Chapter 4 : Membrane bioreactors for bio-artificial pancreas

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Abstract

Designing an efficient and functional bioartificial pancreas (BAP) at human scale to treat type I diabetes remains the Holy Grail in the 2010s, although investigations started in the 1970s. Biomimetic approaches need to be performed and evaluated to offer insulin secreting cells an environment close to the native pancreas, but also accounting for the interactions between the pancreas and other organs, and more specifically liver.

This chapter outlines the concept, development and recent progress of BAP technology, with specific focus on interaction between BAP and the host environment. After the introduction of pancreas anatomy and physiology and the current treatments for diabetic patients, we will study how fulfill (or not) the requirements for an efficient BAP, regarding its different components: cell types, encapsulation methods, membranes and devices dedicated to several implantation sites. We conclude with a short discussion of future directions including BAP revascularization to improve the exchanges with the host and the impact of microtechnologies on the development of next generation of BAP.

1 Introduction: the pancreas

The pancreas is a fundamental organ for coordination and regulation of body metabolism. The main functions of the pancreas are to control glucose homeostasis via endocrine hormones and produce exocrine enzymes necessary for digestion process. Pancreatic dysfunction is responsible for many diseases including diabetes mellitus, one of the most prevalent diseases in the world. This introduction is a brief overview of the anatomy, physiology and principal pathology associated to pancreas.

1.1 Anatomy and physiology

The pancreas is an organ with glandular structure located in the curve of duodenum just behind the stomach (Figure 1). It is divided into three regions(Mahadevan, 2016): i) the head, connected to the duodenum, is the widest and most medial region of the organ; ii) the body is located behind the stomach; iii) the tapered tail region is located in the left side of the abdomen near the spleen. The vascularization of the pancreas is ensured by the anterior pancreaticoduodenal artery (head of pancreas) and multiple

branches of the splenic artery (body and tail of the pancreas). Pancreatic vein joins the splenic vein to form the hepatic portal vein together with the inferior and superior mesenteric veins.

The pancreas is a heterocrine gland involved in both exocrine and endocrine regulation. The exocrine cells of the pancreas represent more than 90% of the pancreatic tissue and are grouped in structures called acini (Figure 1), whose function is the synthesis and secretion of enzymes implicated in the digestion process (pancreatic lipase and amylase, phospholipase, nucleases) (Jouvet and Estall, 2017). Digestive enzymes are drained by the pancreatic ductal tree into the intestine where they aid in nutrient metabolism. The functional units of the endocrine system represent approximately 2% of the pancreas (2 million cells in human adults) and are made up of pancreatic islets or islets of Langerhans. They are clusters of cells whose size varies from 20 to 500 μm, with five different cell types: α-, β-, δ-, ε-, and γ (PP) cells (Jouvet and Estall, 2017; Kumar and Melton, 2003) . The most abundant cells include the glucagon-producing α-cells and insulin-producing ß-cells. The small proportion of δ-, ε-, and γ cells secrete somatostatin, ghrelin and pancreatic polypeptides, respectively. Despite comprising only 2% of the total mass of the pancreas, the islets receive around 15% of the pancreatic blood supply, allowing their secreted hormones ready access to the circulation (Jansson et al., 2016). At the islet level, the oxygen partial pressure (PO2) is about 40 mmHg.

Figure 1 here

1.2 Mechanisms of glycemic regulation

The control of glucose levels in the blood is carried out by the interaction of two antagonistic hormones secreted by pancreatic α and β cells. Glucagon (alpha cells) increases glucose levels in the fasting period activating the glycogenolysis and gluconeogenesis in the liver in coordination with cortisol (hormone secreted by the adrenal gland). While insulin activates the uptake and storage of glucose in the muscle, fatty tissue and most importantly the liver through glycogenesis thereby decreasing blood sugar levels in postprandial (Barrett et al., 2015) (Figure 2).

The mechanism of regulation of blood glucose begins with the stimulation of insulin secretion that intensifies when blood glucose levels increase. The beta cells of the pancreas respond in a biphasic manner to this stimulus. First there is a rapid and brief rise (in the form of a peak) of insulin release, followed by a slower but constant release of the hormone (in the form of a plateau) over time(Tortora and Derrickson, 2013).

The feedback loop that involves carbohydrates as an input signal and the synchronization of the insulin and glucagon release as an output allows the control of blood glucose and insulinemia to occur accurately and precisely (Miller, 1981).

The secretion of the two antagonist hormones is carried out in a pulsatile manner so that a simultaneous peak of insulin and glucagon would never occur. The synchronization of hormones is of great importance for the regulation of blood glucose by the liver.

Figure 2 here

1.3 Physiopathology & treatment

Diabetes mellitus is the most important dysfunction of the endocrine system of the pancreas affecting more than 422 million people worldwide, according to the International Diabetes Federation (IDF) and the World Health Organization (WHO) (IDF and WHO official web sites, 2018). Type I diabetes mellitus (T1DM) affects about 5-10% of diabetes patients, mostly the young population. It is a chronic pathology occurring due to the autoimmune destruction of pancreatic islet beta cells. As a result, there is a disorder in blood glucose levels caused by hyperglycemia and the inability to store glucose due to the absence of insulin. It is a pathology with a complex clinical picture. The breakdown of the control mechanism of blood glucose severely affects other organs and systems on long term basis, causing blindness, kidney failure, cardiac arrest, stroke, limb amputation due to thrombosis and even death (Amer et al., 2014; WHO, global reports in diabetes, 2016).

The function in need of replacement in the case of insulin dependent diabetes is thus primarily the secretion of insulin by the pancreatic islet β cells, which has four characteristics: (a) it is continuous, even in the postabsorptive state, with rapid and transient peaks during meals: (b) it undergoes automatic regulation by blood glucose levels; (c) insulin is delivered into the portal blood system; (d) the endocrine pancreas is (of course) an internal organ placed within the body.

The most widespread treatment of T1DM is the daily and scheduled administration of insulin based on previous monitoring with a glucometer (Klonoff et al., 2017; Stephens, 2015) (Table 1). In the best cases, insulin injections, glucose levels monitoring, and a restrictive diet could successfully keep the patient safe from the risks of the extreme hyperglycemia. However, the variety of the clinical profile of the patients and the age reveals the limitations of insulin injections as a treatment. On the one hand, the production of insulin usually decreases progressively as the disease progresses, so the patient continues to produce their own insulin in small quantities. This makes it difficult to estimate the amount of exogenous insulin to be administered at each moment. On the other hand, due to the nature of the pathology, it usually manifests at an early age. This makes it difficult to control certain variables such as intake and physical exercise especially in neonates and children. In addition, to correctly apply the treatment, continuous education of the patient is required to maintain glucose in the appropriate ranges (Malik and Taplin, 2014).

Another treatment based on the same principle as insulin injections, but with some improvements is the insulin pump or also called "continuous subcutaneous therapy" (Bruttomesso et al., 2009). This approach is based on the subcutaneous delivery of insulin through a catheter connected to a peristaltic pump (Galderisi et al., 2017). This allows the control of the insulinemia 24 hours maintaining the basal level of glucose in the blood. The control carried out by the insulin pump mimics quite well the pattern of glucose concentration given by a healthy pancreas. However, possible infections and fibrosis at the site of catheter insertion are limiting factors of the use of the insulin pump as therapy. Despite the great advances that have been made in recent years for the development of this device (El-Khatib et al., 2017), the response time is another limiting factor in terms of abrupt changes in glucose concentration (Tauschmann and Hovorka, 2014).

Depending on the patient clinical profile of the T1DM, transplantation of the pancreas is sometimes chosen as a strategy to control glycemia. Since 1966, the success rates of transplantation of the pancreas have been increasing thanks to technical improvements in extraction, preservation and implantation. Up to now, more than 1500 pancreas transplants have been carried out according to the Collaborative Islet Transplant Registry (CITR) (Shapiro et al., 2016). However, it remains an invasive intervention that is usually carried out when kidney transplantation is also required. And most importantly, it involves the submission of the patient to immunosuppressants for the rest of his life.

The transplantation of islets of Langerhans is another approach that is applied to the treatment of diabetes (Chang et al., 2017; Ludwig et al., 2013a, 2012; Ludwig and Ludwig, 2015). Since the 1960s, the

purification of pancreatic islets and their transplantation into different animal models have been the objects of many groups of research. Pancreatic islet transplantation is a promising therapy for patients with T1DM difficult to control (Bertuzzi et al., 2018). It is a technique that provides an efficient and robust control of the homeostasis of glucose against the administration of insulin. However, islet transplantation remains controversial because it requires continuous immunosuppression that is harmful to both the graft and the patient (Nourmohammadzadeh et al., 2013).

Table 1 here

2 The concept of bioartificial pancreas (BAP)

In the above-mentioned therapeutic strategies, the objectives are to replace either the structure (transplantation) or some functions (insulin injection) to compensate organ failure. Another approach is the design of a BAP based on the two major pillars in tissue engineering: cells and scaffolds. The objectives would be to mimic as much as possible the physiology of the native organ, using the cells for the production and release of insulin, but also as "glucose sensor" and the scaffold as biocompatible environment and immunoprotection for the cells (Figure 3).

Depending on the amount of tissue to be encapsulated, there are two major configurations of pancreatic islet immunoisolation: macroencapsulation and microencapsulation (Pandolfi et al., 2017) (Figure 4). In addition to the amount of tissue to be encapsulated, the content of the implant also determines the type of encapsulation implemented. It is not the same to encapsulate isolated beta cells than to encapsulate cellular aggregates or islets of Langerhans. In case the islets are directly covered by a polymer, the term of nanoencapsulation is commonly employed.

Macroencapsulation consists in the assembly of a large number of islets or cells within a selectively permeable membrane forming a macrocapsule with a dimension in the centimeter range or even larger. Depending on the site of implantation, macrocapsule-based devices are classified in two categories: intravascular and extravascular ones (Iacovacci et al., 2016; Kepsutlu et al., 2014). Intravascular system is directly connected to the vessels of the host via an arteriovenous shunt (Iacovacci et al., 2016).

Microencapsulation is the entrapment of individual or few islets of Langerhans in a polymeric matrix (Skrzypek et al., 2018). Due to optimal volume-to-surface ratio, microcapsules allow fast exchange of insulin, oxygen and nutrients. Generally, microcapsules are produced from hydrogels like alginate, chitosan, agarose, polyethyleneglycol (PEG), copolymers of acrylonitrile and polyacrylates (de Vos et al., 2002; Skrzypek et al., 2018). The most widely used microcapsules for islet immunoisolation is the ionically crosslinked alginate system (de Vos et al., 2006). In this process, cells are mixed within alginate solution and extruded dropwise into an aqueous calcium chloride gelation solution. The droplet entrapping islets solidify to become hydrogel beads in contact with Ca^{2+} divalent cations (Pandolfi et al., 2017). Finally, alginate beads are coated with cationic poly-amino acid (usually poly (L-lysine)) solution, which forms a semi-permeable membrane around the microcapsule (de Vos et al., 2006, 2002).

To overcome the limitations associated to micro- and macroencapsulation (size, diffusion), the use of nanoscale immune-isolation layer has been developed. This strategy called nanoencapsulation allows the immunoisolation of single islet/β-cells, and the obtained devices are less than 100 µm in diameter (Iacovacci et al., 2016). Different strategies have been developed including photopolymerization of PEG and layer-by-layer deposition of polycation and polyanion (Iacovacci et al., 2016; Kepsutlu et al., 2014; O'Sullivan et al., 2011). The reduced distance between the implanted islet and the host enhances the diffusion of oxygen, nutrients and insulin.

Figure 3 here

Figure 4 here

3 Overview of the specificities of currently developed BAP

The BAP is an implantable device formed by endocrine tissue encapsulated by a semipermeable biomaterial that provides protection against immunological agents and allowing the mass transfer of hormones, nutrients, oxygen and waste. In the process of BAP development, it is essential to know the different variables to be considered (donor, host, material and shape of the BAP, transplantation site ...) and how to combine them to get the optimal design.

There are various requirements depending on the components of the BAP.

1. Cell functions and number: the objective is to get the same type of response (amount of insulin/glucagon synthesized, sensitivity to glucose concentration) than from the native pancreas. Therefore, the cells have to be correctly supplied for nutrients and oxygen, and with kinetics of blood glucose concentration.
2. Immuno-isolation ensured by the material: a compromise has to be found between rapid transfer of low and medium molecular weight solutes (glucose, insulin) and sieving of immunoglobulins and cells such as macrophages and leukocytes (Figure 5).
3. Biocompatible material for the cells and for the host.
4. Adequacy of the implantation site: to mimic the physiology, blood glucose should reach easily the b-cells to stimulate if necessary insulin synthesis and secretion, insulin should be ideally released in the portal system. Minimally invasive surgery should be preferred, and the device should also be easily removable in case of failure.

Figure 5 here

3.1 Number and potential sources of pancreatic islets

Before addressing the cell type to use in a BAP, it is fundamental to answer the question of the number of cells/islets to implement. A human adult pancreas contains about a million and a half islets of Langerhans. However, as for other organs such as kidney or liver, they do not all operate simultaneously. To achieve normoglycemia in human, it is now widely considered that $15x10^3$ islets equivalent (IEQ) per kilogram are needed in a BAP (Kepsutlu et al., 2014). These figures come from experiments performed either in human or in small animals. In the past, our group was interested in BAP mass transfer modeling. In a full model including glucose, insulin and O_2 transfer, we clearly outlined that O_2 was the limiting factor for BAP efficiency, and that oxygen starvation led to significant decrease in insulin release (Dulong and Legallais, 2005). In some cases, most of the implanted islets were necrosed, because their density in the implant was too high. In contrast, implementing a lower number of well oxygenated islets may lead to a better response in term of insulin release. We concluded that about 500,000 islets (i.e. $5x10^3$ IEQ/kg) would be enough for human scale supply, if they maintain their functions.

Concerning primary human cells, it is reported that 2/3 of the endocrine tissue is lost in the purification stage during the pancreatic islet isolation process (Hwang et al., 2016; Ryan et al., 2001; Schweicher, 2014; Shapiro et al., 2016). Therefore, the actual availability of human donor pancreases can never fulfill the requirements for treating more than a small fraction of patients who need islet transplantation (Kepsutlu et al., 2014). Actually, the insufficient number of human donors is the major motives for scientists to focus on exploration of other cell sources to replace the function of insulin secreting beta cells. Table 2 summarizes the advantages and limitations of different types of cells employed up to now in BAP.

The immunoisolation provided by encapsulation within semipermeable membrane indeed enabled investigation into the use of other sources of insulin-secreting cells. In the past, the use of xenogeneic porcine islets represented an interesting alternative because the close homology between porcine and human insulin (O'Sullivan et al., 2011; Song et al., 2017; Sykes et al., 2006). Several porcine islets transplantation demonstrated efficacy (Dufrane et al., 2010, 2006a, 2006c; Dufrane and Gianello, 2012). Studies by Dufrane et al. showed survival and function of encapsulated adult pig islets after implantation without immunosuppression into non-human primates. Diabetes was corrected up 6 months post-transplant in diabetic primates (Dufrane et al., 2010, 2006d, 2006b). However, adult pig islets are expensive, fragile and difficult to maintain in culture after isolation. Alternatively, neonatal porcine islets represent an attractive source of cell for transplantation because of their ability for proliferation and differentiation, ease of isolation/purification and low cost (Nagaraju et al., 2015). Survival and function of encapsulated neonatal porcine islets after transplantation into human and animals were reported by Elliott et al., Matsumoto et al. and Valdés-González et al. (Elliott et al., 2007, 2005b, 2005a; Matsumoto et al., 2014; Valdes-Gonzalez et al., 2005). Despite the encouraging results provided by encapsulated pig islets, new regulations, in Europe, prevent the use of such cells to avoid the risk of zoonosis (Hwang et al., 2016; Lima et al., 2016).

Several autologous alternatives are thus being investigated: differentiation of induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) into beta cells (Espes et al., 2017; Iacovacci et al., 2016), and genetic modification of the exocrine pancreatic tissue in insulin-secreting cells (Iacovacci et al., 2016; Skrzypek et al., 2018). Some of these strategies are in advanced preclinical stages.

The differentiation of stem cells to insulin secreting cells represents an attractive alternative to human islets. Stem cells are able to self-renew and differentiate into specialized cell types, allowing the generation of all cell types of the human body (Chhabra and Brayman, 2013). Among stem cells, ESCs and iPSCs are the most commonly studied for differentiation in pancreatic islets (Amer et al., 2014; Millman et al., 2016). The ideal source to obtain beta cells would be iPSCs since the tissue generated in vitro would be genetically identical to the pancreatic endocrine tissue of the patient. In the last years, several studies reporting insulin-secreting cells production from ESCs (Cavelti-Weder et al., 2017; D'Amour et al., 2006; Kirk et al., 2014; Li et al., 2014; Pepper et al., 2017; Rezania et al., 2014) and iPSCs (Bruin et al., 2015; Chang et al., 2017; Motté et al., 2014; Robert et al., 2018) have been published. Rezania et al. reported the normalization of blood glucose levels in diabetic mice after 120 days of human embryonic stem cells (hESCs) transplantation in vivo (Rezania et al., 2012). After transplantation, the differentiation of hESCs cells was similar to human fetal pancreas development, with similar gene and protein expression profiles. Normalization of hyperglycemia in diabetic mice by hESCS, human induced pluripotent stem cells (hiPSCs) and mouse iPSCs-derived β cells was also demonstrated by Pagliuca et al. (Pagliuca et al., 2014), Yabe et al. (Yabe et al., 2017) and Alipo et al. (Alipio et al., 2010), respectively. However, there are still concerns regarding the ability of β-cells generated from stem cells to regulate insulin physiological levels in response to glucose (Iacovacci et al., 2016).

Exocrine pancreatic tissue is the main part of the pancreas. This tissue, about 95% of total mass of pancreas, is discarded following each islet isolation procedure. Recently, scientists have been interested in a new approach based on reprogramming of exocrine acinar and ductal cells into insulin-secreting β-cells

(Shen et al., 2013). Exocrine cells are close of β-cells and have similar epigenetic profiles since they arise from the same progenitor common for all pancreatic cells ($Pdx1^+$ cells) (Bonal and Herrera, 2008). Moreover, pancreatic exocrine cells are known by plasticity of their phenotype. Therefore, interconversion of exocrine cells in β-cells is easily possible (Minami et al., 2011). Reprogramming of exocrine cells can occur through manipulation of pancreatic transcription factors (Pdx1, Ngn3, MafA, and Pax4), in combination with growth factors (betacellulin, exendin-4 and nicotinamide) (Lima et al., 2016) . *In vitro* and *in vivo* generation of insulin-secreting β-cells from pancreatic exocrine cells has been widely studied and reported in literature (Lemper et al., 2015; Lima et al., 2016; Minami et al., 2011; Zhou et al., 2008). Nevertheless, further developments are needed to guarantee high efficacy and safety of β-cells derived from exocrine cells (O'Sullivan et al., 2011).

In addition to stem, exocrine and xenogenic cells, several other strategies of β cells generation were/are studied. Among these strategies, the most studied are the use of immortalized human pancreatic cell lines and the reprogramming of cells from other organs such as liver cells and gastrointestinal cells (Benthuysen et al., 2016; Cito et al., 2018; Iacovacci et al., 2016).

Table 2 here

3.2 Mass transfer issues in BAP and implantation site

As previously described, islets of Langerhans in a native pancreas are highly vascularized, providing the cells with glucose signal (from systemic circulation), oxygen (local PO2) and releasing insulin directly in the portal system to reach the liver. In addition, in the situation of hyperglycemia, the flow rate can be multiplied by six to improve the response kinetics.

3.2.1 Intravascular systems combining convection and diffusion

Ideally, the BAP should be located at the same position as in the native pancreas, i.e., as a shunt between arterial and venous circulation in the portal area. In such situation, both convective and diffusive bidirectional mass transfer would occur between the blood and the isolated islets.
Local mass transfer (Js) combining diffusion and convection can be described by the following equation:

$$Js = Jf \times S \times Cs + Ds \times \text{grad}(Cs)$$

With:
Js in $kg.m^{-2}.s^{-1}$
Jf: local solvent convective flux ($m.s^{-1}$) : Jf = UFR x ΔP, with ΔP the local transmembrane pressure and UFR the membrane ultrafiltration rate
S: membrane sieving coefficient for the solute of interest
Cs ($kg.m^{-3}$): solute concentration in the compartment from which convection process is issued
Ds ($m.s^{-1}$): diffusive coefficient of the solute between both compartments (NB: this coefficient takes into account resistance in the fluids but also across the scaffold/membrane)
Grad (Cs): concentration gradient between compartments

Design and limits of perfusion chambers

The Figure 6A illustrates in a simple way the exchanges that can take place between the host and the islets isolated in a perfusion chamber, and the associated governing factors. Such chambers, with various

designs, have been investigated since the mid-seventies employing either flat or hollow fiber membrane, inspired from artificial kidney devices (Chick et al., 1975; Reach and Jaffrin, 1990.; Scharp et al., 1984; Sun et al., 1977).

Based on the kinetic modelling of glucose and insulin transfer through the porous structure, the group of Reach designed a system optimizing convective fluxes across the membrane, and yielded excellent kinetics *in vitro* (Reach et al., 1984) and *in vivo* in rats (Reach et al., 1986) and in dogs (Lepeintre et al., 1990). The correction of hyperglycaemia in diabetic rats with this system was demonstrated over a few hours (Reach and Jaffrin, 1987). However, the system was unable to avoid blood clotting inside the fiber. Another major effort in this field was made by the group working with Chick, who used a radically opposite approach. They focused on the haemocompatibility of the system, and reported the successful graft of a vascular device in dogs over several months in the absence of any heparinization of the animals, which only received aspirin (Monaco et al., 1991; Sullivan et al., 1991). Hyperglycemia was corrected, but the authors recognize that improvements in the kinetics of insulin release by this device were still required. Last results showed that a device seeded with xenogeneic porcine islets implanted into pancreatectomized dogs allowed to reduce exogeneous insulin requirement for up to 9 months (Maki et al., 1996). This work led to an FDA authorization to initiate clinical studies. During one of the last pre-clinical transplants, the device failed leading to the death of the animals and the program was cancelled.

A similar system was proposed by Calafiore et al., who implanted micro-encapsulated islets inside the wall of a Dacron-based prosthesis connected to an arterial bypass. Plasma crossed the Dacron meshes and perfused the islets, which were immunoprotected by the membrane of the microcapsules, and which released insulin into the bloodstream. This system was investigated in a small number of dogs (Calafiore et al., 1992) and in two diabetic patients (Calafiore, 1992).

It is obvious that the development of these systems was hindered by the need for vascular access and by its thrombotic risk: indefinite prevention of clotting represents a formidable challenge. This may be one reason why the intravenous route for insulin delivery by implantable pumps has been almost abandoned in the late 90's. More recently, Prochorov et al. revisited the concept using an intravascular device that contains around 6000 IEQ/kg isolated from fetal rabbit (Prochorov et al., 2008). 19 patients with T1DM received a nylon microporous device into the arteria profunda femoris (APF) using autovenous angioplastics (Prochorov et al., 2008). After 18 months, the patients showed no complications related to the transplantation. Although insulin secreted was not enough to reestablish normoglycemia, it helps to reduce the insulin dose injected per day and protect against episodes of hyperglycemia or hypoglycemia.

Direct perfusion of encapsulated islets implanted in vascularized organs

This approach is inspired from the first transplantation of pancreatic islets into the portal vein of the liver which had been carried out successfully in the 90s (Scharp et al., 1990). Choosing the liver as a site of implantation of the BAP is driven by physiology, since liver is the first organ through which the hormones secreted by the pancreas pass. In addition, liver is a major site for glucose storage (glycogenesis) and release (gluconeogenesis). Finally, thanks to the last advances in minimally invasive surgery, BAP implantation could be carried out easily by percutaneous transhepatic portal embolization technique (Goss et al., 2002; Ryan et al., 2001; Scharp et al., 1991). This site required to deploy microencapsulation of the islets, due to the size of the vessels. To overcome mass transfer limitations leading to cell necrosis, several groups even attempted to reduce the thickness of the encapsulating material by surface treatment of the islets directly instead of creating a continuous barrier around them (antibodies, heparin, cells…) (Arifin et al., 2016; Cabric et al., 2007; Giraldo et al., 2017; Lau et al., 2015; Teramura and Iwata, 2010) or by using new improved biomaterials (Mooranian et al., 2016; Teramura and Iwata, 2011, 2009), leading to so-called nano-encapsulation.

The coating or superficial treatment of the islets presents some very promising results after its implantation in rodents. The superficial treatment significantly reduces the size of the implant, allowing its insertion in highly vascularized organs as well as increasing postoperative survival up to 78% (Fotino et al., 2015; Teramura et al., 2013; Teramura and Iwata, 2010, 2009; Tomei et al., 2014). But despite the good glycemic control obtained in diabetic subjects, the long-term stability of this encapsulation technique is quite questionable (Arifin et al., 2016). The deterioration of the protective layer exposes the islets to the attack of the immune system (Giraldo et al., 2017).

However, the liver as an implantation site presents some drawbacks. First, the space available is rather small for the size of the graft; it is necessary to consider that the microencapsulated islets in spheres of material containing one or two islets have a diameter of 400 μm each one. Secondly, microspheres hosting pancreatic islets generate problems of embolization and thrombosis of the small blood vessels around the implantation site induced by the instant blood-mediated inflammatory responses (IBMIR). The third drawback of the intraportal implantation is the partial pressure of oxygen to which the pancreatic islets will be exposed (Zhu et al., 2018). The partial pressure of oxygen in the liver portal system is considerably lower than in the pancreas (5-10 against 40 mmHg) (Carlsson et al., 2001; Olsson et al., 2011; Zhu et al., 2018): the islets are permanently in hypoxia, which affect significantly their viability. Usually, a large amount of IEQ islet per kilogram is needed for the pancreatic islets transplantation, considering that half of them die in a few hours after the intervention (Shapiro et al., 2016).

At first sight, the spleen could be also a good candidate as a BAP implantation site. It is a very vascularized organ with similar characteristics to the portal vein without the risk of hypertension induced after intraportal transplantation. The limited number of publications about intrasplenic transplantation in rodents and dogs shows that it is safe and feasible as a procedure. However, there are not enough studies to corroborate the suitability of the site for the BAP. The lake of studies is due to the small space available to place the majority of the devices, the risk of hemorrhage during surgery, the concentration of the immune system cells that could activate easily the IBMIR and the difficulty to remove the graft in case of failure (Aoki et al., 2005; Gores and Sutherland, 1993; Itoh et al., 2017).

Figure 6 here

3.2.2 Diffusion based extravascular systems

If perfusion cannot be considered, the alternative option is to enhance/promote diffusion, since the substances to exchange present relatively low molecular weight. In this case, the limiting parameter is the diffusion capacity of the solute, which is mostly governed by the diffusivity within the scaffold (Figure 6B). Mass transfer can thus be enhanced either by increasing the porosity of the structure, or by reducing the diffusion length. The diffusion length can be defined as the mean distance between islets and surrounding blood: it can thus be decreased either by decreasing the scaffold/device thickness, or by promoting neovascularization of the implant.

We will see in the following subchapter that these different strategies have been investigated in various implantation sites.

Omental pouch and intraperitoneal transplantation

Intraperitoneal transplantation is the most common site for the BAP in the clinical setting (Basta et al., 2011; Calafiore et al., 2006; Jacobs-Tulleneers-Thevissen et al., 2013a; Soon-Shiong et al., 1994; Tuch et al., 2009). One major advantage is the ease and safety of implantation through minimally invasive surgery

and accessibility to the graft. It is an ideal choice for macroencapsulation systems due to the space available for the placement of the device. It benefits from appropriate environment considering that the encapsulated cells are in contact with the surrounding fluids allowing the exchange of insulin and nutrients.

Takeuchi and his group succeeded in restoring blood glucose level of diabetic rodents by the transplantation of different hydrogel-based microfibers (Onoe et al., 2013; Ozawa et al., 2017a, 2017b; Sugimoto et al., 2011). Hollow fiber devices have been explored since early in the 80's. They give a good responsiveness to changes in glucose blood levels (Jun et al., 2013). However, they had some drawbacks such the little amount of tissue that could be encapsulated in a fiber, requesting to consider significant lengths to be implanted (Lacy et al., 1991). Takeuchi's group proposed an innovative technique based on microtechnology to produce fibers with small diameters without compromising the viability of the tissue (Ozawa et al., 2017b).

Alginate beads as a microencapsulated device seems to be more suitable device for intraperitoneal transplantation than macrodevices in terms of long term viability and performance (Elliott et al., 2007, 2005b, 2005a, Matsumoto et al., 2016, 2014; Ryan et al., 2001; Valdes-Gonzalez et al., 2005). However, microbeads injected in the peritoneal cavity move from their original implantation site and end up in the lower part of the pelvis due to the upright position adopted by human and non-human primates (Dufrane et al., 2006a; Jacobs-Tulleneers-Thevissen et al., 2013; Lanza et al., 1993; Omer et al., 2003; Sun et al., 1996; Vegas et al., 2016; ClinicalTrials.gov NCT01739829).

The peritoneal cavity has also certain drawbacks that do not fully meet to the requirements of the BAP. On the one hand, due tots anatomy and physiology, it has small or null revascularization capacity around the implant, which hinders the exchange of oxygen and nutrients and submits the encapsulated islets to hypoxia. On the other hand, not being in direct contact with the bloodstream limits the ability of the implanted device to respond to changes in glucose concentration is slow and delayed, which subjects the body constantly to hypoglycemia or hyperglycemia.

To mitigate the hypoxia, polydimethylsiloxane (PDMS) based materials with high oxygen permeability have been used for the graft encapsulation (Coronel et al., 2017; McQuilling and Opara, 2017; Pedraza et al., 2012). But the most representative device with an effective mechanism to improve the oxygen supply for islets survival is the β-air (Barkai et al., 2013; Ludwig et al., 2013b, 2012; Neufeld et al., 2013) or its new version beta-O_2 (Ludwig et al., 2017). β-air is a disk diffusion chamber where the islets are loaded in an alginate-based core and a polytetrafluoroethylene (PTFE) based semipermeable membrane. But the most important characteristic is the central oxygen module connected with the outside of the host body that provides more O_2 than the blood transporters.

To improve the neovascularization of the graft, devices in development like Sernova cell pouch (Kriz et al., 2012; ClinicalTrials.gov NCT01652911) and Viacyte (ClinicalTrials.gov NCT02239354) have made interesting progresses in recent years. Both devices are currently in phases I or II of the clinical study. Sernova cell pouch has shown that omental transplantation with a subcutaneous access point (for the subsequent replacement of the islets) can induce a good neovascularization of the device thanks to the close position of the portal vein and the microenvironment that provides the great omentum. The omental pouch can be stimulated by neoangiogenic factors to create new blood vessels in a short time. 70% of the rodents involved in Kriz et al. study have shown long-term normoglycemia (Kriz et al., 2012). Several studies corroborated the suitability of the omentum as a site for the transplantation of encapsulated pancreatic islets (Harrington et al., 2017; Opara et al., 2010; Pareta et al., 2014).

Kidney capsule

The renal subcapsular site is the most widely used for islet transplantation in experimental studies, especially in rodents. Islet transplantation into the kidney is easy and has been reported to restore

normoglycemia (Zhu et al., 2018). Kidney subcapsular space offers good vascular network and desirable growth conditions for islets (Kepsutlu et al., 2014). Previous studies reported that mice and human islets transplanted in kidney subcapsular present better morphology and function, compared with islets implanted in liver, lung and spleen of mice (Hayek and Beattie, 1997; Mellgren et al., 1986). In comparative study between intraportal and kidney subcapsular transplantation in mice, Sakata et al., demonstrated that two hundred islets yielded normoglycemia in renal subcapsular grafts, while minimum 800 islets are required for normoglycemia with intraportal transplantation (Sakata et al., 2009).

Transplantations of encapsulated islets with different shapes into kidney subcapsular space were also studied and have shown their ability to correct glycemia. Dufrane et al. investigated transplantation of pig islets microencapsulated with alginates into Kidney subcapsular space of monkey. The results demonstrated the functionality of alginate microcapsules and the absence of capsule fibrosis (Dufrane et al., 2006a). In other study, the same group has shown that alginate microcapsules transplanted under kidney capsule of rat demonstrate better biocompatibility than capsules transplanted in the peritoneum. In addition, due to restricted mobility of the grafts, alginate microcapsules integrity was preserved to a greater extent in the kidney, compared to peritoneal cavity (Dufrane et al., 2006d). Rat islet cells encapsulated within alginate microfibers and mice islets protected by PEGylation were also transplanted in kidney subcapsular of mice. Islets into alginate microfibers normalized blood glucose concentrations for two weeks in diabetic mice (Onoe et al., 2013). Concerning PEGylated islets, the transplanted diabetic mice exhibited long term normoglycemia (>100 days) (Giraldo et al., 2017).

Despite the promising results observed in animal experiments, clinical transplantation into renal subcapsular would be difficult given the limited space within this site. It is impossible to implant devices with the islets number necessary to correct human glycemia. In addition, renal cortex has an oxygen tension of 15 mmHg, which represents an hypoxic environment for islets (the oxygen partial pressure in pancreas is about 40 mmHg).

Subcutaneous tissues

The first clinical trial of subcutaneous transplantation of a BAP has been carried out by Scharp et al. in 1994. The islets has been encapsulated by semi-permeable membrane in the form of hollow fiber (Scharp et al., 1994). In an attempt to verify the biocompatibility and survival of human pancreatic islets, the results were quite promising. Although not surprisingly, the response time to the stimulus of insulin secretion was slow.

Subcutaneous transplantation is usually carried out for the macroencapsulated devices in the form of hollow fiber, planar or when an external oxygenation mechanism is integrated, like in the β-Air device (Barkai et al., 2013; Ludwig et al., 2017, 2013a, 2012; Neufeld et al., 2013). The advantages of the subcutaneous transplantation are the easy access and monitoring of the graft, the good biocompatibility and the high viability of the islets in the postoperative period (Pepper et al., 2015). However, the difficulty of neovascularization of the macrodevices and the low partial pressure of oxygen remain the major drawbacks in the subucutaneous transplantation.

The most representative device of subcutaneous transplantation is the Theracyte System ™ or its new generations Viacyte and Encaptra® (Robert et al., 2018). The first was initiated by Baxter Healthcare in the late 1990's as a planar device of two composite membranes sealed at all sides with a loading port or ports (Cañibano-Hernández et al., 2018). The outside of the device is designed for strength and to encourage host tissue to incorporate into its outer portions. The other sections are a teflon-based membrane (PTFE) to encourage capillary ingrowth and a hydrogel semipermeable membrane (alginate based) for allograft immune protection. Theracyte has evolved in parallel with the safety level of experiments, from rodents to large animals implementing different cell sources including human cells (Bruin et al., 2013; Elliott et al., 2007; Kirk et al., 2014; Kumagai-Braesch et al., 2013; Motté et al.,

2014).The latest innovation provided by the manufacturers of Viacyte is the device-less character in its new trials thanks to the implemented prevascularization technique whose objective is the preparation of a suitable microenvironment for grafting before the cells implantation to improve the viability and the sensibility of the graft (Kroon et al., 2008; Pepper et al., 2017, 2015).

Another original approach has been described by Farina et al. They implemented a prevascularized polylactic acid (PLA) scaffold printed in 3D (Farina et al., 2017). The porous biomaterial was tested in nude mice with human pancreatic islets. The islets were injected into the device 4 weeks after its transplantation. The angiogenesis of the islets was demonstrated, but it was necessary a second injection of islets to get the same amount of insulin secreted in the positive because of the slow neovascularization.

Subcutaneous transplantation remains controversial regardless the problem of angiogenesis and the mechanical requirements of the BAP. The superficial location of a graft so sensitive and so important for the control of metabolism can suffer irreversible damage due to temperature variations or physical trauma (Zhu et al., 2018).

4 Porous Scaffolds – Membranes

Table 3 here

Different materials have been employed as "membrane" structure. In intravascular devices, islets are encapsulated within hollow semipermeable tubes or fibers made of polymeric materials such as polyacrylonitrile-polyvinylchloride copolymer, polyethylene-vinyl alcohol, polycarbonate and nylon (de Vos et al., 2002; Skrzypek et al., 2018; Song and Roy, 2016). In extravascular devices, two main geometries are used: tubular and planar devices. Various polymeric or inorganic biomaterials have been investigated. However, polymeric materials are the most commonly used. These include alginate, 2-hydroxy-ethyl methacrylate (HEMA), nitro-cellulose acetate, acrylonitrile, sodium-methallylsulfonate, and PTFE (de Vos et al., 2002).

Micro or macroencapsulation using alginate as basic material is probably the best response to biocompatibility since alginate is an inert polysaccharide. However, as material from natural origin, it may contain impurities promoting fibrosis. Alginate, when jellified with calcium or other divalent cations, is also not very stable over time and might lose its polymeric state. Therefore, crosslinking agents or additional layers have been added, changing the overall mass transfer and interactions with the host tissue (Basta et al., 2011; Calafiore et al., 2006; Jacobs-Tulleneers-Thevissen et al., 2013; Soon-Shiong et al., 1994; Tuch et al., 2009; Veiseh et al., 2015). Strand et al. reviewed the progress that have been made in alginate encapsulated pancreatic islets (Strand et al., 2017). The lack of long-term trials and cohort studies plus the fibrosis of the alginate-based capsules are the most important drawbacks to overcome.

According to the BAP requirements, all the scaffolds/membranes entrapping the insulin secreting cells or the islets are designed with the same objectives in term of sieving: allow the exchange of oxygen, nutrients, insulin and waste products and prevent immune response from the host (Fotino et al., 2015).

If this second point is fulfilled by the membrane-based devices, there is no need for immunosuppressive therapy after the implantation. Describing in detail the rejection process of a graft and the factors involved is far beyond the scope of this review. Briefly, this immune response, in the case of type I diabetic patients, can be of two different types : i) allogenic or xenogenic response of the host to the transplanted tissue, leading to the activation of the innate immune system due the detection of foreign cells by the host; ii) auto-immunity (following the same mechanisms than those inducing the pathology

in the native pancreas (Scharp and Marchetti, 2014). The first response is mainly supported by cells (lymphocytes B and T) but can also be mediated by immunoglobulins.

As indicated in Table 3, most of the synthetic polymer based membranes/scaffolds present pore size average 0.2-0.4 µm (Colton, 1995; Schweicher, 2014), which is a sieve for cells only and not immunoglobulins. So far, immune rejection seems to be effective on relatively short-term basis. In these cases, the membrane demonstrated a very high porosity, and the diffusive transport is not hindered. Only the thickness of the device and the seeding density of the islets/cells influenced the mass transfer. In such case, Dulong and Legallais (Dulong and Legallais, 2007) demonstrated that a too high density may lead to islet necrosis in case of implantation in poorly oxygenated sites.

Besides the sieving effect, in most of the case, one has to consider that the membrane is in contact with the host tissues. One major problem in biocompatibility for implanted device is the development of a fibrous and inert structure around the device. It represents an additional resistance to mass transfer and increases the risk of islets' necrosis due to oxygen starvation. A way to circumvent this issue would be to use materials that can promote neovascularization.

5 Conclusions and Future Trends

Pancreatic islet transplantation can successfully controls glucose levels and has been validated as a treatment for type 1 diabetes on short periods. The development of BAP that consists of islets encapsulation within semi-permeable membrane is considered as a promising strategy to overcome some obstacles of classical islet transplantation. Despite the significant progress in the lab, clinical applications of BAP are few. To increase the impact of the BAP translation from the bench to the bed side, it appears necessary to combine the progress made in different disciplines such as nanotechnology, biomaterials, immunology and tissue engineering.

Hypoxia adversely affects the functionality of encapsulated islets and represents a major limitation in the development of efficient BAP devices. Limited oxygen supply causes apoptosis and reduces the capacity of islets to secrete insulin (Barkai et al., 2013). In the last years, different strategies including prevascularization and *in situ* oxygen supply have been investigated to improve encapsulated islet oxygenation. The combination of conformal coating and extravascular microencapsulation has shown some promising results. Other studies reported the use of proangiogenic factors (vascular endothelial growth factor (VEGF)) to induce BAP prevascularization (Pileggi et al., 2006; Trivedi et al., 2000). Several researchers are working on the co-encapsulation of insulin-secreting cells with another cell type in order to improve viability and stimulate graft neovascularization without compromising immunological safety (Valdes-Gonzalez et al., 2005; Vériter et al., 2014). Johansson et al. provided evidence that the coculture of MSCs and endothelial cells with human islets *in vitro* before transplantation initiated the formation of vessel-like structures that may promote further neovascularization (Johansson et al., 2008). In other approach, Barkai et al. developed a device that can be refueled with oxygen via subdermally implanted access ports. The transplantation of this device normalized glucose levels in diabetic rats for 6 months. The authors demonstrated that the functionality of the device was dependent on oxygen supply (Barkai et al., 2013).

In recent years, microfluidic technology has emerged as a valuable tool for a wide range of applications such as biotechnology, tissue engineering and analytical applications. This technology has been used to generate precise micro-scaled encapsulation. Onoe et al. developed microfibers encapsulating ECM proteins and islets cells using microfluidic device (Onoe et al., 2013). The fabricated microfibres reconstitute intrinsic morphologies and functions of living tissues. In other study, Tomei et al. developed an encapsulation method that allows conformal coating of islets through microfluidics and minimizes capsule size, capsule thickness and graft volume. The reduction of capsule thickness improves oxygen and insulin exchange (Tomei et al., 2014). Microfluidic devices can be used in differentiation of stem

cells, which can be alternative sources of islets for transplantation to solve the critical problem of the shortage of human islet donors. Indeed, the destiny of stem cells is highly regulated by microenvironment. Such devices provide a new support of cells culture with unique advantages to mimic complex physiological microenvironments in vivo (Zhang et al., 2017): high oxygenation, 3D tissue reorganisation, dynamic stimulation, continuous nutrient supply and waste removal. Microsystems can be also used to assess islets or beta cells functionality before transplantation, in an environment close to in vivo conditions.

In conclusion, the interactions between the graft and its microenvironment still remain a huge challenge for the BAP. It is well known that the structural organization of the pancreatic beta cells and its interaction with the host cells influences the amount of insulin secreted (Desai and Shea, 2017).

List of symbols

Cs	solute concentration
Ds	*diffusion coefficient of the solute*
Jf	local convective flux of the solvent
Js	local mass transfer
MafA	MAF bZIP transcription factor A
Ngn3	neurogenin 3
P	pressure
ΔP	local transmembrane pressure
Pax4	paired box 4
Pdx1	pancreatic and duodenal homeobox 1
PO2	oxygen partial pressure
S	sieving coefficient of the membrane
UFR	membrane ultrafiltration rate

List of acronyms

APA	alginate-poly-L-ornithine-alginate
APF	arteria profunda femoris
BAP	bioatificial pancreas
CAC	collagen-alginate composite
CITR	collaborative islet transplant registry
ESCs	embryonic stem cells
FDA	food and drug administration
HEMA	2-hydroxy-ethyl methacrylate
hESCs	human embryonic stem cells
hiPSCs	human induced pluripotent stem cells
IBMIR	instant blood-mediated inflammatory responses
IDF	international diabetes federation
IEQ	islets equivalent
IPN	interpenetrating network
iPSCs	induced pluripotent stem cells
LFA-1	function-associated Antigen-1
PDMS	polydimethylsiloxane
PECs	pancreatic endoderm cells
PEG	polyethylene glycol
PLA	polylactic acid

PP	pancreatic polypeptide
PTFE	polytetrafluoroethylene
T1DM	type I diabetes mellitus
TMTD	triazole-thiomorpholine dioxide
VEGF	vascular endothelial growth factor
WHO	world health organization

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Figures

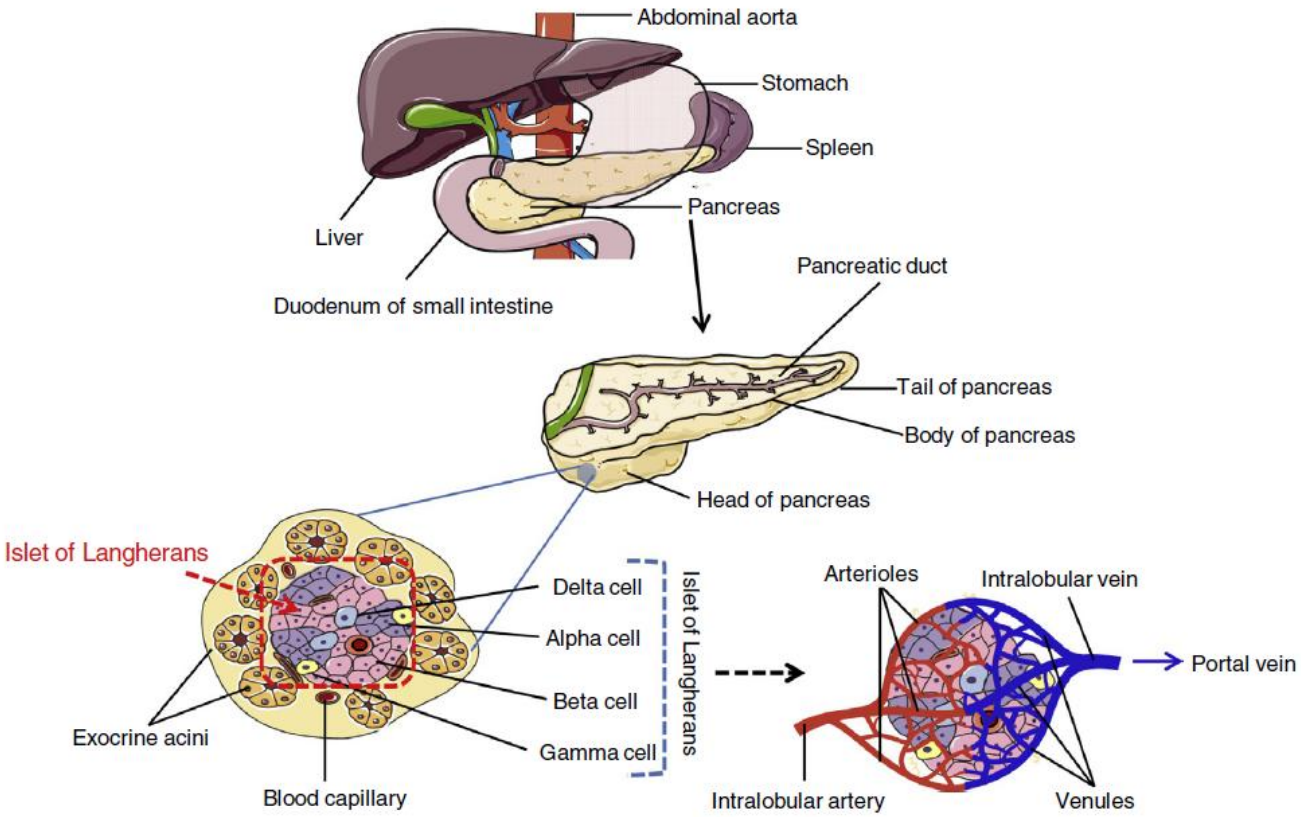

Figure 1. Multiscale description of the systemic and local environment of islets of Langerhans.

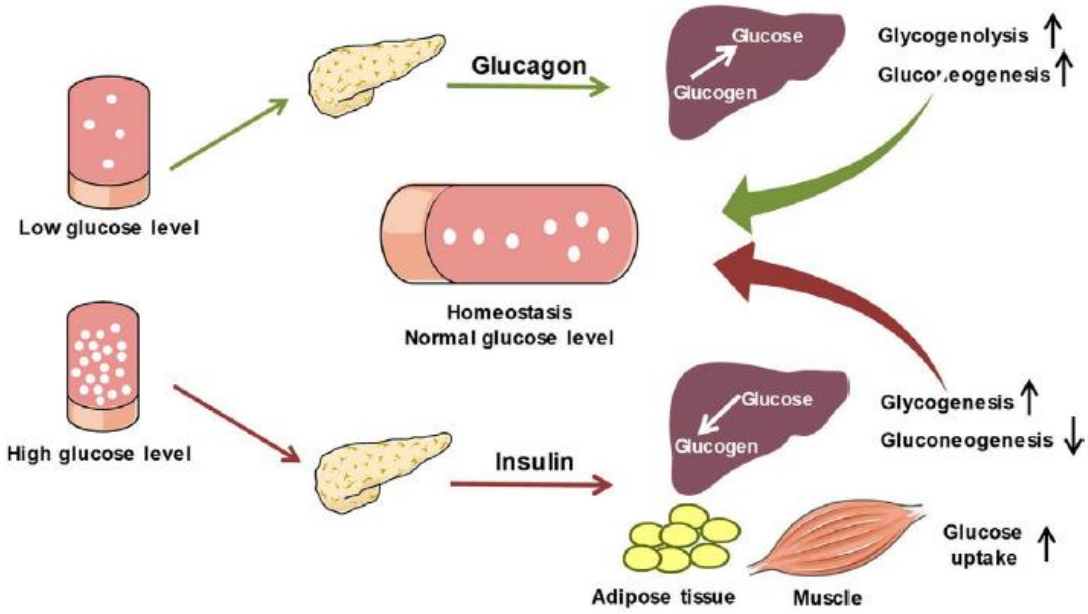

Figure 2. Mechanisms of glycemia regulation by the pancreas and other tissues (liver, adipose, muscle).

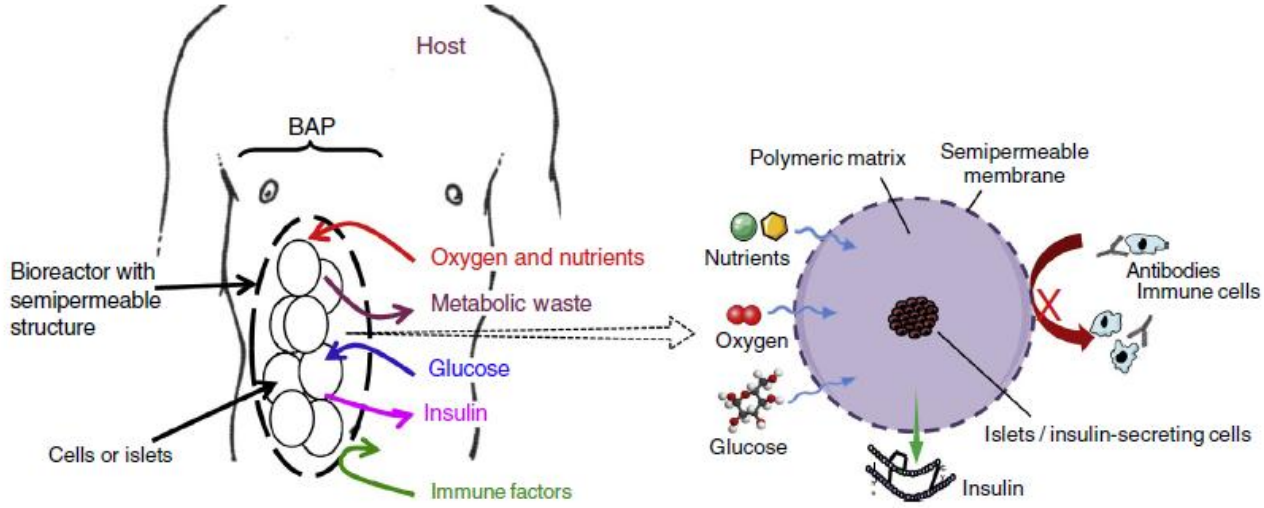

Figure 3. Concept of implantable bioartificial pancreas.

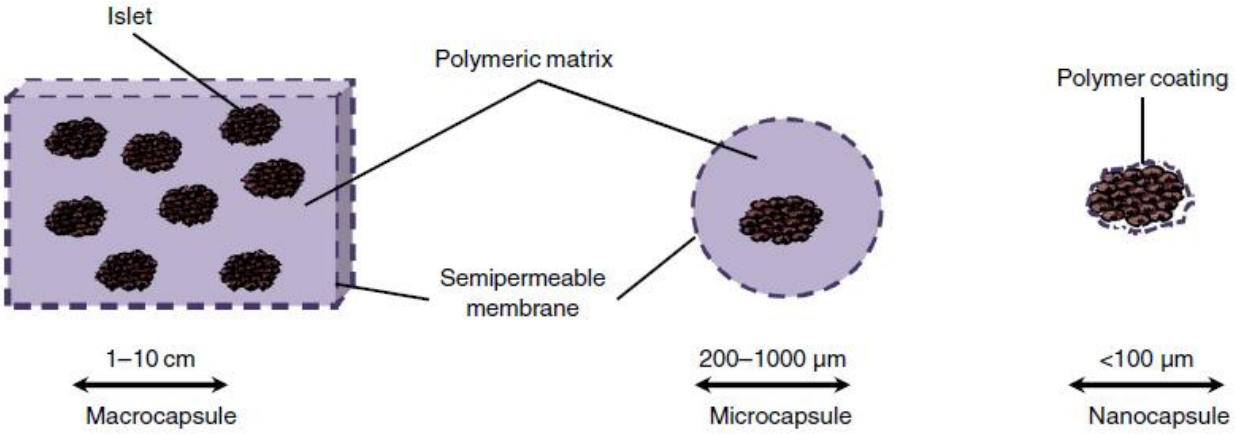

Figure 4. Different concept of islet encapsulation, from macro to nano scale.

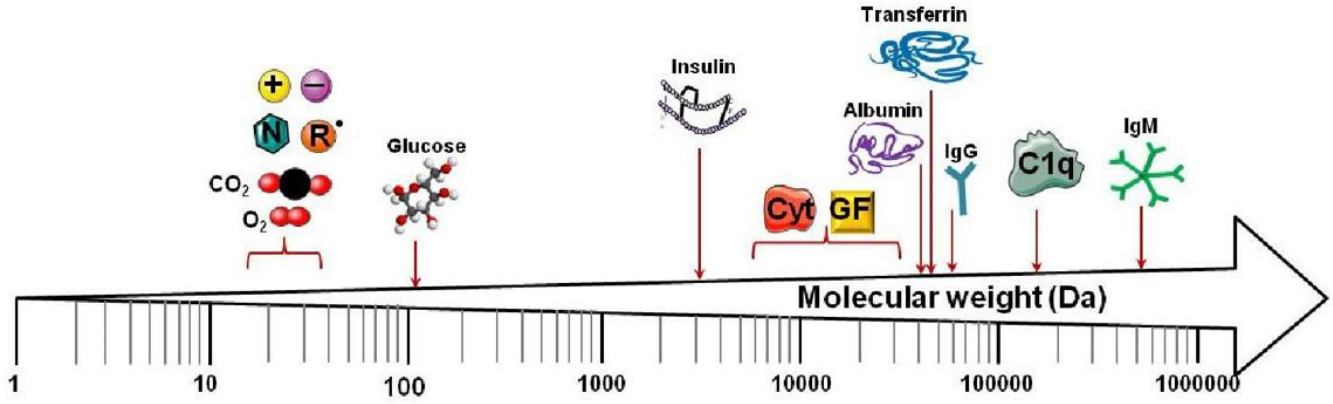

Figure 5. Classification of the elements implicated in BAP inmuno-isolation by their molecular weight (adapted from Schweicher et al., 2014). (R) free radicals; (N) nitrogen metabolites; (+) cation; (-) anion; (Cyt) cytokines; (GF) growth factors; (C1q) complement component 1q.

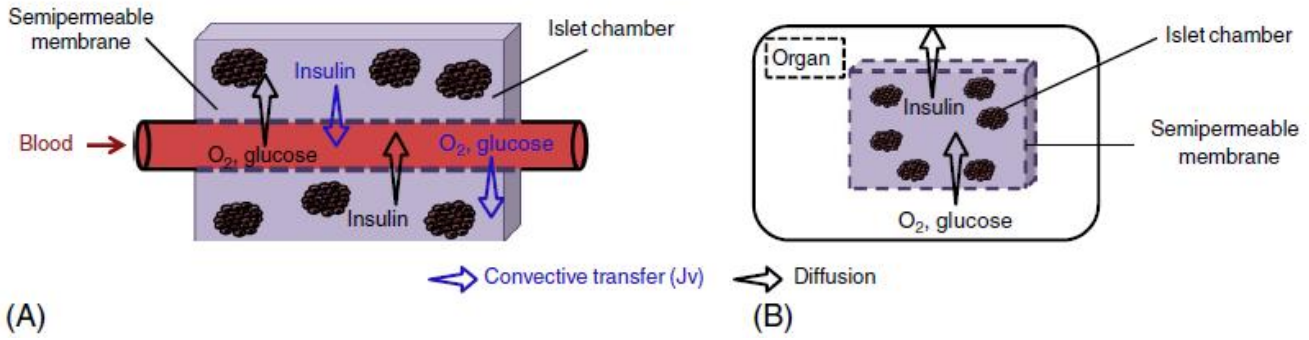

Figure 6. Schematic representation of intravascular BAP (A) and diffusion chamber (B).

Tables

Table 1: Summary of the different treatment available for type I diabetic patients.

Treatment	Advantages	Disadvantages
Insulin injection	• Simple and relatively accessible treatment • Long-term durability in case of T1DM	• Difficult maintaining normoglycemia overnight • Requires user training • It's usually combined with a restrictive diet control
Closed-loop insulin delivery (mechanical pump)	• Ergonomic for the patient • Continuous control of blood glucose levels (overnight) • Telematic follow-up by the therapist	• Fibrosis in the catheter implant site • Slow response to sudden changes in glucose levels • Requires maintenance (battery and insulin)
Pancreas transplantation	• Durability • Full control of normoglycemia	• Quite complex surgery • Donor shortage • Requires immunosuppressants for life
Clinical islets transplantation	• Full control of normoglycemia • Minimally invasive surgery	• Still in development • Requires two donors for one receiver • Loss of functionality in the long term • Requests as transplantation immunosuppressive treatment

Table 2: Cells' sources, pros and cons to be used in BAP.

Cells source	Advantages	Limitations
Porcine	• Homology between porcine and human insulin • Low coast • Availability • Hypoxia tolerance	• Retroviral disease transmission • Fragile during encapsulation • Immune rejection caused by porcine proteins no identified by human system
Stem cells hESCs and hiPSCs	• Sensitiveness as good as the original pancreas • Immunological safety • Unlimited source of human insulin-producing cells	• Risk of teratoma formation • Risk of mutagenesis due to vectors used for reprogramming • Ethical preoccupation • Expansive • Reactivity to glucose
Exocrine	• Available as a by-product of islet transplantation (90% of the pancreatic tissue). • Possibility of differentiation in situ without a surgical intervention. • Full biocompatibility and immunological safety	• Limited source of cells • Difficult control of the differentiation in a specific type of endocrine pancreatic cells • Reactivity to glucose
Immortalized human pancreatic cell lines	• Unlimited sources (easily proliferate) • Low cost • Easy to maintain	• Low insulin production • Low reactivity to glucose • Risk of metastasis • Risk of massive proliferation • Need of a effective encapsulation

Table 3: in vivo studies of some bioartificial pancreas in development.

Cells source	With/without immunosuppressants	Recipient	Inmuno-isolation	Material	Transplantation site	Characteristics	Success	Reference
Porcine			No		Kidney	Fetal porcine islet-like cell clusters (ICC)	Partially. Presence of porcine peptide-C	Groth MD et al. 1994[35]
Porcine			No		Kidney	Fetal porcine islet	Yes	Reinholt et al. 1998
Porcine			yes		subcutaneous autologous	porcine neonatal islets of Langerhans and Sertoli cells	Yes	Valdés-González et al. 2005
Porcine			yes		Peritoneal cavity	neonatal porcine islets	Yes	Matsumoto et al. 2014
Porcine			yes		Peritoneal cavity	neonatal	No, immuno-	Elliott et

						porcine islets	reactive insulin identified as porcine	al. 2007[36]
Porcine		Monkey	Yes	alginate	Kidney and subcutaneous	Adult pig islets encapsulated in alginate	Yes	Dufrane et al. 2006
Porcine		Monkey	Yes	alginate	Kidney and subcutaneous	Adult pig islets encapsulated in alginate	Yes,	Dufrane et al. 2010
Porcine		Rat	Yes	alginate	Peritoneal cavity, Kidney and subcutaneous	Adult pig islets encapsulated in alginate	Yes,	Dufrane et al. 2006
Porcine		Dog	Yes	agarose and polystyrene sulfonic acid (PSSa)	Peritoneal cavity	Pig islets encapsulated in agarose and polystyrene sulfonic acid	yes	Kin et al. 2002
Exocrine	-		-		-	In vivo genetically reprograming mice pancreatic cells	yes	Zhou et al. 2010[37]
Exocrine			No		Kidney	Genetically reprograming human pancreatic cells	Partially	Lemper et al. 2015[38]
Exocrine	-		-		-	In vivo genetically reprograming mice pancreatic cells	Yes	Li et al. 2014[18]
Exocrine	-		-		-	In vivo genetically reprograming mice pancreatic cells	yes	Furuya et al. 2013[19]
Exocrine	-		-		-	In vivo genetically reprograming mice pancreatic cells	yes	Cavelti-Weder et al. 2017[20]
human embryonic stem (hES) cells	-	-	No	-	In vitro	The insulin expression in hES cell–derived is like adult islets	Yes	D'Amour et al. 2006[21]
human embryonic stem (hES) cells	With	Mice	Yes	Polytetrafluoroethylene (PTFE),	Subcutaneous	hESC in Theracyte™ device	Partially	Kirk et al. 2014[22]

human embryonic stem (hES) cells	With	Mice		ViaCyte device	Subcutaneous	50 weeks of metabolic control by insulin release in Viacyte a variant of the Theracyte device	Yes	Robert et al. 2018[23]
human embryonic stem (hES) cells	Without	Mice	Yes	Polytetrafluoroethylene (PTFE); alginate	Subcutaneous	20 weeks of metabolic control by insulin release in the Theracyte device versus alginate	Yes	Motté et al. 2014[24]
human embryonic stem (hES) cells	Without	Mice and rat	No	-	Kidney and Subcutaneous	Comparing 2 animal models and 2 transplantation sites	Yes	Bruin et al. 2015[25]
Human induced pluripotent stem (hiPS) cells	-	-	-	-	In vitro	Functional beta cells like	Yes	Kimura et al. 2017[39]
Human induced pluripotent stem (hiPS) cells	With	mice	No	-	Kidney	Normoglycemia after trqnsplantation	Yes	Pagliuca et al. 2014[40]
Human induced pluripotent stem (hiPS) cells	With	mice	No	-	Kidney	Normoglycemia after transplantation	Yes	Yabe et al. 2017[41]