

New Advances and Future Direction of Islet Xenotransplantation for Type 1 Diabetes

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ABSTRACT

Type 1 Diabetes (**T1D**) is characterized by pancreatic beta (**β**) cell destruction through autoimmunity, leading to a gradual loss of endogenous insulin secretion and ensuing hyperglycemia. Current treatment methods for T1D include the administration of exogenous insulin or the replacement of β -cell mass through either pancreas or islet transplantation. Current β -cell replacement trials have reported a lower incidence of potentially fatal hypoglycemic episodes when compared to exogenous insulin therapy. Islet allotransplants have also shown success in establishing insulin independence during the first-year post-transplant, however, transplant recipients progressively become increasingly dependent on insulin and this therapy has been limited to a selected pool of patients due to a shortage of islet donors. The outcomes of the procedure have also been inconsistent, with the most success coming from highly experienced transplant centers.

Due to these inherent limitations of islet allotransplantation, xenotransplantation has been investigated as a possible alternative, since there are several potential advantages. Xenotransplantation has the potential of offering a reliable and consistent supply of islets. Having a readily available source of islets provides a significant advantage of being able to schedule the transplant procedure in advance. This is of great importance since most immunosuppression induction strategies require pre-dosing patients before the procedure. In addition, the development of specific pathogen free (**SPF**) and designated disease pathogen free (**DPF**) facilities and the propagation of animals with limited or no transmissible zoonotic diseases, make xenotransplantation the treatment of choice for T1D patients.

Keywords: Xenotransplantation; Type 1 Diabetes; Islet Transplantation; Transgenic Pig

INTRODUCTION TO TYPE 1 DIABETES AND TREATMENTS

Current Treatment for Type 1 Diabetes

Type 1 diabetes (**T1D**) patients lack adequate endogenous insulin secretion, caused by immune-mediated destruction of pancreatic beta (**β**) cells [1]. Current treatment for T1DM patients can take the form of either exogenous insulin injections several times a day, or replacement of β -cells by pancreas or islet transplantation, to restore normal blood glucose control. Good blood glucose control helps delay development and progression of chronic complications of T1D [2,3].

β -cells replacement has shown more reliability in achieving good glycemic control and preventing hypoglycemic episodes compared to exogenous insulin injection [4]. The first long term success was in 2000, when the Edmonton islet transplant group at the University of Alberta, Canada achieved insulin independence in 7 patients, using human cadaveric islets combined with a specific steroid-free immunosuppression protocol [5]. Islet transplantation results in fewer complications, with comparable patient outcomes and graft survival to whole pancreas transplant [6], which makes it an appealing alternative [7]. In 2005, University of Minnesota reported that out of the 8 islet transplant recipients, all became insulin independent and 5 out of 8 recipients remained insulin independent after 1 year. All 8 patients also had improved HbA1c levels and demonstrated sustained C-peptide production five years post-transplant [8]. Hering, et al. reported in a 2008 study that of 6 recipients with hypoglycemia unawareness who received one to two islet infusions with immunosuppression protocol, 5 were insulin-independent at 1 year, and 4 continue to be insulin-independent at a mean of 3.4 ± 0.4 years post-transplant [9]. Success of islet transplant has also improved over the years. The 7th Annual Report of CITR (Collaborative Islet Transplant Registry) showed a progressive improvement in achieving insulin independence at 3 years after transplant, from 27% in 1999–2002 to 44% in 2007–2010, and reported improvements in C-peptide levels, reduction of HbA1c, resolution of severe hypoglycemia exhibited, fasting blood glucose stabilization, and less islet reinfusion. In the 8th Annual Report, graft retention rates remains at 80% for 7-8 years depending on favorable factors (immunosuppressive therapy, patient age) [10].

Limitations of Cadaveric Human Islets

Widespread adoption of islet transplantation is limited by availability of cadaveric donors. Pancreases are first offered for whole pancreas transplantation before they're offered to islet isolation centers, because of the longer success record of whole pancreas transplant [11]. In contrast with optimal whole pancreas donor (young donors (<50 years old) with low body mass indexes (BMI <30)), older islet donors (>50 years old) with high BMI (>30) are preferred because of improved islet yield, viability and easier islet isolation process [12,13]. Another factor that negatively affect islet transplant include the associated adverse effects of current immunosuppressive protocols used to prevent transplant rejection [14].

To overcome donor scarcity, xenotransplantation, with the porcine model being the most widely studied due to the genetic similarities of porcine and human insulin [15], are being explored as alternative. Porcine insulin functions in human and are used clinically [16,17], as such, porcine islets should be a reasonable substitute for human islets.

THE XENO OPTION

What is Xenotransplantation?

Xeno or "foreign" transplantation can be defined as the implant, transplantation or infusion of living cells, tissues, or organs from one species to another [18,19]. Xenotransplantation includes a variety of different procedures that can be classified into three categories; external animal therapies, solid organ transplant, and tissue and cellular therapies, and transplants [20].

Islet transplantation is considered tissue and cellular therapies, which include the implant, infusion, or transplantation of animal cells into a human recipient to replenish or compensate for the patient's dysfunctional or diseased cells or tissue. Other examples of tissue and cell therapies are neurons, bone marrow and stem cells.

Although xenotransplantation has the potential to resolve the problem of human organ shortage, it also has the potential for transmitting infectious diseases, both known and undiscovered, from animals to humans [21].

Potential of Xenografts in Organ Transplantation

Porcine tissue offers a scalable source of organs and cells, and are physiologically similar to humans [22]. Over the years there has been an increase in the use of porcine organs and cells in transplantation research, largely due to the increasing availability of specialized pig models [23]. In nonhuman primates, porcine heterotopic heart grafts were reported to have a survival rate of 945 days (median: 298 days) [24]; while primates that received porcine kidney transplants showed function for 136 days [23,25].

One barrier for pig organs is coagulation dysfunction triggered by activation of the host's humoral immune system, resulting in thrombotic microangiopathy [26-29] and consumptive

coagulopathy secondary to antibody deposition in the donor organs [30-32]. This response may be related to molecular incompatibilities in the coagulation systems between pigs and humans [33]. Several solutions have been proposed, focusing on the genetic modification of the cell source, or of the complete organ itself [34]. Studies out of the Massachusetts General Hospital and Harvard Medical School have shown that the use of genetically modified pigs as a donor source for transplant can show improvements in graft function and survival [27]. This includes expression of human complement factors CD55 and CD59, along with the intravenous treatment of antithrombin III, which improved response to genetically modified kidney compared to normal pig kidneys [35]. In diabetic non-human primates transplanted with Gal-deficient islets expressing human CD46, human CD39 and/or human tissue factor pathway inhibitor (**TFPI**), the islets can maintain graft survival, function and establish normoglycemia for up to a year post-transplant [36]. Others examples of transgenic pigs were demonstrated by Klymiuk and by Mohiuddin [37,24].

Encapsulation by creating a biocompatible barrier around the transplanted islets have demonstrated long-term graft survival, without the use of harmful immunosuppression regimes [38]. The most promising encapsulation material is alginate. Encapsulated porcine islets transplanted into diabetic non-human primates resulted in significant reduction in daily insulin requirements when compared to un-transplanted controls [39]. A study by Dufrane, et al. showed survival and function of encapsulated porcine islet grafts up to 6 months post-transplant into *Cynomolgus* maccacus, with detectable C-peptide levels and anti-pig IgM/IgG 1 month after transplantation, although no significant impact on daily exogenous insulin dose after 1 year [40]. A major obstacle found with encapsulated islets transplant is opaque or cloudy capsules, indicating foreign body or immune response, which negatively affects islet survival by decreasing nutrient and waste permeability of encapsulated islets [41,42].

Potential Sources of Islet Donors for Clinical Xenotransplantation

Piscine islets

Tilapia fish islets, known as Brockmann bodies (BBs), can be easily and inexpensively harvested, while the fish is also easily bred [43,44]. BBs are separate organs located near the liver within a triangular region of adipose tissue [45-47]. BBs transplanted into streptozotocin-induced diabetic mice under the kidney capsule, restores and maintain long-term normoglycemia (>50 days) [43,48]; and this is replicated for up to 210 days in NOD-SCID mice [49].

Tilapia insulin differs from human insulin by 17 amino acids, thus requiring modification to become biologically active in human [43-46,50]. Pohajdak et al. achieved the “humanized” tilapia, a transgenic tilapia with Brockmann Bodies secreting [desThrB30] human insulin [51]. Transgenic tilapia can produce humanized insulin with stable inheritance through generations, and could become a viable donor source for clinical islet xenotransplantation [52].

Bovine islets

Bovine islet isolation is similar to human's, using collagenase digestion and density gradient purification, and are functional in diabetic nude mice [53]. Bovine islets can be cultured up to 4 weeks while maintaining glucose responsiveness [54]. Encapsulated bovine islets have also been tested successfully in non-immunosuppressed immunocompetent diabetic mice [55] and rats [56]. However, just as with human islet isolation, bovine islet isolation is difficult, expensive, and labor intensive [57,58]. There is a 3 amino acid difference between bovine and human insulin, leading to different metabolic profile and is immunogenic [59].

Porcine source

Porcine islets have received the most attention as alternative to human's. Porcine insulin differs from human insulin by only one amino acid [60] and has been used clinically. Encapsulated adult pit islets transplanted into the peritoneal cavity of diabetic Lewis rats restores euglycemia within 1 month [56]. Long term study showed that euglycemia was maintained for up to 10 months post-transplant in diabetic Balb/c mice that received a transplant of encapsulated adult porcine islets [61].

Fetal pig islet-like clusters resulted in 20 weeks of normoglycemia following transplantation into diabetic mice [62], while another study found that encapsulated neonatal porcine islets maintained euglycemia for more than 174 days [63]. Other studies also support the conclusion that porcine islets can maintain euglycemia for extended periods of time [62-70].

Recent experiences with juvenile pigs, animals younger than 1 month, may have produced a better source of islet for xenotransplantation [52]. Some advantage in using younger instead of older pigs: less housing cost (adult pigs require 2 years to reach adulthood); and because of their smaller size, pancreas procurement is quicker, with shorter cold ischemia time, increasing the yield of islets. To develop an effective therapy for this disease, a consistent, reliable and scalable source of high-quality islets isolated from designated pathogen-free pigs bred and housed in an SPF facility is required. It is still unknown which porcine islet model and age is "best" for clinical transplant and whether there is a need for encapsulation or immunosuppression regimes at this stage.

LIMITATIONS OF XENOTRANSPLANTATION

Xenotransplantation is still limited by the immunologic and physiologic incompatibilities between animals and humans [71]. In addition, there is the potential of transplanted animal tissue to transmit endogenous retroviruses and other infectious agents across the species barrier, posing significant risk to the patient's health [72,73].

Per the United States Federal Drug Administration (**FDA**)'s guidelines for xenotransplantation process, the potential health risk to the patient and community may include the possible

transmission of infectious agents, which may not be detectable or infectious to the animal host. Also, there is a potential for recombination of animal and human genetic material within the recipient, creating new pathogenic forms [74].

Cross-Species Transmission of Pathogen

Due to the similarities in overall physiology, there is a potential for pathogens to be transmitted from pigs to humans [73]. There has been a special interest in a group of viruses known as Porcine Endogenous Retroviruses (**PERV**). PERV has the potential to infect humans post-transplant, as shown by their ability to infect human cells in vitro, and their continued presence in the donor animal's genome [75-78]. Even though the potential of transmission exists, extensive investigations has uncovered no evidence of a human infection with PERV [79,80]. A recent clinical trial by Living Cell Technologies (**LCT**) in New Zealand with neonatal pig islets showed that the human recipients remained PERV negative after transplant [81].

Considering these risks, the International Xenotransplantation Association (**IXA**) Ethics Committee released a position paper in 2004, stating that there must be strict regulations to minimize the risks of contracting animal pathogens during and after transplantation. This includes the need to ensure appropriate animal husbandry, barrier-contained breeding facilities, stringent controls for surgical procedures, and screening of cells or organs prior to clinical use. To be effective, national and international oversight will be needed [82].

Facility Safety and Regulation

Microbial safety is an important focus when it comes to xenotransplantation, affecting animal housing, surgery, islet isolations and clinical transplant. Many centers have implemented current good manufacturing practices (**cGMP**) for islet processing facilities to provide a clean and safe environment for clinical transplants [83,84] and prevent pathogen transmission.

The Clinical Islet Transplant Center in Edmonton, Canada reported that while there was a 31% microbial contamination in the transplant solution of human pancreases, the process of surface decontamination and islet processing resulted in 92% clearance in microbial load [85]. With proper cGMP precautions, the risk of infection can be lowered significantly. This leads to the wider development of sterile animal housing facilities for breeding and pancreas procurement, along with clean rooms used for islet processing and final product release [86].

One of the first pathogen-free pig farms was implemented in New Zealand by Living Cell Technologies (**LCT**) [87]. This farm holds a herd of rare pathogen-free Auckland Island pigs, housing over 1000 pigs for breeding and islet isolation [87]. In the USA, The Spring Point Project (**SPP**), in Minnesota, has received the Class V medical license from the FDA in Aug 2012 for their pathogen free, medical grade porcine facility capable of breeding, housing and pancreas procurement [88].

Pathogen free facilities require that their sentinel pigs to be tested monthly for a variety of pathogens including *Mycoplasma hyopneumonia* and *Actinobacillus pleuropneumoniae*, and all products or animals leaving the facilities must be tested to confirm a non-disease state [89]. The Public Health Service (**PHS**) Guidelines states that extensive pre-clinical data must be obtained in order to progress to clinical trials and screening must be performed on all source herds and the final product for transplantation, along with stringent testing of clinical patients [90].

All these guidelines cannot remove endogenous virus in the genome. PHS states that a virus-free herd and final product are needed to ensure no endogenous viruses are transferred from the source to the patient [91], leading to research on transgenic pigs.

LARGE ANIMALS AND CLINICAL TRIALS FOR ISLET XENOTRANSPLANTATION

Canine Islet Xenotransplantation

Large animal xenotransplantation trials help collect the requisite pre-clinical data necessary to justify proceeding into clinical trials because of the metabolic and immunological similarities between larger animals and humans. Canines have been used as large animal models because of the ease of training and because they are a well-established diabetes model, either by chemical induction (streptozotocin or alloxan) or by surgical pancreatectomy [92,93]. Many groups have shown positive results using encapsulated porcine islets transplanted into diabetic canines. In 2009 a group from Argentina transplanted microencapsulated adult pig islets and reported decreased insulin requirements and glycosylated hemoglobin (**HbA1c**) for up to 6 to 12 months post-transplantation [94]. Previous articles have reported that encapsulated porcine islets transplanted into diabetic canines can maintain euglycemia for >100 days with detectable porcine C-peptide levels in the serum [95-97]. With these reports and continued interest among researchers, canines offer a valid model for pre-clinical xeno-islet transplantation studies.

Non-human Primate Islet Xenotransplantation

Non-human primate (**NHP**) transplant models offer a stepping-stone to the clinic by offering the closest model to a human for transplant, due to the similarities they share with humans, genetically, immunologically and physically [98]. Studies suggest that there is the potential for long-term survival and function of xenotransplanted islets in NHP, in contrast to studies performed with primate solid organ xenotransplantation [99].

However, a study out of the University of Minnesota reported that when adult porcine islets were transplanted into NHP, the C-peptide levels were lower than NHP's transplanted with cadaveric human islets, thus suggesting lower glucose-stimulated insulin release by the transplanted porcine islets [100]. Although encouraging, these results must be further addressed if porcine islets are to be used as a viable source for transplant and lead to the development of an improved, functional porcine islet type. A study in 2010 reported that without encapsulation,

adult porcine islets are rejected after 7 days when transplanted under the kidney capsule of NHP's without immunosuppression, while the same islets can maintain viability and function in vivo for up to 6 months after encapsulation [101].

In 2012, a comprehensive review in Diabetes reported that several research centers have had successes with pig to NHP islet transplants, with normoglycemia maintained for up to 6 months post-transplant. Out of the six reported studies, five reported the combination of transplants and immunosuppression with porcine donor tissue of varying ages ranging from adult to fetal islet tissue. Most recent of study has achieved normoglycemia up to 603 days [102]. Furthermore, one study even transplanted Gal-knockout (**GTKO**) neonatal porcine islets with two out of the six groups within this study used encapsulation techniques [103].

Clinical Islet Xenotransplantation

Based on pre-clinical data, including success in NHP model, xenotransplantation has been tested in multiple countries, using porcine islets (Table 1).

Table 1: Xenotransplant Clinical Trials: Pig to Human Transplant.

Tissue Type	Country	Trial Period	# Patients (age)	Encapsulation Type	Company/ Author	Results
Neonatal Pig islets	New Zealand	2010-Present	20+ (Adult)	Alginate Capsules	LCT (R.B Elliott) [104]	Improved HbA1c and reduction in hyperglycemia. 2 patients became insulin independent after 4 months.
Neonatal Pig islets	Russia	2007-Present	8 (21-68)	Alginate Capsules	LCT (R.B Elliott) [105]	6 out of the 8 patients had improved blood glucose control, with reduction in both insulin requirements and HbA1c. 2 patients discontinued insulin for 8 months.
Neonatal Pig islets	Argentina	2011-Present	8 (Adult), 20 recruited	Alginate Capsules	LCT (R.B Elliott) [106]	Group 1: 5000 leq/kg x 2, n:4. Group 2: 10.000 leq/kg x 2, n: 4. In the group 2, the Hba1C was minor than 7 % and TEF score was 0.5, both for 2 years. The unawareness hypos were reduced significantly in the group 2.
Porcine Islets	Mexico	2002 & 2005	12 (14.7 mean years)	Collagen devise w/ 2 steel mesh tubes	Valdes Gonzales [107]	All patients are infection free and 2 became insulin independent for several months, 1 continues to be insulin free after 2 years
Pig Islets	Ukraine	1995, In Progress	Unknown	None	I.S. Turchin [108]	Unknown
Fetal pig islet like clusters	Sweden	1979-1993	10	None	C Gustav Groth [109]	No C-peptide detected in plasma, but in detected in Urine after 460 days. Kidney biopsy showed viable cells
Pig Islets	China	2005	22	None; with immunosuppression	W.Wang [110]	Reduction of insulin requirements and lowering of HbA1c. Detection of porcine C-peptide, immunosuppressants stopped after 1 year.

Summary of clinical trials of pig islets for Type 1 diabetes treatment [18, 111].

In 1994, Groth et al. found that isolated fetal porcine islets transplanted into diabetic kidney transplant patients, either intraportal or under the kidney capsule, were able to produce porcine C-peptide for up to 400 days post transplantation [109].

One of the most notable and well-documented clinical trials are the trials being performed by LCT, with clinical trials in three countries for islet xenotransplantation [87]. LCT's clinical trials use pathogen-free, medical grade fetal pigs that have been encapsulated with their "Diabecell" device. Phase 1 clinical trial in Australia demonstrated the safety, as well as improvement in HbA1c levels and decrease in hypoglycemia unawareness [104]. The results of the first trial from Australia led to a phase I/IIa clinical trial in New Zealand, where a total of 14 patients were transplanted with different islet doses: 5,000, 10,000, 15,000, and 20,000 IEQ/kg body weight. A reduction in daily insulin requirements in all groups, with a statistically significant improvement in hypoglycemic unawareness events in the groups transplanted with 5,000 and 10,000 IEQ was reported. In addition, there was no evidence of any transmissible zoonotic infection in the recipients [112].

Between 2011 and 2014, LCT commenced a third phase I/IIa clinical trial in Argentina, using 44 microencapsulated islet xenografts in 22 patients. This trial was authorized by the Ministry of Health of the Province of Buenos Aires [113]. The data of the last 14 patients are still being processed. The first 8 patients were divided into two groups: Group 1: two implants of 5000 IEQ/kg and Group 2: two implants of 10,000 IEQ/kg. In the Group 2, the HbA1c was under 7 % during 2 years. The TEF score was in 0.5 during the same time. PERV was not detected and they observed only one serious event adverse related with the transplant, but resolved in 2 days [106].

Even though most patients saw improvements in their diabetes management, without infection of evidence of PERV infection noted to date, long term studies are still required to confirm improvements in recipient quality of life [72,80,114-116].

RECENT DEVELOPMENTS AND FUTURE APPLICATIONS

Genetically Modified Porcine Islets

Genetically modified porcine islets could offer advantages in graft function and limit the host's immune response to the transplant. Current studies focus on gene transfer techniques to decrease the host response to the graft. The genetic transduction of genes like antiapoptotic and antinecrotic Bcl-2 into porcine islets have been shown to decrease the release of natural reactive antibodies and cell lysis by the complement cascade [117]. Other molecules, like MSPEG (PEG-mono-succinimidyl-succinate) and DSPEG (PEG-di-succinimidyl-succinate), in combination with Bcl-2 transduction have shown no negative effect on islet viability, function or morphology [118]. Results from studies using these methods have also shown that these combinations have positive effects, with a reduction in lactate dehydrogenase release, a marker for cellular necrosis, when transplanted into animal recipients [119]. The use of T-cell inhibitors to limit the graft rejection by the adaptive immune system have also been studied. In a study by Klymiuk et al, neonatal porcine islets were isolated from transgenic pigs that expressed LEA29Y, which inhibits T-cell co-stimulation. In diabetic immunocompetent mice, these islets resulted in complete tolerance [37].

Various genetic modifications with clinical potential, are still under study: incorporation of cytoprotective molecules (heme oxygenase-1 and A20) [102], inhibitors of coagulation and/or inflammation, e.g., CD39, tissue factor pathway inhibitor, human endothelial protein C receptor, human thrombomodulin [120,121], knockout of the xenoantigens: N-glycolylneuraminic acid, [122] and β 1,4N-acetylgalactosaminyltransferase gene [123].

Genetic modification can also be used to improve glucose insulin response. After stimulation with 15 mM glucose, pigs isolated islets secrete insulin 6 times less than human islets. Cooper shows that the stimulation index for neonatal and adult pig islets improved from 3.3 and 3, to 7.3 and 7 respectively, using islets co-expressing glucagon-like peptide-1 and activated muscarinic receptor type 3. This could greatly reduce the number of cells to be transplanted [106].

Gal-Deficient Galactosyl Transferase and Perv Knockout Strains

The first target in antibody-mediated rejection in the pig to human transplant paradigm is the carbohydrate Galactose- α 1,3-galactose (**α -gal**). In porcine islets, α -gal expression varies depending on the size of the islet and not the age of the pig donor [124]. Since nearly all porcine islets express α -gal, there has been recent developments targeted at the creation of a Gal knockout pig (**GTKO**) strain that are deficient in α -gal. Studies characterizing GTKO pig islets have demonstrated insulin independence and establishment of normoglycemia [125]. A study in 2011, compared wild type neonatal porcine islets (non-GTKO islets) with neonatal-GTKO islets, and found an 80% insulin-independence with the GTKO islets compared to 20% insulin-independence with the wild type [125]. This experiment, and the development of GTKO pigs allow for improved consistency and overall transplantation outcomes for the treatment of T1D.

Researchers have also been focusing on limiting or eradicating the occurrence of porcine-specific pathogens, thus creating pathogen-free pigs [80,126]. Controlled environment breeding and housing facilities of porcine donors along with sterile rooms for pancreas procurement allow for a decreased risk of microbial contamination from outside sources and enhanced overall transplantation success [127]. Specific pathogen-free (**SPF**) pig farms have also created a suitable and reliable source for islet transplant that limit the risk of porcine microbe transmission, but are limited because they do not limit PERV that are so well integrated into the pigs genome [80]. Without the development of a cross-species model, the study and validation of PERV transmission rates is nearly impossible [128]. However, in a recent study with use of CRISPR-Cas9 technique, investigators have inactivated all PERV in kidney epithelial cell line (**PK15**) and reduced transmission of PERV in human cells by >1000 fold [129]. This strategy would be the key to eliminate permanently the risk of PERV.

Immuno-Isolation Instead of Immunosuppression

Implementation of xenogeneic islets for transplant therapy of T1D requires a solution to tackle the problem of acute rejection [76,131]. While immunosuppression has previously been

the standard therapy to prevent rejection in human islet allotransplantation, immune-isolation has been studied as an alternative for xenograft islets due to the presence of cell surface antigens such as α -gal [132,133].

A successful immune-isolation technique can allow islets to be transplanted without any immunosuppression. One such in vivo study utilizing porcine islets that have been immune-isolated using encapsulation in alginate showed remarkable longevity in the reversal of diabetes, with euglycemia up to 550 days when transplanted into diabetic rats [134]. There are several factors that influence this potential for success. One major factor involved in transplant success is the quality and purity of the islets that have been isolated, where a purer preparation of islets reduces the chance of extraneous exocrine tissue can protrude out of the encapsulation layer [135,136]. Another factor involved is the chemical composition and purity of the alginate of greater purity has shown to improve the biocompatibility of the capsules, such that the immunoisolated islets are not recognized as foreign bodies [137,138].

The Future of Islet Xenotransplantation

The future of xenotransplantation may lie in the development of a genetically engineered donor animal to reduce immunogenicity post-transplant, or through the development of immunoisolating materials such as alginate to allow the transplanted xenograft to remain undetected by the host immune system. The potential of PERV-free pigs will stimulate the development of clinical trials. Improvements in these technologies could make xenotransplantation a much more attractive option to solve the problems faced when using cadaveric human islets.

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