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Porcine Islet Xenografts: a Clinical Source of ß-Cell Grafts

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Abstract
Purpose of Review Diabetes is medical and social burden affecting millions around the world. Despite intensive therapy, insulin fails to maintain adequate glucose homeostasis and often results in episodes of hypoglycemic unawareness. Islet transplantation is a propitious replacement therapy, and incremental improvements in islet isolation and immunosuppressive drugs have made this procedure a feasible option. Shortage of donors, graft loss, and toxic immunosuppressive agents are few of many hurdles against making human allogenic islet transplantation a routine procedure.
Recent Findings Xenografts—especially pig islets—offer a logical alternative source for islets. Current preclinical studies have revealed problems such as optimal islet source, zoonosis, and immune rejection. These issues are slowing clinical application.
Summary Genetically modified pigs, encapsulation devices, and new immune-suppressive regimens can confer graft protection. In addition, extrahepatic transplant sites are showing promising results. Notwithstanding few approved clinical human trials, and available data from non-human primates, recent reports indicate that porcine islets are closer to be the promising solution to cure diabetes.

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Introduction

Diabetes mellitus (DM) is "a group of metabolic disorders, characterized by hyperglycemia due to deficient insulin release, peripheral insulin resistance or both." The distinctive feature in type 1 diabetes (T1D) is the absolute lack of insulin secretion due to immune destruction of ß-cells. Hence, it is essentially accompanied with long-term complications, and the most prominently affected organs are the heart, kidneys, eyes, nerves, and blood vessels [1]. The International Diabetes Federation (IDF) estimated the number of adults suffering from DM in 2015 by 415 million: this number is expected to increase to 642 million patients in 2040 [2]. During 2015, it was estimated that one in 11 adults became diabetic, and half of these diabetic patients were undiagnosed and unaware of the complications related to chronic hyperglycemia. Moreover, the health expenditure on diabetes worldwide was estimated to be at least USD 673 billion and expected to spike towards USD 802 by 2040, showing that diabetes became a pandemic, and associated morbidities are not the only impacting factors; there are also socioeconomic influences that affect both patients and health care systems [3, 4]. Despite the recent advancements in exogenous insulin manufacturing and the wide array of glucose monitoring systems, unaware hypoglycemia, and glucose level excursions are still the most undesirable complications of diabetes that cannot be fully ameliorated, even with the tight insulin regimens and extensive monitoring.

β-Cell Replacement

A potentially effective alternative to daily insulin injections in T1D is to transplant insulin-producing tissue to reestablish the natural physiological system for glucose homeostasis. Ideally, this will confer endogenous insulin production that resembles the pancreas's response to glucose excursions, eventually leading to long-term insulin independence, normalization of glycated hemoglobin (HbA1c) levels, and prevention of hypoglycemic episodes and might even reverse the metabolic and neurovascular complications of diabetes. Early trials of whole or partial pancreas transplantation often with simultaneous kidney transplant were carried out by Orloff [5], who outlined at least two major conditions where patients with T1D might benefit from a pancreas transplant. Firstly, are patients who need to receive a kidney transplant due to end-stage renal disease, and in this case, a pancreas transplant was considered to be a way to prevent the inevitable deterioration of the new kidney. Secondly, and far more common, are patients with long-standing T1D exhibiting chronic diabetic complications.

In 1966, William Kelly and Richard Lillehei performed the first whole pancreas transplant—simultaneously with kidney transplant at the University of Minnesota. The patient remained insulin-independent for 6 days; after that, the patient had to receive exogenous insulin due to the massive doses of steroids prescribed to prevent graft rejection. Later, the patient developed more post-operative complications, eventually both grafts had to be removed, and the patient died from pulmonary embolism [6]. By the late 1970s, surgeons started to examine the feasibility of segmental pancreas transplantation, to mitigate the immune reaction towards the graft. The longest duration where the recipient remained insulin-independent was 18 years [7]. Pancreas is usually transplanted simultaneously with kidney, or after previous kidney transplantation, and can be transplanted alone in preuremic patients. Recent reports show that 5 years insulin independence rates achieved by islet cell infusions are comparable to rates obtained by solid organ transplantation. Nonetheless, the massive perisurgical burden—such as sepsis, thrombosis, and anastomosis leakage—in addition to complications associated with pancreatic ductal drainage [8, 9, 10•], renders whole organ transplantation a least favorable replacement therapy.

Clinical Islet Transplantation

In contrast to whole pancreas replacement, islet transplantation is a minimally invasive procedure that ameliorates the disease similarly by eliminating the need for exogenous daily insulin injections, without the risk of major surgical procedures. From 1987 to 1998, 300 patients with T1D received a human islet transplant [11]. The International Islet Transplant Registry reported that 40% of the islet grafts lost their function within weeks of the transplant and only 8% of patients remained off insulin for 1 year [11]. There were some centers, including Edmonton, which had a small percentage of patients who achieved long-term insulin independence [12–14].

As reported in 2000, seven islet transplant recipients in Edmonton attained insulin independence by receiving freshly isolated islets from multiple donors and steroid-free anti-rejection therapy—a procedure known as the Edmonton Protocol [15–17]. This protocol set the standard worldwide and now many other groups have attained similar success [18–20], and recent data are showing an increase in median insulin independence periods, associated with massive reduction of hypoglycemic episodes [21, 22].

Clinical Application of Porcine Islet Xenografts

The World Health Organization (WHO) defines xenotransplantation as "any procedure that involves transplantation, implantation or infusion into a human recipient of (i) live cells, tissue or whole organs from non-human source, or (ii) human body fluids, cells, tissues or organs that had ex vivo contact with live non-human animal cells, tissues or organs" [23].

As concluded from current reports of clinical allotransplantation, the key for any successful transplant can be concluded in three main goals:

1. Finding a virtually unlimited donor tissue source, with similar physiological characteristics,
2. Achieving better immune protection and/or tolerance for donor tissue, and
3. Finding the optimal islet graft implantation site.

Therefore, in many current transplant studies, researchers are trying to fulfill this triad, to overcome the increasing demand of tissue for transplantation and the scarcity of human donors.

Xenotransplantation was practiced since the seventeenth century, and Cooper [24] referred in his report to clinical attempts where animal cells/tissues were used in treatment of human patients. Most of these trials failed, while some demonstrated unexpected success. For more than 90 years, porcine insulin has been used as a routine replacement therapy for patients with diabetes. With only one different amino acid residue from the human counterpart, porcine insulin was considered the optimal exogenous replacement therapy for diabetes. Novo Nordisk introduced the unpurified porcine insulin in 1920s and was able to produce it glucagon-free by the 1950s. At the late 1970s, the "very pure insulin" was introduced to clinical practice, diminishing the problems of lipoatrophy/hypertrophy [25]. In addition to insulin, porcine biological heart valves have been used for heart valve replacements [26].

There is a strong rationale to pursue the use of porcine donors for clinical islet xenotransplantation, including: (1) unlimited availability of porcine islets, increasing access to islet transplants and eliminating waiting time; (2) the reproducibility and quality of preparing porcine islets, predictably high and not compromised by comorbidity, brain death, and ischemia related to human islets; (3) porcine insulin has been used to treat human diabetes for more than 60 years; (4) porcine islets respond to glucose in the same physiological range as do human islets; (5) new techniques allow genetic manipulation and cloning of pigs, if it proves necessary or advantageous to do so; and (6) porcine islets are a potential therapy for highly allosensitized patients [27]. Thus, the risk-benefit ratio of porcine islet grafts make them a major therapeutic option to the currently used human islet grafts.

Reproducible isolation of large numbers of islets from adult pigs has been challenging, since adult porcine islets are fragile and difficult to maintain in culture. In recent years, however, there have been some improvements in the methodology and reagents used to isolate adult pig islets [28–33]. Yet, the potential disadvantages of adult porcine islets such as inefficiencies and variability of the isolation process and the practical considerations of maintaining large adult herds make them less desirable transplant donors. Because of these problems, many researchers have focused on developing a translational strategy to use neonatal porcine islets (NPI) instead, to treat patients with T1D. In 1996, Korbutt and his group reported a simple, inexpensive, and reproducible method to isolate large numbers of neonatal porcine islets [34]. These islets are comprised of differentiated endocrine and endocrine precursor cells that both in vitro and in vivo have the potential for proliferation and differentiation and have been shown to reverse hyperglycemia in immunodeficient mice [34], allogeneic outbred pigs [35], and in non-human primates [36, 37]. Furthermore, NPI possess numerous advantages over their adult counterparts, as they exhibit resistance to hypoxia [38], human pro-inflammatory cytokines [39], hyperglycemia [40], and islet amyloid deposition [41], as well as their inherent ability to differentiate and proliferate [34] and achieve transplant tolerance induction in diabetic mice [42]. Taken together, these observations clearly indicate that neonatal porcine islets are a promising tissue source for clinical islet xenotransplantation.

In 1995, a Swedish group led by Groth and colleagues transplanted ten patients with T1D with fetal porcine islets [43, 44]. Although no patient became insulin independent, serum porcine C-peptide was detected [43] as well as surviving islet cells within graft biopsies [44]. Moreover, subsequent follow-up of these patients demonstrated no infection of porcine viruses as a test of the safety of this procedure [45, 46]. The New Zealand Government has also approved clinical trials for the transplantation of neonatal porcine islets in patients with T1D, and these initial studies were conducted by Elliot and colleagues at Living Cell Technologies (http://www.lctglobalcom). To date, this group has transplanted 14 non-immunosuppressed patients with T1D with microencapsulated neonatal porcine islets and was able to alleviate hypoglycemic unawareness in these patients [47, 48]. In addition to this metabolic improvement, none of the recipients exhibited any evidence of infection with porcine viruses, thereby further demonstrating the safety of this procedure. Taken together, these studies provide evidence for the clinical feasibility of neonatal porcine islet transplantation.

Challenges for Porcine Islet Xenograft Survival

IBMIR

Instant blood-mediated inflammatory response (IBMIR) is thought to be a non-specific/non-immune-mediated inflammatory response that results in islet destruction when transplanted directly in the blood stream. It is a significant obstacle in human islet allotransplants, as the portal vein is the standard site for current islet transplantation protocol [49]. IBMIR is thought to be related to tissue factors expressed by isolated islets that stimulate clotting cascades, platelet aggregation, and complement activation. A recent report proposes that xenogeneic-induced IBMIR is platelet independent and involves multiple simultaneous mechanisms and activation pathways, leading to eventual leukocyte/macrophage infiltration, and the ominous fate of inevitable graft loss [50, 51]. Although decreasing the load of xenoantigens by using islets obtained from α1,3-galactosyltransferase gene-knockout (GTKO) pigs has shown better graft survival than wild-type islets, it failed to provide long-term protection against host response [52]. Despite the possibility of experimental control of complement activation via cobra venom factor, and platelet aggregation and coagulation by anti-platelet agents and low molecular weight heparins, these in vitro strategies are not proven safe to be used clinically, and other methods should be investigated to make sure that it is clinically applicable [53, 54].

Donor Age

The age of the donor pig is one of the debatable factors when it comes choose what islets should be used in xenotransplants. As denoted previously, many research groups favor adult pigs, as it can yield high number of adult porcine islets, up to 800,000 islet equivalents per isolation from a single pig's pancreas [55]. These islets are mature and expected to correct diabetes immediately, or within few days, in the recipient [56]. Nonetheless, difficulties in isolation and fragility of the islets during culture make them challenging to use.

On the other hand, neonatal porcine islets are resistant to hypoxia, hyperglycemia, and pro-inflammatory cytokines, and

with a reproducible and simple protocol for isolation, relatively low cost of herd housing, and feasibility of raising in a designated pathogen-free facility, neonatal porcine islets have many benefits over adult porcine islets [34]. When implanted in mice, it is noted that neonatal porcine islets require at least 6–8 weeks to correct diabetes [34]; however, when implanted in allogeneic pigs [35] or non-human primates [36], neonatal porcine islets can correct diabetes with 2 to 3 weeks. This difference in the time to correct diabetes is likely related to the poor efficacy of porcine insulin in mice [57].

Some studies suggest the benefits of fetal porcine islets, such as the incomplete formation of contaminating exocrine tissue, and resistance to hypoxic/ischemic injury makes their isolation easy [58]. However, they pose the same shortcoming of delayed function due to their immaturity. Also as pointed below, their expression of αGal is extremely high, which makes them a target for imminent rejection. Finally, recovery of fetal porcine islets is very low relative to neonatal or adult pancreas, a single transplantation will require more than one fetus, and the necessary sacrificing of the sow makes this approach more expensive [58].

Another potential islet source are juvenile pigs (8–10 weeks old), their housing logistics are easier than adult pigs, and they are capable of reversing diabetes in preclinical animal models [59•]. However, in vitro secretory stimulation assays revealed that there are no added significant benefits when compared to the adult porcine islets [60]. Table 1 demonstrates briefly some of the pig-to-primate preclinical experiments relevant to adult vs. neonatal porcine islets.

Galactose-α-1,3-Galactose

Galactose-α-1,3-galactose (αGal) is a carbohydrate present on the cell membrane of most of living cells, with the exception of primates, including humans. Exposure to αGal typically occurs at an early stage of life, via gut flora, resulting in formation of humoral immunity and reactive xenoantibodies. αGal is highly expressed on porcine endothelial cells, and in pig-to-primate whole organ xenotransplants, occurrence of hyperacute or acute immune rejection is the outcome.

It has been demonstrated that αGal expression is mostly present in immature fetal and neonatal porcine islets, and its expression is lower in more mature and adult porcine islets; moreover, its expression is not restricted to non-endocrine cells and can thereby be present on islet endocrine cells [71–73]. A strategy to overcome this impediment is the generation of GTKO pigs produced by targeted gene modification technology [74] that has been applied to neonatal porcine islets implanted in non-human primates [69]. This allows the production of αGal-free donor pigs, preventing this antigen from being targeted by the host's immune system. Additional gene manipulation and targeting using GTKO background pigs can be adventitious, if combined with expression of human complement-regulatory proteins (hCRPs). Transgenic pigs have been generated to produce islets that express hCD46 a complement-regulatory protein and have demonstrated function when implanted into non-human primates [64].

Table 1 Summary of pig-to-non-human primate islet xenotransplantation reports sorted by islet source (adult versus neonatal)

Year—group	Transplant site	Immune protection technique	Graft survival (days)
Adult			
1996—Sun [61]	Intraperitoneal	Microencapsulation	~800
2006—Hering [31]	Intraportal	Pharmacological	~180
2006—Dufrane [62]	Subcapsular space	Microencapsulation	~180
2007—Cardona [63]	Intraportal	Pharmacological	<345
2009—van der Windt [64]	Intraportal	Pharmacological + GKO	<400
2010—Dufrane [65]	Subcutaneous	Macroencapsulating device	~180
2014—Veriter [66]	Subcutaneous	Coencapsulation with MSC	~210
2014—Bottino [67]	Intraportal	Pharmacological + GKO	Up to 365
2015—Shin [33]	Intraportal	Pharmacological	150–600
Neonatal			
2005—Elliot [68]	Intraperitoneal	Microencapsulation	~250
2006—Cardona [36]	Intraportal	Pharmacological	140–260
2011—Thompson [37]	Intraportal	Pharmacological	90–340
2011—Thompson [69]	Intraportal	Pharmacological + GKO	~250
2012—Thompson [70]	Intraportal	Pharmacological	<100
2014—Hawthorne [52]	Intraportal	Pharmacological	~200

MSC mesenchymal stem cells, *GKO* gene-knockout, ~ an average

Zoonosis and Cross-species Contagion

A considerable limitation to bring porcine xenografts to the clinic is cross-species contamination and introduction to additional morbidities to the recipients. WHO has published a consultation report, listing the possible pathogens that might pose risks to human recipients [75]. Porcine endogenous retrovirus (PERV) is by far the most concerning pathogen in xenotransplantation, as it is present in all porcine cells. PERV is an endogenous viral element and the virus reversely transcripts its RNA into DNA sequence and embeds it into the host genome. There are three classes of PERV: A, B, and C. Both classes A and B are polytropic—they can infect and replicate in non-porcine cells—while class C possesses an ecotropic characters with narrow infectious spectrum [76].

Although multiple studies have been published regarding the capability and positivity of in vitro infection of human cell lines by PERV [77, 78], evidence and conclusions drawn from the few clinical trials and preclinical studies contradict these in vitro findings [43, 79–81]. Cheng [82] discussed the effect of Canadian and Australian public's opinions, regarding their socio-ethical point of view towards xenotransplantation and expanding the clinical use of animal cells and organs. Unfortunately, the outcome resulted in a ban in Australia on clinical xenotransplantation.

However, the development of designated-pathogen free facilities for raising herds is feasible and can control the introduction of unwanted pathogens to the "sterile" animals. Also, the widespread use of good manufacturing practices techniques, facilities, and protocols guarantee the uniform and reproducible quality control required for production of cell products for human use. WHO recommended as well some guidelines for donor/recipient screening, and stressed on the benefits of the communication between centers to exchange information as good tools to examine cross-species contamination. Finally, follow-up for patients and preclinical experimental subjects is a paramount and, all together, are encouraging steps towards more clinical trials of xenotransplantation [83].

Strategies to Improve Porcine Islet Xenograft Survival

Pharmacological Immunosuppression

Earlier, corticosteroids were considered the backbone of any chemical immunosuppressive regimen, due to their superior capabilities to inhibit the immune system. However, this came on the cost of other deleterious global side effects, especially when used chronically in multi-morbidity patients. In modern era, new agents and regimens used in immunosuppression exclude corticosteroids, and as proven by experimental reports, they enabled the sustenance of islet allografts survival in recipients. However, they are still non-patient-friendly agents that pose numerous undesired adverse side effects. Ironically, an effective new agent prescribed routinely, the calcineurin inhibitor tacrolimus, is known to be nephrotoxic and diabetogenic and may adversely affect islet vascularization post-transplantation [84].

The concept of adding protective agents and preconditioning of the islets prior to transplantation is suggested to protect the islets from stress-induced apoptosis and tacrolimus-related toxicity. A study published recently by Gala-Lopez reports that using anti-freeze proteins analogs, also known as anti-aging glycopeptides (AAGP) enhances the survival of engrafted islets. AAGP reduced oxidative stress and interleukin (IL) 1ß and 6 expressions, lowered apoptosis, and enhanced insulin secretion, in both human and murine islets [85]. Alternative method of selective immune suppression is the use of unique and specific monoclonal antibodies (mAbs). This employs the concept of "selective targeting" of receptors and/or ligands involved in the process of graft immune rejection. Examples of these methods were reported in 2006. In two separate studies, Cardona [36], and Hering [31] used specific CD154/CD40L mAbs, to suppress activated T cells in non-human primates (NHP) transplanted with islet xenografts, derived from adult and neonatal pigs, respectively. Although its effective, there are reports about the thrombotic effects of CD154 mAb that preclude its usage in the clinic. Adopting this concept, more selective agents that target specific pathways with more safety outcomes are being explored.

Immuno-isolation

Immuno-isolation or containment of individual/few islets by microencapsulation or numerous islets by macroencapsulation in a polymer or a chamber is considered a valuable method of immune isolation. Early studies of islet macroencapsulation were reported in the mid 1970s, where islets were placed in hollow synthetic capillaries. These capillaries were later connected to vascular system of diabetic rats, and blood flowed inside the capillaries allowing oxygen, nutrients, wastes, and cell products to be exchanged across the capillary walls. However, over time, the capillaries became occluded due to thrombosis and the islet grafts subsequently failed [86]. Over the past 20 years, extensive research has been done to develop better macroencapsulation devices without having adverse side effects on the islet grafts. Many prototypes of devices have been investigated, such as vascularized bioartificial pancreas devices or diffusion chambers. TheraCyte™ is a diffusion chamber that possesses the advantage of having a double layer of polyester-Biopore membrane that allows it to be implanted subcutaneously thereby permitting diffusion from the neovascularization surface. TheraCyte™ devices have been shown to reverse diabetes in rodents and prolong protect islet allograft rejection [87, 88].

The concept of islet microencapsulation began in 1964 by Thomas Chang [89]. He proposed the theory of an "artificial cell" and hypothesized that microencapsulation would not only protect cells against immune rejection but also increase the exchange surface area between the encapsulated cells and surrounding environment, thus enhancing the exchange process [89]. The usage of alginate as a common biopolymer in islet microencapsulation was reported in 1980 [90], where encapsulated islet xenografts were capable of survival and controlling elevated blood glucose in diabetic rats. Since then, multiple reports regarding usage of alginate-encapsulated islet xenografts have been published [91–95], demonstrating the proof of concept. Purity of alginate, cross-linking molecules, surface coatings, and transplantation site are few of many factors that are involved in success and survival of microencapsulated islets. Recently, a group in Massachusetts, USA, published a report about size and shape of microcapsules influence the foreign body immune response in rodents and NHP [96•]. Against what was expected, the larger diameter islet-containing alginate capsules showed significantly lesser fibrous overgrowth and foreign body immune reaction, than their smaller counterparts. This enforces the need to perform similar trials using human patients, to investigate this paradox and see whether the capsules will show the same results or not.

Transplant Site

Transplantation of islets into the portal vein is often associated with life-threatening intraperitoneal bleeding [97], portal vein thrombosis, and hepatic steatosis [98, 99]. The liver may also contribute to the gradual attrition of chronic islet graft function [98]. Pursuit for an alternative, safer site for islet transplantation is therefore desirable and an important issue to address [100]. Furthermore, the use of porcine islets or ß-cell grafts derived from human embryonic or pluripotent stem cells will likely require that these grafts can be retrievable for safe and effective clinical treatment. This prerequisite severely limits the liver's capacity to safely house future xenogeneic ß-cells and insulin-producing cells derived from human embryonic or pluripotent stem cells. Therefore, the concept of developing retrievable scaffolds and devices is a key component for ß-cell replacement therapy for T1D. This model involves "seeding" individual islets onto three-dimensional (3-D) scaffolds that are often made of biopolymer fibers that provide a 3-D support structure for the islets that is deprived during the isolation procedure, and thereby mimics the natural pancreatic microenvironment. It is conceivable that islets will engraft more effectively in a 3-D than 2-D environment, and the scaffolds improve viability by promoting cell adherence and nutrient diffusion, thereby increasing islet survival immediately after transplantation. In addition, a polymer scaffold will prevent direct exposure to blood in the first few weeks after transplantation thereby attenuating IBMIR. Three-dimensional synthetic scaffolds have been reported to provide a protective environment during in vitro culture by preventing islet aggregation and thereby enhancing viability and function [101, 102]. Similar beneficial effects were observed when human islets were cultured on decellularized lung-derived microscaffolds [103]. In 2005 Dufour demonstrated that syngeneic mouse islets seeded onto scaffolds composed of poly-(glycolide-lactide) co-polymer fibers successfully corrected diabetes [104]. Ellis has also developed a highly vascularized matrix for the ectopic transplantation of neonatal porcine islets into the subcutaneous space of mice [105, 106].

The subcutaneous space is an attractive site for islet transplantation, yet poorly vascularized, which is often associated with modest ß-cell survival. It is clear that the subcutaneous site requires optimization to advance the neovascularization process thereby minimizing cell loss in the early post-transplant period. Recently, the Shapiro lab published a "device-less" approach that transforms the inhospitable subcutaneous tissue into a viable and vascularized engraftment location through the temporary implantation of an angiocatheter. The foreign body reaction to the in situ catheter culminates in a cloaking of the catheter in a vascularized collagen scaffold into which the cellular graft is infused, while the simultaneous catheter withdrawal extinguishes this reaction. The Shapiro group has demonstrated that this site is efficacious in reversing diabetes post-transplant of both human and rodent islets, even in models of aggressive foreign body reaction and alloimmunity [107, 108].

Conclusion

The physiological similarities of porcine islets with human islets make them an excellent choice to replace the scarce, non-consistent human islet allografts. Yet, with only few clinical pig-to-human transplants, definite conclusions regarding the consistency and safety cannot be drawn. However, with preclinical experiments, especially involving porcine islets implanted into non-human primates (Table 1), a clinical path is becoming even closer for porcine ß-cell grafts. Pigs represent the most accepted source for islet cell replacement. Their rate of reproduction, the capability of raising them in designated-pathogen free facilities, and the emerging technologies of gene manipulations are just few merits in favor of this "virtually" unlimited source.

Despite the public comfort towards using them—not only as food source but also in biomedical field—there are some obvious concerns regarding ethical and safety issues. Although scientists were able to map a list of potential porcine pathogens, there is no enough data from clinical trials to encourage further advancements in xenotransplantation. The devastating experience swine flu has polarized the public

opinion against xenografts, especially if tissue is coming from pigs.

More scientific hurdles were encountered during preclinical experiments, such as the host's immune system, and disadvantaged transplant sites. However, some of the previously stated ideas and solutions are being extensively studied, with incremental advancement. Also reports from International Xenotransplantation Association and WHO are drawing guidelines and communication tools between different centers and researchers around the globe. The main goal of these guidelines is to establish an ethical platform, based on public involvement in decision-making, and to ensure that all experiments carried out are driven by concept of patient safety.

Compliance with Ethical Standards

Conflict of Interest Bassem F. Salama and Gregory S. Korbutt declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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