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Progress and Challenges in Macroencapsulation Approaches for Type 1 Diabetes (T1D) Treatment: Cells, Biomaterials, and Devices

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ABSTRACT: Macroencapsulation technology has been an attractive topic in the field of treatment for Type 1 diabetes due to mechanical stability, versatility, and retrievability of the macrocapsule design. Macro-capsules can be categorized into extravascular and intravascular devices, in which solute transport relies either on diffusion or convection, respectively. Failure of macroencapsulation strategies can be due to limited regenerative capacity of the encased insulin-producing cells, sub-optimal performance of encapsulation biomaterials, insufficient immunoisolation, excessive blood thrombosis for vascular perfusion devices, and inadequate modes of mass transfer to support cell viability and function. However, significant technical advancements have been achieved in macroencapsulation technology, namely reducing diffusion distance for oxygen and nutrients, using pro-angiogenic factors to increase vascularization for islet engraftment, and optimizing membrane permeability and selectivity to prevent immune attacks from host's body. This review presents an overview of existing macroencapsulation devices and discusses the advances based on tissue-engineering approaches that will stimulate future research and development of macroencapsulation technology.

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KEYWORDS: type 1 diabetes (T1D); islet encapsulation; macroencapsulation devices; immunoisolation; cells and biomaterials; micro-electro-mechanical systems (MEMS)

Introduction

Type 1 diabetes (T1D) mellitus results from autoimmune destruction of insulin-producing β cells in the islets of Langerhans of the endocrine pancreas, causing reduction in β cell mass and dysfunction. Of the more than 366 million people worldwide affected by diabetes today, it is estimated that as many as 40 million patients have T1D (Rewers, 2012). The global incidence of T1D doubles approximately every 20 years (Harjutsalo et al., 2008; Vehik et al., 2008), increasing up to 5% per year (Nokoff et al., 2012).

As the prevalence of T1D increases worldwide, the associated chronic complications are the main cause of morbidity and mortality, which adversely affect the quality of T1D patients' lives (Zhao et al., 2009). Specifically, complications of diabetes have been classified as either microvascular (e.g. retinopathy, nephropathy, and neuropathy) or macrovascular (e.g. cardiovascular disease and peripheral vascular disease) (Melendez-Ramirez et al., 2010; Nathan, 2014). Macrovascular complications in T1D show significant morbidity and mortality in comparison to individuals with Type 2 diabetes. For T1D patients under age 40, the onset of macrovascular complications occur much earlier in life, exacerbate throughout the course of disease, and result in a higher mortality compared to the general population (Melendez-Ramirez et al., 2010). The total estimated financial burden for T1D is $14.9 billion in health care costs in the U.S. each year, including medical costs of $10.5 billion and indirect costs of $4.4 billion (Dall et al., 2009). The economic burden per case of diabetes is greater for T1D than type 2 diabetes and the difference increases with age (Dall et al., 2009). This trend will only continue given the escalation in global incidence and worsen as the T1D population ages and disease progresses, especially for patients in low-resource settings.

Current Treatment Methods

There are currently two dominant paradigms associated with the treatment of T1D: insulin infusion therapy and whole organ transplantation.

Insulin Infusion

Insulin therapy is administered with multiple daily injections or subcutaneous infusion using an insulin pump (Golden et al., 2012; Little et al., 2012; Yardley et al., 2013). To survive, T1D patients must measure their blood glucose levels and administer insulin in response to those glucose levels multiple times per day for the rest of their lives. Even in the most compliant patients, tight glucose control is difficult to maintain. For example, patients must calculate insulin dose at mealtimes by taking in account of several factors, such as blood

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glucose levels, insulin/carbohydrate ratio, carbohydrate intake, intensity of physical exercise after injection, and individual insulin sensitivity. Any small miscalculation can result in episodes of hypo- and hyperglycemia, causing life-threatening conditions. These dangerous fluctuations in glucose levels are the primary cause of diabetic complications (Cryer, 2002; Little et al., 2012). Hypoglycemia can result in cognitive impairment, unconsciousness, seizures, and death (Cryer, 2002). Hyperglycemia leads to similarly devastating complications, such as kidney failure, heart attack, stroke, blindness, nerve damage, and many other diseases (Cryer, 2012). The elevated levels of glucose may induce glycation of various structural and functional proteins that leads to advanced glycation end products (AGES), which are thought to be the major causes of different diabetic complications (Negre-Salvayre et al., 2009).

Although use of insulin injections and insulin pumps are life-prolonging technologies, they do not mimic real-time secretory patterns of pancreatic β cells nor do they prevent long-term complications (Hinshaw et al., 2013; Penfornis et al., 2011). Medtronic has recently designed a new algorithm, Predictive Low Glucose Management (PLGM), which automatically stops the delivery of insulin when a sensor detects a predetermined low glucose level (Danne et al., 2014). However, designing algorithms to make therapeutic decisions with accurate and instantaneous regulation of blood sugar level with minimal human input remains a challenge (Dolgin, 2012).

Pancreas Transplantation

Whole pancreas transplantation presents an alternative intervention for T1D by re-establishing normoglycemia without the excessive need for insulin therapy. From 2004 to 2008, the most common pancreas transplant category was a combined pancreas/kidney transplant (SPK) (∼73%) where immunosuppressives were used for both transplants, followed by a kidney transplant before undergoing a pancreas transplant (PAK) (∼18%), and pancreas transplants alone (PTA) (∼9%) (Gruessner and Sutherland, 2008). Prior to 2000, PTA and PAK transplant categories had experienced more graft loss comparing with SPK (Sutherland, 1998; Sutherland et al., 2001). Graft loss happens frequently in PTA and PAK patients because these patients do not suffer from the uremia associated with renal failure, hence their healthy platelet function places them at a higher risk for thrombosis in the low-flow state of the pancreas graft (Troppmann et al., 1996; Venstrom et al., 2003). Treatment with anti-coagulant agents like heparin and dipyridamole are required during the perioperative period to decrease the likelihood of graft thrombosis, but they increase bleeding risk (Farney et al., 2012). With advances in immunosuppression since 2000, the use of antibody induction and steroid avoidance-based maintenance protocols (Tacrolimus/Mycophenolate Mofetil or Sirolimus) in all transplant categories has been shown to improve the outcome of pancreas transplantation extensively, as illustrated by the pancreas graft survival rates of 85% and 52% in PTA, 81% and 55% in PAK, and 87% and 72% in SPK at one year and five years, respectively (Kandaswamy et al., 2013).

Although pancreas transplantation can achieve insulin-independence with a greater than 80% graft survival rates in all categories after one year, this approach has many drawbacks. First, whole organ transplantation is constrained by the number of donors. Of 8,000 available donors in the US, just around 1,400 donors (16%) are potentially suitable for whole organ transplantation annually (Gruessner et al., 2010). Second, T1D patients with accelerated course of cardiovascular complications are not recommended for such a complex operation due to their underlying cardiovascular disease and increased risk of perioperative complications (Gruessner et al., 2004; Nathan, 2003). The combination of perioperative cardiac risk coupled with surgical complications places whole pancreas transplantation as the procedure with highest morbidity among all routinely performed abdominal solid organ transplantation surgeries (Humar et al., 2000; Schenker et al., 2011).

Alternative Treatment Methods

Cell Therapy

Intraportal alloislet transplantation, as described by The Edmonton Protocol (Shapiro et al., 2000), has shown promise in becoming a viable T1D treatment after demonstrating that a cohort of seven patients remained insulin-independent with an average of 12 months under steroid-free immunosuppressive drugs during the last decade. The Clinical Islet Transplantation Consortium (CIT) created by the US National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) and the US National Institute of Allergy and Infectious Diseases (NIAID) is a network consisting of 13 clinical centers to conduct studies of islet transplantation in T1D patients to improve the safety and long-term success of intraportal islet transplantation. The CIT initiated two Phase III clinical trials to demonstrate that islet transplantation could improve glycemic control in T1D patients with severe hypoglycemia and extreme glycemic lability (CIT-07; NCT00434811) and in T1D patients who had received a kidney transplant (CIT-06; NCT00468117). The CIT-07 protocol markedly improved the beta-cell mass and secretory capacity compared to the Edmonton protocol (Rickels et al., 2013). Islet graft function and insulin independence were achieved for 94% and 52.1% of all participants a year after the first islet transplant (Ricordi et al., 2014). The CIT-07 protocol showed a favorable safety profile and patients experienced substantially reduced insulin use and glycemic lability. Human islet product release can be prepared at multiple manufacturing centers using this standardized protocol. The current islet transplant procedure involves catheter delivery of islets into the liver via the hepatic portal vein under radiological guidance. Once the catheter is in place, a suspension containing islet tissue is infused. Unlike whole organ transplant, the clinical procedure of islet transplant is less invasive and patients require minimal time to recover. The main advantage of using the portal vein is that it allows rapid delivery of insulin to the hepatic portal circulation in response to post-prandial glucose delivery to portal vein from intestine (Rajab, 2010). Other benefits of islet transplantation include reduced need for exogenous insulin administration among recipients, improved blood glucose control, and greatly reduced risk of severe hypoglycemic episodes (Paty et al., 2006).

Islet transplantation based on the Edmonton Protocol possesses limitations. A long-term follow up revealed that only 10% of

patients were free from exogenous insulin use after five years (Ryan et al., 2005a). This technology also faces the donor shortage problem. Islet transplantation requires infusion of high-quality islets isolated from a total of two to four donors to treat one recipient (Markmann et al., 2003). Multiple donors are needed because islet attrition occurs during the islet isolation process where uncontrollable factors such as donor's body mass index, pancreas size, chemical digestion, and pancreatic surface integrity could all damage islet quality (Sakuma et al., 2008). This could also happen during the post transplantation where 50% to 70% of islets die due to the immediate hypoxia and inflammatory response (Lehmann et al., 2007). Similar to whole pancreas transplants, islet transplants require chronic immunosuppression to ensure long-term performance of the grafts (Lehmann et al., 2004). Detrimental side effects of chronic high-dose immunosuppressive regimens can also lead to nephrotoxicity and kidney dysfunction in T1D patients who are already at heightened risk (Hirshberg et al., 2003; Ojo et al., 2003). The high metabolite concentrations in the liver may cause graft failure over time (Pileggi et al., 2006). Hence, the applicability of this type of procedure is still greatly constrained by the limited supply of human donor tissue, graft damage from long-term usage of immunosuppressive regimens, and inadequate implantation sites that result in graft failure from hypoxia.

Insulin Therapy Via Cell Encapsulation

Given the aforementioned deficiencies associated with current transplantation methods in T1D treatment, researchers need to tackle the challenge of immunosuppressives, along with the issues of donor shortage and physiological mimicry of a functional pancreas. An attractive strategy for the development of a bioartificial pancreas that would eliminate the need for immunosuppressives is encapsulation of insulin-producing islets within a semipermeable membrane. The properties of the suitable semipermeable membrane are such that it protects islets from the host's immune system, while allowing the exchange of nutrients and small molecules (including glucose and insulin) between the encapsulated islets and their external environment (Chang, 1964). Successful immunoisolation would potentially allow cells from xenogeneic and stem cell sources to be used as alternatives to standard human pancreatic islets or β cells, thereby significantly easing the donor shortage problem. Stem-derived cell sources or xenotransplantation are, however, highly challenging with respect to safety and immunologic perspectives. The implantable bioartificial pancreas would mimic physiological responses by functioning autonomously and dynamically to the varying state of the human body.

To date, existing semipermeable membranes can be categorized into ultra-thin coatings, microcapsules, and macrocapsules based on differences in diffusion distance (Fig. 1a). Ultra-thin coatings using conformal or Layer-by-Layer (LbL) assembly directly modify the surface of islets to enhance transport and mechanical properties (de Temmerman et al., 2012; Matsusaki et al., 2012; Paulick et al., 2007; Rabuka et al., 2008; Tomei et al., 2014). The conformal coatings aim to cover each islet with a uniform thickness rather than controlling the overall capsule diameter like the microencapsulation. These techniques create polyelectrolyte multilayer thin films based on sequential adsorption of oppositely charged components. However, cytotoxic byproducts released during the manufacturing process could disrupt the integrity of cell membrane, causing cell death (Bieber et al., 2002; de Koker et al., 2007; Godbey et al., 1999; Wilson et al., 2008).

Microencapsulated islets ranging 400-800 μm in diameter rely on diffusive nutrient transport and require minor surgery for implantation in the peritoneal cavity, subcutaneously, or under the renal capsule due to their relatively small size (Maria-Engler et al., 2001). In particular, Calafiore's Minimal Volume Capsules which are small alginate micro-capsules with 300-400 μm in diameter were implanted intraperitoneally in patients under echography guidance and local anesthesia and showed clinical relevance with reduced exogenous insulin requirements (Basta et al., 2011b; Calafiore et al., 2006a,c). The large surface area to volume ratio is advantageous for mass transport in microcapsules; however, limitations of this technology include the need for a large transplantation site that accommodates the necessary number of capsules, a favorable microvascular bed that provides immediate nutrient access, difficulty in microcapsule removal if required, and insufficient long-term survival rates for functional islets to adequately address the daily insulin requirement (Khanna et al., 2010; Levesque et al., 1992; Moya et al., 2010; Shin et al., 2013). Though notable applications of microcapsules have been attempted in large animals (Elliott et al., 2005; Wang et al., 1997) and human subjects (Basta et al., 2011a; Calafiore et al., 2006b; Elliott et al., 2007; Limited, 2012; Soon-Shiong, 1999; Tuch et al., 2009), the challenges such as cell sources, implant location, mass transfer, and vascularization remain unsolved.

Unlike microencapsulation where only few islets are grouped together, the large capsule size of the macroencapsulation strategy requires assembling a greater number of islets, and hence, it imposes an mass transport limitations and challenges conventional sites such as renal capsules for implantation. Specifically, vascular perfusion macrocapsules may cause life-threatening blood coagulation and thrombosis in vascular surgery and surface-induced thrombosis (Chaikof, 1999). Nonetheless, macrocapsules have successfully demonstrated the feasibility of implantation and retrieval (Jain et al., 1995; Suzuki et al., 1998). While far from a comprehensive review of islet encapsulation, Table I summarizes some notable macroencapsulation methods to restore normoglycemia in animals and human.

The goal of this review is to present the development of macroencapsulation devices with an emphasis on its challenges and limitations, progress in generating alternative sources for pancreatic β cells, and the variety of biomaterials used for cell encapsulation. With the great potential of a bioartificial pancreas in mind, a successful macroencapsulation device will depend on the availability of cell sources, the physical and chemical properties of the underlying semipermeable membranes, and the mass transport between cells and their outside environment.

Macroencapsulation of Islets

The early development of macroencapsulation dated from the 1950s (S2.1, S2.2, Fig. 1S). Macroencapsulation devices may possess different geometries such as hollow fibers (Lacy et al., 1991; Monaco

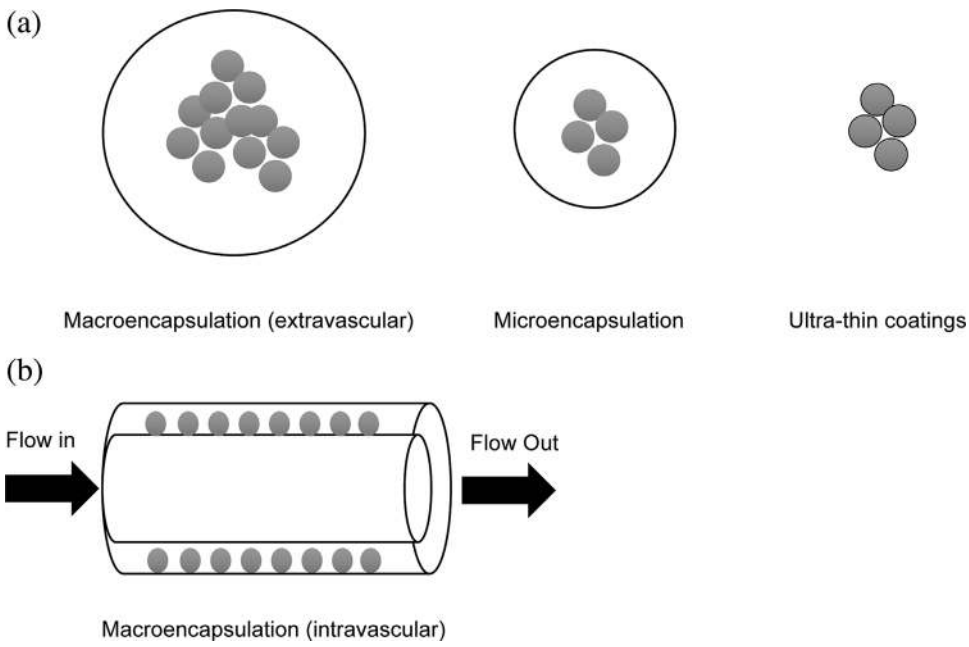

Figure 1. An overview of various encapsulation methods to immunoisolation. Macro-scale encapsulation devices include extravascular (**a**), or vascular perfusion (intravascular) (**b**) which are perfused with body fluid or blood. Micro-scale encapsulation devices typically group a few number of cells into microcapsules (a). Nano-scale encapsulation directly coats surface of the islets with polymeric layers (e.g., conformal coating) (a).

et al., 1991), bag-like structures (Brauker et al., 1995; Toleikis, 2010; Pepper et al., 2015), polymeric hydrogel sheets (Storrs et al., 2001; Stendahl et al., 2009), or planar membranes (Trivedi et al., 2000) for high flow rate or reduced surface area. They can be categorized as either extravascular or vascular perfusion based on their mechanism of transport.

Extravascular Macrocapsules

The concept of extravascular macrocapsules is based on the principle of diffusive transport. Because extravascular devices do not require vascular anastomoses, the corresponding surgical risks are much lower than vascular perfusion devices.

Hydrogels

During the past two decades, there has been a growing interest in using hydrogels as a means to achieve greater biocompatibility for macroencapsulation. Due to the hydrophilic nature of the material, almost no interfacial tension is created with surrounding fluids and tissues, hence, minimizing protein adsorption and cell adhesion. Furthermore, the mechanical properties of hydrogels can be easily controlled via crosslinking to obtain desired selectivity and permeability, allowing the passage of low molecular weight nutrients and metabolites entering the encased cells.

AN69, a copolymer of acrylonitrile and sodium methallyl sulphonate, was one of the early hydrogels studied as a macroencapsulation material (Kessler et al., 1991, 1995, 1997). Early studies reported that AN69 induced only minimal fibrosis in the peritoneal cavity of rats with low permeability for insulin (Kessler et al., 1995, 1997). Application of corona discharge on AN69 caused a more hydrophobic surface with less molecular adhesion. This approach improved both the insulin permeability and the long-term biocompatibility (Kessler et al., 1995, 1997). Poly(vinyl alcohol) (PVA) hydrogel macrocapsules reinforced with mechanically strong support also restored normoglycemia a month after implantation into the abdominal cavity of diabetic rats (Burczak et al., 1994; Lee et al., 1991; Mitsuo et al., 1992b). Other supportive results from Jain and co-workers demonstrated that macrobeads made of agarose contained functional porcine islets for almost 200 days after intraperitoneal transplantation into rats (Fig. 2) (Jain et al., 1999).

One of the most serious problems associated with macro-encapsulated hydrogels is the loss of viability of the transplanted islets due to central necrosis of the tissue clusters. The islet aggregation has been reported to cause hypoxia and result in gradual loss of tissue viability within 1-2 weeks (Mitsuo et al., 1992a). To prevent undesired clustering, islets are usually immobilized in gel matrices prior to encapsulation, as demonstrated by previous studies that cell-matrix interaction could also enhance islet viability (Stendahl et al., 2009).

Sheets and Pouches

Advances in technology and knowledge from studies conducted in the 80s and 90s have pushed the development of extravascular macroencapsulation forward. Islet sheets, developed by Hanuman Medical Foundation, are composed of highly purified alginate (12–45 kDa) with a reinforcing mesh that encapsulates islets (Fig. 3) (Storrs et al., 2001). Lamb and co-workers reported that alginate encapsulated human islets remained both viable and functional

Table I. Macroencapsulation used in animals and human.

Macro-encapsulation	Type of transplant (e.g. allo, xeno)	Device description	Locations	No. of encapsulated islets (IEQ)	Results
Extravascular	Human to mice (xeno)	TheraCyte (PTFE) device with an inner semipermeable membrane (pore size of 0.4 μm) laminated to an outer membrane and covered by a loose polyester mesh. Device is 2-cm long with inner lumen volume of 4.5 μL	Intraperitoneal	70–216	C peptide and responsiveness to glucose changes were not observed in the first 12 weeks of transplantation but were detected after 5 months (Lee et al., 2009a)
	Human to mice (xeno)	Nanogland (silicon membrane: $6 \times 6\,mm^2$) with channel sizes: 3.6, 5.7, 13, 20, and 40 nm nanochannels and 20, 40, and 60 μm microchannels. The membrane has a circular pattern of 161 square islets chambers (200 μm width by 200 μm height) separated by 50-μm walls	Subcutaneous	1000	Detectable insulin production for at least 120 days (Sabek et al., 2013)
	Rat to rat (allo)	Meshed PVA tubings	Peritoneal	2500–3000	Normoglycemia was maintained for 1 month (Mitsuo et al., 1992b)
	Dog, cow, pig to rat (xeno)	Tubular, permselective acrylic-copolymer membrane chambers (2–3 cm long, 1.8–4.8 mm in inner diameter, 69–105 μm in wall thickness)	Intraperitoneal	$4–6/mm^3$ or 20,000	Insulin independence for an average of 138 ± 16 days, and two animals showed 260 days with higher dose (Lanza et al., 1993)
	Pig to rat (xeno)	Agarose macrobeads	Intraperitoneal	1000–1500	Macrobeads remained functional for 199+ days (Jain et al., 1999)
	Human to rats (xeno)	Alginate sheets	Subcutaneous	1000	Encapsulated islets were viable and functional after 8 weeks (Lamb et al., 2011)
	Dog to dog (allo)	Wider-bore tubular membrane made of acrylic-copolymer with a 1.7–4.8 mm in inner diameter and a wall thickness of 69–105 μm	Peritoneal	300,000	70 days insulin free (Lanza et al., 1992a)
	Pig to monkey (xeno)	A monolayer of islet-seeded human acellular collagen matrix covered in alginate	Subcutaneous	30,000/kg	Diabetes was corrected for a maximum of 6 months in 5 animals (Dufrane et al., 2010)
	Human to human (allo)	Acrylic-copolymer hollow fiber (1.5-cm length, 800 μm in inner diameter, and 100 μm in wall thickness)	Subcutaneous	150–200	14 days with 90% viability (Scharp et al., 1994)
Vascular Perfusion (intravascular)	Rat to rat (allo)	Hollow-fiber setup with 100 11-cm capillary fibers of polyacrylonitrile-PVC copolymer sealed into cylindrical glass with 0.5 cm inner dimaeter. Isets were seeded at the outside surface of the fiber bundles	Silastic iliac	180 neonatal rats	90-min decrease in plasma blood glucose (Chick et al., 1977)
	Dog, cow, pig to dog (allo & xeno)	A single-coiled tubular membrane made of acrylic-copolymer. The coil membrane contained disk-shaped acrylic islet housing. The membrane has a normial molecular weight cutoff of 50 kDa, an internal diameter of 5–6 mm, and a wall thickness of 120–140 nm. The islet compartment was 5–6 mL in volume.	External iliac artery and common iliac vein	220,000–320,000	Zero or minimal insulin required for ∼50 weeks (Maki et al., 1991a,b, 2003)
					Reduced exogenous insulin after 284 days and 106 days (Monaco et al., 1991)
				114,000–341,000	Minimal insulin required for 57–366 days (Maki et al., 1996b)
	Rabbit to dog (xeno)	Polyamide or nylon capsules with 1–2 mm pore dimension, 20 mm in length, and 5 mm in diameter	Abdominal Aortic lumen	500,000	Normoglycemia restored after 12 days of tranpslantation. About 60% of encapsulated cells were functional after 13 months. (Prochorov et al., 2004, 2005)
	Rabbit to human (xeno)	Nylon macrocapsule with 1–2 μm in pore size, 30–40 mm in length, and 3–4 mm in diameter	Deep femoral artery or fore arm cubital vein	6000/kg	2 years with reduced insulin requirement for 73.7% recipients (Prochorov et al., 2008)

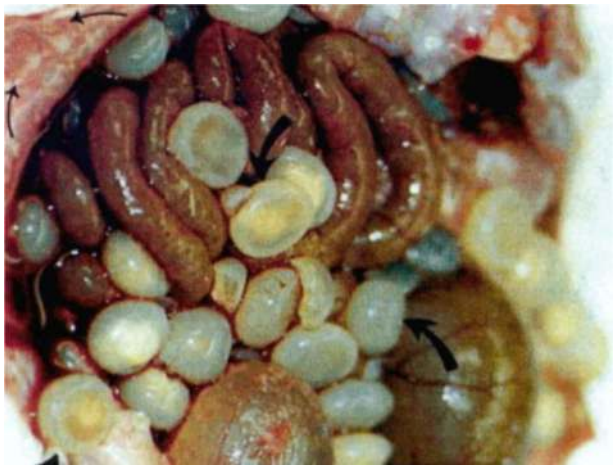

Figure 2. A number of agarose macrobeads retrieved from the peritoneal cavity of a diabetic rat 145 days after implantation (Jain et al., 1999). None of the macrobeads showed any fibrosis but small eruptions were detected on the wall of the peritoneal cavity (indicated by black arrows). Image reproduced with copyright permission.

after 8 weeks in culture and in the subcutaneous space of rats (Lamb et al., 2011). The team has since moved to large-animal efficacy studies using a canine model. Dufrane and co-workers developed a similar system where porcine islets were seeded on a human acellular collagen matrix to create a cell monolayer before covering with high mannuronic acid alginate (Dufrane et al., 2010). Alginate macrocapsules that were then transplanted into abdominal subcutaneous tissue of cynomolgus monkey showed metabolic control over the glucose course with an acute stimulation (Dufrane et al., 2010). Encapsulated adult pig islets corrected streptozotocin-induced diabetes up to a maximum of 6 months in five animals, in spite of the strong humoral response that was elicited (Dufrane et al., 2010). The authors concluded that failure at 6 months was possibly due to the lifespan of adult pig islets (Dufrane et al., 2010).

Sernova's Cell Pouch^{TM}, made from FDA approved materials, consists of a multi-channel sheet inserted with an array of rods (Toleikis, 2010). The pouch creates a favorable pre-vascularized environment but it does not offer an immune-barrier to protect cells from the host immune system. This device is first placed under the skin for better vascular integration with the surrounding tissues for a month. Once microvasculature is developed around the device, the rods are removed to expose channels that allow the infusion of transplanted islets into the device. Sernova devices were pre-implanted in mice four weeks before diabetes induction and transplantation. The implanted mouse islets restored glycemic control and maintained normoglycemia until graft explantation after 100 days (Pepper et al., 2015). Although there was a 20-day delay in the initial engraftment, the implants responded well to glucose challenge and islets within the cell pouch stained positively for insulin, glucagon, and microvessels. Glycemic control by cell pouch encapsulated islets was also demonstrated in pigs for two months, along with high infiltration of blood vessels to promote survival of encapsulated islet autografts (Toleikis, 2010). Currently, this device has moved to a three-year Phase I/II clinical study with human patients under standard immunosuppressive regimes from the Edmonton Protocol and an estimated date of completion in 2016 (Toleikis, 2010).

The TheraCyte device (Fig. 4) produced by Baxter Healthcare is an example of pouch encapsulation that aims to promote angiogenesis and immunoisolation (Brauker et al., 1995). TheraCyte is a planar pouch featuring a double membrane of polytetrafluoroethylene (PTFE) with its inner 30-μm thick membrane of 0.4 μm in pore size for selectivity and immunoisolation, and its outer 15-μm thick membrane of 5 μm in pore size for angiogenesis through an alternative foreign body response. (Lee et al., 2009b; Trivedi et al., 2000). Undoubtedly, enhancing microvasculature plays an essential role in promoting survival of macroencapsulated islets (Thomlinson and Gray, 1955). The outer membrane consisting of 5-μm pores showed a 80 to 100-fold more vascular structure with much improved biocompatibility compared with the 0.02-μm pores (Brauker et al., 1995). The vascular structures were adjacent to the membrane surface and fibrosis occurred beyond the vessels. It is also possible to integrate angiogenic factors to further enhance vascularization of the device. For example, the infusion of VEGF greatly enhanced angiogenesis by increasing the number of surrounding blood vessels and promoting insulin diffusion from the TheraCyte device (Trivedi

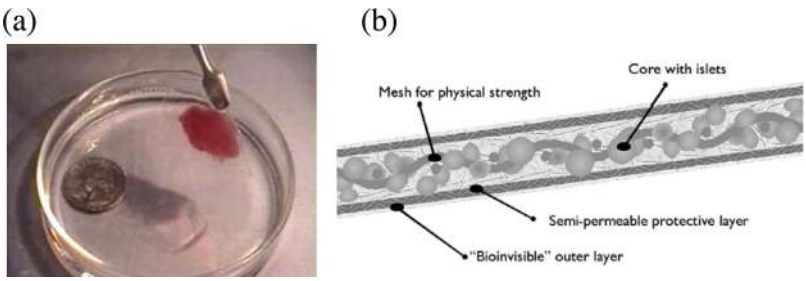

Figure 3. Diagrams of an Islet Sheet (**a**) and its cross-sectional view (**b**) (Lamb et al., 2011; Storrs et al., 2001). Islets-encapsulated alginate is enclosed between acellular immunoprotective alginate layers. A polymer mesh can be included in the sandwiched layer to provide physical strength. Islet Sheets measure approximately 4×8 cm$^2 \times$ 250 μm. Molecular weight cutoff depends on the modification of the alginate chemistry and its processing conditions. Images by courtesy of Dr. Scott King and reproduced with copyright permission.

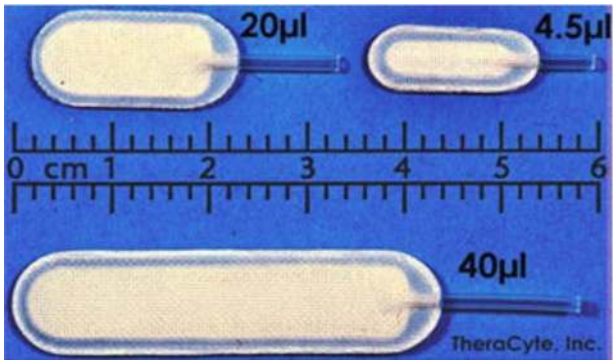

Figure 4. Diagram of TheraCyte devices (Lee et al., 2009b; Trivedi et al., 2000). The device was a planar pouch made of bilaminar polytetrafluoroethylene (PTFE) with its inner membrane for immunoisolation, and the outer membrane for tissue integration. The inner membrane was 30 µm in thickness with 0.4 µm in pore size. The outer membrane was 15 µm in thickness with 5 µm in pore size. Image by courtesy of TheraCyte, Inc.

et al., 2000). Lee and co-workers reported that transplant of TheraCyte with human fetal pancreatic islet-like cell clusters led to maturation of β-cells and correction of diabetes for at least 10 days in immunodeficient mice (Lee et al., 2009b). ViaCyte has developed an encapsulation system called Encaptra that is designed to be implanted subcutaneously. This device (based on the TheraCyte) is also a planar pouch with a single layer of membrane which will protect transplanted cells from host's immune system while allowing oxygen and nutrients freely transport through the membrane. This system will allow the encapsulation of stem cells or pancreatic progenitor cells to differentiate into functioning insulin-producing cells (Agulnick et al., 2015; Kroon et al., 2008). ViaCyte recently announced a Phase I/II clinical trial using Encaptra with stem cell-derived cell sources to assess safety and efficacy of the system with an expected completion in 2017.

Beta-O_2 is an implantable device composed of a central gas cavity that connects to access ports for refueling oxygen from the outside (Fig. 5) (Neufeld et al., 2013). Surrounding the central gas cavity are the gas permeable membranes that house alginate-immobilized pancreatic islets with 0.4 µm PTFE porous membranes covering the external surfaces. After implantation of the device in the abdomen,

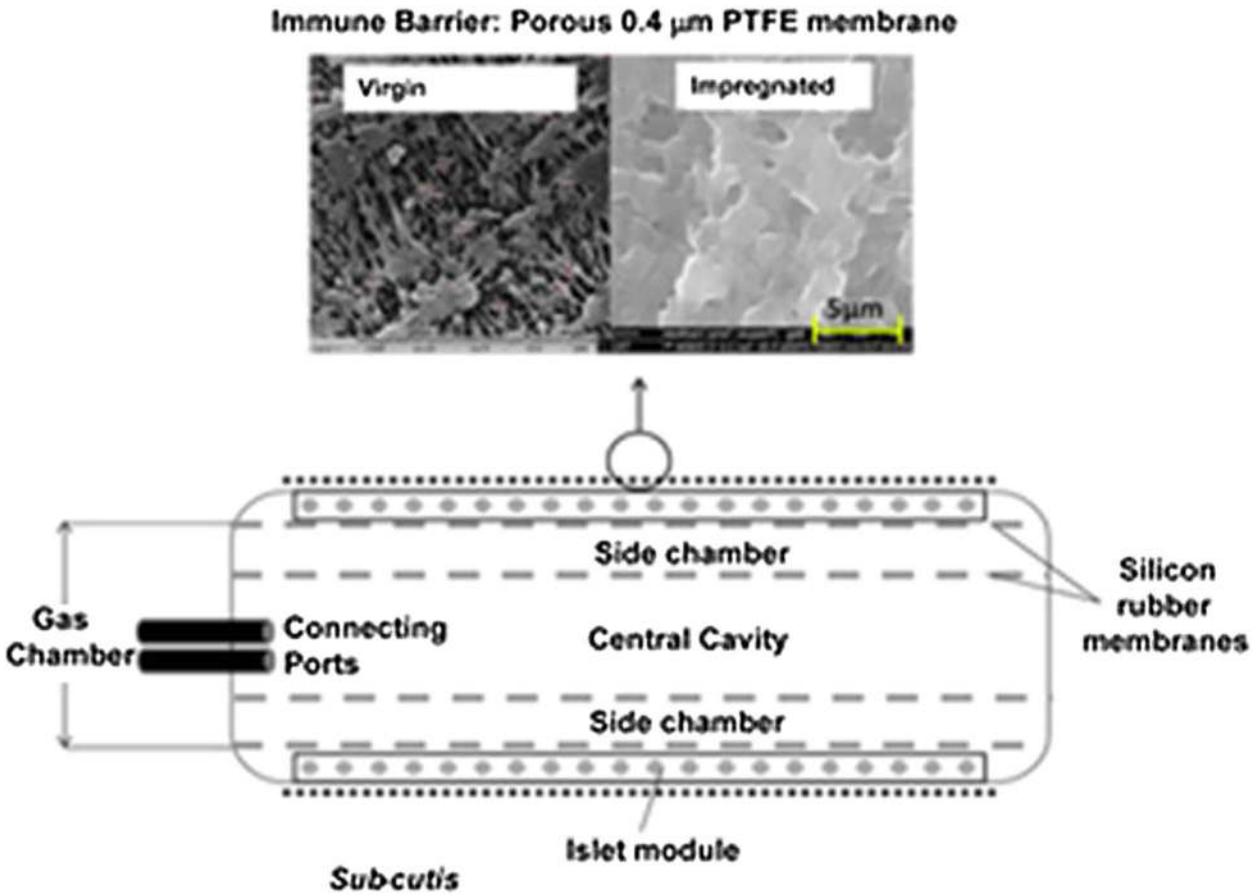

Figure 5. A schematic of the Beta O_2 device (Neufeld et al., 2013). The center of the device was built as an oxygen chamber, connected to access ports for exogenous oxygen refueling. The oxygen chamber was sandwiches between two alginate-immobilized islets layers separated by gas permeable silicon membranes. The external surfaces were coved by hydrophylized polytetrafluoroethylene (PTFE) membranes of 0.4 µm in pore size. Image reproduced with copyright permission.

oxygen is pumped daily to support islet viability. Results showed that rat islets corrected glucose levels in diabetic mini-pigs for 90 days with no signs of islet disintegration (Neufeld et al., 2013). One human case study using this device reported that encapsulated islets were functional over the entire period of 10 months with moderate reduction of insulin requirement (Ludwig et al., 2013).

Although remarkable progress has been made in autologous and allogeneic cell transplantation without immunosuppression (Calafiore et al., 1998; Lanza et al., 1999; Siebers et al., 1997; Weber et al., 1995), overcoming immunologic rejection of xenogeneic cells still remains as a great obstacle (Lacy et al., 1991; Lanza et al., 1995b, 1997; Marchetti et al., 1996) due to the mechanical rupture of the membranes, biochemical instability, islet cell heterogeneity, and the broad distribution of pore sizes in the encapsulation materials (Colton and Avgoustiniatos, 1991; Kajita and Hugli, 1991; Lanza and Kuhtreiber, 1999; Soon-Shiong et al., 1991). It is known that cross-linking macrocapsules does not provide precise control over molecular weight cutoff, so antibodies and cytokines cannot be sufficiently excluded in many hydrogel macrocapsules (Cui et al., 2004; Sakai et al., 2006; Zhang et al., 2008). For example, large PEG microbeads that were manufactured with poor porosity exhibited hindered molecular transport (Weber et al., 2007).

These issues have brought interest from scientists and engineers to apply a more controlled, fabrication technology, associated with the production of Micro-Electro-Mechanical Systems (MEMS), to produce biocompatible materials with features in the range of micro- and nanometers for biomedical applications (Das et al., 2007; Edell et al., 1992; Kim et al., 2011; Kipke et al., 2003; Kovacs et al., 1994; Kristensen et al., 2001; Lee et al., 2011; Li et al., 2011) . Desai and co-workers utilized bulk and surface micro-machining to produce biocapsules with uniform and well-controlled pore sizes, channel lengths, and surface properties (Chu et al., 1996; Desai et al., 1999, 2004; Leoni and Desai, 2004). The nanoporous biocapsule consisted of two permeable silicon membranes with specific pore sizes, which can be as small as 7 nm (Fig. 6). They reported that upon transplantation in peritoneal cavity, encapsulated insulinoma cells reversed diabetes in rats for at least 14 days using this nanoporous biocapsule (Desai et al., 2004). Capsules made of 20-nm barriers maintained secretory output whereas 66-nm capsules led to loss of cell function. They also developed nanoporous alumina capsules with nominal pore size of 75 nm where diffusion of glucose was undisturbed but the transport of immunoglobulin G (IgG) was impeded (La Flamme et al., 2005, 2007). Nanoporous alumina encapsulated MIN6 cells secreted insulin with dosage-dependent response (La Flamme et al., 2007). Nanogland, another device produced using MEMS technology, consists of parallel nanochannels and perpendicular microchannels to the islet chamber (Fig. 7) (Sabek et al., 2013). The membranes present a 6 by 6 mm surface area with channel size ranges from 3.6

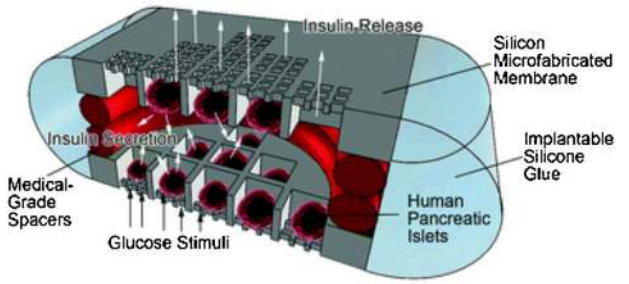

Figure 7. An image of the Nanogland device (Sabek et al., 2013). The Nanogland device consisted of two silicon membranes glued together with implantable silicone. The active membrane area is 6 × 6 mm. The islet chambers were microfabricated for a channel size of 20, 40, 60 μm and a pore size of 3.6, 5.7, 13, 20, and 40 nm. Image reproduced with copyright permission.

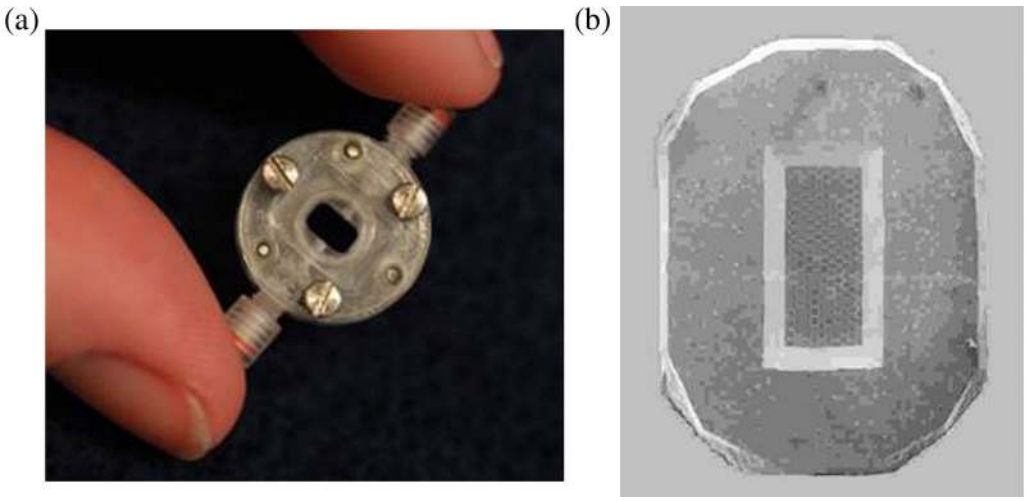

Figure 6. An image of a nanoporous biocapsule (Desai et al., 2004). The nanoporous biocapsule consisted of two nanoporous silicon membranes, gaskets, and protective screens on both side of the device. The injection ports allow the sampling and replenishing of the islets (a). The dimension of the nanoporous silicon membranes, including the support ridge, was 6 × 8 mm. The active membrane area was 3.5 × 2 mm with a thickness of 5 μm (b). Images by courtesy of Dr. Tejal A. Desai.

to 40 nm for nanochannels and 20–60 μm for microchannels. All membranes have a circular pattern of 161 square islet chambers (200 × 200 μm; W × H) separated from each other by 50 μm walls. Subcutaneous implantation of the Nanogland with human islets in mice showed survival of implants over 120 days with endothelial cell infiltration, suggesting potential vascularization of the device (Sabek et al., 2013). These encouraging results demonstrated the feasibility of using MEMS technology to precisely control pore dimension to achieve immunoisolation and sustain cell viability.

In summary, a major advantage of extravascular macro-devices is the feasibility of replenishing islets without removing the device in case of experimental analysis or surgical complications. Because of their large sizes, extravascular macrocapsules face difficulties in maintaining high permeability to diffusive transport necessary to support encased islets while ensuring mechanical strength of the membrane to prevent graft failure. As a result, large volume of macrocapsules is proposed to support sufficient masses of insulin-producing islets. This requirement challenges the conventional sites such as the limited space in renal capsules, and even the relatively large space in the peritoneal cavity may not satisfy the volume required for the long-term function of macroencapsulated islets (de Vos and Marchetti, 2002).

Vascular Perfusion Devices

To circumvent hypoxia and necrosis of cells located at the center of extravascular devices (Chaikof, 1999), the development of vascular perfusion devices struggled to overcome issues with diffusive transport but achieved limited success (Leoni and Desai, 2004; Tibell et al., 2001). Islet density of the extravascular macrocapsules is suggested to be 5-10% of the volume fraction in order to ensure the adequate exchange of nutrients and waste of the islets, (de Vos and Marchetti, 2002).

It is well-recognized that delay of insulin secretion in response to glucose (>20 min) has been a common problem encountered in the early extravascular hollow-fiber systems (Orsetti et al., 1981; Sparks et al., 1982). One of the crucial tasks is to minimize the volume of islet encapsulating compartment to reduce the lag in insulin release (Sparks et al., 1982). To satisfy this requirement, thinner and longer hollow fibers are needed to accommodate a large number of cells to maintain normoglycemia in the body. However, thin fibers are prone to rupture under physical stress and demand enormous area for implantation, making implantation of these types of fibers impractical. The delay in glucose-insulin response further prompted scientists to design vascular perfusion devices directly connected with blood circulation (Fig. 1b) relying on convective movements of glucose and insulin carried by ultrafiltration, instead of passive diffusion in the case of extravascular devices, to provide a faster glucose-insulin response.

In the 1970s, Chick and co-workers first reported diabetic rats connected ex vivo to an intravascular hollow fiber device consisting of neonatal islets (Chick et al., 1977). When implanted ex vivo as arteriovenous (AV) shunts, the plasma glucose decreased to normal range (100–130 mg/100 mL). This approach provides the encapsulated islets in close contact with the blood circulation. It also allows fast exchange of glucose and insulin to correct blood glucose levels in almost real time. Similar studies using this approach ex vivo or in vivo also restored short-term normoglycemia in chemically or surgically induced diabetic animals (Colton and Avgoustiniatos, 1991; Lanza et al., 1992b). In contrast to a pure diffusion process under extravascular conditions, this device utilized the physiological pressure difference between the artery and vein to reduce the overall insulin response time. The unidirectional blood flow causes the pressure of the first part of the lumen to be greater than the pressure in the periphery of the islet compartment, and therefore, ultrafiltrate crosses from the bloodstream to the islet graft. Because the hydrostatic pressure drops as a function of flow distance within the lumen, hydrostatic pressure becomes lower in the second half of the fiber, which creates an equal, reverse flux where ultrafiltrate moves from the islet compartment to the bloodstream. The resulting effect is that the ultrafiltrate in the shell compartment first stimulates islets to release insulin in response to glucose challenge, and then carries insulin back to the bloodstream. Specifically, vascular perfusion devices are developed as shunts that connect to the systemic circulation and allow blood perfusion through the devices. Despite the promise and potential of vascular perfusion devices, anticoagulant requirements have limited the utility of this approach, especially for pediatric patients.

First demonstration of the long-term use of a bioartificial pancreas in a large animal using a vascular perfusion device was demonstrated in the 1990s (Maki et al., 1991a, b, 1993, 1996b). Maki and co-workers developed a hybrid pancreas device, which contains an acrylic housing with islets separated from the common iliac artery and vein in dogs through the semipermeable membrane (80kDa) (Fig. 8). They showed that allogeneic islets could control diabetes induced by total pancreatectomy for up to 1 year with zero or minimal exogenous insulin in dogs (Maki et al., 1991a,b, 1993). Devices retrieved from two recipient dogs showed a 50–70% viability of islets after 1 year. They also observed that insulin requirements were greatly reduced by 50% in the allogeneic and xenogeneic recipients after 284 days and 106 days, respectively (Monaco et al., 1991). No gross fibrosis observed throughout the membrane, except for thin layers of fibrin-like material adhered to the luminal surface of the membrane. Importantly, clotting occurred at either the anastomosis sites or the junction of the PTFE graft and tubular acrylic copolymer membrane. These findings were considered to be remarkable because of the difficulty in maintaining the patency of vascular device in dogs (McMillan, 1992). However, vascular perfusion devices have been perceived to be risky as demonstrated that hybrid pancreas device failed immediately in 3 dogs due to excessive clotting and thrombosis, collapse of membrane and vascular connection, and loss of islet function related to device patency in this study. Additional modifications to devices such as increasing the length of semipermeable membrane coil and the size of acrylic housing to accommodate more islets showed improvement in glycemic control and reduced insulin requirements for up to 9 months in pancreatectomized diabetic dogs without immunosuppression (Maki et al., 1996a). Specifically, nine out of 17 dogs had a marked reduction in exogenous insulin requirements by porcine islet xenograft. Monaco and co-workers found out that only 4–16 IU insulin per day was needed for 57–366 days in half of the pancreatectomized dogs that received between 114,000–341,000 IEQ.

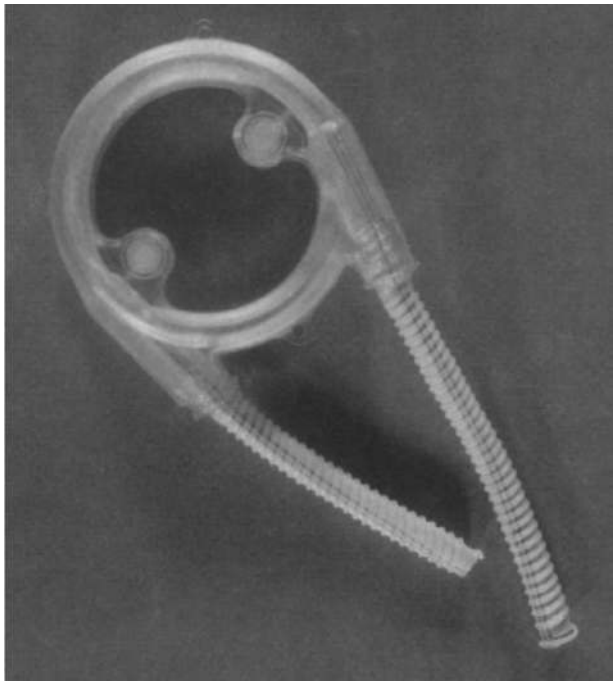

Figure 8. An image of the hybrid artificial pancreas device (Monaco et al., 1991). The device consisted of a coiled, hollow fiber membrane on top of a disk-shaped, islet compartment. Two seeding ports allowed direct injection of islets into the compartment. The hollow fiber was connected to vascular graft. The membrane has a normial molecular weight cutoff of 50 kDa, an internal diameter of 5–6 mm, and a wall thickness of 120–140 nm. Image reproduced with copyright permission.

These studies demonstrated the feasibility and clinical applicability of the intravascular hybrid artificial pancreas; however, it did not move to the clinical stage due to potential risks associated with thrombosis and hemorrhage. Other blood contacting devices such as the polyacrylonitrile and polyvinylchloride copolymer (PAN-PVC) ultrafiltration capillary design, a hollow-fiber shaped tube with islets at the outside of the artificial capillaries, also failed due to excess clotting of the blood in the lumen of those small diameter artificial capillaries, in spite of anticoagulant medication in massive doses (Colton, 1995). As a summary, the advantages of vascular perfusion devices include the high oxygen tension of the arterial blood exposed to islets. The disadvantages of this type of system are risks associated with the surgery required for creating AV or AA shunts, vascular thrombosis, and potential risks in cardiac stress and diversion of large volume of blood from the distal extremity.

Challenges to Successful Macroencapsulation

Cell Source

The clinical application of encapsulated islets requires an inexhaustible source of cells or tissues capable of delivering therapeutic agents in response to physiological changes. Insufficient number of human donors and long-term immunosuppression are the major motives for scientists to focus on alternative sources of insulin-producing cells for future transplants. New advances in the field of stem cell differentiation and regeneration therapy suggest use of xenogenic islets, immortalized β cell lines (Narushima et al., 2005), embryonic stem cells (ESC), adult stem cells (ASC), and progenitor cells that reside in the pancreas for generating insulin-producing cells. Cells from allogenic or xenogenic sources will require protection from the host immune system, and thus, efforts directed toward an encapsulation method will prove highly valuable as various cell sources gain significance in clinical relevance. Another feature of encapsulation is the improved safety of cell-based therapies since cells can be readily retrieved and separated from patients in the case of malignancy.

Xenogenic porcine islets. Using islets from non-human sources for transplantation has been explored to supplement the insufficient supply of donor tissue. The porcine islet is the most popular animal candidate because porcine insulin differs from human insulin by one amino acid, a higher islet yield per animal, and hypoxia tolerance observed in different age groups of pig islets with neonatal porcine islets being the most resilient (Emamaullee et al., 2006). If not immune-protected, porcine islets in non-immunosuppressed nonhuman primates can be rejected by both humoral and cellular immune reactions (Cantarovich et al., 2002; Kirchhof et al., 2004; Soderlund et al., 1999). After a 72 hour transplant of fetal pig islets under the kidney capsule of primates, a large number of macrophages and T cells were observed at the periphery of and within transplanted islets (Soderlund et al., 1999). Infiltration of neutrophils caused tissue damage by releasing enzymes and producing chemokines that directed T cells and dendritic cells (Soderlund et al., 1999).

In addition, the risks associated with porcine tissues include endogenous virus transfer from porcine cells to human. These may impede the use of this porcine islets in clinical applications. However, a prospective pig-to-primate islet xenotransplantation study consisting of gene expression and serology for potentially xenotic viruses such as porcine cytomegalovirus (PCMV), porcine endogenous retrovirus (PERV), porice lymphotropic herpesvirus (PLHV) and porcine circovirus (PCV) showed no evidence of pig virus transmission to primate recipients (Garkavenko et al., 2008).

Embryonic Stem Cells (ESCs). Stem cells have the ability to self-regenerate and differentiate into specialized cell types under appropriate external niche and signaling cues (Smith, 2006). They have the potential to provide a sufficient supply of insulin-producing source (Street et al., 2004). ESCs derived from the inner cell mass of pre-implantation blastocysts are self-renewing and have the intrinsic capacity to generate all types of differentiated cells (Weissman, 2000). Due to the pluripotent nature in ESCs, several groups have attempted to direct differentiation of ESC into functional β cells (Baetge, 2008; Best et al., 2008; D'Amour et al., 2006; Kelly et al., 2011; Kroon et al., 2008). Insulin-expressing cells were initially produced from murine (Soria et al., 2000) and human (Assady et al., 2001) ESCs through the formation of an embryoid body, but this method was insufficient to generate a large amount of insulin-positive cell formation (Soria et al., 2000). It is now understood that β cells are derived from controlled formation of the definitive endoderm (D'Amour et al., 2006) followed by a sequential

and transient activation of specific transcription factors like Pdx1, NeuroD/Beta 2, Isl1, Nkx6.1, Nkx2.2, Mafa, Pax4, and Pax6 (Kroon et al., 2008). However, these derived cells were not very responsive to glucose in vitro, but they could mature and restore euglycemia after being transplanted into diabetic animals (Assady et al., 2001; Baetge, 2008; Best et al., 2008; D'Amour et al., 2006; Kelly et al., 2011; Kroon et al., 2008; Soria et al., 2000).

In addition to the need for stem-cell differentiation into insulin-producing cells, the ability of insulin-producing cells to replicate is also very important as observed during human normal growth (Matveyenko et al., 2008), pregnancy (Sorenson and Brelje, 1997; van Assche et al., 1978), and obesity (de Koning et al., 1993). High-throughput screens of chemical libraries could potentially identify small molecules that can stimulate the propagation of such cells in vitro or in vivo (Bonner-Weir et al., 2000; Chen et al., 2009).

Despite the versatility of ESCs, ethical concerns and possible teratoma formation limit the usage of ESCs (Ensenat-Waser et al., 2006; Fujikawa et al., 2005). To address the ethical concerns with ESCs, induced pluripotent stem cells (iPS) were generated by reprogramming adult somatic cells after ectopic expression of stem cell transcription factors Oct4, Sox3, c-myc and Klf4 (Takahashi and Yamanaka, 2006; Wernig et al., 2007; Yamanaka, 2007; Yu et al., 2007). The initial mouse and human fibroblast reprogramming has now extended to other somatic cells including stomach (Aoi et al., 2008) and pancreatic epithelium (Stadtfeld et al., 2008). Furthermore, mature exocrine pancreas was transformed into functional β cells through expression of endocrine transcription factors (Ngn 3, Pdx1, and Mafa) (Zhou et al., 2008). Although the transformed cells secreted insulin and relieved diabetes in animals, an underlying mechanism study showed that the cells lacked glucose-sensitive insulin secretion and critical aspects of the β cell phenotype (Akinci et al., 2012). In addition, transplantation of undifferentiated iPS containing derived insulin-producing cells could also result in teratoma formation.

In 2014, ViaCyte launched a Phase I/II clinical trial using a pouch approach with human embryonic stem cell-derived, encapsulated cell replacement therapy (Agulnick et al., 2015; Kroon et al., 2008). It is known that insulin producing cells previously generated from human stem cells lack many functional characteristics of beta cells. In the same year, The Kieffer group published a seven-stage protocol that described embryonic stem cell-derived insulin-producing cells not only responded to glucose challenge in vitro, but also reversed diabetes in mice within 40 days, roughly four times faster than pancreatic progenitors (Rezania et al., 2014). The Melton group also reported a human stem cell differentiation protocol that could generate glucose-responsive beta-cells to treat hyperglycemia in diabetic mice (Pagliuca et al., 2014). The Hebrok group used a pancreatic differentiation protocol that enables temporal activation of endocrine differentiation in the progenitor cells to produce glucose-responsive beta-like cells, which reduced blood glucose levels in diabetic mice after short-term transplantation (Russ et al., 2015). Successful differentiation of stem cells into functional insulin-producing cells has significant clinical relevance and could potentially solve the shortage of donor tissues. However, safety issues such as the propensity of cells to form tumors have to be addressed before using ESCs and iPS in the clinical setting. Again, encapsulation could accelerate the acceptance of cell-based therapies because devices can be readily removed without spreading of tumors to the host.

Adult stem cells (ASCs). ASCs are multipotent cells that are capable of self-renewal but limited in their pluripotent potential. ASCs can be differentiated to specialized cell types under appropriate signaling cues and microenvironment (Barry and Murphy, 2004; Zhao et al., 2002). The relative ease of isolation and expansion of ASCs makes them a potential cell based therapy for T1D treatment.

The ability to control growth and differentiation of pancreatic stem cells provides an attractive islet source for β cell reconstitution. Human ductal structures of the adult pancreas contain stem cells that differentiate into islets of Langerhans. Propagation and differentiation of these islet-like cells demonstrated insulin production in vitro to normalize blood glucose levels for more than 3 months in non-obese diabetic mice (Ramiya et al., 2000). Nestin positive derived islet cell clusters expressed pancreatic endocrine markers like Glut2, glucagon, Pdx1, and exocrine genes (Zulewski et al., 2001). Exocrine pancreatic tissue (Baeyens et al., 2005) and neurogenin 3 (ngn 3) positive cells (Gu et al., 2002) could also be used as an alternative source to β cells. However, the harvest procedure of pancreatic stem cells from the pancreas is very invasive. The number of isolated precursor cells is few and heterogeneously distributed in the body, thus, restricting the actual application in the clinical setting.

There have been controversies regarding the origin of neonatal β cells during the normal pancreatic tissue maintenance, the role of the regenerating cells after injury, and the signaling mechanism by which they regenerate (Kushner et al., 2010; Szabat et al., 2012). It is known that the adult pancreas has a capacity to respond to changing physiological needs. Lineage tracing experiments after partial pancreatectomy suggested that the majority of new β cells is from the proliferation of pre-existing β cells rather than stem cell differentiation (Dor et al., 2004; Georgia and Bhushan, 2004). However, other evidence demonstrated that stem cells or progenitor cells expressing markers cytokeratin-19 (CK) give rise to new β cells after 90% pancreatectomy or treatment with streptozotocin (Bonner-Weir et al., 1993; Gao et al., 2003; Wang et al., 1995). Despite the recent debates, there is little doubt that both replication and neogenesis (the differentiation of new islet cells form progenitors or stem cells) pathways play an important role in maintaining an adequate β cell mass after birth. However, the degree of replication of β cells or differentiation of progenitors/stem cells in a particular model system depends on the species (e.g. human vs. mice, transgenic vs non-transgenic animals), the pathophysiological conditions, and the physiological states (Bonner-Weir et al., 2010).

Biomaterials

To date, a variety of polymeric and inorganic materials have been utilized to create the semipermeable membranes with immuno-protective barriers characteristics. The materials required for encapsulation must demonstrate adequate permselectivity—high selectivity excludes immune components and high permeability supports the metabolic needs of encapsulated cells. Some of the commonly used biomaterials for macroencapsulation are alginate

(Lamb et al., 2011; Lanza et al., 1995a, 1996a,b; Storrs et al., 2001), agarose (Iwata et al., 1992; Jain et al., 1999; Luan and Iwata, 2012), nitro-cellulose acetate (Algire, 1943), 2-hydroxy-ethyl methacrylate (HEMA) (Klomp et al., 1979; Sefton, 1993), acrylonitrile and sodium-methallylsulfonate (Kessler et al., 1991), and PTFE (Agulnick et al., 2015; Brauker et al., 1995; Lee et al., 2009a; Trivedi et al., 2000). Unlike materials used for microencapsulation, polymers for macroencapsulation are mechanically more stable with thicker capsule walls. However, thicker walls can actually impair diffusion across the membrane, threatening the viability of transplant tissue. Many techniques have been used to improve the survival rate of macroencapsulated islets such as smoothened capsule surface and hydrophilic materials with low interfacial energy to reduce protein adsorption, cell adhesion and fibrosis (Narang and Mahato, 2006; Zhang et al., 2008).

Alginate. Alginate is a polysaccharide whose biocompatibility and gelling properties make it the most popular choice for encapsulation. The final gelled polymers form many non-uniform alginate strands that serve as a barrier to the movement of molecules passing from the outside of the capsule to the tissue within or vice versa (de Vos et al., 2009). These non-uniform alginate strands create a wide distribution of pore sizes, which can greatly affect the diffusion of molecules. Therefore, rigorous purification of the naturally occurring compound is required. Otherwise, inadequate alginate purification can cause increased alginate immunogenicity and splenocyte proliferation, and decreased encapsulated islet viability (De Vos et al., 1997). Highly purified alginate does not interfere with islet function and shows good stability (de Vos et al., 2002). Moreover, various biomaterials such as polyethylene glycol (PEG) and poly-L-lysine (PLL) have been used to improve the permeability and selectivity of alginate with reduced plasma absorption. Cui et al. demonstrated that grafting PEG chains onto alginate capsules increased in vivo viability of islet cells (Cui et al., 2004). The Stabler group further improved the cross-linking process of alginate/PEG by Staudinger ligation (Hall et al., 2011). Goosen et al. reported alginate/PLL/alginate capsules blocked diffusion of serum immunoglobulin, albumin, and hemoglobin (Goosen et al., 1985). The Anderson group showed that larger alginate capsules of 1.5-mm in size restored blood-glucose control for up to 180 days in diabetic C57BL/6 mice, which was five times longer than the conventionally sized 0.5-mm alginate capsules (Veiseh et al., 2015). They reported that alternating the spherical dimension of implanted devices can significantly improve the device biocompatibility in vivo.

Agarose. Agarose is a thermo-sensitive, linear polymer made of repeating monomeric unit of agarobiose. The gelling temperature of agarose used in encapsulation is 15–30°C, but it is dependent on the concentration of agarose used. Often, droplet extrusion followed by hardening with reduction in temperature is used to create an encapsulation capsule. Agarose has been shown to be biocompatible and prevent extrusion of cells (Wong and Chang, 1991). Selectivity increases as the concentration of agarose rises (Iwata et al., 1994). Although it has not been studied intensively as alginate, agarose-macroencapsulated porcine islets remained viable and functional for almost 200 days after intraperitoneal transplantation in rat recipients (Jain et al., 1995, 1999).

PTFE. PTFE is a fluorocarbon-based polymer which is very stable both thermally and chemically. This polymer is hydrophobic, biologically inert, and non-biodegradable which gained popularity as a vascular graft material in the expanded form (ePTFE), due to greater porosity, better tissue adhesion, and improved pliability (Berardinelli, 2006; Elliott et al., 1977). Microporosity of this material can be controlled through processing techniques including mixing resin with a solvent binder, cold extrusion of a billet, and mechanical expansion and stretching followed by sintering (Snyder, 1982). A notable example of using this material to encapsulate cells is the Baxter TheraCyte System, which was also an expanded PTFE structure that enhanced blood vessel formation with 5 days of implantation (Brauker et al., 1995) and prevented allograft rejection in non-immunized recipients for 6 months (Kumagai-Braesch et al., 2013) and xenograft rejection for up to 8 weeks in a porcine-to-cynomolgus monkey model (Elliott et al., 2005).

Immune Response

The principle of immunoisolation is based on physical separation of graft cells from the host immune system to prevent direct cell-to-cell contact, thereby circumventing the direct antigen pathway that causes activation of cytotoxic CD8+ T cells by donor major histocompatibility complex (MHC)-peptide complexes expressed on the surface of antigen presenting cells (Gill, 1999; Gray, 1997). Allograft rejection is primarily mediated by such aforementioned process through cellular immunity. To prevent the macrophage and T cell reaction to allografts, allotransplantation of islets with testicular Sertoli cells or genetically engineered cells induced with Fas ligand (FasL) have been shown to protect islets (Calafiore et al., 2001; Korbutt et al., 1997; Lau et al., 1996). Antigens shredded from encapsulated cells could also trigger T cell activation resulting in a series of cytotoxic granules and cytokine release. Therefore, it is important to consider using size exclusion to prevent graft rejection. For example, TheraCyte device with 0.4 μm in pore size protected against allograft rejection in non-immunized recipients for 6 months (Kumagai-Braesch et al., 2013). TheraCyte device also provided effective immunoisolation that allowed neonatal porcine islets to survive in cynomolgus monkeys for up to 8 weeks (Elliott et al., 2005). The pore size of this membrane is insufficient for long-term xenograft protection.

Rejection of non-vascularized xenografts includes both the humoral immunity (involving IgG and IgM antibodies and complement) and cellular immunity (involving T-cells and macrophages, cytokines, free radicals, and NO) (Duvivier-Kali et al., 2004; Mikos et al., 1998; Rokstad et al., 2001; Siebers et al., 1999; Weber et al., 1999). For the humoral immune system, complement reaction is initiated either by the classic pathway that involves binding of the complement component C1q to an IgM or IgG molecule, or by the alternate pathway which involves C3 (Iwata et al., 1999). The final result of the cascade of events is the lysis of cells. In the cellular immunity system, host antigen presenting cells display peptides from donor proteins to engage CD4+ helper T cells which develop into Th2 cells. These cells produce cytokines that

stimulate the maturation of B cells into plasma cells, which secrete xenoantigen-specific antibodies (Gill, 1999; Gray, 1997). CD4+ T cells also induce production of additional cytokines (IFN-γ, IL-2, IL-5) and pro-inflammatory molecules by macrophages (TNF-α, IL-1β, histamine), which can be highly destructive to encapsulated cells through oxidative and endoplasmic reticulum stress pathways (Barshes et al., 2005; Cnop et al., 2005; Montolio et al., 2007; Rabinovitch and Suarez-Pinzon, 1998). Effects of the indirect antigen pathway with humoral and cellular responses on the transport characteristics of immunobarriers have been discussed in many studies (Colton, 1995; Colton and Avgoustiniatos, 1991). Complement reaction can be prevented by using a membrane with a maximum effective pore diameter of 30 nm to hinder passage of complement and antibodies to islets (Colton, 1995), or using molecules that inhibit a step in the formation of the membrane attack complex on encapsulated tissue (Iwata et al., 1999; White and Yannoutsos, 1996). However, the physical nature of immunocellular components presents an enormous challenge to the size-selective based immunoisolation techniques, as shown by dimensions of glucose, insulin and other inflammatory mediators in Table II. While some immunoisolation membranes have managed to protect cells from IL-1β and/or TNF-α (de Haan et al., 2003; Kulseng et al., 1997), blockade of free radical diffusion is very unlikely as demonstrated by Wiegand et al. (Wiegand et al., 1993) and Chae at al. (Chae et al., 2004) that, despite its short half-life, nitric oxide (NO) can still destroy encapsulated islets. This observation was also supported by a mathematical model of free radical diffusion through a spherical matrix containing pancreatic islets (Kavdia and Lewis, 2002). New paradigms in the development of immunoisolation barriers must be explored in the case of indirect antigen presentation for the use of xenografts. As ESC-based cell therapies develop, immunoprotection of xenogeneic cells may not be as critical. Alloprotection may offer sufficient immunoisolation and improved nutrient transport given the pore size used for this type of immunoisolation.

Table II. Glucose, insulin and soluble inflammatory mediators expressed by pancreatic islets.

Molecule	Molecular weight (Da)	Ref.
IgG	150,000	Iizuka et al. (1994)
IL-6	21,500–28,000	Berney et al., (2001); Bottino et al. (2004)
IL-1β	17,500	Berney et al. (2001); Ehrnfelt et al. (2004); Johansson et al. (2003); Matsuda et al. (2005)
TNF-α	17,300	Beutler et al. (1985); Old (1985)
IFN-γ	15,500–25,000	Kelker et al. (1984)
Macrophage migration inhibitory factor (MIF)	12,000	Johansson et al. (2003)
CXCL9 (MIG)	11,700	Schroppel et al. (2005)
CXCL10	10,000	Schroppel et al. (2005)
IL-8	8,000	Bottino et al. (2004); Johansson et al. (2003)
CCL5 (RANTES)	8,000	Schroppel et al. (2005)
MIP-1α	7800	Lewis et al. (2005)
MCP-1	6000–7000	Bottino et al. (2004); Chen et al. (2001); Ehrnfelt et al. (2004); Johansson et al. (2003); Piemonti et al. (2002)
CXCL2 (MIP-2α)	6000	Schroppel et al. (2005)
Insulin	5,087	Gutfreund (1948)
Glucose	180	Khanna et al. (2008)
Nitric oxide (NO)	30	Matsuda et al. (2005); Thomas et al. (2002)

Inflammatory Response

Acute Response

Non-specific inflammatory responses occur at the transplant site immediately after implantation of immunoisolated or naked islets, mediated by activated macrophages that produce cytokines, free radicals, and NO to damage islet cells. The inflammatory milleu is very metabolically active, and therefore, oxygen is rapidly consumed, which further reduces the amount of oxygen available to islets, resulting in hypoxia and death. Not surprisingly, reduction of these effects and prolonged engraftment of both encapsulated and non-encapsulated cells were observed following macrophage depletion (Bottino et al., 1998).

Foreign Body Response

Foreign body response to implanted biomaterials can be described as initial recruitment of neutrophils and macrophages by non-specific adsorption of proteins on the material surface, which leads to subsequent attachment and overgrowth of the device by macrophages, foreign body giant cells, and fibroblasts (Anderson, 1988). The severity of foreign body responses to immunoisolation devices depends on transplantation site and material properties, such as surface charge and chemistry, porosity, roughness, and implant size (Babensee et al., 1998). Capsular overgrowth of the implanted devices inhibits nutrient transport to the islets and cause hypoxia and necrosis that lead to islet destruction and graft failure (de Vos et al., 2006). The biocompatibility of immunoisolating materials could be improved by using highly purified materials (De Vos et al., 1997) or by engendering an alternative foreign body response as illustrated by the TheraCyte device, which encourages blood vessel growth at the capsule surface (Brauker et al., 1995).

Instant Blood-Mediated Inflammation Reaction

In addition to the challenge associated with complex immune responses aforementioned, vascular perfusion macrocapsules face another big hurdle because implantation of vascular perfusion devices injures vessel walls, which, in turn, induces significant platelet adhesion and activation, and blood coagulation. Instant blood mediated inflammation reaction (IBMIR) is another mechanism for acute graft rejection that involves platelet consumption, complement activation and the initiation of the coagulation cascade (van der Windt et al., 2007). To prevent acute rejection as a result of direct contact with the blood, conjugation of thrombomodulin (Feng et al., 2002; Tseng et al., 2006a; Wilson et al., 2010) and anti-coagulation agents such as heparin and warfarin (Edens et al., 1994; Maillet et al., 1988; Tseng et al., 2006b,

c; Wang et al., 2013), use of low-molecular weight dextran sulfate (Goto et al., 2004; van der Windt et al., 2007), and genetic modifications of islets such as adenoviral transduction of complement regulatory factors (CD55, CD59) (Schmidt et al., 2003; van der Windt et al., 2007) have been investigated.

Hypoxia/Implantation Site

Progressive islet graft dysfunction and loss occurs due to many reasons as summarized in Figure 9: absent re-innervations, chronic hypoxia due to poor vascularization, premature apoptosis, lack of regeneration in insulin-producing cells, pro-inflammatory milieu, coagulation and thrombosis in vascular perfusion devices, and mechanical failure of the encapsulation membrane. When islets are transplanted, many of them die in the first few days due to hypoxic death before vascularization develops (O'Sullivan et al., 2010). Cell necrosis occurs when islets are placed beyond the diffusion limit of tissue (>150–200 μm away from the nearest blood vessels) (Thomlinson and Gray, 1955). Vascularization only occurs in 7–10 days after transplant (Johansson et al., 2009; Moya et al., 2010). This delayed and insufficient vascularization creates low oxygen tension, resulting in cell death and graft failure (Figliuzzi et al., 2009). The Sernova and TheraCyte devices have the capability to pre-vascularize the system prior to cell insertion to overcome the low oxygen tension.

To avoid hypoxia, vascular perfusion devices can be connected by vascular anastomoses to the vessels of the host with either AV or AA connection (Elliott et al., 2005; Sun et al., 1996), where oxygen and nutrients directly passed to the cells. Numerous vascular perfusion devices were developed to overcome transport challenges. Common iliac artery and the common iliac vein are the popular sites to use (Maki et al., 1991a,b, 1993, 1996b) in addition to aortic lumen (Prochorov et al., 2004, 2005) in canine models. vascular perfusion devices were also grafted into the deep femoral artery or the forearm cubital vein after performing AV anastomosis in patients (Prochorov et al., 2008). The method of islet transplantation into the forearm cubital vein with AVA formation was less traumatic and more physiological such that patients showed a faster and larger decrease of insulin demand, and euglycemia was maintained for two years with 14 recipients (73.7%) (Prochorov et al., 2008).

Extravascular macrocapsules require large volumes to accommodate sufficient masses of insulin-producing islets, and therefore, locations with established vascular beds are preferred. Peritoneal cavity offers less restriction on the volume of encapsulated islets that can be transplanted, and the procedure can be invasive compared to subcutaneous implantation (Ryan et al., 2005b; Shapiro et al., 2006). However, the lack of vascularization and gravity-induced clumping of islets on the pelvic floor in upright primates, if not immobilized within macrocapsules, are the main issues concerning this location (O'Sullivan et al., 2011). Kidney subcapsular space also offers good vascular network, but the space is quite limited (Biarnes et al., 2002; Potter et al., 2010). Subcutaneous tissue such as epididymal fat pad is close to

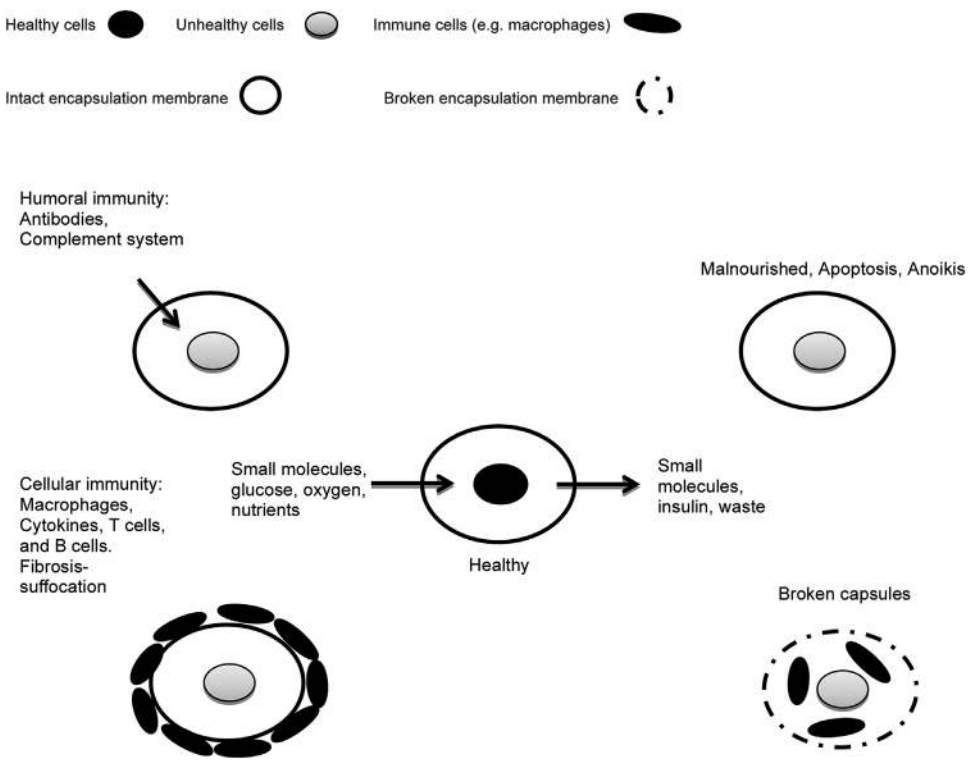

Figure 9. Possible causes for encapsulation failure.

vasculature, but a large surface area may be required for transplantation (Chang, 1964; Chick et al., 1977; Lim and Sun, 1980). Other possible locations include omentum (Browning and Resnik, 1951; Dufrane et al., 2006), muscle (Berman et al., 2009), and intraocular sites (Hathout et al., 2003), but vascularization and space limitation make implantation of extravascular macrocapsules impractical.

New Solution for Macroencapsulation

There are two major areas to be considered for making the successful design of next generation of islet macroencapsulation devices, namely providing effective immunoisolation and presenting sufficient mass transfer between the outside environment and the encased islets. As previously discussed, semipermeable membranes must exhibit precisely controlled pore size to separate soluble inflammatory mediators (Table II) that are on a scale of nanometer in size while exhibiting exceptional uniformity in pore size distribution to provide suitable immunoisolation. Microfabricated silicon membranes can be used to achieve such level of high precision control over pore sizes, as illustrated by examples like nanoporous biocapsule (Desai et al., 1999, 2004; Leoni and Desai, 2004) (Fig. 6) and Nanogland (Sabek et al., 2013) (Fig. 7). The nanoporous biocapsule and Nanogland were designed with L-shaped pore paths with perpendicular microchannels and parallel nanochannels to the membrane surface. This L-shaped design effectively prevented diffusion of larger immune components, but hindered diffusion of small molecules due to the indirect, long diffusion distance. This effect was observed in the Nanogland device where nanochannels with 3.6 and 5.7 nm pore sizes showed a reduction in glucose diffusivity by 40% and 25% compared with the molecule in the bulk medium (Sabek et al., 2013). Besides the long diffusion distance, solutes also face reduced diffusion as their size approach the molecular dimension of the pores. Dechadilok and Deen reviewed hindered transport theory for both diffusive and convective hindrance factors in which uncharged, spherical particles travel in the long cylindrical and slit pores of uniform cross-section (Dechadilok and Deen, 2006). Depending on the mode of transport, it is crucial to design immunoisolating membranes with size exclusion properties for the larger immune components (e.g. cytokines, antibodies) while still permit the passage of smaller molecules (e.g. glucose, insulin). The surfaces of silicon membranes can also be selectively grafted with biocompatible polymer thin films to ensure functional performance over extended time periods, making them suitable for biological applications (Li et al., 2010; Melvin et al., 2010; Zhu and Marchant, 2006). Although nano-sized pores are ideal to restrict the passage of immune components, encased islet functions and viability could be greatly impacted under the diffusive transport approach. A faster mass transfer of oxygen and nutrients to the encapsulated islets is needed given the size constraints on the pores. To monitor vessel stenosis and prevent thrombosis in vascular devices, advances including the use of intra-access blood flow and pressure measurements and duplex ultrasound (Allon, 2007) could further shed light on the optimal vascular perfusion design (e.g. pressure drop, blood flow path) for macroencapsulation devices.

Conclusions

To date, the pursuit of bioartificial pancreas devices that restore glucose homeostasis without the need for immunosuppression still remains one of the most challenging goals within the field of regenerative medicine and tissue engineering. With more than 50 years of intensive research directed at developing encapsulation methods for immunoisolation of transplanted cells, both promise and inherent challenges, particularly related to macroencapsulation, have been discussed within this review. The progress on macroencapsulation has been limited due to inefficient mass transport of oxygen and nutrients under extravascular setting and problematic blood coagulation and thrombosis under intravascular environment in large animals. But advances in membrane development such as use of MEMS technology have the potential to improve macroencapsulation. In addition to the maintenance of adequate oxygen and nutrient transport, inflammatory response also plays a pivotal role in reacting with any implanted cell-material composite, and therefore, a proper control of membrane transport properties to prevent host responses is of paramount importance. Given the promising potential of encapsulation based bioartificial pancreas, successful devices will depend on merging knowledge from cell-based therapeutics with advanced engineering approaches to overcome several major obstacles: first, the development of a renewable, alternative insulin-producing cell source to solve the current donor organ shortage; second, enhanced biocompatibility and permselectivity of immunobarriers to reduce deleterious host immune response; and thirdly, improved mass transport characteristics of existing encapsulation techniques using advanced engineering approach. Therefore, a synergistic effort between biological and physical scientists, physician-scientists, and engineers will be essential for the development of novel life-saving technologies in the field of T1D research.

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References

Agulnick AD, Ambruzs DM, Moorman MA, Bhoumik A, Cesario RM, Payne JK, Kelly JR, Haakmeester C, Srijemac R, Wilson AZ, Kerr J, Frazier MA, Kroon EJ, D'Amour KA. 2015. Insulin-producing endocrine cells differentiated in vitro from human embryonic stem cells function in macroencapsulation devices in vivo. Stem Cells Transl Med 4(10):1214–1222.

Akinci E, Banga A, Greder LV, Dutton JR, Slack JM. 2012. Reprogramming of pancreatic exocrine cells towards a beta (beta) cell character using Pdx1, Ngn3 and MafA. Biochem J 442(3):539–550.

Algire GH. 1943. An adaptation of the transparent-chamber technique to the mouse. J Natl Cancer Inst 4(1):1–11.

Allon M. 2007. Current management of vascular access. Clin J Am Soc Nephrol 2(4):786–800.

Anderson JM. 1988. Inflammatory response to implants. ASAIO. Trans 34:101–107.

Aoi T, Yae K, Nakagawa M, Ichisaka T, Okita K, Takahashi K, Chiba T, Yamanaka S. 2008. Generation of pluripotent stem cells from adult mouse liver and stomach cells. Science 321(5889):699–702.

Assady S, Maor G, Amit M, Itskovitz-Eldor J, Skorecki KL, Tzukerman M. 2001. Insulin production by human embryonic stem cells. Diabetes 50(8):1691–1697.

Babensee JE, Anderson JM, McIntire LV, Mikos AG. 1998. Host response to tissue engineered devices. Adv Drug Deliv Rev 33(1–2):111–139.

Baetge EE. 2008. Production of beta-cells from human embryonic stem cells. Diabetes Obes Metab 10(Suppl 4):186–194.

Baeyens L, De Breuck S, Lardon J, Mfopou JK, Rooman I, Bouwens L. 2005. In vitro generation of insulin-producing beta cells from adult exocrine pancreatic cells. Diabetologia 48(1):49–57.

Barry FP, Murphy JM. 2004. Mesenchymal stem cells: clinical applications and biological characterization. Int J Biochem Cell Biol 36(4):568–584.

Barshes NR, Wyllie S, Goss JA. 2005. Inflammation-mediated dysfunction and apoptosis in pancreatic islet transplantation: implications for intrahepatic grafts. J Leukoc Biol 77(5):587–597.

Basta G, Montanucci P, Luca G, Boselli C, Noya G, Barbaro B, Qi M, Kinzer KP, Oberholzer J, Calafiore R. 2011a. Long-term metabolic and immunological follow-up of nonimmunosuppressed patients with type 1 diabetes treated with microencapsulated islet allografts: four cases. Diabetes Care 34(11):2406–2409.

Basta G, Montanucci P, Luca G, Boselli C, Noya G, Barbaro B, Qi MRG, Kinzer KP, Oberholzer J, Calafiore R. 2011b. Long-term metabolic and immunological follow-up of nonimmunosuppressed patients with type 1 diabetes treated with microencapsulated islet allografts. Diabetes Care 34(11):2406–2409.

Berardinelli L. 2006. Grafts and graft materials as vascular substitutes for haemodialysis access construction. Eur J Vasc Endovasc Surg 32(2):203–211.

Berman DM, O'Neil JJ, Coffey LC, Chaffanjon PC, Kenyon NM, Ruiz P, Jr., Pileggi A, Ricordi C, Kenyon NS. 2009. Long-term survival of nonhuman primate islets implanted in an omental pouch on a biodegradable scaffold. Am J Transplant 9(1):91–104.

Berney T, Molano RD, Cattan P, Pileggi A, Vizzardelli C, Oliver R, Ricordi C, Inverardi L. 2001. Endotoxin-mediated delayed islet graft function is associated with increased intra-islet cytokine production and islet cell apoptosis. Transplantation 71(1):125–132.

Best M, Carroll M, Hanley NA, Piper Hanley K. 2008. Embryonic stem cells to beta-cells by understanding pancreas development. Mol Cell Endocrinol 288(1–2):86–94.

Beutler B, Greenwald D, Hulmes JD, Chang M, Pan YCE, Mathison J, Ulevitch R, Cerami A. 1985. Identity of tumor necrosis factor and the macrophage-secreted factor cachectin. Nature 316(6028):552–554.

Biarnes M, Montolio M, Nacher V, Raurell M, Soler J, Montanya E. 2002. Beta-cell death and mass in syngeneically transplanted islets exposed to short- and long-term hyperglycemia. Diabetes 51(1):66–72.

Bieber T, Meissner W, Kostin S, Niemann A, Elsasser HP. 2002. Intracellular route and transcriptional competence of polyethylenimine-DNA complexes. J Control Release 82(2–3):441–454.

Bonner-Weir S, Baxter LA, Schuppin GT, Smith FE. 1993. A second pathway for regeneration of adult exocrine and endocrine pancreas. A possible recapitulation of embryonic development. Diabetes 42(12):1715–1720.

Bonner-Weir S, Taneja M, Weir GC, Tatarkiewicz K, Song KH, Sharma A, O'Neil JJ. 2000. In vitro cultivation of human islets from expanded ductal tissue. Proc Natl Acad Sci USA 97(14):7999–8004.

Bonner-Weir S, Li WC, Ouziel-Yahalom L, Guo LL, Weir GC, Sharma A. 2010. Beta-cell growth and regeneration: Replication is only part of the story. Diabetes 59(10):2340–2348.

Bottino R, Fernandez LA, Ricordi C, Lehmann R, Tsan MF, Oliver R, Inverardi L. 1998. Transplantation of allogeneic islets of Langerhans in the rat liver: effects of macrophage depletion on graft survival and microenvironment activation. Diabetes 47(3):316–323.

Bottino R, Balamurugan AN, Tse H, Thirunavukkarasu C, Ge X, Profozich J, Milton M, Ziegenfuss A, Trucco M, Piganelli JD. 2004. Response of human islets to isolation stress and the effect of antioxidant treatment. Diabetes 53(10):2559–2568.

Brauker JH, Carr-Brendel VE, Martinson LA, Crudele J, Johnston WD, Johnson RC. 1995. Neovascularization of synthetic membranes directed by membrane microarchitecture. J Biomed Mater Res 29(12):1517–1524.

Browning H, Resnik P. 1951. Homologous and heterologous transplantation of pancreatic tissue in normal and diabetic mice. Yale J Biol Med 24(2):140–152.

Burczak K, Fujisato T, Hatada M, Ikada Y. 1994. Protein permeation through poly(vinyl alcohol) hydrogel membranes. Biomaterials 15(3):231–238.

Calafiore R, Basta G, Luca G, Boselli C, Bufalari A, Giustozzi GM, Gialletti R, Moriconi F, Brunetti P. 1998. Transplantation of allogeneic/xenogeneic pancreatic islets containing coherent microcapsules in adult pigs. Transplant Proc 30(2):482–483.

Calafiore R, Luca G, Calvitti M, Neri LM, Basta G, Capitani S, Becchetti E, Brunetti P. 2001. Cellular support systems for alginate microcapsules containing islets, as composite bioartificial pancreas. Ann N Y Acad Sci 944:240–251.

Calafiore R, Basta G, Luca G, Lemmi A, Montanucci MP, Calabrese G, Racanicchi L, Mancuso F, Brunetti P. 2006a. Microencapsulated pancreatic islet allografts into nonimmunosuppressed patients with type 1 diabetes - First two cases. Diabetes Care 29(1):137–138.

Calafiore R, Basta G, Luca G, Lemmi A, Montanucci MP, Calabrese G, Racanicchi L, Mancuso F, Brunetti P. 2006b. Microencapsulated pancreatic islet allografts into nonimmunosuppressed patients with type 1 diabetes: first two cases. Diabetes Care 29(1):137–138.

Calafiore R, Basta G, Luca G, Lemmi A, Racanicchi L, Mancuso F, Montanucci MP, Brunetti P. 2006c. Standard technical procedures for microencapsulation of human islets for graft into nonimmunosuppressed patients with type 1 diabetes mellitus. Transplant Proc 38(4):1156–1157.

Cantarovich D, Blancho G, Potiron N, Jugeau N, Fiche M, Chagneau C, Letessier E, Boeffard F, Loth P, Karam G, Soulillou JP, Le Mauff B. 2002. Rapid failure of pig islet transplantation in non human primates. Xenotransplantation 9(1):25–35.

Chae SY, Lee M, Kim SW, Bae YH. 2004. Protection of insulin secreting cells from nitric oxide induced cellular damage by crosslinked hemoglobin. Biomaterials 25(5):843–850.

Chaikof EL. 1999. Engineering and material considerations in islet cell transplantation. Annu Rev Biomed Eng 1:103–127.

Chang TM. 1964. Semipermeable microcapsules. Science 146(3643):524–525.

Chen MC, Proost P, Gysemans C, Mathieu C, Eizirik DL. 2001. Monocyte chemoattractant protein-1 is expressed in pancreatic islets from prediabetic NOD mice and in interleukin-1 beta-exposed human and rat islet cells. Diabetologia 44(3):325–332.

Chen S, Borowiak M, Fox JL, Maehr R, Osafune K, Davidow L, Lam K, Peng LF, Schreiber SL, Rubin LL, Melton D. 2009. A small molecule that directs differentiation of human ESCs into the pancreatic lineage. Nat Chem Biol 5(4):258–265.

Chick WL, Perna JJ, Lauris V, Low D, Galletti PM, Panol G, Whittemore AD, Like AA, Colton CK, Lysaght MJ. 1977. Artificial Pancreas Using Living Beta Cells - Effects on Glucose Homeostasis in Diabetic Rats. Science 197(4305):780–782.

Chu WH, Huen T, Tu J, Ferrari M. 1996. Silicon-micromachined, direct-pore filters for ultrafiltration. SPIE Proc. of Micro-and nanofabricated structures and devices for biomedical environmental applications. Int Soc Optic Engin 2978:111–122.

Cnop M, Welsh N, Jonas JC, Jorns A, Lenzen S, Eizirik DL. 2005. Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: many differences, few similarities. Diabetes 54(Suppl 2):S97–107.

Colton CK, Avgoustiniatos ES. 1991. Bioengineering in development of the hybrid artificial pancreas. J Biomech Eng 113(2):152–170.

Colton CK. 1995. Implantable biohybrid artificial organs. Cell Transplant 4(4):415–436.

Cryer PE. 2002. Hypoglycaemia: The limiting factor in the glycaemic management of Type I and Type II Diabetes. Diabetologia 45(7):937–948.

Cryer PE. 2012. Minireview: Glucagon in the pathogenesis of hypoglycemia and hyperglycemia in diabetes. Endocrinology 153(3):1039–1048.

Cui W, Barr G, Faucher KM, Sun XL, Safley SA, Weber CJ, Chaikof EL. 2004. A membrane-mimetic barrier for islet encapsulation. Transplant Proc 36(4):1206–1208.

D'Amour KA, Bang AG, Eliazer S, Kelly OG, Agulnick AD, Smart NG, Moorman MA, Kroon E, Carpenter MK, Baetge EE. 2006. Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol 24(11):1392–1401.

Dall TM, Mann SE, Zhang Y, Quick WW, Seifert RF, Martin J, Huang EA, Zhang S. 2009. Distinguishing the economic costs associated with type 1 and type 2 diabetes. Popul Health Manag 12(2):103–110.

Danne T, Tsioli C, Kordonouri O, Blaesig S, Remus K, Roy A, Keenan B, Lee SW, Kaufman FR. 2014. The PILGRIM study: in silico modeling of a predictive low glucose management system and feasibility in youth with type 1 diabetes during exercise. Diabetes Technol Ther 16(6):338–347.

Das M, Wilson K, Molnar P, Hickman JJ. 2007. Differentiation of skeletal muscle and integration of myotubes with silicon microstructures using serum-free medium and a synthetic silane substrate. Nat Protoc 2(7):1795–1801.

de Haan BJ, Faas MM, de Vos P. 2003. Factors influencing insulin secretion from encapsulated islets. Cell Transplant 12(6):617–625.

de Koning EJ, Bodkin NL, Hansen BC, Clark A. 1993. Diabetes mellitus in Macaca mulatta monkeys is characterised by islet amyloidosis and reduction in beta-cell population. Diabetologia 36(5):378–384.

De Koker S, De Geest BG, Cuvelier C, Ferdinande L, Deckers W, Hennink WE, De Smedt SC, Mertens N. 2007. In vivo cellular uptake, degradation, and biocompatibility of polyelectrolyte microcapsules. Adv Funct Mater 17(18): 3754–3763.

De Temmerman ML, Demeester J, De Smedt SC, Rejman J. 2012. Tailoring layer-by-layer capsules for biomedical applications. Nanomedicine (Lond) 7(5):771–788.

de Vos P, Marchetti P. 2002. Encapsulation of pancreatic islets for transplantation in diabetes: the untouchable islets. Trends Mol Med 8(8):363–366.

de Vos P, De Haan BJ, Wolters GH, Strubbe JH, Van Schilfgaarde R. 1997. Improved biocompatibility but limited graft survival after purification of alginate for microencapsulation of pancreatic islets. Diabetologia 40(3):262–270.

de Vos P, Hamel AF, Tatarkiewicz K. 2002. Considerations for successful transplantation of encapsulated pancreatic islets. Diabetologia 45(2):159–173.

de Vos P, Faas MM, Strand B, Calafiore R. 2006. Alginate-based microcapsules for immunoisolation of pancreatic islets. Biomaterials 27(32):5603–5617.

de Vos P, Bucko M, Gemeiner P, Navratil M, Svitel J, Faas M, Strand BL, Skjak-Braek G, Morch YA, Vikartovska A, Lacik I, Kollarikova G, Orive G, Poncelet D, Pedraz JL, Ansorge-Schumacher MB. 2009. Multiscale requirements for bioencapsulation in medicine and biotechnology. Biomaterials 30(13):2559–2570.

Dechadilok P, Deen WM. 2006. Hindrance factors for diffusion and convection in pores. Ind Eng Chem Res 45(21):6953–6959.

Desai TA, Chu WH, Rasi G, Sinibaldi-Vallebona P, Guarino E, Ferrari M. 1999. Microfabricated biocapsules provide short-term immunoisolation of insulinoma xenografts. Biomed Microdevices 1(2):131–138.

Desai TA, West T, Cohen M, Boiarski T, Rampersaud A. 2004. Nanoporous microsystems for islet cell replacement. Adv Drug Deliv Rev 56(11):1661–1673.

Dolgin E. 2012. Medical devices: Managed by machine. Nature 485(7398):S6–S8.

Dor Y, Brown J, Martinez OI, Melton DA. 2004. Adult pancreatic beta-cells are formed by self-duplication rather than stem-cell differentiation. Nature 429(6987): 41–46.

Dufrane D, Goebbels RM, Saliez A, Guiot Y, Gianello P. 2006. Six-month survival of microencapsulated pig islets and alginate biocompatibility in primates: proof of concept. Transplantation 81(9):1345–1353.

Dufrane D, Goebbels RM, Gianello P. 2010. Alginate macroencapsulation of pig islets allows correction of streptozotocin-induced diabetes in primates up to 6 months without immunosuppression. Transplantation 90(10):1054–1062.

Duvivier-Kali VF, Omer A, Lopez-Avalos MD, O'Neil JJ, Weir GC. 2004. Survival of microencapsulated adult pig islets in mice in spite of an antibody response. Am J Transplant 4(12):1991–2000.

Edell DJ, Toi VV, McNeil VM, Clark LD. 1992. Factors influencing the biocompatibility of insertable silicon microshafts in cerebral cortex. IEEE Trans Biomed Eng 39(6):635–643.

Edens RE, Linhardt RJ, Bell CS, Weiler JM. 1994. Heparin and derivatized heparin inhibit zymosan and cobra venom factor activation of complement in serum. Immunopharmacology 27(2):145–153.

Ehrnfelt C, Kumagai-Braesch M, Uzunel M, Holgersson J. 2004. Adult porcine islets produce MCP-1 and recruit human monocytes in vitro. Xenotransplantation 11(2):184–194.

Elliott MP, Gazzaniga AB, Thomas JM, Haiduc NJ, Rosen SM. 1977. Use of expanded polytetrafluoroethylene grafts for vascular access in hemodialysis: laboratory and clinical evaluation. Am Surg 43(7):455–459.

Elliott RB, Escobar L, Tan PL, Garkavenko O, Calafiore R, Basta P, Vasconcellos AV, Emerich DF, Thanos C, Bambra C. 2005. Intraperitoneal alginate-encapsulated neonatal porcine islets in a placebo-controlled study with 16 diabetic cynomolgus primates. Transplant Proc 37(8):3505–3508.

Elliott RB, Escobar L, Tan PL, Muzina M, Zwain S, Buchanan C. 2007. Live encapsulated porcine islets from a type 1 diabetic patient 9.5 yr after xenotransplantation. Xenotransplantation 14(2):157–161.

Emamaullee JA, Shapiro AM, Rajotte RV, Korbutt G, Elliott JF. 2006. Neonatal porcine islets exhibit natural resistance to hypoxia-induced apoptosis. Transplantation 82(7):945–952.

Ensenat-Waser R, Vicente-Salar ASN, Cigudosa JC, Roche E, Soria B, Reig JA. 2006. Isolation and characterization of residual undifferentiated mouse embryonic stem cells from embryoid body cultures by fluorescence tracking. In Vitro Cell Dev Biol Anim 42(5–6):115–123.

Farney AC, Rogers J, Stratta RJ. 2012. Pancreas graft thrombosis: causes, prevention, diagnosis, and intervention. Curr Opin Organ Transplant 17(1):87–92.

Feng J, Tseng PY, Faucher KM, Orban JM, Sun XL, Chaikof EL. 2002. Functional reconstitution of thrombomodulin within a substrate-supported membrane-mimetic polymer film. Langmuir 18(25):9907–9913.

Figliuzzi M, Cornolti R, Perico N, Rota C, Morigi M, Remuzzi G, Remuzzi A, Benigni A. 2009. Bone marrow-derived mesenchymal stem cells improve islet graft function in diabetic rats. Transplant Proc 41(5):1797–1800.

Fujikawa T, Oh SH, Pi L, Hatch HM, Shupe T, Petersen BE. 2005. Teratoma formation leads to failure of treatment for type I diabetes using embryonic stem cell-derived insulin-producing cells. Am J Pathol 166(6):1781–1791.

Gao R, Ustinov J, Pulkkinen MA, Lundin K, Korsgren O, Otonkoski T. 2003. Characterization of endocrine progenitor cells and critical factors for their differentiation in human adult pancreatic cell culture. Diabetes 52(8): 2007–2015.

Garkavenko O, Dieckhoff B, Wynyard S, Denner J, Elliott RB, Tan PL, Croxson MC. 2008. Absence of transmission of potentially xenotic viruses in a prospective pig to primate islet xenotransplantation study. J Med Virol 80(11):2046–2052.

Georgia S, Bhushan A. 2004. Beta cell replication is the primary mechanism for maintaining postnatal beta cell mass. J Clin Invest 114(7):963–968.

Gill RG. 1999. Antigen presentation pathways for immunity to islet transplants. Relevance to immunoisolation. Ann N Y Acad Sci 875:255–260.

Godbey WT, Wu KK, Mikos AG. 1999. Size matters: molecular weight affects the efficiency of poly(ethylenimine) as a gene delivery vehicle. J Biomed Mater Res 45(3):268–275.

Golden SH, Brown T, Yeh HC, Maruthur N, Ranasinghe P, Berger Z, Suh Y, Wilson LM, Haberl EB, Bass EB. 2012. Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Rockville (MD).

Goosen MF, O'Shea GM, Gharapetian HM, Chou S, Sun AM. 1985. Optimization of microencapsulation parameters: Semipermeable microcapsules as a bioartificial pancreas. Biotechnol Bioeng 27(2):146–150.

Goto M, Johansson H, Maeda A, Elgue G, Korsgren O, Nilsson B. 2004. Low molecular weight dextran sulfate prevents the instant blood-mediated inflammatory reaction induced by adult porcine islets. Transplantation 77(5):741–747.

Gray DW. 1997. Encapsulated islet cells: the role of direct and indirect presentation and the relevance to xenotransplantation and autoimmune recurrence. Br Med Bull 53(4):777–788.

Gruessner AC, Sutherland DE. 2008. Pancreas transplant outcomes for United States (US) cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). Clin Transpl 45–56.

Gruessner RW, Sutherland DE, Gruessner AC. 2004. Mortality assessment for pancreas transplants. Am J Trans 4(12):2018–2026.

Gruessner AC, Sutherland DER, Gruessner RWG. 2010. Pancreas transplantation in the United States: a review. Curr Opin Organ Transplant 15(1):93–101.

Gu G, Dubauskaite J, Melton DA. 2002. Direct evidence for the pancreatic lineage: NGN3+ cells are islet progenitors and are distinct from duct progenitors. Development 129(10):2447–2457.

Gutfreund H. 1948. The molecular weight of insulin and its dependence upon pH, concentration and temperature. Biochem J 42(4):544–548.

Hall KK, Gattas-Asfura KM, Stabler CL. 2011. Microencapsulation of islets within alginate/poly(ethylene glycol) gels cross-linked via Staudinger ligation. Acta Biomater 7(2):614–624.

Harjutsalo V, Sjoberg L, Tuomilehto J. 2008. Time trends in the incidence of type 1 diabetes in Finnish children: A cohort study. Lancet 371(9626):1777–1782.

Hathout E, Lakey J, Shapiro J. 2003. Islet transplant: an option for childhood diabetes? Arch Dis Child 88(7):591–594.

Hinshaw L, Dalla Man C, Nandy DK, Saad A, Bharucha AE, Levine JA, Rizza RA, Basu R, Carter RE, Cobelli C, Kudva YC, Basu A. 2013. Diurnal pattern of insulin action in type 1 diabetes: Implications for a closed-loop system. Diabetes 62(7):2223–2229.

Hirshberg B, Rother KI, Digon BJ, Lee 3rd, Gaglia J, Hines JL, Read K, Chang EJ, Wood R, Harlan BJ. 2003. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: The National Institutes of Health experience. Diabetes Care 26(12):3288–3295.

Humar A, Kandaswamy R, Granger D, Gruessner RW, Gruessner AC, Sutherland DE. 2000. Decreased surgical risks of pancreas transplantation in the modern era. Ann Surg 231(2):269–275.

Iizuka K, Ikebe M, Somlyo AV, Somlyo AP. 1994. Introduction of high molecular weight (IgG) proteins into receptor coupled, permeabilized smooth muscle. Cell Calcium 16(6):431–445.

Iwata H, Takagi T, Amemiya H. 1992. Agarose microcapsule applied in islet xenografts (hamster to mouse). Transplant Proc 24(3):952.

Iwata H, Kobayashi K, Takagi T, Oka T, Yang H, Amemiya H, Tsuji T, Ito F. 1994. Feasibility of agarose microbeads with xenogeneic islets as a bioartificial pancreas. J Biomed Mater Res 28(9):1003–1011.

Iwata H, Murakami Y, Ikada Y. 1999. Control of complement activities for immunoisolation. Ann N Y Acad Sci 875:7–23.

Jain K, Yang H, Cai BR, Haque B, Hurvitz AI, Diehl C, Miyata T, Smith BH, Stenzel K, Suthanthiran M, Rubin AL. 1995. Retrievable, replaceable, macroencapsulated pancreatic islet xenografts. Long-term engraftment without immunosuppression. Transplantation 59(3):319–324.

Jain K, Asina S, Yang H, Blount ED, Smith BH, Diehl CH, Rubin AL. 1999. Glucose control and long-term survival in biobreeding/Worcester rats after intraperitoneal implantation of hydrophilic macrobeads containing porcine islets without immunosuppression. Transplantation 68(11):1693–1700.

Johansson U, Olsson A, Gabrielsson S, Nilsson B, Korsgren O. 2003. Inflammatory mediators expressed in human islets of Langerhans: implications for islet transplantation. Biochem Biophys Res Commun 308(3):474–479.

Johansson A, Olerud J, Johansson M, Carlsson PO. 2009. Angiostatic factors normally restrict islet endothelial cell proliferation and migration: implications for islet transplantation. Transpl Int 22(12):1182–1188.

Kajita T, Hugli TE. 1991. Evidence for in vivo degradation of C3a anaphylatoxin by mast cell chymase. I. Nonspecific activation of rat peritoneal mast cells by C3ades Arg. Am J Pathol 138(6):1359–1369.

Kandaswamy R, Stock PG, Skeans MA, Gustafson SK, Sleeman EF, Wainright JL, Carrico RJ, Ghimire V, Snyder JJ, Israni AK, Kasiske BL. 2013. OPTN/SRTR 2011 Annual Data Report: Pancreas. Am J Transplant 13:47–72.

Kavdia M, Lewis RS. 2002. Free radical profiles in an encapsulated pancreatic cell matrix model. Ann Biomed Eng 30(5):721–730.

Kelker HC, Le J, Rubin BY, Yip YK, Nagler C, Vilcek J. 1984. Three molecular weight forms of natural human interferon-gamma revealed by immunoprecipitation with monoclonal antibody. J Biol Chem 259(7):4301–4304.

Kelly OG, Chan MY, Martinson LA, Kadoya K, Ostertag TM, Ross KG, Richardson M, Carpenter MK, D'Amour KA, Kroon E, Moorman M, Baetge EE, Bang AG. 2011. Cell-surface markers for the isolation of pancreatic cell types derived from human embryonic stem cells. Nat Biotechnol 29(8):750–756.

Kessler L, Pinget M, Aprahamian M, Dejardin P, Damge C. 1991. In vitro and in vivo studies of the properties of an artificial membrane for pancreatic islet encapsulation. Horm Metab Res 23(7):312–317.

Kessler L, Legeay G, Jesser C, Damge C, Pinget M. 1995. Influence of corona surface treatment on the properties of an artificial membrane used for Langerhans islets encapsulation: permeability and biocompatibility studies. Biomaterials 16(3):185–191.

Kessler L, Legeay G, West R, Belcourt A, Pinget M. 1997. Physicochemical and biological studies of corona-treated artificial membranes used for pancreatic islets encapsulation: mechanism of diffusion and interface modification. J Biomed Mater Res 34(2):235–245.

Khanna P, Strom JA, Malone JI, Bhansali S. 2008. Microneedle-based automated therapy for diabetes mellitus. J Diabetes Sci Technol 2(6):1122–1129.

Khanna O, Moya ML, Opara EC, Brey EM. 2010. Synthesis of multilayered alginate microcapsules for the sustained release of fibroblast growth factor-1. J Biomed Mater Res A 95(2):632–640.

Kim H, Lee TJ, Kim S, Lee H. 2011. Modification of silicon substrate using low-energy proton beam for selective growth of CNTs. J Nanosci Nanotechnol 11(5):4378–4383.

Kipke DR, Vetter RJ, Williams JC, Hetke JF. 2003. Silicon-substrate intracortical microelectrode arrays for long-term recording of neuronal spike activity in cerebral cortex. IEEE Trans Neural Syst Rehabil Eng 11(2):151–155.

Kirchhof N, Shibata S, Wijkstrom M, Kulick DM, Salerno CT, Clemmings SM, Heremans Y, Galili U, Sutherland DE, Dalmasso AP, Hering BJ. 2004. Reversal of diabetes in non-immunosuppressed rhesus macaques by intraportal porcine islet xenografts precedes acute cellular rejection. Xenotransplantation 11(5):396–407.

Klomp GF, Ronel SH, Hashiguchi H, D'Andrea M, Dobelle WH. 1979. Hydrogels for encapsulation of pancreatic islet cells. Trans Am Soc Artif Intern Organs 25:74–76.

Korbutt GS, Elliott JF, Rajotte RV. 1997. Cotransplantation of allogeneic islets with allogeneic testicular cell aggregates allows long-term graft survival without systemic immunosuppression. Diabetes 46(2):317–322.

Kovacs GT, Storment CW, Halks-Miller M, Belczynski CR, Jr., Della Santina CC, Lewis ER, Maluf NI. 1994. Silicon-substrate microelectrode arrays for parallel recording of neural activity in peripheral and cranial nerves. IEEE Trans Biomed Eng 41(6):567–577.

Kristensen BW, Noraberg J, Thiebaud P, Koudelka-Hep M, Zimmer J. 2001. Biocompatibility of silicon-based arrays of electrodes coupled to organotypic hippocampal brain slice cultures. Brain Res 896(1–2):1–17.

Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, Young H, Richardson M, Smart NG, Cunningham J, Agulnick AD, D'Amour KA, Carpenter MK, Baetge EE. 2008. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol 26(4):443–452.

Kulseng B, Thu B, Espevik T, Skjak-Braek G. 1997. Alginate polylysine microcapsules as immune barrier: permeability of cytokines and immunoglobulins over the capsule membrane. Cell Transplant 6(4):387–394.

Kumagai-Braesch M, Jacobson S, Mori H, Jia X, Takahashi T, Wernerson A, Flodstrom-Tullberg M, Tibell A. 2013. The TheraCyte device protects against islet allograft rejection in immunized hosts. Cell Transplant 22(7):1137–1146.

Kushner JA, Weir GC, Bonner-Weir S. 2010. Ductal origin hypothesis of pancreatic regeneration under attack. Cell Metab 11(1):2–3.

La Flamme KE, Mor G, Gong D, La Tempa T, Fusaro VA, Grimes CA, Desai TA. 2005. Nanoporous alumina capsules for cellular macroencapsulation: Transport and biocompatibility. Diabetes Technol Ther 7(5):684–694.

La Flamme KE, LaTempa TJ, Grimes CA, Desai TA. 2007. The effects of cell density and device arrangement on the behavior of macroencapsulated beta-cells. Cell Transplant 16(8):765–774.

Lacy PE, Hegre OD, Gerasimidi-Vazeou A, Gentile FT, Dionne KE. 1991. Maintenance of normoglycemia in diabetic mice by subcutaneous xenografts of encapsulated islets. Science 254(5039):1782–1784.

Lamb M, Storrs R, Li S, Liang O, Laugenour K, Dorian R, Chapman D, Ichii H, Imagawa D, Foster C, 3rd, King S, Lakey JR. 2011. Function and viability of human islets encapsulated in alginate sheets: in vitro and in vivo culture. Transplant Proc 43(9):3265–3266.

Lanza RP, Kuhtreiber WM. 1999. Xenotransplantation and cell therapy: progress and controversy. IBC's 4th International Conference on Xenotransplantation and Cell Therapy. Boston, MA, USA, 10-11 December 1998. Mol Med Today 5(3): 105–106.

Lanza RP, Sullivan SJ, Chick WL. 1992a. Perspectives in diabetes. Islet transplantation with immunoisolation. Diabetes 41(12):1503–1510.

Lanza RP, Sullivan SJ, Monaco AP, Chick WL. 1992b. The hybrid artificial pancreas: Diffusion and vascular devices. Pancreatic islet cell transplantation. R.G. Landes Company ed. p 223–237.

Lanza RP, Beyer AM, Staruk JE, Chick WL. 1993. Biohybrid artificial pancreas. Long-term function of discordant islet xenografts in streptozotocin diabetic rats. Transplantation 56(5):1067–1072.

Lanza RP, Ecker D, Kuhtreiber WM, Staruk JE, Marsh J, Chick WL. 1995a. A simple method for transplanting discordant islets into rats using alginate gel spheres. Transplantation 59(10):1485–1487.

Lanza RP, Kuhtreiber WM, Ecker D, Staruk JE, Chick WL. 1995b. Xenotransplantation of porcine and bovine islets without immunosuppression using uncoated alginate microspheres. Transplantation 59(10):1377–1384.

Lanza RP, Hayes JL, Chick WL. 1996a. Encapsulated cell technology. Nat Biotechnol 14(9):1107–1111.

Lanza RP, Kuhtreiber WM, Ecker DM, Marsh JP, Staruk JE, Chick WL. 1996b. A simple method for xenotransplanting cells and tissues into rats using uncoated alginate microreactors. Transplant Proc 28(2):835.

Lanza RP, Cooper DK, Chick WL. 1997. Xenotransplantation. Sci Am 277(1):54–59.

Lanza RP, Ecker DM, Kuhtreiber WM, Marsh JP, Ringeling J, Chick WL. 1999. Transplantation of islets using microencapsulation: Studies in diabetic rodents and dogs. J Mol Med 77(1):206–210.

Lau HT, Yu M, Fontana A, Stoeckert CJ, Jr. 1996. Prevention of islet allograft rejection with engineered myoblasts expressing FasL in mice. Science 273(5271) :109–112.

Lee WA, Narog BA, Patapoff TW, Wang YJ. 1991. Intranasal bioavailability of insulin powder formulations: Effect of permeation enhancer-to-protein ratio. J Pharm Sci 80(8):725–729.

Lee SH, Hao E, Savinov AY, Geron I, Strongin AY, Itkin-Ansari P. 2009a. Human beta-cell precursors mature into functional insulin-producing cells in an immunoisolation device: Implications for diabetes cell therapies. Transplantation 87(7):983–991.

Lee SH, Hao EG, Savinov AY, Geron I, Strongin AY, Itkin-Ansari P. 2009b. Human beta-cell precursors mature into functional insulin-producing cells in an immunoisolation device: Implications for diabetes cell therapies. Transplantation 87(7):983–991.

Lee MH, Chang ST, Hsieh BF, Huang JJ, Lee CC. 2011. Analysis and modeling of nanocrystalline silicon TFTs on flexible substrate with mechanical strain. J Nanosci Nanotechnol 11(12):10485–10488.

Lehmann R, Weber M, Berthold P, Zullig R, Pfammatter T, Moritz W, Madler K, Donath M, Ambuhl P, Demartines N, Clavien PA, Andreia SG. 2004. Successful simultaneous islet-kidney transplantation using a steroid-free immunosuppression: Two-year follow-up. Am J Trans 4(7):1117–1123.

Lehmann R, Zuellig RA, Kugelmeier P, Baenninger PB, Moritz W, Perren A, Clavien PA, Weber M, Spinas GA. 2007. Superiority of small islets in human islet transplantation. Diabetes 56(3):594–603.

Leoni L, Desai TA. 2004. Micromachined biocapsules for cell-based sensing and delivery. Adv Drug Deliv Rev 56(2):211–229.

Levesque L, Brubaker PL, Sun AM. 1992. Maintenance of long-term secretory function by microencapsulated islets of Langerhans. Endocrinology 130(2): 644–650.

Lewis EC, Shapiro L, Bowers OJ, Dinarello CA. 2005. Alpha1-antitrypsin monotherapy prolongs islet allograft survival in mice. Proc Natl Acad Sci USA 102(34):12153–12158.

Li L, Marchant RE, Dubnisheva A, Roy S, Fissell WH. 2010. Anti-biofouling sulfobetaine polymer thin films on silicon and silicon nanopore membranes. J Biomater Sci Polym Ed.

Li DH, Lin J, Lin DY, Wang XX. 2011. Synthesized silicon-substituted hydroxyapatite coating on titanium substrate by electrochemical deposition. J Mater Sci Mater Med 22(5):1205–1211.

Lim F, Sun AM. 1980. Microencapsulated Islets as Bioartificial Endocrine Pancreas. Science 210(4472):908–910.

Limited LCT. 2012. LCT's DIABECELL trial extension approved. http://www.lctglobal.com/html/blob.php/120518%20LCT%20to%20extend%20DIABECELL%20trial. pdf?attach=0&documentCode=4527&elementId=20084

Little S, Chadwick T, Choudhary P, Brennand C, Stickland J, Barendse S, Olateju T, Leelarathna L, Walkinshaw E, Tan HK, Marshall SM, Thomas RM, Heller S, Evans M, Kerr D, Flanagan D, Speight J, Shaw JA. 2012. Comparison of optimised MDI versus pumps with or without sensors in severe hypoglycaemia (the Hypo COMPaSS trial). Bmc Endocrine Disorders 12.

Luan NM, Iwata H. 2012. Xenotransplantation of islets enclosed in agarose microcapsule carrying soluble complement receptor 1. Biomaterials 33(32): 8075–8081.

Ludwig B, Reichel A, Steffen A, Zimerman B, Schally AV, Block NL, Colton CK, Ludwig S, Kersting S, Bonifacio E, Solimena M, Gendler Z, Rotem A, Barkai U, Bornstein SR. 2013. Transplantation of human islets without immunosuppression. Proc Natl Acad Sci 110(47):19054–19058.

Maillet F, Petitou M, Choay J, Kazatchkine MD. 1988. Structure-function relationships in the inhibitory effect of heparin on complement activation—independency of the anti-coagulant and anti-complementary sites on the heparin molecule. Mol Immunol 25(9):917–923.

Maki T, Ubhi CS, Sanchez-Farpon H, Sullivan SJ, Borland K, Muller TE, Solomon BA, Chick WL, Monaco AP. 1991a. The biohybrid artificial pancreas for treatment of diabetes in totally pancreatectomized dogs. Transplant Proc 23(1 Pt 1): 754–755.

Maki T, Ubhi CS, Sanchez-Farpon H, Sullivan SJ, Borland K, Muller TE, Solomon BA, Chick WL, Monaco AP. 1991b. Successful treatment of diabetes with the biohybrid artificial pancreas in dogs. Transplantation 51(1):43–51.

Maki T, Lodge JP, Carretta M, Ohzato H, Borland KM, Sullivan SJ, Staruk J, Muller TE, Solomon BA, Chick WL, Monaco AP. 1993. Treatment of severe diabetes mellitus for more than one year using a vascularized hybrid artificial pancreas. Transplantation 55(4):713–717.

Maki T, Otsu I, O'Neil JJ, Dunleavy K, Mullon CJ, Solomon BA, Monaco AP. 1996a. Treatment of diabetes by xenogeneic islets without immunosuppression. Use of a vascularized bioartificial pancreas. Diabetes 45(3):342–347.

Maki T, Otsu I, ONeil JJ, Dunleavy K, Mullon CJP, Solomon BA, Monaco AP. 1996. Treatment of diabetes by xenogeneic islets without immunosuppression—Use of a vascularized bioartificial pancreas. Diabetes 45(3):342–347.

Marchetti P, Scharp DW, Finke EH, Swanson CJ, Olack BJ, Gerasimidi-Vazeou D, Giannarelli R, Navalesi R, Lacy PE. 1996. Prolonged survival of discordant porcine islet xenografts. Transplantation 61(7):1100–1102.

Maria-Engler SS, Mares-Guia M, Correa ML, Oliveira EM, Aita CA, Krogh K, Genzini T, Miranda MP, Ribeiro M, Vilela L, Noronha IL, Eliaschewitz FG, Sogayar MC. 2001. Microencapsulation and tissue engineering as an alternative treatment of diabetes. Braz J Med Biol Res 34(6):691–697.

Markmann JF, Deng S, Huang X, Desai NM, Velidedeoglu EH, Liu C, Frank A, Markmann E, Palanjian M, Brayman K, Wolf B, Bell E, Vitamaniuk M, Doliba N, Matschinsky F, Barker CF, Naji A. 2003. Insulin independence following isolated islet transplantation and single islet infusions. Ann Surg 237(6):741–749.

Matsuda T, Omori K, Vuong T, Pascual M, Valiente L, Ferreri K, Todorov I, Kuroda Y, Smith CV, Kandeel F, Mullen Y. 2005. Inhibition of p38 pathway suppresses human islet production of pro-inflammatory cytokines and improves islet graft function. Am J Transplant 5(3):484–493.

Matsusaki M, Ajiro H, Kida T, Serizawa T, Akashi M. 2012. Layer-by-layer assembly through weak interactions and their biomedical applications. Adv Mater 24(4):454–474.

Matveyenko AV, Veldhuis JD, Butler PC. 2008. Adaptations in pulsatile insulin secretion, hepatic insulin clearance, and beta-cell mass to age-related insulin resistance in rats. Am J Physiol Endocrinol Metab 295(4):E832–E841.

McMillan DE. 1992. Clotting isorders in diabetes. In: Alberti KGMM, DeFonzo RA, Keen H, Zimmer P, editors. International textbook of diabetes mellitus. Chichester: John Wiley BT & Sons Ltd. p 1447.

Melendez-Ramirez LY, Richards RJ, Cefalu WT. 2010. Complications of type 1 diabetes. Endocrinol Metab Clin North Am 39(3):625–640.

Melvin ME, Fissell WH, Roy S, Brown DL. 2010. Silicon induces minimal thromboinflammatory response during 28-day intravascular implant testing. ASAIO J 56(4):344–348.

Mikos AG, McIntire LV, Anderson JM, Babensee JE. 1998. Host response to tissue engineered devices. Adv Drug Deliv Rev 33(1–2):111–139.

Mitsuo M, Inoue K, Nakai I, Oda T, Gu Y, Shinohara S, Kogire M, Fujisato T, Maetani S, Ikada Y, Tobe T, Oka T. 1992a. Efficacy of mesh reinforced polyvinylalcohol tube as a novel device for bioartificial pancreas: a functional study of rat islets in vivo. Transplant Proc 24(6):2939–2940.

Mitsuo M, Inoue K, Nakai I, Oda T, Gu Y, Shinohara S, Kogire M, Fujisato T, Maetani S, Ikada Y, Tobe T, Oka T. 1992b. Efficacy of mesh reinforced polyvinylalcohol tube as a novel device for bioartificial pancreas - a functional-study of rat islets in vivo. Transplant Proc 24(6):2939–2940.

Monaco AP, Maki T, Ozato H, Carretta M, Sullivan SJ, Borland KM, Mahoney MD, Chick WL, Muller TE, Wolfrum J, Solomon B. 1991. Transplantation of islet allografts and xenografts in totally pancreatectomized diabetic dogs using the hybrid artificial pancreas. Ann Surg 214(3):339–360.

Montolio M, Biarnes M, Tellez N, Escoriza J, Soler J, Montanya E. 2007. Interleukin-1beta and inducible form of nitric oxide synthase expression in early syngeneic islet transplantation. J Endocrinol 192(1):169–177.

Moya ML, Garfinkel MR, Liu X, Lucas S, Opara EC, Greisler HP, Brey EM. 2010. Fibroblast growth factor-1 (FGF-1) loaded microbeads enhance local capillary neovascularization. J Surg Res 160(2):208–212.

Narang AS, Mahato RI. 2006. Biological and biomaterial approaches for improved islet transplantation. Pharmacol Rev 58(2):194–243.

Narushima M, Kobayashi N, Okitsu T, Tanaka Y, Li SA, Chen Y, Miki A, Tanaka K, Nakaji S, Takei K, Gutierrez AS, Rivas-Carrillo JD, Navarro-Alvarez N, Jun HS, Westerman KA, Noguchi H, Lakey JR, Leboulch P, Tanaka N, Yoon JW. 2005. A human beta-cell line for transplantation therapy to control type 1 diabetes. Nat Biotechnol 23(10):1274–1282.

Nathan DM. 2003. Isolated pancreas transplantation for type 1 diabetes: a doctor's dilemma. JAMA 290(21):2861–2863.

Nathan DM. 2014. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: Overview. Diabetes Care 37(1):9–16.

Negre-Salvayre A, Salvayre R, Auge N, Pamplona R, Portero-Otin M. 2009. Hyperglycemia and glycation in diabetic complications. Antioxid Redox Signal 11(12):3071–3109.

Neufeld T, Ludwig B, Barkai U, Weir GC, Colton CK, Evron Y, Balyura M, Yavriyants K, Zimermann B, Azarov D, Maimon S, Shabtay N, Rozenshtein T, Lorber D, Steffen A, Willenz U, Bloch K, Vardi P, Taube R, de Vos P, Lewis EC, Bornstein SR, Rotem A. 2013. The efficacy of an immunoisolating membrane system for islet xenotransplantation in minipigs. PLoS ONE 8(8):e70150.

Nokoff NJ, Rewers M, Cree Green M. 2012. The interplay of autoimmunity and insulin resistance in type 1 diabetes. Discov Med 13(69):115–122.

O'Sullivan ES, Johnson AS, Omer A, Hollister-Lock J, Bonner-Weir S, Colton CK, Weir GC. 2010. Rat islet cell aggregates are superior to islets for transplantation in microcapsules. Diabetologia 53(5):937–945.

O'Sullivan ES, Vegas A, Anderson DG, Weir GC. 2011. Islets transplanted in immunoisolation devices: a review of the progress and the challenges that remain. Endocr Rev 32(6):827–844.

Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. 2003. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med 349(10):931–940.

Old LJ. 1985. Tumor Necrosis Factor (Tnf). Science 230(4726):630–632.

Orsetti AB, Crespy S, Perez R. 1981. Analyse critique de la valeur fonctionnelle d'un pancreas bio-artificial (modele a fibres creuses). C. R. Soc. Biol. (Paris) 175:228–234.

Pagliuca FW, Millman JR, Gurtler M, Segel M, Van Dervort A, Ryu JH, Peterson QP, Greiner D, Melton DA. 2014. Generation of functional human pancreatic beta cells in vitro. Cell 159(2):428–439.

Paty BW, Senior PA, Lakey JR, Shapiro AM, Ryan EA. 2006. Assessment of glycemic control after islet transplantation using the continuous glucose monitor in insulin-independent versus insulin-requiring type 1 diabetes subjects. Diabetes Technol Ther 8(2):165–173.

Paulick MG, Forstner MB, Groves JT, Bertozzi CR. 2007. A chemical approach to unraveling the biological function of the glycosylphosphatidylinositol anchor. Proc Natl Acad Sci USA 104(51):20332–20337.

Penfornis A, Personeni E, Borot S. 2011. Evolution of devices in diabetes management. Diabetes Technol Ther 13(Suppl 1):S93–102.

Pepper AR, Pawlick R, Gala-Lopez B, MacGillivary A, Mazzuca DM, White DJ, Toleikis PM, Shapiro AM. 2015. Diabetes is reversed in a murine model by marginal mass syngeneic islet transplantation using a subcutaneous cell pouch device. Transplantation 99(11):2294–300.

Piemonti L, Leone BE, Nano R, Saccani A, Monti P, Maffi P, Bianchi G, Sica A, Peri G, Melzi R, Aldrighetti L, Secchi A, Di Carlo V, Allavena P, Bertuzzi F. 2002. Human pancreatic islets produce and secrete MCP-1/CCL2: Relevance in human islet transplantation. Diabetes 51(1):55–65.

Pileggi A, Molano RD, Ricordi C, Zahr E, Collins J, Valdes R, Inverardi L. 2006. Reversal of diabetes by pancreatic islet transplantation into a subcutaneous, neovascularized device. Transplantation 81(9):1318–1324.

Potter KJ, Abedini A, Marek P, Klimek AM, Butterworth S, Driscoll M, Baker R, Nilsson MR, Warnock GL, Oberholzer J, Bertera S, Trucco M, Korbutt GS, Fraser PE, Raleigh Dp, Verchere CB. 2010. Islet amyloid deposition limits the viability of human islet grafts but not porcine islet grafts. Proc Natl Acad Sci USA 107(9):4305–4310.

Prochorov AV, Tretjak SI, Roudenok VV, Goranov VA. 2004. Long-term normalization of diabetes mellitus after xenotransplantation of fetal pancreatic islet cells into the blood stream without immunosuppresive therapy. Transplant Proc 36(9):2855–2856.

Prochorov AV, Roudenok VV, Goranov VA. 2005. Histological study of macro-encapsulation of pancreatic islet cells after transplantation into the bloodstream. Transplant Proc 37(10):4446–4448.

Prochorov AV, Tretjak SI, Goranov VA, Glinnik AA, Goltsev MV. 2008. Treatment of insulin dependent diabetes mellitus with intravascular transplantation of pancreatic islet cells without immunosuppressive therapy. Adv Med Sci 53(2):240–244.

Rabinovitch A, Suarez-Pinzon WL. 1998. Cytokines and their roles in pancreatic islet beta-cell destruction and insulin-dependent diabetes mellitus. Biochem Pharmacol 55(8):1139–1149.

Rabuka D, Forstner MB, Groves JT, Bertozzi CR. 2008. Noncovalent cell surface engineering: Incorporation of bioactive synthetic glycopolymers into cellular membranes. J Am Chem Soc 130(18):5947–5953.

Rajab A. 2010. Islet transplantation: Alternative sites. Curr Diab Rep 10(5):332–337.

Ramiya VK, Maraist M, Arfors KE, Schatz DA, Peck AB, Cornelius JG. 2000. Reversal of insulin-dependent diabetes using islets generated in vitro from pancreatic stem cells. Nat Med 6(3):278–282.

Rewers M. 2012. Challenges in diagnosing type 1 diabetes in different populations. Diabetes Metab J 36(2):90–97.

Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, Asadi A, O'Dwyer S, Quiskamp N, Mojibian M, Albrecht T, Yang YH, Johnson JD, Kieffer TJ. 2014. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol 32(11):1121–1133.

Rickels MR, Liu C, Shlansky-Goldberg RD, Soleimanpour SA, Vivek K, Kamoun M, Min Z, Markmann E, Palangian M, Dalton-Bakes C, Fuller C, Chiou AJ, Barker CF, Luning Prak ET, Naji A. 2013. Improvement in beta-cell secretory capacity after human islet transplantation according to the CIT07 protocol. Diabetes 62(8):2890–2897.

Ricordi C, Hering B, Bridges N, Eggerman T, Naji A, Posseit A, Stock P, Kaufman D, Larsen CP, Turgeon N, Oberholzer J, Barbaro B, Korsgren O, Markmann J, Alejandro R, Rickels MR, Senior PA, Luo X, Zhang X, Bellin M, Lei J. 2014. Completion of the first Fda phase 3 multicenter trial of islet transplantation in type 1 Diabetes by the Nih Cit Consortium. Cytotherapy 16(4):S14.

Rokstad AM, Kulseng B, Strand BL, Skjak-Braek G, Espevik T. 2001. Transplantation of alginate microcapsules with proliferating cells in mice: Capsular overgrowth and survival of encapsulated cells of mice and human origin. Ann N Y Acad Sci 944:216–225.

Russ HA, Parent AV, Ringler JJ, Hennings TG, Nair GG, Shveygert M, Guo T, Puri S, Haataja L, Cirulli V, Blelloch R, Szot GL, Arvan P, Hebrok M. 2015. Controlled induction of human pancreatic progenitors produces functional beta-like cells in vitro. EMBO J 34(13):1759–1772.

Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JR, Shapiro AM. 2005a. Five-year follow-up after clinical islet transplantation. Diabetes 54(7):2060–2069.

Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, Lakey JRT, Shapir AMJ. 2005b. Five-year follow-up after clinical islet transplantation. Diabetes 54(7):2060–2069.

Sabek OM, Ferrati S, Fraga DW, Sih J, Zabre EV, Fine DH, Ferrari M, Gaber AO, Grattoni A. 2013. Characterization of a nanogland for the autotransplantation of human pancreatic islets. Lab Chip 13(18):3675–3688.

Sakai S, Mu C, Kawabata K, Hashimoto I, Kawakami K. 2006. Biocompatibility of subsieve-size capsules versus conventional-size microcapsules. J Biomed Mater Res A 78(2):394–398.

Sakuma Y, Ricordi C, Miki A, Yamamoto T, Pileggi A, Khan A, Alejandro R, Inverardi L, Ichii H. 2008. Factors that affect human islet isolation. Transplant Proc 40(2):343–345.

Scharp DW, Swanson CJ, Olack BJ, Latta PP, Hegre OD, Doherty EJ, Gentile FT, Flavin KS, Ansara MF, Lacy PE. 1994. Protection of encapsulated human islets implanted without immunosuppression in patients with type I or type II diabetes and in nondiabetic control subjects. Diabetes 43(9):1167–1170.

Schenker P, Vonend O, Kruger B, Klein T, Michalski S, Wunsch A, Kramer BK, Viebahn R. 2011. Long-term results of pancreas transplantation in patients older than 50 years. Transpl Int 24(2):136–142.

Schmidt P, Goto M, Le Mauff B, Anegon I, Korsgren O. 2003. Adenovirus-mediated expression of human CD55 or CD59 protects adult porcine islets from complement-mediated cell lysis by human serum. Transplantation 75(5):697–702.

Schroppel B, Zhang N, Chen P, Chen D, Bromberg JS, Murphy B. 2005. Role of donor-derived monocyte chemoattractant protein-1 in murine islet transplantation. J Am Soc Nephrol 16(2):444–451.

Sefton MV. 1993. The good, the bad and the obvious: 1993 Clemson Award for Basic Research-Keynote Lecture. Biomaterials 14(15):1127–1134.

Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. 2000. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 343(4):230–238.

Shapiro AMJ, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson P, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Aleijandro R, Ryan EA,

DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbutt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, Lakey JR. 2006. International trial of the edmonton protocol for islet transplantation. New England Journal of Medicine 355(13):1318–1330.

Shin S, Shin JE, Yoo YJ. 2013. Attachment of alginate microcapsules onto plasma-treated PDMS sheet for retrieval after transplantation. Biotechnol Appl Biochem 60(6):617–622.

Siebers U, Horcher A, Bretzel RG, Federlin K, Zekorn T. 1997. Alginate-based microcapsules for immunoprotected islet transplantation. Bioartificial Organs 831:304–312.

Siebers U, Horcher A, Brandhorst H, Brandhorst D, Hering B, Federlin K, Bretzel RG, Zekorn T. 1999. Analysis of the cellular reaction towards microencapsulated xenogeneic islets after intraperitoneal transplantation. J Mol Med (Berl) 77(1):215–218.

Smith A. 2006. A glossary for stem-cell biology. Nature 441(7097):1060–1060.

Soderlund J, Wennberg L, Castanos-Velez E, Biberfeld P, Zhu S, Tibell A, Groth CG, Korsgren O. 1999. Fetal porcine islet-like cell clusters transplanted to cynomolgus monkeys: an immunohistochemical study. Transplantation 67(6):784–791.

Soon-Shiong P, Otterlie M, Skjak-Braek G, Smidsrod O, Heintz R, Lanza RP, Espevik T. 1991. An immunologic basis for the fibrotic reaction to implanted microcapsules. Transplant Proc 23(1 Pt 1) 758–759.

Soon-Shiong P. 1999. Treatment of type I diabetes using encapsulated islets. Adv Drug Deliv Rev 35(2–3):259–270.

Sorenson RL, Brelje TC. 1997. Adaptation of islets of Langerhans to pregnancy: beta-cell growth, enhanced insulin secretion and the role of lactogenic hormones. Horm Metab Res 29(6):301–307.

Soria B, Roche E, Berna G, Leon-Quinto T, Reig JA, Martin F. 2000. Insulin-secreting cells derived from embryonic stem cells normalize glycemia in streptozotocin-induced diabetic mice. Diabetes 49(2):157–162.

Sparks RE, Mason NS, Finley TC, Scharp DW. 1982. Development, testing and modeling of an islet transplantation chamber. Trans Am Soc Artif Intern Organs 28:229–231.

Stadtfeld M, Brennand K, Hochedlinger K. 2008. Reprogramming of pancreatic beta cells into induced pluripotent stem cells. Curr Biol 18(12):890–894.

Stendahl JC, Kaufman DB, Stupp SI. 2009. Extracellular matrix in pancreatic islets: relevance to scaffold design and transplantation. Cell Transplant 18(1):1–12.

Stipa S, Cavallaro A. 1982. Fabrication and testing of vascular prostheses. Peripheral arterial diseases: medical and surgical problems 44:259.

Storrs R, Dorian R, King SR, Lakey J, Rilo H. 2001. Preclinical development of the Islet Sheet. Ann N Y Acad Sci 944:252–266.

Street CN, Sipione S, Helms L, Binette T, Rajotte RV, Bleackley RC, Korbutt GS. 2004. Stem cell-based approaches to solving the problem of tissue supply for islet transplantation in type 1 diabetes. Int J Biochem Cell Biol 36(4):667–683.

Sun Y, Ma X, Zhou D, Vacek I, Sun AM. 1996. Normalization of diabetes in spontaneously diabetic cynomologus monkeys by xenografts of micro-encapsulated porcine islets without immunosuppression. J Clin Invest 98(6): 1417–1422.

Sutherland DER, Gruessner RWG, Dunn DL, Matas AJ, Humar A, Kandaswamy R, Mauer SM, Kennedy WR, Goetz FC, Robertson RP, Gruessner AC, Najarian JS. 2001. Lessons learned from more than 1,000 pancreas transplants at a single institution. Annals of Surgery 233(4):463–501.

Sutherland DE. 1998. Pancreas and pancreas-kidney transplantation. Curr Opin Nephrol Hypertens 7(3):317–325.

Suzuki K, Bonner-Weir S, Trivedi N, Yoon KH, Hollister-Lock J, Colton CK, Weir GC. 1998. Function and survival of macroencapsulated syngeneic islets transplanted into streptozocin-diabetic mice. Transplantation 66(1):21–28.

Szabat M, Lynn FC, Hoffman BG, Kieffer TJ, Allan DW, Johnson JD. 2012. Maintenance of beta-cell maturity and plasticity in the adult pancreas: developmental biology concepts in adult physiology. Diabetes 61(6):1365–1371.

Takahashi K, Yamanaka S. 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126(4):663–676.

Thomas HE, Darwiche R, Corbett JA, Kay TW. 2002. Interleukin-1 plus gamma-interferon-induced pancreatic beta-cell dysfunction is mediated by beta-cell nitric oxide production. Diabetes 51(2):311–316.

Thomlinson RH, Gray LH. 1955. The histological structure of some human lung cancers and the possible implications for radiotherapy. Br J Cancer 9(4):539–549.

Tibell A, Rafael E, Wennberg L, Nordenstrom J, Bergstrom M, Geller RL, Loudovaris T, Johnson RC, Brauker JH, Neuenfeldt S, Wernerson A. 2001. Survival of macroencapsulated allogeneic parathyroid tissue one year after transplantation in nonimmunosuppressed humans. Cell Transplant 10(7):591–599.

Toleikis P. 2010. Sernova's Diabetes Cell Therapy Platform Technologies. Coporate Presentation: Sernova Corp.

Tomei AA, Manzoli V, Fraker CA, Giraldo J, Velluto D, Najjar M, Pileggi A, Molano RD, Ricordi C, Stabler CL, Hubbell JA. 2014. Device design and materials optimization of conformal coating for islets of Langerhans. Proc Natl Acad Sci USA 111(29):10514–10519.

Trivedi N, Steil GM, Colton CK, Bonner-Weir S, Weir GC. 2000. Improved vascularization of planar membrane diffusion devices following continuous infusion of vascular endothelial growth factor. Cell Transplant 9(1):115–124.

Troppmann C, Gruessner AC, Benedetti E, Papalois BE, Dunn DL, Najarian JS, Sutherland DE, Gruessner RW. 1996. Vascular graft thrombosis after pancreatic transplantation: Univariate and multivariate operative and nonoperative risk factor analysis. J Am Coll Surg 182(4):285–316.

Tseng PY, Jordan SW, Sun XL, Chaikof EL. 2006a. Catalytic efficiency of a thrombomodulin-functionalized membrane-mimetic film in a flow model. Biomaterials 27(13):2768–2775.

Tseng PY, Rele SM, Sun XL, Chaikof EL. 2006b. Fabrication and characterization of heparin functionalized membrane-mimetic assemblies. Biomaterials 27(12): 2627–2636.

Tseng PY, Rele SS, Sun XL, Chaikof EL. 2006c. Membrane-mimetic films containing thrombomodulin and heparin inhibit tissue factor-induced thrombin generation in a flow model. Biomaterials 27(12):2637–2650.

Tuch BE, Keogh GW, Williams LJ, Wu W, Foster JL, Vaithilingam V, Philips R. 2009. Safety and viability of microencapsulated human islets transplanted into diabetic humans. Diabetes Care 32(10):1887–1889.

van Assche FA, Aerts L, De Prins F. 1978. A morphological study of the endocrine pancreas in human pregnancy. Br J Obstet Gynaecol 85(11):818–820.

van der Windt DJ, Bottino R, Casu A, Campanile N, Cooper DK. 2007. Rapid loss of intraportally transplanted islets: An overview of pathophysiology and preventive strategies. Xenotransplantation 14(4):288–297.

Vehik K, Hamman RF, Lezotte D, Norris JM, Klingensmith GJ, Rewers M, Dabelea D. 2008. Trends in high-risk HLA susceptibility genes among Colorado youth with type 1 diabetes. Diabetes Care 31(7):1392–1396.

Veiseh O, Doloff JC, Ma M, Vegas AJ, Tam HH, Bader AR, Li J, Langan E, Wyckoff J, Loo WS, Jhunjhunwala S, Chiu A, Siebert S, Tang K, Hollister-Lock J, Aresta-Dasilva S, Bochenek M, Mendoza-Elias J, Wang Y, Qi M, Lavin DM, Chen M, Dholakia N, Thakrar R, Lacik I, Weir GC, Oberholzer J, Greiner DL, Langer R, Anderson DG. 2015. Size- and shape-dependent foreign body immune response to materials implanted in rodents and non-human primates. Nat Mater 14(6):643–651.

Venstrom JM, McBride MA, Rother KI, Hirshberg B, Orchard TJ, Harlan DM. 2003. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. JAMA 290(21):2817–2823.

Wang RN, Kloppel G, Bouwens L. 1995. Duct- to islet-cell differentiation and islet growth in the pancreas of duct-ligated adult rats. Diabetologia 38(12): 1405–1411.

Wang T, Lacik I, Brissova M, Anilkumar AV, Prokop A, Hunkeler D, Green R, Shahrokhi K, Powers AC. 1997. An encapsulation system for the immunoisolation of pancreatic islets. Nat Biotechnol 15(4):358–362.

Wang T, Ji X, Jin L, Feng Z, Wu J, Zheng J, Wang H, Xu ZW, Guo L, He N. 2013. Fabrication and characterization of heparin-grafted poly-L-lactic acid-chitosan core-shell nanofibers scaffold for vascular gasket. ACS Appl Mater Interfaces 5(9):3757–3763.

Weber CJ, Hagler M, Konieczny B, Chryssochoos J, Rajotte R, Lakkis F, Lowry R. 1995. Encapsulated islet iso-, allo-, and xenografts in diabetic NOD mice. Transplant Proc 27(6):3308–3311.

Weber CJ, Safley S, Hagler M, Kapp J. 1999. Evaluation of graft-host response for various tissue sources and animal models. Ann N Y Acad Sci 875:233–254.

Weber LM, Hayda KN, Haskins K, Anseth KS. 2007. The effects of cell-matrix interactions on encapsulated beta-cell function within hydrogels functionalized with matrix-derived adhesive peptides. Biomaterials 28(19):3004–3011.

Weissman IL. 2000. Stem cells: Units of development, units of regeneration, and units in evolution. Cell 100(1):157–168.
Wernig M, Meissner A, Foreman R, Brambrink T, Ku M, Hochedlinger K, Bernstein BE, Jaenisch R. 2007. In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state. Nature 448(7151):318–324.
White DJ, Yannoutsos N. 1996. Production of pigs transgenic for human DAF to overcome complement-mediated hyperacute xenograft rejection in man. Res Immunol 147(2):88–94.
Wiegand F, Kroncke KD, Kolb-Bachofen V. 1993. Macrophage-generated nitric oxide as cytotoxic factor in destruction of alginate-encapsulated islets. Protection by arginine analogs and/or coencapsulated erythrocytes. Transplantation 56(5):1206–1212.
Wilson JT, Cui W, Chaikof EL. 2008. Layer-by-layer assembly of a conformal nanothin PEG coating for intraportal islet transplantation. Nano Lett 8(7):1940–1948.
Wilson JT, Haller CA, Qu Z, Cui W, Urlam MK, Chaikof EL. 2010. Biomolecular surface engineering of pancreatic islets with thrombomodulin. Acta Biomater 6(6):1895–1903.
Wong H, Chang TM. 1991. A novel two step procedure for immobilizing living cells in microcapsules for improving xenograft survival. Biomater Artif Cells Immobilization Biotechnol 19(4):687–697.
Yamanaka S. 2007. Strategies and new developments in the generation of patient-specific pluripotent stem cells. Cell Stem Cell 1(1):39–49.
Yardley JE, Iscoe KE, Sigal RJ, Kenny GP, Perkins BA, Riddell MC. 2013. Insulin pump therapy is associated with less post-exercise hyperglycemia than multiple daily injections: An observational study of physically active type 1 diabetes patients. Diabetes Technol Ther 15(1):84–88.
Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin II, Thomson JA. 2007. Induced pluripotent stem cell lines derived from human somatic cells. Science 318(5858):1917–1920.
Zhang X, He H, Yen C, Ho W, Lee LJ. 2008. A biodegradable, immunoprotective, dual nanoporous capsule for cell-based therapies. Biomaterials 29(31):4253–4259.
Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC. 2002. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. Exp Neurol 174(1):11–20.
Zhao Y, Ye W, Boye KS, Holcombe JH, Swindle R. 2009. Healthcare charges and utilization associated with diabetic neuropathy: impact of Type 1 diabetes and presence of other diabetes-related complications and comorbidities. Diabet Med 26(1):61–69.
Zhou Q, Brown J, Kanarek A, Rajagopal J, Melton DA. 2008. In vivo reprogramming of adult pancreatic exocrine cells to beta-cells. Nature 455(7213):627–632.
Zhu J, Marchant RE. 2006. Dendritic saccharide surfactant polymers as antifouling interface materials to reduce platelet adhesion. Biomacromolecules 7(4):1036–1041.
Zulewski H, Abraham EJ, Gerlach MJ, Daniel PB, Moritz W, Muller B, Vallejo M, Thomas MK, Habener JF. 2001. Multipotential nestin-positive stem cells isolated from adult pancreatic islets differentiate ex vivo into pancreatic endocrine, exocrine, and hepatic phenotypes. Diabetes 50(3):521–533.

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