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Review

Islet Xenotransplantation for the Treatment of Type 1 Diabetes

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Abstract:

More than 10 million people worldwide suffer from type 1 diabetes mellitus (T1DM). Allogeneic islet transplantation has been established to prevent severe hypoglycemia in unstable T1DM patients although there is a serious shortage of donors. Islet xenotransplantation using porcine islets is a promising solution to this issue. Porcine islets offer several advantages over human islets, including unlimited and on-demand supplies, a higher quality of islets from healthy donors, greater safety with designated pathogen-free (DPF) donor pigs and the potential to improve survival with gene modification technologies. Compared with embryonic stem (ES) cell- and induced pluripotent stem (iPS) cell-derived insulin producing cells, porcine islets are associated with a depth of clinical experience and evidence of safety and efficacy. One of the major concerns of islet xenotransplantation is zoonotic infection. DPF status donor pigs and monitoring for the presence of porcine endogenous retrovirus (PERV) are necessary to prevent this complication. In addition, compliance with regulatory guidance is important to prevent the spread of zoonotic infections.A clinical trial of encapsulated porcine islet xenotransplantation for the treatment

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of T1DM under comprehensive regulation was reported in 2014. This study demonstrated the safety of islet xenotransplantation although the efficacy was limited. In 2016, encapsulated porcine islet xenotransplantation was reported to provide clinical benefit for T1DM patients. Encapsulated porcine islet xenotransplantation seems a promising therapeutic approach and recent scientific advances, including immune suppression protocols, gene editing technologies, and blastocyst complementation technology, offer the potential to further promote this technique for the treatment of T1DM.

Keywords
Islet xenotransplantation; porcine islets; donor shortage; porcine endogenous retrovirus (PERV); designated pathogen free pig; severe hypoglycemic episodes; type 1 diabetes

1. Introduction

Intensive insulin therapy is the standard treatment for type 1 diabetes mellitus (T1DM). Although this approach reduces HbA1c, the increasing the frequency of hypoglycemic events is a disadvantage [1]. Hypoglycemia can be a serious issue; especially hypoglycemia with a lack of unawareness and severe hypoglycemia, which are life-threatening complications. Beta-cell replacement therapy, including pancreas and islet transplantation, is the best treatment to avoid severe hypoglycemia while maintaining normal HbA1c [2]. Islet transplantation alone is the most frequently adopted form of islet transplantation, while simultaneous pancreas and kidney transplantation, which has been established for the treatment of diabetic nephropathy, is the most frequently adopted form of pancreas transplantation. Since pancreas transplantation requires major surgery, pancreas transplantation alone for the treatment of severe hypoglycemia is less common.

Donor shortage is the major limitation to the promotion of islet transplantation for the treatment of unstable T1DM. Islet xenotransplantation using porcine islets is an attractive approach to overcoming the challenge of donor shortage [2].

In this review article, we describe the current status of islet transplantation and future direction of islet xenotransplantation.

2. Current Status and Challenges to Allogeneic Islet Transplantation

The first clinical allogeneic islet transplantation was performed at the University of Minnesota (USA), but with limited efficacy [3]. Since then, islet transplantation had been conducted as an experimental treatment. In 2000, a group from the University of Alberta (Canada) demonstrated that all seven T1DM patients who received islet transplantation achieved insulin-independence [4]. In this study, freshly isolated islets were transplanted on multiple occasions using an induction and maintenance immunosuppression; this method is known as the Edmonton protocol, for which the details of long-term efficacy was published in 2005 [5]. Insulin-free status was maintained in less than 10% of patients; however, excellent glycemic control was maintained in more than 80%. Since then, islet transplantation has been considered to maintain excellent glycemic control in unstable T1DM patients. Recently, the outcomes of a Phase 3 clinical trial of allogeneic islet

transplantation were published [6]. In this clinical trial, HbA1c <7% and no severe hypoglycemic episodes (SHEs) until 1 year after the first islet transplantation was used as a composite primary endpoint. This study clearly demonstrated that allogeneic islet transplantation effectively prevented SHEs with excellent maintenance of HbA1c levels. In addition, data from the collaborative islet transplant registry show the long-term effects of SHE prevention (**Table 1**). The rate of SHE prevention is higher than the positive C-peptide rate, indicating that minimum insulin secretion below the detection level prevents SHEs after allogeneic islet transplantation.

Table 1 Effect of allogeneic islet transplantation

	C-peptide-positive		Prevention of severe hypoglycemic episodes (SHE)	
	1 year % (N)	3 years % (N)	1 year % (N)	3 years % (N)
Islet transplant alone (ITA)	80 (599)	61 (376)	94 (431)	88 (267)
Islet after kidney transplant (IAK)	76 (133)	69 (109)	96 (111)	93 (75)

More than 10 million people are affected by T1DM, with donor shortage representing a serious challenge to the promotion of allogeneic islet transplantation. We have performed islet transplantation using a single donor [7], non-heart beating donor [8] and a live donor [9] but despite these approaches, it is not possible to overcome the issue of donor shortages using human organ donors.

3. Overcoming the Donor Shortage

Islet xenotransplantation using porcine islets is a promising solution to the donor shortage issue. Porcine islets offer several advantages over human islets including unlimited and on-demand supplies, higher quality of islets from healthy donor, greater safety with designated pathogen-free (DPF) donor pigs and the potential to improve survival with gene modification technologies (**Table 2**).

Table 2 Advantages of porcine islets

Advantages	**Explanation**
Unlimited and on-demand donor supply	No need to wait for a brain-dead donor
Healthy donor	Completely healthy donor can be used
Gene modification	CRISPR/Cas9 system can be used to edit genes reliably to improve quality and reduce immunogenicity
Clinical experience	Initiated in the1990s

Compared with embryonic stem (ES) cell- and induced pluripotent stem (iPS) cell-derived insulin producing cells, porcine islets are associated with a depth of clinical experience and evidence of safety and efficacy since their initial use in the 1990s.

4. History of Islet Xenotransplantation

The first islet xenotransplantation was reported from Sweden in 1994 [10]. Ten insulin-dependent diabetic kidney-transplanted patients received fetal porcine islet-like cell clusters (ICCs) transplanted under immunosuppression via the portal vein in eight patients and under the kidney capsule in two patients. Four patients who received ICCs via the portal vein secreted porcine C-peptide into the urine for 200 to 400 days. This study demonstrated porcine ICCs can survive following transplantation into humans.

In 1996, encapsulated neonatal porcine islets were transplanted into a T1DM patient in New Zealand [11]. Since the islets were delivered in immune-isolated capsules, no immunosuppressive drugs were used. Insulin-stained encapsulated islets were identified 9.5 years after transplantation [11], thus indicating the long-term survival potential of encapsulated porcine islets.

In 2005, a study of 12 adolescents with T1DM who received macroencapsulated neonatal porcine islets and Sertoli cells was reported [12]. Two devices were initially implanted subcutaneously and left for 2 months to allow the formation of vascularized collagen tissue. Subsequently, islets (250,000) and Sertoli cells (30–100) were transplanted into the devices. Eleven patients underwent a second transplantation 6 to 9 months after the first procedure. Daily insulin doses were reduced in six patients and increased in six patients. Of note, two patients achieved insulin-independence. However, this clinical trial was criticized for a number of reasons, including the participation of young patients [13, 14].

5. Porcine Endogenous Retrovirus (PERV) Infection

When co-cultured with pig kidney cell line PK-15 infected with PERV, it has been demonstrated that the virus can be transferred to human kidney 293 cells [15]. Van der Laan et al. also demonstrated that porcine pancreatic islets release PERVs, which infected human cells in culture [16]. Thus, the risk of PERV infection related to porcine islet xenotransplantation in immunosuppressed patients became a major concern leading to a substantial reduction in clinical xenotransplantation. However, a rigorous survey among the patients who received porcine organs or cells and their close contacts [17] revealed that there were no xenotransplantation-related PERV infections. Since then several reports have refuted the existence of PERV infection after porcine xenotransplantation [18], leading to the publication of a consensus statement among key opinion leaders related to the prevention of PERV infection in this context [19].

Detecting PERV infected cells after co-culture of porcine cells and human kidney 293 cells is the standard method used to assess PERV infectivity. When the absence of PERV infection is confirmed, the pig is assigned non-transmitter status, which is required for medical grade pigs. There are three types of PERV: PERV-A, B and C, with PERV-A and B incorporated into all pig genomes. To prevent PERV infection, donor pigs should have low copy numbers of all PERVs and PERV-C-free pigs are preferable [19].

After xenotransplantation, monitoring of PERV copy numbers in the patients and their close contacts is required. PERV may be detected in the transplanted porcine cells or organs (known as the chimeric condition) and it is necessary to distinguish between the chimeric condition and infection. This is achieved by the comparison of PERV copy numbers with those of a ubiquitous porcine gene (for example, the cytochrome oxidase gene: COX gene) [19]. Positive detection of ubiquitous porcine genes indicates micro-chimerism, whereas positive detection of PERV at higher

levels than the ubiquitous porcine gene indicates PERV infection. Some patients who received porcine cell transplantation were reported to be micro-chimerism-positive, but none were PERV infection-positive.

6. DPF Pigs

The source pig must be depleted of infectious agents that can be transmitted to the recipient and cause disease [20]. Regulatory guidance states that donor animals must qualify for DPF status [20]. The term DPF is used to describe animals, animal herds, or animal facilities that have been rigorously documented to be free of specified infectious agents (bacteria, fungi, protozoa, and viruses) using well-defined routine tests performed conducted according to standard operating procedures following the implementation of practices of herd husbandry and veterinary care to assure the absence of the designated pathogens [20]. Importantly, the list of designated pathogen can vary depending on location and the emergence of new or modified pathogens over time [20]. Therefore, pathogens that do not exist in the area are not included in the designated pathogen list. It is important to create a designated pathogen list that is appropriate to the area to avoid the need to conduct overwhelmingly exhaustive pathogen checks while ensuring all possible pathogens are covered. Among the published lists of designated pathogens, the list in New Zealand is the shortest because the country has fewer pathogens compared to other areas (**Table 3**) [18].

Table 3 Designated pathogen list for New Zealand herds

Bacteria	Viruses	Protozoa
Leptospira tarrasovi	PCV2	Toxoplasma
Leptospira hardjo	PCV1	
Leptospira pomona	PLHV2	
Mycoplasma	RotaV A-C	
hyopneumoniae	Reo V	
Campylobacter	PTV	
Isospora	PEVB	
Cryptosporidium	PHEV	
Yersinia	HEV	
Escherichia coli K88	BVD	
Salmonella	AujD	
	PPV	
	PRRSV	
	EMCV	

PCV2, Porcine Circovirus Type 2; PCV1, Porcine Circovirus Type 1; PLHV2, Porcine Lymphotrophic Herpesvirus Type 2; PCMV, Porcine Cytomegalovirus; RotaV A-C, Rotavirus A, Rotavirus B and Rotavirus C; ReoV, Reovirus (all types); PTV, Porcine Teschovirus; PEVB, Porcine Enterovirus B; PHEV, Porcine Hemagglutinating Encephalomyelitis Virus; HEV, Hepatitis E Virus; BVD, Bovine Virus Diarrhea; AujD, Aujesky's Disease; PPV, Porcine Parvovirus; PRRSV, Porcine Reproductive and Respiratory Syndrome Virus; EMCV, Encephalomyocarditis Virus.

To ensure DPF status of the donors of neonatal porcine islets for clinical use, three levels of screening have been applied [18] that involve sequential checking of the donor herd, the donor animals and the products. This vigorous checking system is important to avoid zoonosis.

7. Non-human Primate Studies of Porcine Islet Xenotransplantation

In 2006, two reports indicated the potential of porcine islet transplantation to reverse T1DM in non-human primate (NHP) models. Hering et al. demonstrated that intraportal transplantation of NHPs with wild-type adult porcine islets reversed T1DM for more than 100 days. CD25-specific and CD154-specific monoclonal antibodies, FTY720 (or tacrolimus), everolimus and leflunomide were used for immunosuppression [21]. Groups from Emory University and the University of Alberta demonstrated that transplantation of neonatal porcine islets with a CD28-CD154 costimulation blockage reversed T1DM for more than 140 days in a NHP model [22].

In 2015, a group from Seoul National University demonstrated that wild-type adult porcine islet transplantation reversed T1DM for more than 6 months in four out of five NHP. Islets were isolated from DPF miniature pigs and transplanted into streptozotocin-induced diabetic rhesus monkeys via the portal vein. Cobra venom factor, ATG, anti-CD154 monoclonal antibody and low dose sirolimus were used to prevent rejection. Impressively, the longest graft survival exceeded 600 days [23].

These three reports demonstrated the ability of porcine islets to reverse diabetes in a NHP model; however, all three protocols involved the use of a CD-154-specific monoclonal antibody that is not clinically available due to its side-effects in humans. A replacement for CD-154-specific monoclonal antibodies is, therefore, required.

In 2018, a group from Seoul National University demonstrated that an anti-CD40 antibody can be used as a replacement for the CD154-specific monoclonal antibody [24], although it is less effective. Nonetheless, clinically available immunosuppressive protocols have been established for porcine islet xenotransplantation in a NHP model [24].

Immune isolation of islets without immune suppression is an attractive approach to overcoming the problem of immunogenicity in porcine xenotransplantation. Delivery of porcine islets in an alginate-coated collagen matrix cellular device showed correction of STZ-induced diabetes in five NHPs (5 out of 5, 100%) for up to 6 months [25]. Two of these animals received second transplants, and diabetes was controlled for another 5 months. Further studies using the same device showed that co-transplantation of mesenchymal stem cells and islets [26] improved the oxygen supply to encapsulated islets, with a slight improvement in long-term graft survival.

8. Clinical Application of Porcine Islets

Encapsulated neonatal porcine islet xenotransplantation has been conducted clinically in New Zealand and Argentina. The inclusion and exclusion criteria of the most recent trial are shown in **Table 4** (ClinicalTrials.gov Identifier: NCT01739829).

Table 4 Inclusion and exclusion criteria of a clinical trial of encapsulated porcine islet xenotransplantation

Inclusion criteria:

1. Adults (males or females) in the age range 18 to 65 years.
2. Diagnosis of T1DM (minimum duration of 5 years) in accordance with the American Diabetes Association's criteria. Patients should have been treated continuously with insulin since diagnosis (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 2002).
3. Patients with established brittle T1DM and a well-documented chronic history of metabolic instability who cannot achieve acceptable metabolic control (which may include treatment with the use of a continuous insulin infusion pump) without experiencing multiple episodes of hypoglycemia, often with lack of unawareness.
4. Patients should have HbA1c ≥7% and ≤15% calculated as the average of the last four consecutive HbA1c readings during the 8-week baseline run-in period. The difference between the highest and lowest of the four HbA1c reading should not exceed 1.0%.
5. Plasma C-peptide <0.3 ng/ml following a glucagon stimulation test (Scheen et al. 1996).
6. If female, no childbearing capability (those who are more than two years post-menopausal or have undergone voluntary sterilization can be considered for enrolment).
7. Provision of written informed consent. Patients will be required to agree to comply with all tests and visits specified in the protocol, and they (and their partners/close contacts) will also be required to consent to long-term microbiological monitoring, which is an integral part of the study.

Exclusion criteria:

1. Type 2 diabetes, defined as age of onset >30 years and/or a history of treatment with oral hypoglycemic medication and/or insulin resistance (defined as an insulin dose requirement ≥1.2 U/kg/day).
2. Average HbA1c < 7% and >15% during the 8-week baseline run-in period.
3. Body mass index (BMI) ≥30 kg/m^2 or ≤9 kg/m^2.
4. Active infection, with plasma C-reactive protein ≥10 mg/L at baseline.
5. Previous receipt of an organ, skin graft, or other tissue transplant from a human or animal donor.
6. Treatment with immunosuppressive medication for another medical condition.
7. Previous history of peritoneal disease or abnormal findings at baseline laparoscopy.
8. Previous abdominal surgery, excluding uncomplicated appendectomy, cholecystectomy or cesarean section.
9. History of pelvic inflammatory disease or endometriosis.
10. Inability to tolerate oral medication or a history of significant malabsorption.
11. HIV antibody and/or risk factors for HIV infection.

12. Hepatitis C antibody-positive, hepatitis B surface antigen and hepatitis B core antibody-positive.
13. Kidney disease, defined as serum creatinine >130 µmol/L in men and >110 µmol/L in women and/or urinary albumin >500 mg/L and/or hematuria and/or active urinary sediment or casts.
14. Diabetes microvascular complications defined as untreated, potentially vision-threatening proliferative or pre-proliferative retinopathy or maculopathy; painful peripheral neuropathy; autonomic neuropathy manifesting as postural hypotension; gastroparesis or diabetic enteropathy.
15. Diagnosis of coeliac disease and history of gastrointestinal symptoms including chronic or recurrent diarrhea, malabsorption, weight loss and abdominal distension or bloating on exposure to gluten products in the diet.
16. Serious comorbid conditions that are likely to affect participation in the study.
17. History of drug, substance or alcohol addiction.
18. Any factor detected from psychometric evaluation at Visit 2 pre-transplantation during the screening period that may, in the opinion of the Clinical Psychologist, affect an individual's ability to participate fully in the study.
19. Any other condition that, in the opinion of the Investigator, may interfere with adherence to the study protocol, including dementia, mental illness, or a history of non-adherence to appointments or treatments.

In a New Zealand trial, four doses (5,000 IEQ/kg, 10,000 IEQ/kg, 15,000 IEQ/kg and 20,000 IEQ/kg) of encapsulated neonatal porcine islets were transplanted into the peritoneal the cavity without immunosuppressive drugs [27]. No PERV infection was detected [18]. Furthermore, the number of hypoglycemic episodes with a lack of unawareness were reduced in all groups at 1 year after transplantation, with the greatest efficiency observed in the low dose groups (5,000 IEQ/kg and 10,000 IEQ/kg). On the other hand, there were no changes in the HbA1c levels and daily insulin dose. To detect the efficacy of transplanted encapsulated neonatal porcine islets, Transplant Estimated Function (TEF) was calculated [28] using daily insulin dose (DIR: IU/kg) and HbA1c levels pre- and post-transplantation (tx) as follows:

TEF = [DIRpre-tx+HbA1c pre-tx/5.43]-[DIR+HbA1c/5.43]

A TEF value of 0.3 reflects C-peptide-positivity, and 0.5 reflects insulin-independent status. Average TEFs were 0.2, 0.0, 0.0 and 0.1 in the 5,000, 10,000, 15,000 and 20,000 IEQ/kg groups and one patient in the 5000 IEQ/kg group had a TEF value of 0.6, indicating insulin-independence. Although the safety of the intervention was suggested, only a limited number of patients showed clinical benefit in this trial.

After the New Zealand clinical trial, several modifications were introduced to improve clinical outcomes. The Ricordi islet isolation method [29] was introduced to improve the quality and quantity of isolated islets. Reversal of diabetes was confirmed in diabetic B6 mice following implantation of encapsulated neonatal porcine islets, with excellent glucose profiles observed in oral glucose tolerance tests (OGTT) conducted at day 32 post-transplantation [27]. Low doses (5,000 IEQ/kg and 10,000 IEQ/kg) of encapsulated neonatal porcine islets were transplanted twice.

It can be speculated that transplantation of large volumes of encapsulated islets into peritoneal cavity leads to aggregation as well as nutrient and oxygen deprivation, resulting in cell death.

In the Argentinian clinical trial, encapsulated neonatal porcine islets were transplanted into peritoneal cavity twice at doses of 5,000 IEQ/kg and 10,000 IEQ/kg [30]. Again, no PERV infection was detected in any of the patients [31]. Furthermore, significantly reduced HbA1c was achieved in 50% (2 of 4) of patients in the 5,000 IEQ/kg group after transplantation and significantly reduced daily insulin doses were achieved in 75% (3 of 4) of patients in the 10,000 IEQ/kg group. TEF values were also significantly increased in all patients. The frequency of hypoglycemic episodes with a lack of unawareness per month was significantly decreased in the 10,000 IEQ/kg group. OGTT performed 15 months after the first transplantation confirmed islet function in five patients (1 of 4 patients in the 5,000 IEQ/kg group and all 4 patients in the 10,000 IEQ/kg group). Therefore, this clinical trial demonstrated the clinical benefit of encapsulated neonatal porcine islet transplantation without immune suppressive drugs for the treatment of T1DM.

9. Next Steps

CRISPR technology facilitates simple and stable gene editing [32]. In fact, it was demonstrated that PERVs were completely eliminated with CRISPR technology [33], leading to the establishment of the venture company eGenesis, which specializes in the generation of PERV-free donor pigs for the provision of human compatible porcine cells.

Furthermore, creation of autologous functional islets by interspecies organogenesis has been reported [34]. In this study, iPS cells from a mouse were implanted into a blastocyst of PDX-1 knockout apancreatic rat. The islets isolated from the pancreas of the resulting neonatal rat were then transplanted into diabetic mice of the same strain from which the iPS cells were derived. The transplanted islets reversed diabetes in these mice without immunosuppression. Eventually, a human pancreas might be created inside a pig using the blastocyst complementation technology that enables autologous islet transplantation.

10. Conclusion

The establishment of allogeneic islet transplantation as the main treatment for unstable T1DM is limited by a donor shortage. Islet xenotransplantation is attractive solution to this problem and current clinical trials have shown safety and efficacy. The use of recent technological advances should improve the efficacy and promote the application of islet xenotransplantation for the treatment of T1DM in the clinic.

Author Contributions

Shinichi Matsumoto: Creating concept and design of this review paper, collection of relevant papers and analysis of collected papers, and writing this original manuscript; Masayuki Shimoda: Creating concept and design of this review paper, collection of relevant papers and analysis of collected papers, and revising the original manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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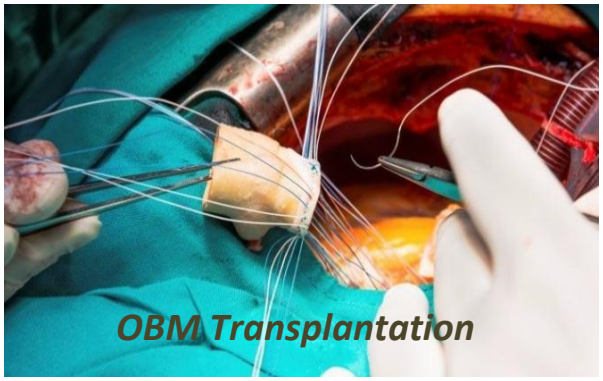

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