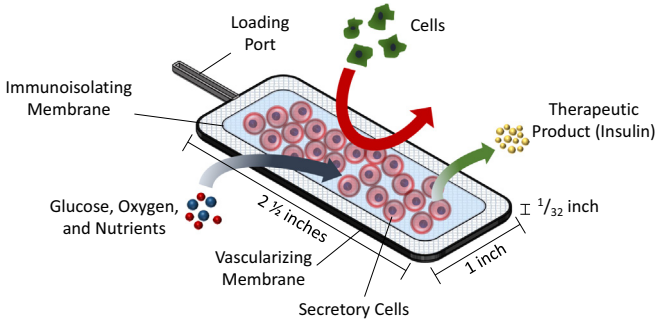


**Fig. 2.** Schematic depicting a generic vascularizing macroencapsulation immunoisolation device based on the one developed and tested by Baxter [TheraCyte™] to protect allogeneic cells from rejection without immunosuppression: An immunoisolation membrane has small enough pores to block immune cells from entering the device thereby protecting the transplanted cells from allogeneic rejection. The device simultaneously allows small molecules like glucose and oxygen to freely enter and be utilized by the encapsulated cells. Insulin released by the encapsulated cells in response to glucose will escape the device and enter the bloodstream. Insulin escaping from the device is taken up quickly by small blood vessels surrounding it, which are formed with the help of a specially designed outer vascularizing membrane.

**Table 1**
Development of key human stem cell lines for cell therapy for diabetes. Transplantation examples using renewable sources of insulin-producing cells including hESCs and hPSCs.

| Cell type | Cell line/tissue source | Implantation modality | Species implanted | Reference |
|---|---|---|---|---|
| hESC | CyT203 | NA | NA | [73] |
| hESCs | hES-PE | Macroencapsulation (TheraCyte™ device) | Athymic rats | [74] |
| hESC | H1 | NA | NA | [44]; [75] |
| hESC | S7 | Kidney capsule | NOD-SCID STZ-diabetic mice | [48] |
| hESC | H1 | Macroencapsulation (TheraCyte™ device) | STZ-diabetic mice | [41] |
| hESCs | CyT49 | Macroencapsulation (TheraCyte™ device) | Alloxan-diabetic mice | [46] |
| hESCs | CyT49 | Macroencapsulation (TheraCyte™ device) | NOD-SCID mice | [47] |
| hPSCs | hiPSC-1, hiPSC-2 | Kidney capsule | SCID-Beige mice | [45] |
| hESCs | Cyt 49 | Prevascularized subcutaneous site | STZ-induced diabetic mice | [76] |
| hESCs | hES-PE | NA | NA | [77] |
| hESCs, hPSCs | iPS-17b, H1, HUES 8 | NA | NA | [78] |
| hPSCs | TID SC-b | NA | NA | [79] |
| hESCs | $INS^{GFP/w}$ | NA | NA | [80] |
| hESCs | HUES8 | Microencapsulation (alginate) | STZ-induced diabetic mice | [81] |
| hPSCs | Fibroblasts | Kidney capsule | STZ-treated diabetic mice | [82] |

*Abbreviations*: hESC: human embryonic stem cells; NA: not applicable; hPSCs: human pluripotent stem cells; SCID: severe combined immunodeficiency; STZ: streptozotocin.

include human and porcine mesenchymal stem cells (MSCs) [41,64–66], and porcine neonatal [49] and fetal islets [67,68]. Co-transplantation of MSCs with islets is a strategy that has also been explored with results suggesting improved vascularization and survival [65,69–71]. However, the feasibility and scalability of this approach have not yet been demonstrated. As the cell supply challenge is being addressed, the challenge of maintaining viability and function of insulin-producing cells post-transplant, especially when such cells are transplanted within immunoisolation devices, must also be addressed for practical clinical translation [20].

Without intra-islet vascularization (Fig. 3A), oxygen supply to the islet core is severely hampered because it relies on diffusion of oxygen from the islet surface to the core through multiple layers of oxygen-consuming cells. Furthermore, the higher the seeding density of islets within immunoisolation devices (to enable the use of smaller and reasonably-sized devices while avoiding rejection without the use of immunosuppression), the steeper the oxygen gradient within them and the higher the need for enhanced oxygen delivery (Fig. 3B). The use of stem cell-derived islets instead of primary human islets in immunoisolation devices can address both, the issue of the limited supply of human islets and the requirement for immunosuppression. However, as in the case with primary human islets, with immunoisolation human stem cell-derived islets will not be allowed to vascularize (Fig. 3B) to avoid rejection but also to minimize the chances of cell escape and potential cell migration to another location. Under these circumstances, enhanced oxygen delivery is needed to preserve cell viability and function within reasonably-sized immunoisolation devices. Therefore, enhanced oxygen delivery is key to addressing the a) cell supply issue (with the use of stem cell-derived islets in immunoisolation devices) and, b) rejection without immunosuppression (with the use of immunoisolation membranes so as to block the immune system from attacking the transplanted cells without the need for immunosuppressive drugs).

The sections that follow outline some of the remaining challenges (with a focus on oxygen demand and supply) along with possible solutions.

### 2.2. Islet microarchitecture/essential role of oxygen

Islets of Langerhans are highly vascularized multicellular spheroidal cell clusters ranging from 50-400 μm in diameter containing a variety of cell types that include insulin-producing β-cells, the most abundant cell type, glucagon-producing alpha cells, somatostatin-producing delta cells, ghrelin-producing epsilon cells, and pancreatic polypeptide cells [72]. Islets also contain immune cells and autonomic innervation [73]. The islet microarchitecture and extensive microvascular network within it support islet function, which is tightly regulated by autocrine, paracrine and endocrine signals [72]. Although the islet cellular composition and spatial organization may vary among species, β-cells are in close contact with capillaries branching from the afferent arteriole [74] and may exhibit hormone secretion polarity [74,75]. Parasympathetic cholinergic axons are sparse within the islet, whereas sympathetic nerve endings innervate vascular smooth muscle cells [73]. The tight sympathetic control of the islet's vascular tone suggests that local blood flow and oxygen supply play a key role in hormone secretion regulation. It is also well documented that the islet microvasculature (Fig. 3A) is critically important for providing access to glucose (and

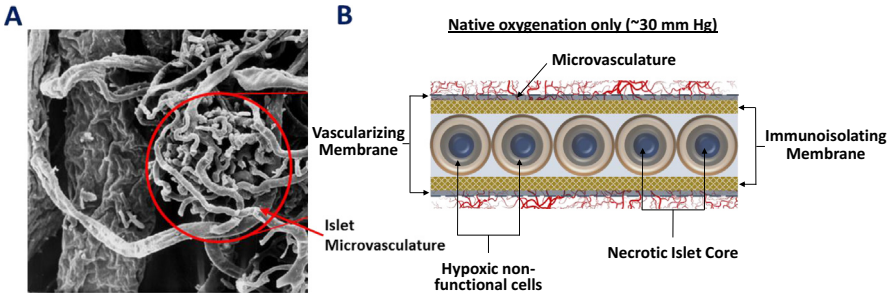


**Fig. 3.** A. Islet microvasculature (with permission from Bonner-Weir and Orci, 1982 [193]). The extensive vasculature is a key element to support islet function in metabolic regulation of glucose levels through production and release of insulin, glucagon and other hormones B. Scheme representing a longitudinal section of a TheraCyte™ device showing the immunoisolation membrane and the vascularization that occurs around the device with the help of the vascularizing membrane after implantation, which is not sufficient given the $pO_2$ level at the transplant site (Table 1–Table 4) to support oxygenation of islets within it when they are at high density in a single layer configuration resulting in necrotic and hypoxic cores.

**Table 2**
Selected measurements of *in vivo* $pO_2$ at prospective islet transplant sites with animal breathing ambient room air ($pO_2$ ~160 mm Hg).

| Transplant site | Model | Method | Range and/or Mean ± SD $pO_2$ [mm Hg] | Reference |
|---|---|---|---|---|
| Intrahepatic | | | | |
| | Rat | Microelectrode | 3-4 | [108] |
| Intramuscular | | | | |
| | Rat | $^{19}$F NMR Spectroscopy | 41 ± 10 | [109] |
| | Rat | $^{19}$F NMR Spectroscopy | 18 ± 16 (day 2), 5 ± 11 (day 90) | [110] |
| Intraperitoneal | | | | |
| | Rat | $^{19}$F NMR Spectroscopy | 52 ± 7 | [109] |
| | Rat | $^{19}$F NMR Spectroscopy | 26 ± 34 (day 1), 21 ± 13 (day 54) | [110] |
| | Mouse | $^{19}$F NMR Spectroscopy | 51-58 | [111] |
| Pancreatic | | | | |
| Islet | Rat | Microelectrode | 37-42 | [108] |
| Acinar | Rat | Microelectrode | 26-33 | [108] |
| Renal | | | | |
| Subcapsular | Rat | $^{19}$F NMR Spectroscopy | 8-33 | [110–112] |
| Cortical | Rat | Microelectrode | 13-14 | [108] |
| Spleen | | | | |
| | Rat | Microelectrode | 28-32 (non-diabetic), 18-22 (diabetic) | [108] |
| Subcutaneous | | | | |
| | Rat | $^{19}$F NMR Spectroscopy Optical probe | 8-14 22-30 | [105] |

*Abbreviations*: $^{19}$F NMR: fluorine nuclear magnetic resonance; PFC, perfluorocarbon; $pO_2$, oxygen partial pressure; SD, standard deviation.

oxygen), as well as other nutrients and signaling molecules involved in hormone release regulation.

The critical need for oxygen is highlighted by the fact that islet cells (especially β-cells) are particularly sensitive to hypoxia, in part because they express low levels of the enzyme lactate dehydrogenase-α (LDHα), which enables energy generation (adenosine triphosphate, ATP) via conversion of pyruvate to lactate under anaerobic conditions [76–81]. The inability to generate ATP under conditions of oxygen deprivation results in cell death. Mature, differentiated β-cells are defined by their ability to secrete insulin in response to glucose (glucose-stimulated insulin secretion, GSIS). In addition to its effect on viability, oxygen deprivation has a dramatic negative effect on the ability of β-cells to synthesize and secrete insulin, especially in response to glucose. This effect is manifested at oxygen levels higher than those needed to affect viability, for example at a $pO_2$ around 10 mm Hg as opposed to 0.1 mm Hg, which is assumed to be the critical value for cellular viability [82–91]. Furthermore, β-cell overexpression of LDHα, the enzyme that would enable energy production under hypoxia/anoxia, disrupts GSIS [76,77,79,81]. Therefore, β-cell function (or GSIS) is more vulnerable to hypoxia than β-cell/islet viability. Even if anti-apoptotic agents or other approaches that block cell death were to be successfully used to minimize the effects of hypoxia on islet viability, the effect of hypoxia on islet function may still severely impair outcomes. More importantly, it appears that even if β-cells survive a hypoxic insult, they may exhibit persistently impaired function, even after re-oxygenation [29,32,92,93]. This is consistent with emerging literature on islets, which suggests that even brief exposure to hypoxia may be sufficient to impair GSIS in the long-term via a hypoxia-induced genetic signature [32,77,78,80,92,94]. Moreover, exposure to hypoxia or ischemia appears to induce a pro-inflammatory signature in the islets, which may further trigger the immune system if transplanted [32]. Experiments in which targeted delivery of ATP to β-cells was able to minimize the effect of hypoxia on viability were unable to block the negative effect of hypoxia on GSIS (even after re-oxygenation) [29]. In fact, although viability was protected, GSIS was impaired even after several days of re-oxygenation.

Isolated islet function (GSIS) becomes affected at $pO_2$ levels below 38 mm Hg, highlighting the limits of oxygen transfer to the islet interior by diffusion alone when the natural intra-islet vasculature (Fig. 3A) is collapsed or not connected to the blood supply [83–86,88]. It is important to recognize that the $pO_2$ is lower than 38 mm Hg at certain prospective transplantation sites including the subcutaneous pocket in animals (Table 2 and Table 3) and humans (Table 4). Furthermore, when $pO_2$ was measured non-invasively with $^{19}$F NMR spectroscopy within fully vascularized empty Baxter TheraCyte™ devices implanted subcutaneously in rats it was found to range from 8-14 mm Hg, which is substantially lower than that apparently available at this transplant site, highlighting the need for such measurements not only at transplant sites but within encapsulation devices [95] (Table 2).

Even though the threshold "minimum allowable" surface $pO_2$ value in isolated islets or in freshly transplanted islets may vary due to factors that include islet size, islet cell packing density and islet cell oxygen consumption rate [20,29–31], the low $pO_2$ reported to be available at prospective transplant sites is unlikely to support full viability and function of transplanted islets without intra-islet vasculature. Taken together, these data suggest that enhanced oxygenation may be necessary in order to obtain full function from transplanted islets.

The effects of hypoxia are by now well established and characterized with adult islets (e.g., rat, human and porcine). However, there is limited data with immature islets and β-cells (such as stem cell-derived β-cells or neonatal porcine islets). The limited literature available suggests that immature islets (or β-cells) may be less sensitive to hypoxia, but this may be temporary and not true when β-cells ultimately mature

**Table 3**
Selected measurements of *in vivo* $pO_2$ at prospective islet transplant sites in animal breathing pure oxygen gas ($pO_2$ ~760 mm Hg) or other mixtures of gas.

| Transplant site | Model | Method | Range and/or Mean ± SD $pO_2$ [mm Hg] | Reference |
|---|---|---|---|---|
| Intramuscular | | | | |
| | Rat | $^{19}$F NMR Spectroscopy | Oxygen: 70 ± 23[a] Hypoxic: 7 ± 6[a] | [109] |
| | Rat | $^{19}$F NMR Spectroscopy | Oxygen: 237 ± 61 (day 2), 12±7 (day 90)[b] | [110] |
| Intraperitoneal | | | | |
| | Rat | $^{19}$F NMR Spectroscopy | Oxygen: 88 ± 14[a] Hypoxic: 19 ± 7[a] | [109] |
| | Rat | $^{19}$F NMR Spectroscopy | Oxygen: 56 ± 62 (day 1), 69 ± 40 (day 54)[c] | [110] |
| | Mouse | $^{19}$F NMR Spectroscopy | Carbogen: 16-213[d] | [113] |
| Renal | | | | |
| Subcapsular | Rat | $^{19}$F NMR Spectroscopy | Oxygen: 43±20[e] | [110] |

*Abbreviations*: $^{19}$F NMR: fluorine nuclear magnetic resonance; PFC, perfluorocarbon; $pO_2$, oxygen partial pressure; SD, standard deviation.
[a] Recipients breathing either pure oxygen gas ($pO_2$ ~760 mm Hg) or hypoxic gas mixture ($pO_2$ ~76 mm Hg).
[b] Days 2 and 90 after implantation with recipients breathing pure oxygen gas ($pO_2$ ~760 mm Hg).
[c] Days 1 and 54 after implantation with recipients breathing pure oxygen gas ($pO_2$ ~760 mm Hg).
[d] Days 0, 1, 2, 6 and 7 after implantation with recipients breathing carbogen gas mixture ($pO_2$ ~720 mm Hg).
[e] Four month period following implantation with recipients breathing pure oxygen gas ($pO_2$ ~760 mm Hg).

**Table 4**
Selected measurements of *in vivo* $pO_2$ at prospective islet transplant sites in humans.

| Transplant site | Method | Range and/or Mean ± SD $pO_2$ [mm Hg] | Reference |
|---|---|---|---|
| Bone marrow | | | |
| | Microelectrode | 52 ± 15 | [114,115] |
| Intestine | | | |
| Small bowel serosa | Microelectrode | 53-71 | [116] |
| Intrahepatic | | | |
| | Microelectrode | 55 ± 21 | [117] |
| | Microelectrode | 30% oxygen: 20-41[a]<br>100% oxygen: 29-39[a] | [118] |
| Intramuscular | | | |
| | Microelectrode | 32 ± 14 | [114,119] |
| | Microelectrode | 34 ± 11 | [114,120] |
| Renal | | | |
| Cortical | Microelectrode | 72 ± 20 | [121] |
| Skin | | | |
| Superficial | Microelectrode | 8 ± 3 | [114,122] |
| Dermis | Microelectrode | 24 ± 6 | [114,122] |
| Subdermis | Microelectrode | 35 ± 8 | [114,122] |

*Abbreviations*: $^{19}F$ NMR: fluorine nuclear magnetic resonance; PFC, perfluorocarbon; $pO_2$, oxygen partial pressure; SD, standard deviation.
[a] Measurements done while patient inspiring 30% or 100% oxygen gas.

[96,97]. Further systematic study of the effects of oxygen on viability and function of less mature β-cells and islets is needed given the clinical relevance of such cell sources.

### 2.3. Cell Encapsulation

The development and testing of encapsulation (immunoisolation) approaches incorporating insulin-secreting tissue from a variety of (renewable) sources aiming at reversing diabetes in humans without the need for immunosuppression is currently an active area of worldwide research [98]. Significant progress has been made over the past several years [20,33,38–40,43–47,99–132] and some encapsulation approaches have demonstrated immunoprotection without immunosuppression in multiple preclinical models and in a limited number of clinical cases in the allogeneic [133,134] and xenogeneic setting [132,135].

These approaches include intravascular and extravascular capsules and devices, all of which have been reviewed in the past [98,102,125,136,137]. The sections that follow will provide a brief overview of the different major encapsulation approaches with special reference to oxygen delivery and will focus on extravascular macroen capsulation approaches (Fig. 2 and Fig. 3B), which appear to be more clinically relevant and more easily amenable to enhanced oxygen delivery [107,113,136,138].

#### 2.3.1. Intravascular approaches

Intravascular devices consist of arteriovenous (AV) shunts with porous tubular structures containing cells/islets in an external chamber separated from luminal blood flow by immunoisolating biomaterials [139,140]. Intravascular devices may be more effective at delivering oxygen and nutrients to islets and may have better glucose sensing and insulin release kinetics relative to extravascular devices due to the proximity of the cells to blood flow, however, they are also more prone to devastating vascular complications (e.g., thrombosis), which may require systemic pharmacological anticoagulation, especially when small diameter tubular structures are used [102,141].

In a pivotal paper published over 40 years ago, Chick *et al* demonstrated that β-cells cultured in semipermeable hollow fibers implanted as AV shunts were able to restore euglycemia in alloxan-induced diabetic rats [142]. Although later studies confirmed the restoration to normoglycemia in small and large animals, insulin secretion decreased over time, and thrombus formation was reported as a complication [143–146].

Intravascular devices were extensively investigated in the early 90s with some exceptional preclinical data reported in terms of functionality but were ultimately abandoned due to issues with coagulation and thrombosis, and AV shunt rupture [102,125]. Intravascular device designs have recently resurfaced, with some promising preclinical results [147–149]. Interestingly, some of these designs incorporate small diameter tubes that were previously found to be problematic [102]. It remains to be seen whether this new generation of intravascular devices, perhaps incorporating new and improved biomaterials [147–149] can be translated into a successful and especially long-term clinical application by avoiding the thrombotic complications and other limitations of their predecessors [102,125].

#### 2.3.2. Extravascular approaches

A variety of extravascular approaches to encapsulated cell transplants with varying geometrical configurations have been explored over the past several decades [102,125,145,150,151]. Geometry has the potential to significantly affect outcomes especially in extravascular approaches that rely on diffusion for the transfer of nutrients to cells within the capsules. Spherical geometry is advantageous because it provides for a higher surface area to volume ratio compared to a cylindrical or a planar slab geometry [82,102]. Extravascular approaches can be categorized based on size as micro- and macroencapsulation and have been previously reviewed elsewhere [102,125]. In the sections below, we will discuss recent developments in extravascular approaches and their remaining challenges and limitations with an emphasis on oxygen availability.

*2.3.2.1. Microencapsulation.* Transplantation of microencapsulated islets has been explored as a treatment for diabetes without immunosuppression for more than three decades. The early work of Lim and Sun demonstrating successful diabetes reversal in rodents with microencapsulated islets in spherical alginate-poly-L-lysine capsules in 1980 [152] was in effect the catalyst behind the appeal and exploration of this approach.

Since then, microencapsulation of insulin-secreting cells and islets has been widely explored by numerous investigators using a variety of natural and synthetic polymers in several models of T1D [102,109,125,148,149,152–175]. Although the ideal size of microcapsules has not yet been defined, the majority of the published research has been conducted with cells and islets immobilized within spherical capsules ranging from 200 to 1000 μm in diameter [156,157]. Capsules 2-3 mm in diameter or larger have also been investigated but to a more limited degree, perhaps due to the negative effect of the larger diffusional distances on the viability and function of cells within them [176].

One of the most utilized natural polymers for microencapsulation is alginate [102,109,125,131,152,154,161,163,167–169]. Alginate is derived from seaweed (brown algae) that gels without apparent effects on cell survival in the presence of ions such as calcium and barium [158,159]. Islets have also been co-encapsulated with photosynthetic, microalga-based, oxygen generators that are activated upon illumination [177]. Alginate capsules can be used uncoated [154] or coated with synthetic polymers such as poly-L-lysine or poly-L-ornithine [161,163,167–169]. Synthetic coatings are believed to increase the mechanical stability and adjust the molecular weight cut-off of microcapsules but they may affect biocompatibility and immunogenicity [102,125,145,172]. A valid source of apprehension in the use of alginate for cell encapsulation in the clinical setting is the high variability in current product composition and manufacturing practices. Impurities present in alginate and different contents of mannuronic and glucuronic acid may be responsible for low biocompatibility when alginate microcapsules are implanted in animals [159,171,172]. Localization of the islets within the microcapsule (with islets/cells protruding) may also be a factor triggering immune responses. Confinement of islets or cells to the core region using a co-axial electrojetting system or encapsulation in double capsules (capsule within a capsule) was reported to improve performance [125,173].

To address some of the inherent limitations of alginate, numerous other natural and synthetic materials have also been explored for microencapsulation. These include collagen, gelatin, fibrin, copolymers of acrylic acid and methacrylic acid, poly(alkylene oxides), poly(vinyl acetate), polyethylene glycol (PEG), polysaccharides such as agarose, cellulose sulfate, chondroitin sulfate, chitosan and hyaluronan [157,174]. PEG has been reported to have higher biocompatibility than poly-L-lysine [175], and can be used to encapsulate islets with multiple techniques [178,179], including electrodynamic spraying [180] and 3D bioprinting [181,182]. The use of combined biomaterials has opened the field to customized encapsulation methods aimed at preventing inflammatory and immune reactions [183,184]. Adding immunosuppressive drugs to microencapsulated cells or islets is a strategy that might prevent side effects that result from systemic drug administration, however, the release of these drugs may only be sustainable for short periods of time. Dexamethasone, curcumin, and rapamycin have been combined with alginate alone or alginate and PEG [185,186]. Physicochemical properties of microcapsules formed with different materials have been extensively reviewed elsewhere [102,125,137,141,145,156–161] and will not be further discussed here.

Based on the published literature with a variety of microencapsulation approaches and models, microencapsulated islets and β-cells are highly successful in reversing diabetes in rodents and in some cases larger animals such as dogs [109,153,154,160–165]. Normalization of diabetes has also been reported in diabetic cynomolgus monkeys without the need for immunosuppression when transplanted intraperitoneally with islets microencapsulated in alginate-poly-L-lysine [163]. However, these remarkable results have not been reproduced by other investigators [102], and attempts to reverse diabetes in humans with this approach have so far been met with very limited and inconsistent success [102,109,125,131].

A major factor contributing to the limited success with microencapsulated islets in non-human primates and humans may be the sedimentation and aggregation of microcapsules leading to severe encapsulated cell hypoxia when injected in the peritoneum [109,131]. Although microencapsulation of individual pancreatic islets results in a relatively large surface area to volume ratio, thereby offering the prospect of maximum diffusion of nutrients and oxygen to the encapsulated tissue, this advantage is eliminated when multiple capsules aggregate *in vivo* leading to severe hypoxia and ischemia.

Integration of perfluorocarbons,which have higher oxygen solubility than water, within capsules, has been explored [102] as an approach to improve oxygenation of cells by increasing oxygen permeability within microcapsules. However, this approach is limited by the volume fraction of perfluorocarbon that can be incorporated in the capsule without compromising cell loading and capsule integrity. This approach is also limited by the oxygen level surrounding the capsule at the transplant site (Table 2 and Table 4). Another approach involves the incorporation of oxygen-generating materials (e.g., calcium peroxide) within the layers of natural or synthetic polymers that form the microcapsule. This strategy would limit the hypoxia-induced cell death particularly during the early post-transplant period [122], however, it cannot be utilized for long-term delivery. Additionally, the generation of oxygen and other potentially toxic byproducts in the vicinity of the encapsulated cells may ultimately limit its efficacy. Therefore, neither approach would be able to overcome issues associated with continuous and prolonged aggregation of multiple capsules *in vivo* [109,131].

Cell microencapsulation has additional limitations when considered for clinical translation. This approach suffers from the inherent disadvantage of injecting large numbers of potentially irretrievable microcapsules into the peritoneum [152,187]. Microcapsules bound to tissues in the peritoneal cavity often became covered by fibrotic tissue leading to the death of the encapsulated islets [188], which cannot be retrieved should replacement be necessary. The inability to retrieve microencapsulated islets/cells implanted in either hepatic and extrahepatic sites remains a major concern with potential regulatory implications [33].

In summary, despite extensive testing of microencapsulated islets using natural and synthetic polymers, clinical translation, has been slow and unsuccessful. Multiple barriers persist [131], particularly incomplete retrievability, sedimentation and aggregation of intraperitoneally transplanted microcapsules in humans [102,109,125,131] and difficulties associated with delivering high levels of oxygen to the local microenvironment [102,189].

*2.3.2.2. Macroencapsulation.* The shortcomings of microencapsulation led several groups to explore macroencapsulation methods that would allow high packing density in a retrievable encapsulation format. Such macroencapsulation has generally been pursued using hollow fibers or planar membrane devices [125,145,190] containing islets or islet-like cell clusters implanted in the peritoneal cavity of animals or in subcutaneous sites of animals and humans. Subcutaneous placement of devices is preferred because of the minimally invasive surgery required and ease of retrieving or refilling the implants. The subcutaneous site also offers the possibility of implanting an empty device prior to islet/β-cell implantation, thus allowing time for the surrounding tissue to heal and vascularize before introducing insulin-secreting islets or β-cells into the lumen (see prevascularization section below).

In all macroencapsulation configurations designed for immunoisolation, the insulin-secreting tissue is separated from the host by one or more membranes that block cells from the recipient's immune system from coming into contact with the encapsulated tissue. The pores of such immunoisolation membranes must be sufficiently large to allow rapid diffusion of nutrients and oxygen into the device to support tissue viability. However, many early studies using macroencapsulation revealed that such implanted devices quickly became surrounded by a poorly vascularized fibrotic capsule [150,151,191,192]. This resulted in insufficient levels of nutrients and oxygen reaching the encapsulated tissue ultimately leading to cell death. Pancreatic islets are highly vascularized [193], so it became evident that separation of the tissue from the vasculature by intervening membranes would stress the tissue. Moreover, it was well known that, in culture, pancreatic islets developed necrotic cores whose size increased with the size of the islet due to greater diffusion distances for oxygen and other nutrients [194].

In an effort to minimize the fibrotic encapsulation of implantable devices and bring the vasculature as close to the implant as possible, an *in vivo* screening study of different membranes based on polymer chemistry and three-dimensional architecture was performed by researchers at Baxter Healthcare Corporation in the 1990s. Those studies showed that the key determining feature in prevention of fibrotic encapsulation at the membrane-host tissue interface was the microarchitecture of the synthetic membranes and not the polymer chemistry [195]. Fig. 4 shows an example of the vascularizing effect of the Baxter TheraCyte™ membrane microarchitecture.

The structure of the membranes identified at Baxter that prevented fibrotic capsule formation at the synthetic membrane-host tissue interface and allowed the formation of close vascular structures had large pores, generally in the 1 to 15 μm range and allowed cellular penetration. Such structures would not prevent cells from the immune system of the host from gaining access to the encapsulated insulin-secreting tissue, so they were laminated to much smaller pore membranes that served as the immunoisolation barrier. The laminated membranes were used to fabricate macroencapsulation devices of many different designs. A key advantage of macroencapsulation over microencapsulation is the ability to fabricate implantable devices that provide a means of introducing supplemental oxygen to the system. The ease of fabricating laminated sheet membranes into a multitude of designs offers the potential to create macroencapsulation devices with unique supplemental features designed to enhance tissue survival and function. One example of supplemental support is under development by Beta-$O_2$ Technologies, Ltd. The company is developing an oxygenated

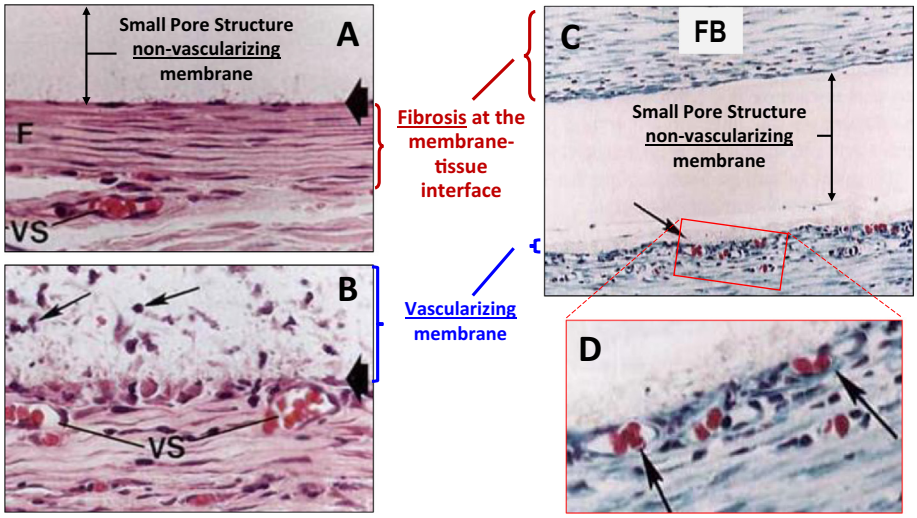


**Fig. 4.** Panel A shows the fibrotic response of subcutaneous (SQ) tissue in a rat to a small pore structure membrane (**upper half of image**). Panel B shows the much more desirable vascularizing response to an open structure with cellular penetration into the membrane (**upper half of image**), F=fibrotic response; VS=vascular structures. The membranes in panels A and B were implanted SQ in Sprague-Dawley rats and were explanted 3 weeks post-implantation. Panel C shows histology from an explanted membrane composite of a small pore (thicker) membrane with a large pore (thinner) vascularizing membrane laminated to the bottom side. Note that on the top side showing the non-vascularizing membrane, a fibrotic layer (FB) of cells has formed. However, on the bottom side showing the vascularizing membrane, there is no fibrotic capsule, and vascular structures have developed at the membrane-tissue interface. The membrane composite was implanted SQ in Sprague-Dawley rats and was explanted 3 weeks post-implantation. Panel D shows a higher magnification view of a portion of the vascularizing membrane (bottom of the laminate) seen in Panel C; thin arrows show red blood cells in vascular structures. A small separation between the tight and more open structure membranes in the laminate seen in the bottom left of panel C is an artifact created during sectioning for histology. Images from Brauker *et al*, 1992 [195].

macroencapsulation device that contains islets embedded in an alginate slab separated from an oxygen-containing chamber by a gas permeable membrane [102,107,196], which is discussed in more detail in a later section. TheraCyte™ macroencapsulation devices have been used to successfully transplant pancreatic islets in an allogeneic diabetic rat model in which the recipients had been preimmunized to the transplanted tissue [197]. Boettler and colleagues used TheraCyte™ macroencapsulation devices to transplant neonatal mouse tissue into a mouse model of immune-mediated diabetes and showed protection of the tissue from β-cell specific immune attack and prevention of hyperglycemia [39]. Lee and colleagues have shown that β-cell precursors can survive and mature within TheraCyte™ macroencapsulation devices [68]. Other groups have shown survival and function of insulinomas [198], genetically engineered cells expressing human Factor IX [199], hGH [200], GLP-1 [201,202], parathyroid cells [203,204], and human embryonic stem cell-derived pancreatic progenitors [45,46,68,205] within TheraCyte™ devices.

Macroencapsulation devices have been used in limited human studies to test the ability to maintain tissue viability and protect the implanted cells from destruction by the recipient's immune system. Scharp and colleagues implanted low numbers of human islets contained within acrylic-copolymer hollow fibers in T1D and T2D patients, as well as in nondiabetic controls without immunosuppression [206]. After two weeks, the fibers were explanted, and the islets were examined for viability and insulin secretory response. Viable tissue was evident in all three groups, however, only the islets in the nondiabetic control group displayed GSIS. Tibell and colleagues at the Karolinska Institute implanted allogeneic parathyroid tissue contained within Baxter TheraCyte™ devices in nonimmunosuppressed patients for up to 14 months [38]. Fig. 5 shows a photograph of a patient's forearm with the implanted devices outlined. Histology of the explanted devices revealed viable allogeneic endocrine tissue in all devices. However, successful and consistent clinical translation of scaled-up macroencapsulation devices for the treatment of diabetes in humans has yet to be achieved. Major efforts (discussed in later sections) aimed at overcoming oxygen supply limitations by delivering oxygen to macroencapsulated cells *in vivo* are currently under development and evaluation. Additional information on macroencapsulation can be found in the comprehensive reviews by Scharp [125] and Colton [145].

## 3. Challenges of oxygen delivery with encapsulation

Islet macroencapsulation prevents cell-cell contact and the penetration of host blood vessels within the encapsulated islets. In this case, oxygen must diffuse from the outside of the capsule to the surface of the islet and then to its core. The penetration depth of oxygen within encapsulated islets at a given oxygen tension at the surface of the encapsulation device also depends to a great extent on the oxygen demand (oxygen consumption rate) of the islets within the device. Oxygen availability at the chosen site for transplantation along with oxygen consumption by the transplanted tissue are among the key critical determinants of the number of viable and functional islets (cells) that can be supported per unit surface area within a planar macroencapsulation device (e.g. TheraCyte™).

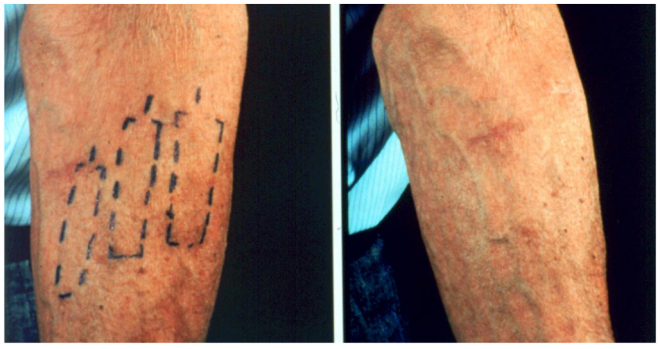

**Fig. 5.** Photographs of the forearm of a patient who had three TheraCyte™ devices implanted in the subcutaneous tissue (outlined with dotted lines on the left image; notice the dark scar line on the right image). The devices contained allogeneic parathyroid tissue and the patient was not immunosuppressed. Photographs were taken at 12 months post-implant. Images from Tibell *et al*, 2001 [38].

Measurements of tissue oxygen concentration or partial pressure at transplant sites *in vivo* are challenging to perform, with the most commonly used modalities being microelectrodes [207], $^{19}F$ NMR spectroscopy [95,208–210] and optical probes [95]. Table 2–Table 4 summarize prior studies performed in animals and humans to measure oxygen availability at several possible islet transplant sites, including (but not limited to): liver, renal capsule, peritoneal cavity, muscle and subcutaneous tissue. Universally, and regardless of location, the measured $pO_2$ is much lower than that measured in venous blood (<40 mm Hg).

Historically, many different potential (unmodified) transplant sites have been explored empirically for their use for islet transplantation and several of them have also been explored for encapsulated islet transplantation. This was performed without the benefit of theoretical modeling taking advantage of knowledge on oxygen levels at the transplant sites and oxygen demand by the transplanted tissue. In 1972, Ballinger and Lacy performed the first successful islet transplant into muscle and the peritoneal cavity of rats [211]. Their group then directly compared the efficacy of islet transplantation into different recipient sites, namely comparing the subcutaneous pocket, peritoneal cavity and the liver (via intraportal injection) [212,213]. They observed diabetes reversal only following transplant into the liver. It was based on these data, and from findings of the early clinical experience by Sutherland and colleagues [214] that the intraportal route of islet transplant became the preferred option. It was also at this time that the focus was shifted to better understanding the impact of immune rejection on allo-islet transplant outcomes, from which stemmed the development of auto-islet transplantation, and much later, the Edmonton protocol [215,216]. Islet autotransplantation (for example, islets that are isolated from patients with chronic pancreatitis, whose pancreata were surgically removed to alleviate intractable pain, are then infused intraportally into their own livers) helped evaluate the survival of intraportally transplanted islets without confounding factors associated with allo- and auto-immunity [217,218] and paved the way for the Edmonton Protocol [215,216]. Since then, extrahepatic sites of islet transplant have been revisited. However, these attempts have resulted in minimal success, largely due to a limited understanding of the poor oxygen availability accompanying alternative recipient sites. In fact, there is growing evidence that the intraportal transplant site may itself have inadequate oxygen supply to support transplanted islets [30,31].

Even in the case of non-encapsulated ITx in the liver, which is considered superior than other sites in terms of oxygen availability, it is currently believed that more than 40% of the islets may die shortly post-transplant due to oxygen starvation prior to vascularization [20,30,31]. This effect appears to be islet size dependent, pointing to limited penetration of oxygen to the core of larger islets as it was predicted by mathematical models and recently demonstrated in the clinical islet auto-transplant setting [20,30,31]. The mathematical models used for the predictions indicated above benefited from the recent development of technology to directly and accurately measure specific islet oxygen consumption rate [219–222], which has enabled calculation of the oxygen required by islets immediately following isolation and after transplantation [30,31].

The low oxygen levels at the transplant site and the immunoisolation requirement, which prohibits the ingrowth of vessels into the islet (Fig. 6A) restrict the number of islets that can be loaded per device while retaining β-cell viability and function (GSIS). This results in an unacceptably large human-sized device (Fig. 7A), unless adequate oxygen is delivered to allow for high-density islet seeding and device size reduction (Fig. 7B) [20]. Measured oxygen demand of the transplanted tissue (e.g., oxygen consumption rate), when integrated with oxygen measurements at transplant sites and used in conjunction with appropriate mathematical diffusion/reaction models can guide device design and loading for optimal viability and function [20]. For example, such models can be used to guide device cell loading and estimate device footprint with and without enhanced oxygen supplementation to devices *in vivo*, taking into consideration the available oxygen at the transplant site and the measured oxygen demand by the tissue. The predicted impact of oxygen supplementation on the footprint of a subcutaneously transplanted device based on modeling of the Baxter TheraCyte™ device is demonstrated in Fig. 7.

In the future, precise determinations of oxygen need within devices and temporal monitoring of local oxygen levels will enable adjusting concentrations that will enhance viability and function of encapsulated cells at any given recipient site [20,32,219]. There may be situations in which enhanced oxygen delivery to encapsulated tissue may not be necessary after a period, even if oxygen demand by the transplanted cells remains unchanged.

An example is the case of autologous transplants (or allotransplanted islets under immunosuppression), when immunoisolation is not needed and blood vessels are allowed to penetrate the device and get close to and within the islets (Fig. 6B). In this case, enhanced oxygen delivery may be terminated once the intra-islet vascularization is sufficient to maintain viability and function. It is important to recognize that oxygen delivery cannot be interrupted in densely packed devices [108,223] unless intra-islet vasculature is adequately formed. This is also true for "device-less" approaches [224] or in prevascularized devices without immunoisolation membranes that enable intra-islet vascularization [108,223]. In these cases, when islets are placed near each other to

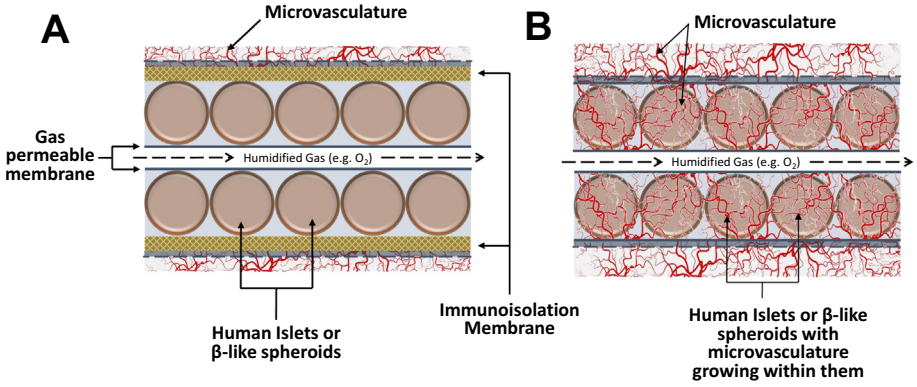


**Fig. 6.** A. Scheme depicting an oxygen-enabled immunoisolation device [two chambers containing a monolayer of islets each (top and bottom) on top of each other, with oxygen gas delivered to the implanted islets through a chamber in the middle. Such devices can be implanted in an animal or a human subject using islets from the same species without immunosuppression. In this case, immunoisolation is required and cells and blood vessels from the recipient cannot be allowed to enter the transplanted islets. Therefore, intra-islet vascularization is not allowed and oxygen may need to be delivered indefinitely so as to support viability and function of the islets at this loading *in vivo*. B. The device can be implanted without the immunoisolation membrane in islet autotransplants to allow the vascular network to invade the device, get closer to the islets and reduce the diffusional distance simulating the situation the islets experience in the native pancreas or in intraportal islet transplantation after vascularization is allowed. In this case, oxygen delivery may be stopped after the intraislet vasculature has formed.

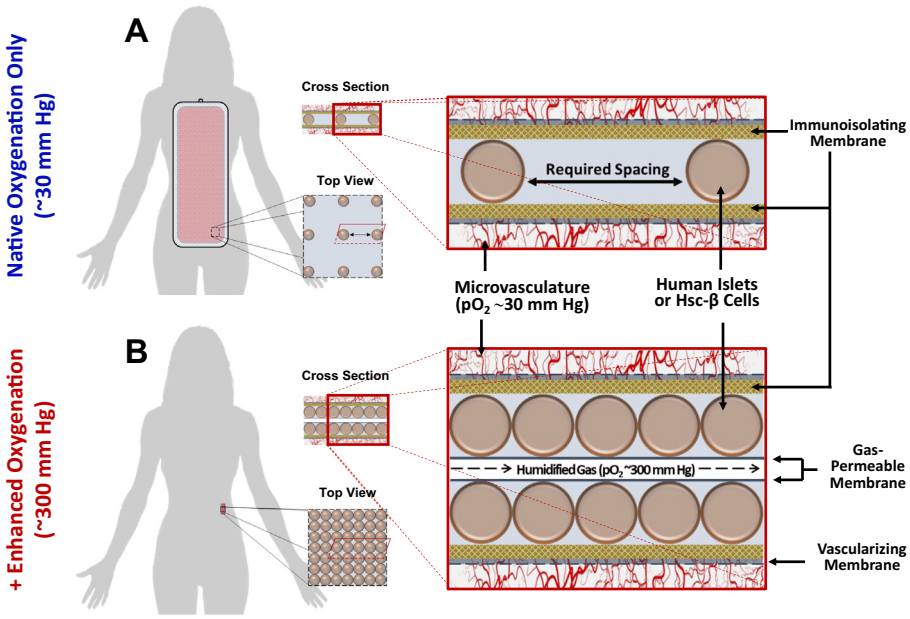


**Fig. 7.** Effect of oxygen supply on the size of implantable islet-containing encapsulation devices. Oxygen delivery as described in Fig. 6 can dramatically reduce the size of the device required.

minimize device footprint, hypoxia and necrotic cores would be expected to be formed as the cells within the islets compete for available oxygen. Unfortunately, this is often overlooked in clinical trials leading to unsuccessful outcomes that could have been predicted and avoided in the first place [103,108,223].

Our current understanding of the need for adequate oxygenation of cells within devices *in vivo* and the challenges associated with it have prompted substantial investment and effort to provide solutions. The sections that follow summarize and review these attempts.

## 4. Strategies for addressing oxygen limitations to improve β-cell survival and function in implanted devices

Sufficient supply of oxygen to encapsulated β-cells to support their viability and function *in vivo* is now recognized as a critical factor for success but has been challenging to achieve [20,31–34,36,82–84,101,102,145,150]. A variety of approaches are being explored to mitigate this problem. These approaches include molecular and pharmacological interventions aimed at protecting islets from hypoxic/ischemic stress and a variety of temporary and more permanent ways to enhance oxygen delivery to encapsulated therapeutic cells *in vivo*. Enhanced oxygen supply to implantable devices via replenishable oxygen chambers [101,107] or external/implantable electrochemical generators [91,225] combined with immunoprotective membranes are sound approaches successfully tested in rodent and large animal models of diabetes [196] — and to a limited extent in humans. The sections that follow summarize these approaches, which have also been addressed elsewhere [98,100,226].

### *4.1. Cytoprotective/antiapoptotic and vascularization promoting agents and approaches*

Numerous molecular approaches have been attempted to render β-cells more resistant to the deleterious effects of hypoxia. On the gene therapy front, adeno-, adeno-associated and retroviral vectors have been utilized to transfer angiogenic and antiapoptotic genes [227]. Transient expression of human VEGF to murine islets stimulated graft angiogenesis and enhanced islet revascularization [228]. Expression of human VEGF-A in transgenic mice also stimulated islet vascularization and β-cell proliferation [229]. Improved revascularization and islet engraftment were achieved by inhibiting the expression of thrombospondin-1 (TSP-1) with TSP-1 siRNA [230]. Adenoviral-mediated expression of A20 and upregulation of heme oxygenase-1 (HO-1) protected islets and β-cells against proapoptotic and proinflammatory cytokines (e.g., IL-1b, INFg) [231,232]. Carbon monoxide (CO), a product of HO activity also protected cells from apoptosis [233,234]. Diabetic mice treated with an IL-1b receptor antagonist prevented β-cell apoptosis induced by IL-1b *in vitro* [235] and prolonged islet allograft survival [236]. Mouse islets treated with alpha 1-antitrypsin (AAT) had reduced expression levels of inflammation-related molecules [237]. Transduction of X-linked inhibitor of apoptosis protein (XIAP) to human islets reduced significantly the number of apoptotic cells and improved islet function and viability [238]. Other apoptosis inhibitors shown to enhance β-cell survival by reducing apoptosis include Val-Pro-Met-Leu-Lys (V5), a pentapeptide that improved the recovered islet mass during isolation and graft function after transplantation [239]. Treatment of human and murine islets with deferoxamine, an iron chelating agent, increased HIF-1a and improved outcomes presumably by decreasing apoptosis and increasing β-cell mass [240]. Simultaneous delivery of CXCL12 (SDF1) and Exendin-4, a GLP-1 receptor analog to β-cells (betaTC-tet) under hypoxic conditions resulted in improved cell survival and function [241]. Alginate microcapsules containing CXCL2, or islets directly coated with the chemokine, induced a sustained local immune-isolation response allowing for long-term survival and function [242].

Preconditioning animals to ischemia before islet isolation has also been studied in several species. Systemic donor or recipient exposure to carbon monoxide (CO) protected cells from apoptosis [234]. Islets isolated from mice preconditioned with a PKCε activator transplanted under the kidney capsule of diabetic mice exhibited improved insulin responses [243]. A similar approach using a caspase-3 inhibitor was also found to be cytoprotective [244]. Repeated rounds of encapsulation in alginate microbeads and peritoneal transplantation in mice resulted in increased rat insulinoma cell (INS-1) resistance to hypoxia [245]. Rodent pancreatic islets have also been reported to be protected from ischemia-reperfusion injury during islet isolation by diazoxide, an ATP-sensitive K+ channel opener [246].

It is important to note that the majority of the molecular approaches evaluated are aimed at protecting cells from death — if hypoxia or ischemia persist, it is unlikely that β-cell function (GSIS) will be regained.

Perhaps future work should focus on identifying molecular and biochemical approaches that may enable islets (or β-cells) to not only survive but also function in the long-term under hypoxic or ischemic conditions, especially within immunoisolation devices. If possible, this could be a major breakthrough for the field.

### 4.2. Enhanced oxygen delivery to implanted capsules and devices

Enhanced oxygen delivery approaches to therapeutic cells within capsules and devices include: prevascularization or enhanced vascularization of the transplant site and or the encapsulation device containing the therapeutic cells, reduction of diffusional distances within capsules and encapsulation devices, enhancing the permeability of oxygen within cell-containing capsules and matrices (e.g., with perfluorocarbons [102]) or by increasing $pO_2$ around or within the encapsulation device, for example with oxygen inhalation or with direct oxygen gas delivery within a chamber in the devices. Biological, photosynthetic oxygen generators have also been co-encapsulated with islets [177].

#### 4.2.1. Prevascularization/enhanced vascularization

Most efforts on islet transplantation in unmodified subcutaneous sites have failed [212,247–249]. In the absence of a prevascularized site, there is an increased susceptibility to islet loss due to ischemic and hypoxic injury. Development of a vascular bed with equivalent or possibly a higher blood flow compared to the native tissue has been explored as a strategy to enhance free and encapsulated islet engraftment and physiological insulin release kinetics.

Transplantation of an explanted kidney containing porcine islets already transplanted and vascularized beneath the kidney capsule and reconnecting the kidney to the blood supply of the new host, demonstrated better function than the same number of porcine islets transplanted under the kidney capsule without prevascularization [250]. Although this approach highlights the importance of prevascularization, it differs from less surgically-involved successful strategies followed by other investigators, including the use of subcutaneous or intramuscular implantations of stainless-steel mesh, polyethylene terephthalate bags, vascular catheters and cell pouch and polylactic acid-based encapsulation devices a few days or weeks prior to islet transplantation to create a prevascularized bed [223,224,251–253]. The main difference in these approaches is that the islets still will need several days to several weeks to vascularize internally (intra-islet vascularization) even if they are placed in a prevascularized site. In the case of the prevascularized islets in the explanted kidney, the intra-islet vasculature was formed and immediately available and functional upon reconnecting the transplanted kidney to the host blood supply [250].

Numerous studies have been performed over the years with a variety of strategies and approaches aimed at prevascularizing encapsulating devices or tissue-engineered chambers in rodents and have generally demonstrated enhanced islet survival and engraftment [251,252,254–261].

Other investigators have succeeded at reversing diabetes in mouse models using a prevascularized subcutaneous site created with a vascular catheter [224], or a cell pouch device implanted 4 weeks before islet transplantation [223]. A refinement of the 'device-less' method where a 5-Fr nylon catheter was used to create a vascularized subcutaneous site [224] resulted in long-term (over a year) glycemic control [262]. However, it is important to recognize the limits of scalability arising from the limitations outlined earlier when islets are packed at substantially high densities [20].

To highlight the importance of this, we utilize the published data on the pre-implantation and prevascularization of a Baxter TheraCyte™ device [126] [153]. Prevascularization of this device reduced the curative dose of macroencapsulated islets in diabetic mice to approximately 2500 IE/Kg BW [126], which is substantially lower than the marginal mass currently used in intraportal islet transplants. However, the number of islets per unit surface area utilized was very low (e.g. ~50 islets per $cm^2$ device). While sufficient for the mouse model, if the number of islets were to be scaled up to a human dose, 5,000-10,000 of such 1-$cm^2$ devices would be needed to harbor 250,000-500,000 IE to reverse diabetes. Thus, an unacceptably large device size would be required because, even with prevascularization, the number of supported islets (β-cells) is limited by the oxygen availability at the transplant site (Fig. 7). Delivering oxygen to the device could dramatically increase the supported tissue but oxygen toxicity limits the thickness of the islet tissue that can be supported within the immunoisolation device. Relatively short-term exposures (24 hours) to 95% or 100% oxygen are highly toxic to human and rat islet tissue.

In summary, although prevascularization is helpful and can reduce the marginal islet (β-cell) dose for diabetes reversal at low device loadings, it is not sufficient and cannot support the high device loadings required for reasonably sized devices in humans without enhancing oxygen delivery to the transplant site. The ease of access of the subcutaneous space makes it an ideal site for implantation, monitoring with non-invasive (e.g., imaging) and minimally invasive (e.g., biopsy) methods, as well as site manipulation and graft retrieval. Therefore, the subcutaneous space merits further consideration as a transplant site for implantable encapsulation devices, especially when coupled with methods for enhanced oxygen delivery.

#### 4.2.2. Reduction in diffusional distances within capsules and devices/enhancement of oxygen permeability

The reduction of diffusional distances within capsules and devices is a logical step in mitigating issues with oxygen supply to encapsulated cells. A variety of approaches and geometries have been considered and have been recently reviewed elsewhere [82–84,102,145,150] along with the practical and technical challenges and limitations associated with them. The enhancement of oxygen permeability within capsules and devices by including a perfluorocarbon within the encapsulating matrix is also a logical approach. This method has the potential to improve the viable and functional β-cell mass by enhancing the permeability of oxygen within encapsulation devices [102]. The impact of this approach is highly dependent on and limited by the $pO_2$ at the transplant site, which is typically low (Table 2–Table 4). It also depends on the volume fraction of the agent that enhances solubility (such as a perfluorocarbon) within the matrix [102]. However, higher volume fractions may have a negative impact on the mechanical properties of the encapsulation matrix and compromise stability. Overall, for the reasons stated above and described in more detail elsewhere [82–84,102,145,150], these approaches may have limited clinical impact and utility, especially in the absence of exogenous oxygen delivery to increase the $pO_2$ at the transplant site.

#### 4.2.3. Delivery of exogenous oxygen to increase $pO_2$ within capsules and devices in vivo

Direct delivery of exogenous oxygen to increase $pO_2$ (to non-toxic levels) within capsules and devices *in vivo* may be the most effective way to enable high islet/β-cell loadings without compromising viability and function within encapsulation devices so as to minimize their footprint (Fig. 7). A variety of approaches are being explored; some (oxygen inhalation, oxygen generating biomaterials) enable temporary gas oxygen delivery as a bridge to vascularization while others enable more permanent oxygen delivery (oxygen gas injection, or electrochemical oxygen generation from water). These approaches along with potential advantages and disadvantages are discussed in the sections that follow.

*4.2.3.1. Oxygen inhalation therapy.* Oxygen inhalation by the transplant recipient [111] is a relatively simple approach that has been explored as a way to enhance oxygen levels at transplant sites, with encouraging results in a rodent model. However, this approach may not be practical for extended periods of time, and even as a bridge to vascularization

may be problematic as short interruptions in the oxygen supply can have significant negative implications on the implanted islet viability and function. Interestingly, oxygen (100%) inhalation in a human study did not appear to increase the intrahepatic $pO_2$ [Table 4]. Furthermore. it may be more limited in its ability to deliver oxygen to the implanted encapsulated cells that need it, especially before devices are vascularized.

*4.2.3.2. Oxygen-generating biomaterials and constructs.* Oxygen can be generated and delivered directly to capsules and devices *in vivo* by co-implanted oxygen generating biomaterials typically entrapped within a scaffold [112,117,263–268]. Sodium percarbonate (SPO), calcium peroxide (CPO), and hydrogen peroxide ($H_2O_2$) are perhaps the most extensively studied molecules [117]. SPO produces oxygen through the generation of hydrogen peroxide as shown below. SPO has been used in various tissue engineering applications [117,264].

$$2[Na2CO3 \cdot 1.5H2O2] \rightarrow 2\ Na2CO3 + H2O2 \quad (1)$$

$$2H2O2 \rightarrow 2H2O + O2 \quad (2)$$

In the presence of water, calcium peroxide (CPO) also generates hydrogen peroxide and oxygen in a two-step reaction:

$$CaO2 + 2H2O \rightarrow Ca(OH)2 + H2O2 \quad (3)$$

$$2H2O2 \rightarrow 2\ H2O + O2 \quad (4)$$

Encapsulation of solid CPO within hydrophobic polydimetylsiloxane (PDMS) (PDMS-CaO2) in a 3D construct sustained β-cell (MIN6) proliferation for over 3 weeks in hypoxic culture conditions [122]. Oxygen-generating agents have been integrated with tissue engineering constructs including hydrogen peroxide-releasing microspheres [265], films of poly(D,L-lactide-co-glycolide (PLGA) [264], polycaprolactone (PCL) nanofibers [266], electrosprayed nanoparticles [267] and PLGA scaffolds [268].

Recent applications of such oxygen-generating biomaterials with encapsulated β-cell systems *in vitro* and *in vivo* produced some encouraging results. Hydrogen peroxide embedded in PDMS used to oxygenate a 3D culture of β-cells showed improved biological function [269]. OxySite, a silicone-peroxide polymeric construct that supplies oxygen, improved graft survival by islet pre-incubation and prevention of hypoxia-induced damage [263]. Oxygen-generating biomaterials may need to be further engineered to provide a gradual release of oxygen to prevent excessive, and possibly damaging, free radical formation.

Biomaterials that generate oxygen from a non-regenerating chemical source may only be able to deliver oxygen relatively short-term (days/weeks) and in a non-controlled fashion. They may also produce high, toxic levels of oxygen (nearly 100%) and potentially other harmful byproducts. For oxygen-generating materials to produce molecular oxygen for extended periods (months/years) and at the scale needed to treat human diabetes, significant size requirements may become major technical limitations. Despite the limitations mentioned above, this approach warrants further experimentation and development and may be able to serve as a bridge to vascularization in selected applications, for example, when immunoisolation is not required and intra-islet vascularization is a possibility (Fig. 6B).

*4.2.3.3. Oxygen gas injection into gas chambers within implanted devices.* Direct oxygen gas injection into a chamber within an immunoisolation device has been championed by Beta-$O_2$ with some promising preclinical data [100–102,113,114,120,196]. This approach in its reported form required daily injections of oxygen. Even though inconvenient, these daily injections can essentially provide indefinite "refueling" and permanent oxygen supply to the device, which may be needed in immunoisolation cases where intra-islet vascularization is not allowed. The prototype Beta-$O_2$ device used in the first clinical case reported [134] was able to maintain human islet survival, and avoid rejection without immunosuppression in a T1D recipient for a period of 10 months. The islet dose used was below the marginal required for diabetes reversal (~2100 IE/Kg BW) and the impact on glycemic control was limited. However, a reduction in insulin requirements and levels of hemoglobin A1c (HbA1c) was reported, which is important and a significant achievement, especially given the low islet dose and the absence of immunosuppression. Beta-$O_2$ devices have essentially the same immunoisolation membrane as the original Baxter TheraCyte™ devices [38] previously reported to protect allogeneic cells from rejection without immunosuppression in human subjects. The Beta-$O_2$ device does not have the additional layer of the vascularizing membrane of the Baxter TheraCyte™ device, which was found to be critically important to prevent the "fibrotic response" and for bringing functional blood vessels near the immunoisolation membrane [38]. The presence of the vascularizing membrane may confer additional significant advantages, including improved glucose and insulin kinetics.

More recent results in another clinical trial of Beta-$O_2$ devices were not as encouraging in terms of efficacy, despite the fact that human islets were not rejected and oxygen supply appeared to maintain viability [133]. The absence of the vascularizing membrane from the Beta-$O_2$ device may partially explain the less than ideal clinical outcomes, despite the absence of rejection and good survival of the islets due to oxygen supplementation [133]. It is also possible that the quality and purity of the human islets utilized may have been a contributing factor. The Beta-$O_2$ device in the form reported is rather large (approximately 36 $cm^2$ in surface area, with ~17 ml of internal volume for the gas chamber) and required general anesthesia. The Beta-$O_2$ device as designed and constructed cannot be prevascularized prior to the infusion of cells. Prevascularization of subcutaneous sites may enable a substantial reduction in the β-cell dose required for diabetes reversal relative to the doses required for intra-portal islet transplantation, especially when combined with oxygen delivery.

*4.2.3.4. Electrochemical oxygen generators.* Permanent oxygen delivery to implanted devices via electrochemical oxygen generation from water is another approach explored either utilizing an implantable oxygen generator or an external wearable oxygen generator [91,225,270,271]. There are no published reports of a fully implantable oxygen generator tested *in vivo* in this context. Some limited *in vitro* results showed promise but also pointed to potential issues with oxygen toxicity [91]. Reports on an external, wearable oxygen generator coupled to a modified Baxter TheraCyte™ device that has the vascularizing membrane in addition to the immunoisolation membrane show promise, with the ability to reverse diabetes with allogeneic islets in non-immunosuppressed rats with a dose below 5,000 IE/Kg BW [225,270,271]. Furthermore, studies demonstrate that oxygen can be delivered to implanted devices via an external wearable electrochemical oxygen generator (wEOG) and be maintained at the desired level for periods of at least 30 days [270] and in some cases more than 90 days. Importantly, the EOG technology may be able to continuously generate and supply the small amounts of oxygen needed, as opposed to requiring daily oxygen injections of large volumes of gas (Beta-$O_2$ device). Therefore, an EOG device may reduce the internal gas volume within the device to the microliter level, as opposed to the milliliter range required by the current prototypes with the reported Beta-$O_2$ approach.

This approach is expected to be superior at the front end by enhancing graft function but also over the life of the implant by improving the kinetics of glucose sensing and insulin bioavailability due to its vascularizing membrane. Continuous oxygen supply at levels below toxicity (40% oxygen) and minimal added volume (gas continuously delivered) as opposed to being stored and refueled, are also important factors to consider.

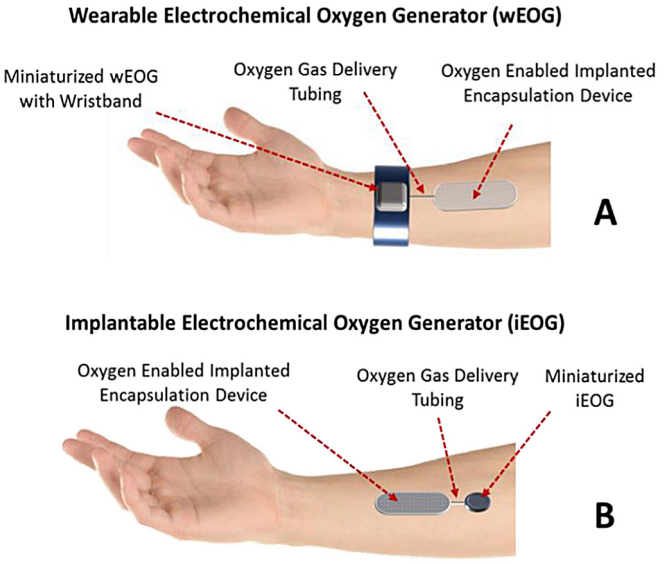


**Fig. 8.** Concept of a prototype cellular implant device connected to a wearable $O_2$ generator, wEOG (A) and ultimately to a fully implantable $O_2$ generator iEOG (B). The battery to support the generator can potentially last many years and should be rechargeable as needed from the outside.

A wearable oxygen generator smaller than an insulin pump is currently available and can be further miniaturized to the size of a wristwatch (Fig. 8A), and it is able to support the islet numbers needed to reverse diabetes in a human and can be tested for proof-of-concept in the porcine model. If these proof-of-concept studies are successful, pilot clinical studies can be quickly undertaken while a fully implantable, miniaturized battery-operated EOG is being developed (Fig. 8B). A battery-operated EOG will permanently deliver oxygen at the desired levels for the lifetime of the implant, which is anticipated to be at least several years. A water source and periodic recharging of the battery through transcutaneous energy transfer will be required and the frequency of recharging will be proportional to the battery size. These technical challenges do not appear to be insurmountable and it is believed that they can be addressed with appropriate expertise and investment.

## 5. Perspective

Even though immunoprotection has been demonstrated in multiple cases, the effective use of encapsulation approaches to convincingly and consistently treat T1D in humans has yet to be demonstrated [100,102,103,106,108,109,115,116,119,129,131–134]. There are a variety of reasons for this depending on the encapsulation approach, transplant site, and origin and maturation stage of the encapsulated cells used; possible explanations have been provided, which include poor islet purity and quality, fibrotic response, inadequate device vascularization, and inadequate oxygen supply [20,103,131].

There is increasing consensus in the field indicating that the efficacy of encapsulation approaches with immunoisolation is compromised by inadequate oxygen supply, especially when scaled for human use, thereby limiting their clinical translation and routine implementation. Enhanced oxygen delivery to encapsulated tissues in immunoisolation implantable devices is critical for the maintenance of tissue viability and function, especially within densely packed insulin-secreting cells in reasonably-sized devices aimed at treating diabetes in humans [20,82–91,97,100–103,107,110–114,117,118,120,122,131,133,134,145,272,273] (Fig. 6). However, despite its critical importance, oxygen is not the only factor limiting success for implantable devices. The quantity and quality — purity, viability and potency — of the transplanted islet (β-cell) product are also of critical importance. Even if a macroencapsulation device delivers effective immunoprotection, or it is well-vascularized and/or well-oxygenated, if the quantity and quality of encapsulated β-cells are insufficient, the outcome will ultimately be poor.

In conclusion, the development and implementation of meaningful real-time islet (β-cell) product characterization assays in terms of quantity and quality [34,95,219–221,274–282], pre- and post-encapsulation, as well as post-transplant is of paramount importance, and will be required prior to successful large-scale implementation of encapsulated cell therapies for the treatment of diabetes. In addition, the presence of support extracellular matrices for the encapsulated cells [64,283–301], is emerging as another component of relevance along with a functional vasculature [20,38,126,302–304] around the encapsulation device to provide key nutrients (other than oxygen) and enable clearance of toxic byproducts, as well as adequate exposure of cells to circulating stimuli (e.g., glucose) for delivery of therapeutic products (e.g., insulin). The absence of any one of these critically needed elements can ultimately lead to poor results and device failure, even in the presence of presumably adequate oxygen supply as evidenced by the limited clinical experience with encapsulated cell transplants to date [20,103,106,108,109,115,116,119,129,131–134].

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## Conflicts of interest

Klearchos K. Papas is the co-founder and CEO of Procyon Technologies, LLC, a startup company focused on the development of oxygenated cell encapsulation devices. Hector De Leon, Thomas M. Suszynski, and Robert C. Johnson have no competing financial interests to disclose.

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