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Review Article

Overcoming Hypoxia: Review of the Encapsulation System to Increase Survival and Viability of Stem Cells

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Abstract

Islet encapsulation technologies aim to protect insulin-producing cells from immune attack while supporting their metabolic function. Two main strategies are currently pursued: microencapsulation and macroencapsulation. Microencapsulation offers a favorable surface to volume ratio, allowing sufficient nutrient and oxygen diffusion to individual or clustered islets. In contrast, macroencapsulation systems enclose larger cell masses within a single device, simplifying retrieval but creating pronounced diffusion limitations, particularly for oxygen. These hypoxic conditions often lead to central necrosis and loss of islet function. To overcome this, various oxygen delivery strategies have been explored, including oxygen-generating materials and external oxygen refueling chambers. However, many of these approaches are limited by uncontrolled release kinetics, cytotoxic byproducts, and poor long-term stability. Perfluorocarbons (PFCs) offer an elegant alternative. These synthetic compounds can physically dissolve and gradually release oxygen in response to local gradients, without generating reactive intermediates. Their compatibility with encapsulation matrices and potential for repeated oxygen loading make them ideal candidates for improving islet survival, especially in macroencapsulation formats. This review highlights current advances in encapsulation technology, compares oxygenation strategies, and explores the potential of PFCs to overcome one of the most persistent barriers in islet transplantation: the challenge of maintaining viability in oxygen-restricted environments.

Introduction

The continued successes and concomitant advances in islet transplantation, have established it as a promising therapeutic strategy for individuals with severe type 1 diabetes mellitus (T1D), particularly those experiencing recurrent hypoglycemia and unstable glycemic control. Historically, long-term insulin independence following allogeneic islet transplantation was rare, with fewer than 10% of recipients remaining insulin-free one-year post-procedure. However, the introduction of the Edmonton protocol marked a significant inflection point [1]. By employing a glucocorticoid-free immunosuppressive regimen and transplanting a sufficient islet mass [2], the Edmonton group achieved substantially improved outcomes, including high rates of one-year insulin independence [3] and sustained partial islet function at five years [4]. This protocol has since been validated and replicated successfully at multiple international clinical sites1, underscoring its reproducibility and therapeutic potential.

The success of this approach relies on achieving an adequate islet mass in combination with steroid-sparing immunosuppression. While the protocol facilitates restoration of endogenous insulin secretion and stabilizes glycemic fluctuations, full endocrine reserve is rarely observed, with most patients eventually experience a gradual decline in insulin independence, highlighting the limitations of current immunosuppressive strategies and islet viability over time. Moreover, the need for islets from multiple donors to achieve therapeutic thresholds significantly limits scalability and widespread clinical application, given the limited availability of suitable pancreatic donors.

As such, islet transplantation remains a developing, adjunctive therapy best reserved for a subset of highly selected T1D patients who have failed conventional medical approaches and exhibit life-threatening metabolic instability. At present, whole-organ pancreas transplantation is still the definitive treatment option, offering superior long-term metabolic reserve [3], albeit with greater surgical risks and is associated with significant surgical complications.

Enhancing therapeutic success of islet transplantation for patients with T1D demands an inexhaustible source of functional islet cell masses and efficient islet cell preservation procedures to optimize islet survival after transplantation [5]. A key obstacle in achieving better outcomes in clinical islet transplantation is the maintenance of islet viability during long-term implantation.

Emerging strategies to enhance the efficacy and durability of islet transplantation such as xenotransplantation, microencapsulation, and oxygen delivery technologies, despite inherent complexities, have introduced new opportunities in the field. A critical determinant of long-term graft function remains the successful engraftment of transplanted islets. This requires not only immune protection but also sufficient nutrients and oxygen diffusion to sustain islet viability and insulin secretion. In the field of islet transplantation, encapsulation technologies have become essential tools to protect insulin-producing cells from immune-mediated destruction while still allowing the exchange of essential molecules such as oxygen, glucose, and insulin. Two main strategies are being explored: microencapsulation and macroencapsulation. Microencapsulation involves enclosing individual islets or small islet clusters in semi-permeable hydrogel spheres, commonly made from alginate or related biomaterials. This format ensures a high surface to volume ratio, which promotes sufficient diffusion of oxygen and nutrients to the encapsulated cells. Because of this efficient exchange, microencapsulated islets can often survive and function without the need for externally supplied oxygen, as demonstrated in various preclinical and clinical settings, including work from our group [6,7].

Macroencapsulation, in contrast, involves placing a substantial number of islets within a single device or chamber. Although this approach allows easier retrieval and offers structural protection, it comes with a significantly lower surface to volume ratio. This poor ratio restricts diffusion, particularly of oxygen, and often leads to hypoxic conditions within the core of the device. These conditions can compromise islet viability and impair insulin secretion. Therefore, macroencapsulation almost always requires exogenous oxygen supply. This can be achieved through oxygen-refillable chambers or by incorporating oxygen-generating components into the device. Our own studies have shown that insufficient oxygenation remains a critical challenge in macroencapsulation and is directly linked to reduced graft function and survival [8-10].

While both approaches aim to provide immune protection and sustain islet function, their biological implications and technical constraints are fundamentally different. The future of the field may depend on combining the advantages of both formats, ideally through the integration of smart oxygenation strategies and materials that support host integration and immune modulation.

To address the issue of islet hypoxia and ischemia, a leading cause of early graft failure, novel approaches such as emulsified perfluorocarbons (PFCs) have been investigated for their ability to act as efficient oxygen carriers [11]. These agents may improve local oxygenation during the critical engraftment phase, thereby enhancing islet survival and function. Despite these promising avenues, the successful clinical translation of these technologies will require further refinement in biomaterial design, immunomodulatory strategies, and oxygenation platforms. This review aims to synthesize recent advances in clinical islet transplantation and explore adjunctive technologies to highlight the future direction of emulsified PFCs as oxygen carriers research aimed at overcoming the current limitations of islet-based therapies for T1D.

Clinical Islet Transplantation

National and international reports demonstrated sustained islet graft function lasting over 4 years in select recipients [12,13].

However, the Edmonton protocol introduced a paradigm shift in 2000 which markedly improved clinical outcomes of islet transplantation [1,13]. Subsequent studies reported that islet transplantation could achieve complete insulin independence, in 60% to 90% of recipients, depending on factors such as islet mass, immunosuppression regimen, and patient selection [1,3,4,14,15]. While islet transplantation has shown the ability to restore near-normal glycemic control, as evidenced by normalized HbA1c durability remains limited with insulin free survival rate decreasing to 15% at five years [3]. Importantly, recipients who retain partial graft function, as indicated by persistent C-peptide positivity, maintained better glycemic control than those who experience complete graft failure [16]. The mechanisms underlying progressive graft dysfunction remain incompletely understood but may include chronic alloimmune or recurrent autoimmune responses, direct toxicity from immunosuppressive agents, or beta cell apoptosis resulting from hypoxic injury during pancreas procurement, islet isolation, and engraftment. These challenges underscore the need for continued innovation in islet preservation, immunomodulation, and graft protection strategies to enhance long-term outcomes [3,4].

The restricted availability of viable tissue represents a critical limitation. Islets isolated from a single pancreas are typically insufficient to achieve insulin independence, necessitating the use of islets from multiple donors for a single recipient [3]. This limitation is compounded by a global shortage of organ donors, as well as suboptimal pancreas preservation and islet isolation techniques that compromise cell viability and yield. Stringent donor selection criteria based on overall health status as well as age and body mass index (BMI), further reduce the eligible donor pool [17]. To address these challenges, ongoing efforts have focused on enhancing islet yield and viability through improved pancreas procurement, preservation, and enzymatic digestion protocols. In particular, advances in the utilization of marginal donor pancreata, coupled with refined isolation methods, have shown promise in increasing the likelihood of achieving insulin independence using islets from a single donor. Success in improving the rate of single donor transplantations using the two-layer method (TLM) of pancreas preservation included University of Wisconsin solution (UW) and perfluorocarbon (PFC) [18]. PFC, immiscible with water, contributes to the success of organ preservation due to its ability to store high levels of oxygen and its low oxygen-binding constant [11]. The viability and function of islet cells are highly dependent on a reliable oxygen source to prevent damage and death [13]. To mitigate ischemic injury, perfluorocarbon (PFC)-based methods facilitate efficient oxygen delivery to the ischemic organ [19]. The TLM has been demonstrated to enhance islet yield, viability, and functional capacity following isolation. Moreover, the TLM shows potential in resuscitating marginal pancreata that would otherwise be deemed unsuitable for transplantation. Importantly, the application of TLM has expanded the utilization of pancreata from donors over 50 years old, thereby increasing the pool of eligible donors and addressing the scarcity of islet cells available for transplantation. Notwithstanding, the persistent shortfall in viable islet mass necessitated exploration of xeno-islets as an alternative source for transplantation [20].

Xenotransplantation

Pigs are considered the preferred source species for clinical xenotransplantation due to their physiological and anatomical similarities to humans, including comparable organ size and metabolic function [21]. Their relatively short gestation period and large litters facilitate rapid breeding, making them particularly amenable to genetic modifications aimed at reducing immunogenicity and improving graft compatibility. Importantly, pigs maintain blood glucose levels within a range similar to that of humans, and historical studies have demonstrated that porcine insulin can be effective in therapy in humans [22,23]. Although early efforts at pancreatic islet xenotransplantation were unsuccessful, there has been at least one report documenting the long-term survival of encapsulated porcine islets in a human recipient. Recent advances in preclinical models have renewed interest in porcine islet transplantation [22]. For instance, studies in diabetic non-human primates have demonstrated the potential of porcine islets to restore normoglycemia and maintain graft survival for extended periods [24]. A recent clinical trial using combined neonatal porcine pancreatic islet and sertoli-cell implantation into subcutaneous collagen-covered devices in Mexican children with type 1 diabetes failed to demonstrate meaningful xenograft function [12]. Notably, this trial lacked a robust preclinical evidence base, and the ethics of proceeding to human experimentation under such conditions have been widely criticized. As a result, the study was suspended by the National Commission of Bioethics in Mexico [25] Nevertheless, additional evidence from preclinical studies continues to emerge. For example, a recent study evaluated the capacity of neonatal porcine islets to engraft and restore glucose control in pancreatectomized rhesus macaques, further supporting the potential for clinical translation [26]. Thus, porcine islets continue to represent a potential solution to the limited supply problem in clinical islet transplantation [27].

Microencapsulation Technology

Considerable effort has gone into the development of encapsulation techniques for pancreatic islet transplantation, which allows protection of the pancreatic islets from immune-mediated destruction without the requirement for chronic immunosuppression therapy. Encapsulation could allow for the transplantation of islets from non-human donors (i.e., pigs) by preventing immune rejection. The identification of novel polymers with improved biocompatibility and optimal pore size for efficient nutrient exchange allowing the incorporating factors to promote blood vessel formation around the encapsulated islets is a key challenge.

A recent report demonstrated that encapsulation of adult porcine pancreatic islets with an alginate matrix can significantly prolong the survival in non-human primates for up to six months [28]. While these findings are promising, no current encapsulation technology has yet provided adequate immune protection or metabolic support for long-term treatment of T1D in humans [29]. The encapsulation of cells in semi-permeable matrices that maintain cell viability and metabolic functionality has extensive clinical applications and is likely to play a major role in cell and transplantation therapy over the next decade [30]. Additionally, cell encapsulation has also proven valuable in the development of *in vitro* 3D culture systems that better replicate the physiological microenvironment than traditional monolayer cultures. The success of an encapsulation device depends on a combination of critical factors: permeability to essential small molecules (e.g., oxygen, glucose, electrolytes), mechanical integrity, immune exclusion (particularly of antibodies and cytotoxic T cells), and overall biocompatibility. The matrix must facilitate bidirectional transport facilitating the entry of nutrients and oxygen and the exit of waste metabolites, hormones, and therapeutic products, while preventing immune-mediated damage to the encapsulated cells.

A variety of materials, especially alginate-based hydrogels, have been evaluated for these purposes, along with diverse cell configurations, including flat, multilayer, and three-dimensional microencapsulated formats. Microencapsulation has shown therapeutic potential not only for type 1 diabetes but also for conditions such as central nervous system malignancies and liver disease. However, several key issues need to be addressed before the clinical use of this technology can be fully realized. These include the availability of transplantable cells, protection from immune rejection, maintenance of cell viability, long term functionality, and the overall biocompatibility of the encapsulation system. Metabolic functionality within these devices is governed by the diffusion of oxygen and nutrients, with oxygen availability being the most critical limiting factor. Inadequate oxygenation often leads to hypoxia-induced cell death or impaired function, making optimization of oxygen transport a central priority. Without sufficient oxygen, even well-protected and immune-isolated cells will fail. Preventing the formation of necrotic or hypometabolic zones requires careful consideration of both material properties and device architecture.

Macroencapsulation platforms have been designed with retrievability and immune shielding in mind. However, due to their unfavorable surface to volume ratio, they are especially prone to oxygen limitations. Several advanced macroencapsulation systems have been developed to address this challenge. The β Air device (Beta-O_2 Technologies) incorporates an oxygen chamber that requires periodic refueling and allows continuous diffusion of oxygen to the encapsulated islets. This system has shown promising preclinical and early clinical results by maintaining viability and insulin production in a macroenvironment that would otherwise be severely hypoxic [31-33].

Another notable example is the Encaptra device developed by Via Cyte, which uses a flat planar design and a selectively permeable membrane to enclose stem cell derived insulin-producing cells [34]. This system aims to provide immune protection while allowing vascularization around the device. However, despite this design, oxygen limitations remain a concern and have contributed to the mixed outcomes seen in clinical trials [35]. Materials used in these devices range from medical grade alginates to expanded polytetrafluoroethylene (ePTFE), polyethersulfone, and polyurethane-based polymers [36]. Each of these materials offers specific advantages in terms of mechanical strength, permeability, and immune modulation, but all must be balanced against the risk of fibrosis and foreign body response, which can further impair oxygen diffusion.

Our own group has explored the effect of oxygen tension and hydrogel composition on islet viability, demonstrating that even minor changes in material density or porosity can have substantial effects on cell survival and function [7,9]. Oxygen generating materials such as calcium peroxide have also been investigated to support local oxygenation, although their safety and long-term performance still require careful validation [37]. In conclusion, macroencapsulation offers a structured and scalable solution for immune isolation, but only when oxygen availability and biocompatibility are adequately addressed. The field is progressing towards more sophisticated devices that combine physical protection, controlled oxygen delivery, and long term retrievability.

Internal oxygen mass transfer limitations are associated with significant oxygen deficiencies with most cell encapsulation devices. One of the primary causes of hypoxia is the restricted diffusion of oxygen to the core of the capsules; as a result, cells located centrally within the microbead often experience oxygen deprivation and undergo apoptosis or necrosis [38]. For example, bTC3 cells encapsulated in alginate have significantly lower oxygen uptake rates than cells grown in a monolayer culture, highlighting the critical influence of the encapsulation environment on cellular metabolism. The survival and function of encapsulated cells depend not only on the physicochemical properties of the matrix but also on the availability of nutrients and oxygen within the encapsulation device and the surrounding medium [39]. Strategies to improve oxygen delivery and mitigate hypoxia include sparging oxygen into the culture medium, perfusing oxygen through silicone tubing, minimizing the size and diffusion distance within the encapsulation geometry, and incorporating oxygen-generating or oxygen-permeable membranes into the device design [40], Optimizing perfusing oxygen through silicone tubing [41], minimizing encapsulation geometry [42] or using oxygen-rich membranes [43,44] is essential for enhancing cell viability and achieving long-term therapeutic efficacy of microencapsulated islet transplants. These approaches are particularly critical because hypoxia arises when oxygen delivery fails to meet the metabolic demands of encapsulated cells.

Islets and Ischemia

Hypoxia arises when oxygen delivery is insufficient to meet the metabolic demands of cells. During pancreas procurement, interruption of the oxygen-rich blood supply to the organ initiates ischemic injury, which may persist following transplantation. In the hypoxic environment, cells are unable to sustain the energy demand for active ion-transport, leading to energy failure and subsequent apoptosis [45]. In early stages of ischemia, cellular ATP consumption remains relatively constant, resulting in a mismatch between energy supply and demand. To compensate, cells shift to anaerobic ATP production. However, the anaerobic pathway is inefficient, rapidly depleting glucose and glycogen while toxic byproducts, lactate and protons (H^+) accumulate, further compromising cellular homeostasis. The metabolic imbalance progressively suppresses mitochondrial oxidative phosphorylation triggering cell death through necrotic or apoptotic pathways, depending on the extent and duration of injury (Figure 1) [46]. The excess lactic acid generated by lactate dehydrogenase (LDH), which catalyzes the conversion of pyruvate to lactate, exacerbates intracellular and extracellular acidosis. This acidic environment not only impairs normal cellular function but also promotes sterile inflammation by activating macrophages and stimulating pro-inflammatory cytokine release. Together, these events contribute to islet graft dysfunction and loss [47].

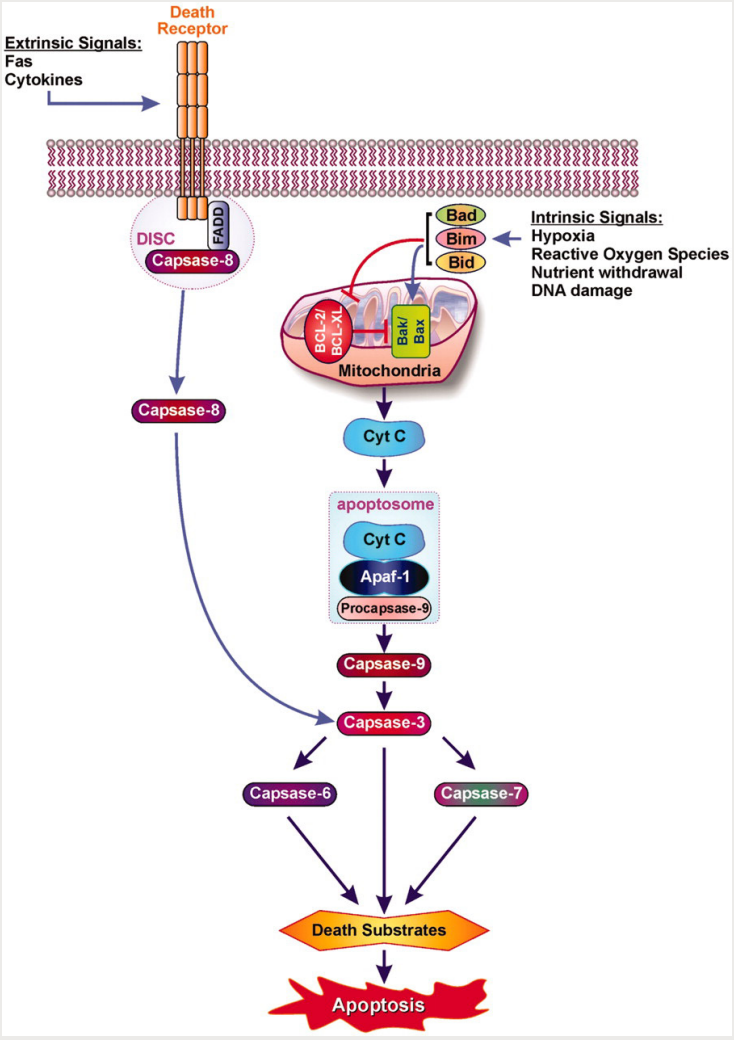

Figure 1: Intrinsic and extrinsic pathways leading to apoptosis.

Ischemia Reperfusion Injury

When blood flow and the supply of oxygen are re-established, the low oxygen availability in tissues in conjunction with accumulated anaerobic metabolites leads to the production of harmful oxygen free radicals via the hypoxanthine-xanthine oxidase reaction [48] (Figure 2). The oxidative stress induces protein peroxidation, direct DNA damage, and/or lipid peroxidation augmenting the potential for cell injury [49] (Figure 3). Reactive oxygen species (ROS) also

can cross-link membrane proteins, cleave peptide bonds, alter the function of glycosaminoglycans, and promote DNA disruption [50]. Concurrently, prolonged ischemia depletes the tissue of protective antioxidants.

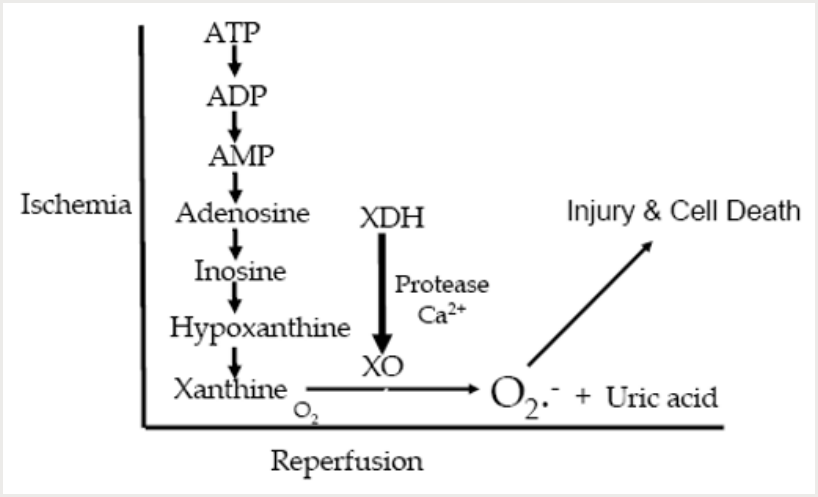

Figure 2: Mechanism of ischemia reperfusion injury.

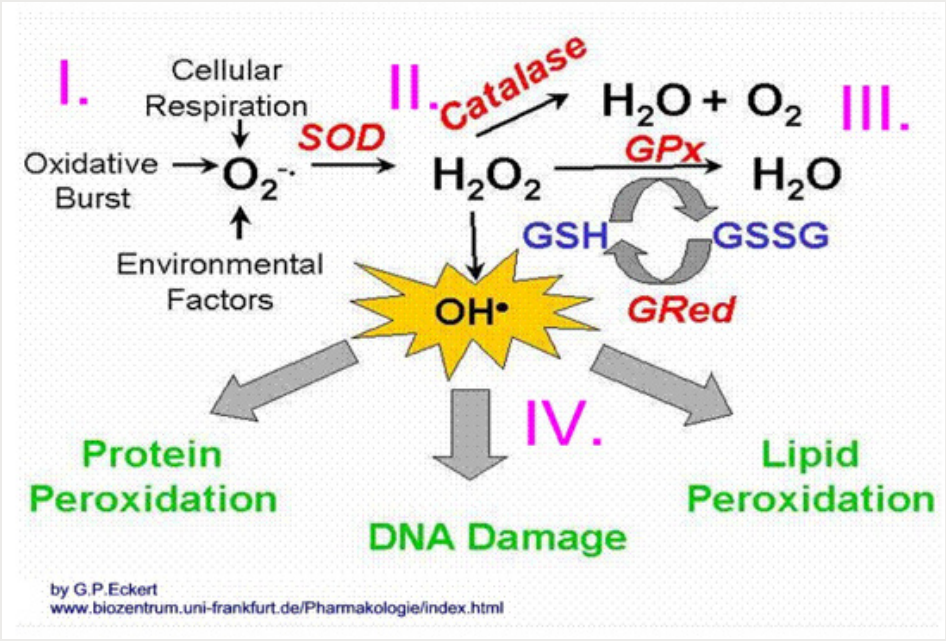

Figure 3: different steps of ischemia reperfusion injury.

Administration of exogenous antioxidants, such as glutathione, plays a critical role in mitigating reperfusion injury in ischemic tissues. Glutathione is commonly included as an additive in organ preservation solutions due to its ability to neutralize ROS and free radicals, thereby limiting oxidative damage [51]. In its reduced form (GSH), glutathione directly scavenges hydroxyl radicals, hydrogen peroxide, and lipid peroxides, preventing oxidative injury to cellular membranes and proteins. Several organ preservation solutions incorporate GSH to enhance cellular redox buffering capacity during cold storage and reperfusion. Other antioxidant agents have also been investigated or incorporated into preservation fluids [52]. These include superoxide dismutase (SOD), which catalyzes the dismutation of superoxide radicals into hydrogen peroxide and oxygen; allopurinol, a xanthine oxidase inhibitor that reduces the formation of superoxide during reperfusion; prostaglandin synthesis inhibitors, which may reduce inflammation-associated oxidative stress; and lipid-soluble vitamin E (α-tocopherol), which protects cellular membranes from lipid peroxidation. The inclusion of these agents reflects a multifaceted approach to mitigating ischemia-reperfusion injury through the reduction of oxidative

stress and inflammation [53].

Perfluorocarbons as Oxygen Carriers

Building on these principles, efforts in the late 1980s, *Kuroda, et al*. led to the development of a two-layer cold storage method (TLM) using perfluorocarbon (PFC) and University of Wisconsin UW solution to enhance oxygen delivery and improve whole-pancreas preservation [54]. PFC is a hyper-oxygen carrier designed to release oxygen into the surrounding tissue more effectively [19] (Figure 4). PFC is immiscible with aqueous systems and has a high density, clearly separated from UW in the TLM method. Unlike hemoglobin-based oxygen carriers, PFCs are fully synthetic compounds derived from halogenated hydrocarbons and do not chemically bind oxygen. Instead, PFCs physically dissolve oxygen in accordance with Henry's law, where oxygen solubility is directly proportional to its partial pressure (pO_2) [11]. This stands in contrast to hemoglobin, which exhibits cooperative oxygen binding characterized by the sigmoidal Barcroft curve. As a result, PFCs offer a linear and predictable oxygen loading and unloading profile, making them advantageous for controlled oxygen delivery in static preservation systems such as TLM (Figure 5) [55]. The oxygen-carrying capacity of PFC is minimally affected by physiological variables such as pH (acidosis or alkalosis) and temperature, making PFCs particularly well-suited for use during cold organ preservation [56]. By maintaining consistent oxygen delivery under hypothermic conditions, PFC-based storage systems such as the TLM can significantly extend the permissible cold ischemia time. This prolonged preservation window enhances islet viability and increases the likelihood of successful transplantation following tissue transport. During ischemia, the availability of endogenous substrates required for ATP synthesis is significantly diminished due to impaired oxygen delivery and metabolic downregulation [57]. However, in the context of organ preservation using the TLM, ATP regeneration can occur through direct phosphorylation of adenosine present in the UW solution. This mechanism enables the synthesis of ATP even in ischemically injured pancreatic tissue [58]. Given that ATP is a critical energy source for maintaining cellular integrity and supporting repair processes, its regeneration during cold storage likely plays a pivotal role in preserving pancreatic viability and function. *Hiraoka, et al*. achieved insulin independence in patients with T1D after single-donor islet transplantation using less than eight hours of cold storage with TLM and new immunosuppression protocols [58]. *Ricordi, et al*., demonstrated significantly improved islet recovery from marginal "older" donors by using TLM [59]. Further, despite a small sample size, *Matsumoto, et al*., demonstrated significantly improved islet recovery by using TLM after six to eight hours of cold storage in UW solution with short and prolonged total cold storage time [18]. Further, *Brandhost, et al*., provided compelling evidence that oxygenated PFCs can be used in a one-layer method (OLM) with comparable outcomes to TLM preservation solution [60]. Using the OLM method is more cost effective and simple compared to the TLM method61. In a recently published paper, the pO_2 was measured using fiber optic sensors in the core of porcine pancreatic tissue preserved with TLM in a media saturated with 100% oxygen. Experimental measurements have confirmed that the pO_2 approaches zero at the core of a 1 cm-thick pancreatic tissue sample preserved using the TLM, highlighting the limitations of passive oxygen diffusion in larger tissue volumes [61] Oxygen content within the core of encapsulated tissues or dense organ sections remains limited due to the inherently poor diffusion capacity of oxygen. This diffusion barrier significantly compromises tissue viability, particularly at the center of microbeads or organ slices. Therefore, more efficient oxygenation strategies are required to overcome this limitation and improve outcomes. Notably, this study found no significant benefit of the TLM on islet isolation or transplantation efficacy, underscoring the need for improved oxygen delivery models [62]. Further evidence from *in vitro* studies investigating the impact of various perfluorochemicals (PFCs) on cultured dorsal root ganglion (DRG) cells suggests that specific compounds, such as perfluorodecalin (PFD) and perfluorooctylbromide (PFO), may be unsuitable for long-term clinical use [63]. For example, in the context of vitreoretinal surgery, both PFD and PFO have been associated with adverse cellular responses, including foam cell formation in co-cultured macrophages—an effect resembling *in vivo* reactions to persistent PFC presence in the vitreous body Importantly, these adverse effects are largely attributed to the use of non-emulsified PFCs in culture. Emulsification of PFCs is therefore necessary to reduce macrophage activation and improve biocompatibility in tissue culture systems.

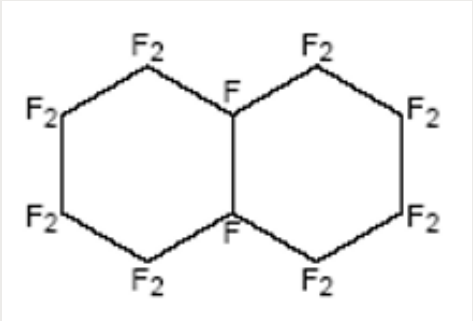

Figure 4: Bicyclic perfluorocarbon.

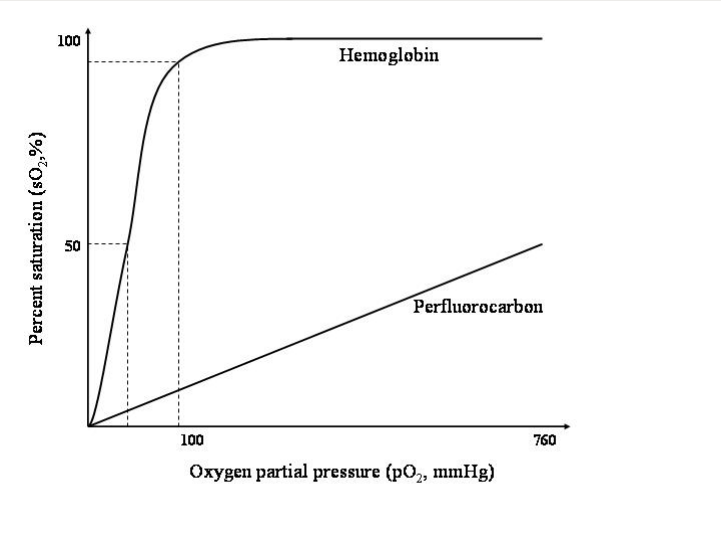

Figure 5: Oxygen diffusion in PFC as compared to hemoglobin.

Emulsified Perfluorocarbons

The ability to dissolve large volumes of oxygen and other gases, inertness in the body and excretion primarily as a vapor during exhalation are important qualitative aspects of PFCs. Liquid PFCs are immiscible with blood and other body fluids but allow for safe intravenous injection as submicron emulsions. Emulsified PFCs have been evaluated in clinical trials as temporary, intravascular tissue-oxygenating fluids. One such emulsion, a commercial perflubron-based, phospholipid-stabilized formulation, is currently being evaluated as an alternative to transfusing donated blood during surgery in a late-phase clinical trial. The use of synthetic blood will reduce the need for donors and reduce other transfusion-associated risks such as the spread of blood-borne disease. Clinical studies have shown that this emulsion can adequately maintain tissue oxygenation during acute blood loss with no abnormal hemodynamics. The utility of PFC's as blood substitutes in the early 1980's was limited due to low concentration and short half-life. Improved emulsion design has attenuated limitations related to chemical properties, producing a more effective agent [64]. Contemporary PFC emulsions are non-toxic and have been utilized to prolong the fertilizing capacity [65] highlighting application of PFCs as oxygen carriers for clinical uses beyond organ preservation [66]. Further experimentation is still warranted to assess the effects of PFC emulsion components on growth and structure of microbial cells [67]. PFC emulsions intended for clinical use have traditionally relied on surfactants such as Pluronic F-68 and egg yolk phospholipids (EYP). However, both surfactants have been associated with adverse immunological effects, including inflammatory and allergic responses upon intravenous administration. These reactions are primarily mediated by the phagocytosis of emulsified PFC microparticles by innate immune cells, particularly macrophages. To mitigate these adverse effects, more biocompatible surfactants that are less prone to phagocytic uptake are being developed. One such candidate is a perfluoroalkylated polyethylene glycol (PEG)-based surfactant, which was synthesized and used to formulate a PFC emulsion via ultrasonic homogenization. The resulting emulsions were incubated with murine macrophage cells to evaluate phagocytic activity. Results demonstrated significantly higher phagocytosis in cultures containing EYP-based emulsions compared to those stabilized with PEG, suggesting improved biocompatibility of the PEG-based formulation [68].

While PFCs have been employed in both liquid and gel emulsion formats, their integration into islet encapsulation devices as a strategy to enhance local oxygen delivery remains largely unexplored. Conceptually, PFCs embedded within encapsulation matrices could act as oxygen reservoirs, gradually releasing O_2 based on concentration gradients and diffusion kinetics. In a recent study, alginate, a widely used hydrogel in tissue engineering, [65] was employed to encapsulate metabolically active and oxygen demanding liver HepG2 cells, which have high oxygen demands [31,33]. Incorporation of PFCs into the alginate matrix improved cellular metabolic function, as evidenced by decreased extracellular lactate production and reduced intracellular lactate dehydrogenase (LDH) activity, indicating a shift away from anaerobic glycolysis. These findings suggest that PFC-alginate composite hydrogels may hold promise for enhancing the viability and function of encapsulated islets or for supporting oxygen-sensitive processes in stem cell differentiation and tissue regeneration applications.

Conclusion

PFCs have been widely investigated across a range of biomedical and bioprocessing applications due to their exceptional capacity to dissolve and transport gases, particularly oxygen. PFC-based

formulations have shown promise as synthetic blood substitutes in clinical trials, and several have received FDA approval for use in specialized settings such as intraoperative blood oxygenation during cardiopulmonary bypass or organ preservation. There is growing evidence that PFC emulsions may play a critical role in the management of ischemic tissues and oxygen-restricted cell systems. In the context of islet cell culture and transplantation oxygen diffusion remains a major limiting factor, often leading to central necrosis within the islet core. Our group and others have demonstrated that PFCs support islet viability, reduce anaerobic glycolysis, and prevent central necrosis in metabolically active tissues encapsulated in alginate matrices (*Smink, et al.,* 2017; *de Vos, et al.,* 2022; *Lakey, et al.,* 2025). This review reinforces and expands the growing body of evidence positioning PFC–infused biomaterials as a transformative solution to the chronic challenge of oxygen deprivation in encapsulated islet transplantation. Conventional oxygen-generating additives such as peroxides fail to sustain long-term viability due to erratic release profiles, toxic byproducts, and microenvironmental acidity. In stark contrast, PFCs function as biocompatible, chemically inert oxygen carriers: they dissolve O_2 proportional to its partial pressure without generating reactive intermediates, enabling steady oxygen delivery even under hypoxic or ischemic conditions. Embedding PFCs (i.e., perfluorooctylbromide (PFOB), within alginate encapsulation matrices significantly enhances local oxygenation, maintains islet viability, and preserves function during *in vivo* transplantation. For instance, enhanced glycemic control was achieved in diabetic mice using PFOB-alginate macrocapsules over several weeks. This design is further supported by modeling studies which predict substantial improvements in mass transfer and oxygen diffusion in dynamic systems containing circulating PFC emulsions. Additionally, PFCs bring practical advantages over hemoglobin-based carriers, including chemical inertness and easier reusability. Given that PFC-based formulations already have FDA approval for critical biomedical applications, such as organ preservation and cardiopulmonary support, translating them into clinical-grade biomaterials for islet transplantation is a logical next step. Their unique ability to be externally reoxygenated also aligns them perfectly with macroencapsulation formats, addressing the limitation of poor oxygen diffusivity inherent in larger device volumes.

Moving forward, optimizing PFC emulsification, dosing, and integration into encapsulation platforms is essential. Investigating species-specific and tissue-level responses will help refine biomaterial designs. Importantly, our findings underscore that PFC-infused encapsulation platforms should be prioritized in future islet transplantation research, and potentially expanded into broader regenerative medicine contexts where oxygen diffusion remains a fundamental limitation. This strategy holds significant promise for advancing the clinical viability and long-term success of cell-based therapies.

Conflict of Interest

None.

Acknowledgement

None.

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