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MINIREVIEW

Polymer scaffolds for pancreatic islet transplantation – Progress and challenges

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Pancreatic-islet transplantation is a safe and noninvasive therapy for type 1 diabetes. However, the currently applied site for transplantation, ie, the liver, is not the optimal site for islet survival. Because the human body has shortcomings in providing an optimal site, artificial transplantation sites have been proposed. Such an artificial site could consist of a polymeric scaffold that mimics the pancreatic microenvironment and supports islet function. Recently, remarkable progress has been made in the technology of engineering scaffolds. The polymer-islet interactions, the site of implantation, and scaffold prevascularization are critical factors for success or failure of the scaffolds. This article critically reviews these factors while also discussing translation of experimental studies to human application as well as the steps required to create a clinically applicable prevascularized, retrievable scaffold for implantation of insulin-producing cells for treatment of type 1 diabetes mellitus.

KEYWORDS

artificial organs/support devices: pancreas, diabetes: type 1, islet transplantation, islets of Langerhans, translational research/science

1 | INTRODUCTION

Islet transplantation is a promising treatment for type 1 diabetes. Conventionally, islets are transplanted in the human liver by infusion via the portal vein. Here islets are revascularized and integrated into the liver parenchyma. This results in insulin independence in the first year after transplantation but less than 50% the islet grafts are still fully functional after 5 years.¹ Multiple factors seem to play a role. Current insight suggests that the liver is not the optimal site for functional survival of islets as grafts are destroyed by instant blood-mediated inflammatory responses, low oxygen tension, and invasion by natural killer (T) cells.² Many

other sites were investigated as alternative, eg, the omentum,³ spleen,⁴ kidney capsule,⁵ bone marrow,⁶ and muscle,⁷ but none of them appeared to be more successful in humans than the liver.² Because the human body has several shortcomings in providing an optimal transplantation site for islets, polymeric scaffolds are proposed to mimic the pancreatic environment.

Engineering polymeric scaffolds for islets is challenging, as it requires knowledge about the properties, advantages and disadvantages of various polymers, and geometries. The choice of the polymer has been shown to be a critical parameter in the success and failure of scaffolds as islets are extremely sensitive for cell-biomaterial interactions. Furthermore, scaffolds have different efficacies subcutaneously, intraperitoneally, in the omentum, and in the epididymal fat pad. We critically review the biomaterial choice and sites for implantation in approaching a clinical application. Based on current advances, we recommend some critical research targets that might expedite clinical islet transplantation.

Abbreviations: DAMP, danger-associated molecular pattern; dsDNA, double-stranded DNA; hESCs, human embryonic stem cells; IEQ, islet equivalence; NHPs, nonhuman primates; PCL, polycaprolactone; PDLLCL, poly(D,L-lactide-co-ε-caprolactone); PDMS, polydimethylsiloxane; PEOT/PBT, poly(ethylene oxide terephthalate)/polybutylene terephthalate; PLG, poly(lactide-co-glycolide); PTFE, polytetrafluoroethylene; PVA, polyvinyl alcohol.

2 | SELECTION OF BIOMATERIALS

During recent years several polymeric biomaterials have been tested for application in scaffolds. The polymers should not interfere with functional islet survival, because this can contribute to graft failure.^{8,9} These polymers with adequate islet interaction can be broadly classified as two types: natural and synthetic.

Some examples of synthetic polymers that were applied for islet scaffolds are polydimethylsiloxane (PDMS),¹⁰⁻¹² polytetrafluoroethylene (PTFE),¹³⁻¹⁶ poly(D,L-lactide-co-ε-caprolactone) (PDLLCL),^{8,17} poly(ethylene oxide terephthalate)/polybutylene terephthalate (PEOT/PBT),¹⁸ and polysulfone.¹⁹ Not all polymeric scaffolds have the same degree of success, which may be caused by nonoptimal islet-biomaterial interactions.^{8,9} To illustrate the importance of islet-biomaterial interaction, we have examined effects of PDLLCL, PEOT/PBT, and polysulfone on functional islet survival.⁸ Repeatedly, we found strong effects of the polymers on islet function and release of “danger signals” such as double-stranded DNA (dsDNA), a so-called danger-associated molecular pattern (DAMP).⁸ DAMPs, such as dsDNA, HMGB1, uric acid, and HSP70 are known to bind to receptors of immune cells and trigger the release of cytokines, leading to undesired immune responses (Figure 1). Of the 3 tested polymers, we found only PDLLCL to be nontoxic and suitable for application in scaffolds. PDLLCL promoted functional survival of islets and low release of dsDNA and was associated with minor tissue reactions in rats after 28 days.⁸ Not many research groups have tested the direct effects of polymers on islets despite the well-known adverse effects they may have.^{8,9} The foregoing should not be interpreted as a suggestion that PDLLCL is the best or the only applicable polymer for islet scaffolds. We tested 3 polymers of different chemical structures but other polymers such as PDMS and PTFE may be suitable as well.^{10-12,15,16}

Natural polymers are known for their biodegradability and biocompatibility. Fibrin is a frequently used natural polymer in scaffold fabrication^{3,20}; it is formed after polymerization of fibrinogen by the enzyme thrombin. This reaction naturally occurs during wound healing, thrombosis, and other biological processes.²¹ Fibrin is used for a broad variety of medical applications and is also successfully applied within the islet field.³ Other examples of natural polymers that are used as scaffold material for islets are extracellular matrix components and silk.²²⁻²⁷ This review focuses on scaffolds that allow islet vascularization. Polymers solely used for immunoisolation that do not allow vascularization are not discussed.

3 | CHOICE OF IMPLANTATION SITE

For clinical application, the site of implantation should be easily accessible by minimal invasive surgery, have enough volume to bear adequate numbers of islets, have a dense vascular network, and minimally activate the immune system, and islets should be retrievable in case of failure.² In recent years several different implantation sites have been tested (Figure 2, Table 1), the different scaffolds are discussed subsequently in the context of these sites.

3.1 | Subcutaneous scaffolds

The unmodified subcutaneous site is not favorable for transplants because of low oxygen tension and a poorly developed vascular network.²⁸ Transplantation of islets under the unmodified skin rarely results in normoglycemia.¹⁷ However, renewed attention recently has been given to this site as it might be successful when the site is modified by implantation of a scaffold that changes the microenvironment by enhancing the vascular density.^{17,22,29} Major advantages

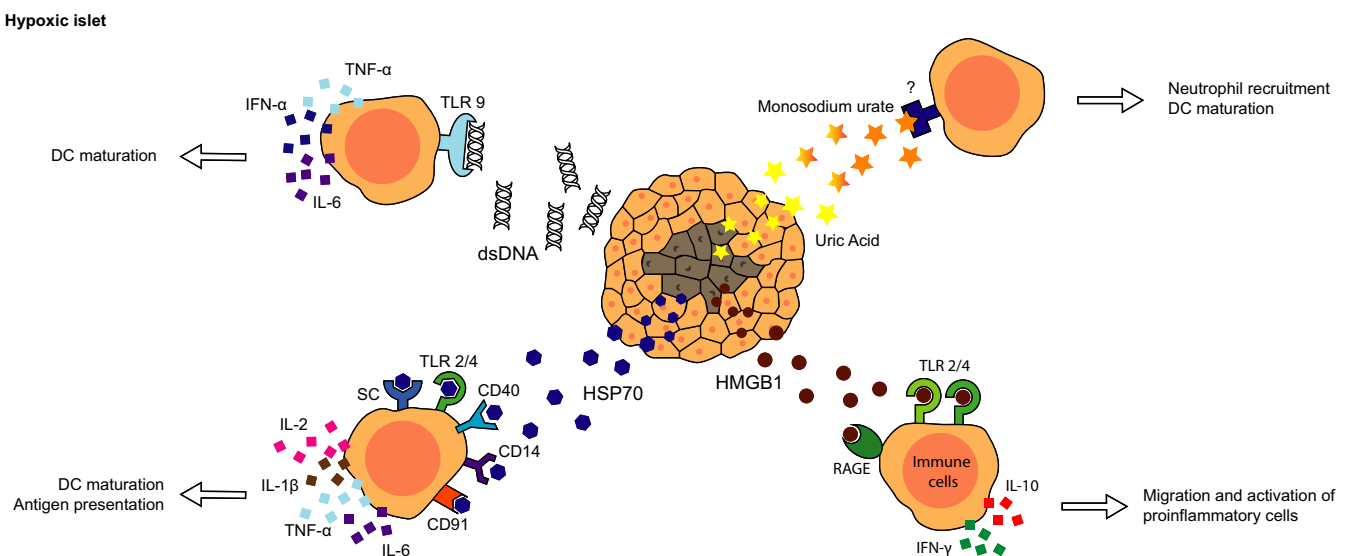


FIGURE 1 The release of DAMPs from islets during hypoxia. During hypoxia the core of the islet will undergo necrosis. As a result, DAMPs such as dsDNA, uric acid, HSP70, and HMGB1 will be released. These DAMPs bind to receptors on different types of immune cells leading to a proinflammatory response

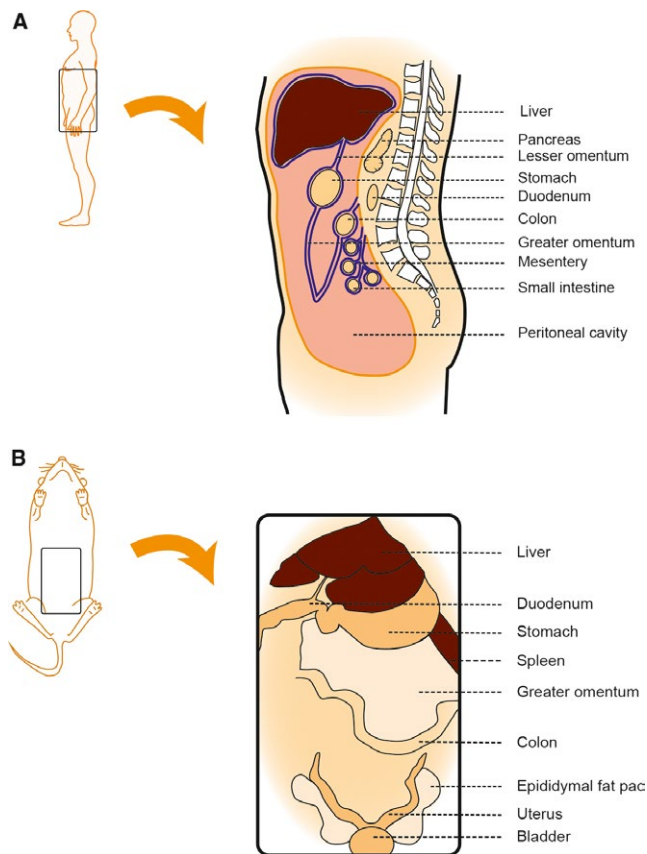


FIGURE 2 The different transplantation sites for islet scaffolds. (A) A membrane called the peritoneum surrounds the abdominal cavity and abdominal organs. The peritoneum consists of the parietal (outlining the abdominal cavity, orange) and visceral (outlining the abdominal organs, blue) peritoneum; the space in between them is called the peritoneal cavity (red). A double layer of visceral peritoneum between the liver, stomach, and colon is called the omentum. The omentum between the liver and stomach is the lesser omentum; the part between the stomach and the colon is referred to as the greater omentum. (B) The omentum of rodents is much smaller and thinner than that of humans. Therefore, the epididymal fat pads are often used in rodents as an alternative for the omentum; these fat pads exist of visceral adipose tissue, which is located around the gonads. Humans do not have epididymal fat pads

of the subcutaneous site are the relatively large surface area, ease of access, ease of graft monitoring, and retrievability without damaging any other organs.

Prevascularization of the scaffold has been shown to be a critical prerequisite for success of scaffolds under the skin.^{17,22,29,30} This prevascularization of the scaffold stimulates revascularization of the islets. The native islet vasculature is disrupted during islet isolation and therefore it is important that revascularization occurs rapidly after transplantation to avoid necrosis. Perteghella and coworkers²² demonstrated the need for prevascularization of silk scaffolds. Islets in prevascularized silk scaffolds performed significantly better than those without a prevascularization period.²² Prevascularization may even facilitate success without a polymeric biomaterial. Pepper and

coworkers implanted a nylon catheter under the skin of mice and removed it 1 month later before islets were transplanted.^{29,31} The foreign body reaction against the catheter created a highly vascularized subcutaneous space for islets. Islet transplantation into this space induced normoglycemia. Pepper et al³² also performed syngeneic islet transplantation in mice using the prevascularized Sernova's Cell Pouch System™ (London, Ontario, Canada). With a marginal dose of 200 islets, mice became normoglycemic.³² But clinical trials with this system showed massive islet death due to hypoxia, illustrating the need for optimization in humans.³⁰

Another approach to make the subcutaneous site more efficacious for islets is by preventing cell loss during early posttransplant ischemia by enhancing oxygen supply. Beta-O₂ Inc. (Rosh Ha'ayin, Israel) developed a subcutaneous macrochamber of PTFE that provides physiologic oxygen levels to islets during the period of implantation and revascularization of the device.^{13,15} The macrochamber contains a gas compartment with oxygen, which can diffuse over a gas-permeable membrane to the islets in the adjacent compartment. Islet-containing devices were subcutaneously implanted resulting in long-term normoglycemia in diabetic rats, pigs, and nonhuman primates.¹⁵ Success was also shown in type 1 diabetic patients for up to 10 months.³³

A pertinent advantage of the skin as transplantation site is that retrievability of the graft is feasible. This is especially important when replenishable cell sources for treatment of type 1 diabetes such as beta cells derived from stem cells become available.³⁴ Many stem cell-derived transplants still suffer from issues such as teratoma formation, malignant transformation, and abnormal hormone releases.³⁵⁻³⁸ This makes retrievability mandatory. Although requirements of islets and beta cells derived from stem cells for scaffolds might differ, current efforts of transplanting progenitor cells in scaffolds are discussed as these studies deliver important insight in scaffold efficacy and field of application. To facilitate retrievability, Viacyte (San Diego, CA) developed the PTFE-based Encaptra® drug delivery system and tested this approach for subcutaneous transplantation of pancreatic progenitor cells derived from human embryonic stem cells (hESCs).¹⁴ The cells had to mature in vivo to become glucose-responsive betalike cells. It took 12 weeks of implantation in mice before the cells started to produce human C-peptide.¹⁴ Viacyte is now testing the device in phase I and II studies.³⁴ Others have recently published similar results with hESC-derived cells transplanted in the PTFE based TheraCyte scaffolds (TheraCyte, Laguna Hills, CA).¹⁶

3.2 | Omentum scaffolds

Because the omentum (Figure 2) is characterized by a naturally rich vascular network and drained via the portal system, it is preferred by some groups as implantation site.^{28,39} Some success has been shown after transplantation in the unmodified omentum, but high amounts of islets are needed.⁴⁰ Fewer islets might be needed when a prevascularized scaffold is placed in the omentum. Several groups developed macroporous PDMS scaffolds to improve islet graft function

TABLE 1 An overview of different islet transplantation approaches including a polymer scaffold

| Implantation site | Polymer | Tested in | Beta-cell source | Type of transplantation | Immunocompetent animal model | Reference |
|------------------------|----------|--------------------------|-----------------------------|-------------------------|------------------------------|-----------|
| Under the skin | PDLLCL | Mice, rats | Islets | Allogeneic | No | 8,17 |
| | Nylon | Mice | Islets | Syngeneic | Yes | 29,31 |
| | PTFE | Mice, rats, pigs, humans | Islets, hESCs derived cells | Xenogeneic, allogeneic | No/Yes | 13-16,33 |
| | Silk | Mice | Pancreatic endocrine cells | Syngeneic | Yes | 22 |
| Omentum | PDMS | Mice, rats | Islets | Syngeneic | Yes | 10,11 |
| | Collagen | Mice, rats | Islets | Allogeneic, syngeneic | No/Yes | 25,42 |
| | Fibrin | Mice, rats, NHPs, humans | Islets | Syngeneic, allogeneic | Yes | 3,20 |
| Epididymal fat pad | PEOT/PBT | Mice | Islets | Syngeneic | Yes | 18 |
| | Silk | Mice | Islets | Syngeneic | Yes | 23,24 |
| | PDMS | Mice | Islets | Syngeneic | Yes | 12 |
| | PLG | Mice | Islets | Xenogeneic | No | 44,45 |
| Intraperitoneal cavity | PVA | Mice | Islets | Allogeneic | Yes | 9 |
| | PTFE | Rat | Islets | Syngeneic | Yes | 46 |
| | PCL | Mice | hESCs derived cells | Xenogeneic | Yes | 47 |

PDLLCL, poly(D,L-lactide-co- ϵ -caprolactone); PTFE, polytetrafluoroethylene; hESCs, human embryonic stem cells; PDMS, polydimethylsiloxane; NHPs, nonhuman primates; PEOT/PBT, poly(ethylene oxide terephthalate)/polybutylene terephthalate; PLG, poly(lactide-co-glycolide); PVA, polyvinyl alcohol; PCL, polycaprolactone.

in the omentum.^{10,41} Pedraza and coworkers¹⁰ transplanted 1800 rat islets in a PDMS scaffold placed in the omentum of diabetic rats. Although some improvement was observed, overall the PDMS scaffold did not provide an advantage over transplantation directly in the unmodified omentum. Further improvement of the PDMS scaffold by inclusion of a growth factor containing fibrin resulted in long-term normoglycemia with a marginal dose of 250 islet equivalence (IEQ) whereas the mice with islets in the unmodified omentum did not become normoglycemic.¹¹

The Miami group is currently testing the omentum as transplantation site for scaffolds in a clinical trial. A biodegradable scaffold manufactured of the natural polymer fibrin is applied in the omentum to enhance survival of human islets (ClinicalTrials.gov number: NCT02213003). They recently reported a successful case in a type 1 diabetic patient that received 602 395 IEQ in a fibrin scaffold in the omentum.³ The patient became normoglycemic and insulin independent for a period of 12 months. This approach has also shown success in diabetic rodents.²⁰ The structure and bioactivity of fibrin stimulate ingrowth of blood vessels,²¹ but they will degrade over time. This biodegradability holds a disadvantage for application of replenishable cell sources that might require retrievability.

To further enhance efficacy of islet grafts, technologies to enhance oxygen supply have been tested in the omentum. Montazeri and coworkers⁴² have transplanted oxygen-generating microparticles together with islets in a porous collagen scaffold to prevent ischemia and support survival in the first few weeks after islet transplantation,⁴² which resulted in a higher percentage of mice that were

normoglycemic than without microparticles. In addition, vascularization was stimulated by inclusion of fibrin-conjugated heparin for the controlled release of vascular endothelial growth factor, which induced normoglycemia in diabetic nude mice with a marginal dose of 250 rat IEQ.

3.3 | Epididymal fat pad scaffolds

Like the omentum, the epididymal fat pad (Figure 2B) is well vascularized. In rodents, this is an easily accessible and spacious site and allows removal of scaffolds without damaging vital organs. Unlike the omentum, the epididymal fat pad does not have portal drainage.⁴³ PDMS scaffolds containing 500-600 syngeneic IEQ placed in the epididymal fat pad resulted in borderline normoglycemia (blood glucose levels of 200 mg/dL) in 2 different mouse studies.¹² Comparison of efficacy of the PDMS scaffolds revealed that the epididymal fat pad performed better than the omentum. This efficacy may be further enhanced by selecting polymers that enhance vascularization.^{18,23,24} Mao et al²³ developed a silk fibroin scaffold, ie, a natural polymer from the insect *Bombyx mori*, which was tested in the epididymal fat pad in mice. All mice became normoglycemic after transplantation of 300 islets and maintained normoglycemic for over a year. Hamilton et al²⁴ showed similar efficacy of the epididymal fat pad with just 200 islets with their silk fibrin gels. Decellularized tissue can also function as natural material for scaffolds. Wang and coworkers²⁷ transplanted 250 syngeneic islets into epididymal fat pad-placed decellularized pericardium scaffolds. In 83% of the

mice diabetes was reversed, including 47% with a minimal number of 150 islets. Furthermore, a poly(lactide-co-glycolide) has been shown to facilitate islet transplantation in the epididymal fat pad.⁴⁴ Transplantation of 2000 human islets in mice resulted in fast reversal of diabetes and this was maintained for 140 days. When this scaffold was adapted for localized protein delivery in order to enhance islet engraftment, mice did not become normoglycemic anymore,⁴⁵ illustrating that other physicochemical factors in addition to the type of polymer determine the success of transplantation outcome.

Furthermore, the design of the scaffold can also play an important role. Studies using a microwell scaffold have shown that the microwell pore structure prevents islet clumping and stimulates ingrowth of blood vessels in individual islets.¹⁸ Reportedly transplantation of 300 islets within a microwell scaffold placed on the epididymal fat pad resulted in normoglycemia in 6 out of 8 diabetic mice.¹⁸ The microwell structure enhanced islet engraftment in the epididymal fat pad by improving islet organization.

3.4 | Intraperitoneal scaffolds

In the past, many researchers including our group focused on the intraperitoneal site (Figure 2A) for islet transplantation because this site provides reasonable space and portal drainage.⁴⁶ We showed that the success rates after islet transplantation were significantly better when transplanted in a PTFE scaffold coated with collagen type IV compared with the unmodified peritoneal cavity of diabetic rats.⁴⁶ For unknown reasons, only a few researchers tested their scaffolds in the intraperitoneal site during recent years. Yoshimatsu et al⁹ developed a polyvinyl alcohol (PVA) scaffold. However, intraperitoneal transplantation of 1500 rat islets into this device could not reverse diabetes in mice.⁹ This was not related to the implantation site but to polymer toxicity as culturing islets in PVA scaffolds was detrimental for islet function and survival.⁹ Recently, Chang et al⁴⁷ developed a polycaprolactone scaffold for intraperitoneal transplantation of hESC-differentiated beta-cell clusters. Their scaffold showed long-term engraftment, viability, and functions of these cells in diabetic mice.⁴⁷ Furthermore, Abualhassan and coworkers²⁶ infused 500 mouse islets into intraperitoneal-placed decellularized lung scaffolds. In 67% of the mice normoglycemia was observed, whereas this was only 13% without the scaffold. As the peritoneal site is easy accessible and allows beta-cell survival,^{46,47} it should receive more attention as transplantation site.

TABLE 2 Challenges for clinical islet transplantation

| Major research questions | |
|--------------------------|--|
| 1. | What are the optimal polymer properties for creating a scaffold for human islet transplantation? |
| 2. | Which geometry is adequate to carry large enough volumes of islets or other beta-cell sources needed to cure human diabetes? |
| 3. | Which geometry allows rapid ingrowth of vessels in upscaled scaffolds for human application? |
| 4. | Which transplantation sites are translatable to humans? |

4 | CONCLUDING REMARKS AND PERSPECTIVES

Selecting adequate polymers, prevascularizing the scaffolds, choosing a geometry allowing fast engraftment, and selecting efficacious transplantation sites are crucial for success of islet scaffolds. Despite many advances in recent years, several major research questions need to be addressed before large-scale clinical application becomes a realistic option (Table 2).

Current insight suggests that *in vitro* pretesting of polymers is a mandatory step. We have shown that minor modifications in chemistry affect functional islet survival.⁸ Islets are equipped with integrins and pattern recognition receptors that interact with the microenvironment.⁴⁸ When these receptors encounter polymers that are not compatible with functional survival, adverse intracellular processes may occur with cell death and endothelial-to-mesenchymal cell transition as a consequence.⁴⁸ These processes will take weeks to months *in vivo* but inevitably lead to graft failure.

Animal studies with scaffolds might be done in a more systemic way to allow judgment and comparison of scaffold efficacy. Tissue response against the polymers might destroy the islets.⁴⁹ All scaffolds currently studied do provoke tissue responses,⁸ but these are usually dampened and not affecting the grafts after the prevascularization periods. It is essential to determine how long the scaffold should be implanted before tissue responses are dampened and prevascularization is completed. After these steps, it is advisable not to progress to allogeneic transplantation models but to first explore efficacy with syngeneic settings to exclude negative influence of possible allogeneic immune responses on islet survival. By performing syngeneic islet transplantations with graded doses of islets or with minimal volume models,¹⁷ the efficacy of the engraftment can be judged. By a follow-up for several months and repeated glucose tolerance testing, maintenance of graft function and possible adverse effects of the scaffold on long-term islet function can be studied.^{8,17} Preferably the scaffolds should be tested at different sites to determine the most optimal site in the host.

The geometry of the scaffolds for future human application also warrants some further considerations. The scaffolds need to bear adequate numbers of islets to cure diabetes. The larger the scaffold, the more important adequate ingrowth of blood vessels will be. In animals, it has been shown that oxygen supply and adequate prevascularization can be achieved by implanting the scaffold several weeks before islet transplantation.^{17,22,25,29,50} In larger experimental

animals and humans this might take longer and will probably be closer to several months than weeks. A conceivable approach to expedite the vascularization process is cotransplantation of angiogenic cells⁵¹ or temporary inclusion of oxygen-generating particles to supply the islets with oxygen might be a solution.

A discussion that needs to be started before the preclinical studies is the human applicability of the scaffold implantation sites. One of the most efficacious sites in rodent studies does not exist in humans, ie, the epididymal fat pad.^{12,18,23,24} Although important lessons have been learned from testing scaffold geometries in the epididymal fat pad, the site itself is of little value for human translation as there are no analogous sites available in humans. Furthermore, there are principal differences between the human and rodent omentum that should be taken into account in the experimental studies.⁴³ Adequate choices for animal models are in that respect very relevant. For example, for subcutaneous scaffolds the pig might be a more adequate model than other large animal models such as nonhuman primates because of the similarity of pig and human skin structure.⁵²

Despite the differences between animals and humans, important advances have been made in the design and testing of polymeric scaffolds for islet transplantation. Many studies showed that it might serve as an alternative for the intraportal route. Interaction of cells and polymers are well studied, but which polymer and geometry are most relevant for human application remain to be determined. Also, the human transplant site for the scaffolds is still subject of debate. Further improvement of these scaffolds may contribute to a more widespread application of islet transplantation.

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REFERENCES

- Hering BJ. Achieving and maintaining insulin independence in human islet transplant recipients. *Transplantation*. 2005;79(10):1296-1297.
- Smink AM, Faas MM, de Vos P. Toward engineering a novel transplantation site for human pancreatic islets. *Diabetes*. 2013;62(5):1357-1364.
- Baidal DA, Ricordi C, Berman DM, et al. Bioengineering of an intraabdominal endocrine pancreas. *N Engl J Med*. 2017;376(19):1887-1889.
- White SA, Davies JE, Pollard C, et al. Pancreas resection and islet autotransplantation for end-stage chronic pancreatitis. *Ann Surg*. 2001;233(3):423-431.
- Groth CG, Korsgren O, Tibell A, et al. Transplantation of porcine fetal pancreas to diabetic patients. *Lancet*. 1994;344(8934):1402-1404.
- Maffi P, Balzano G, Ponzoni M, et al. Autologous pancreatic islet transplantation in human bone marrow. *Diabetes*. 2013;62(10):3523-3531.
- Rafael E, Tibell A, Ryden M, et al. Intramuscular autotransplantation of pancreatic islets in a 7-year-old child: a 2-year follow-up. *Am J Transplant*. 2008;8(2):458-462.
- Smink AM, Hertsig DT, Schwab L, et al. A retrievable, efficacious polymeric scaffold for subcutaneous transplantation of rat pancreatic islets. *Ann Surg*. 2017;266(1):149-157.
- Yoshimatsu G, Sakata N, Tsuchiya H, et al. Development of polyvinyl alcohol bioartificial pancreas with rat islets and mesenchymal stem cells. *Transplant Proc*. 2013;45(5):1875-1880.
- Pedraza E, Brady AC, Fraker CA, et al. Macroporous three dimensional PDMS scaffolds for extrahepatic islet transplantation. *Cell Transplant*. 2013;22:1123-1135.
- Brady AC, Martino MM, Pedraza E, et al. Proangiogenic hydrogels within macroporous scaffolds enhance islet engraftment in an extrahepatic site. *Tissue Eng Part A*. 2013;19(23-24):2544-2552.
- Jiang K, Weaver JD, Li Y, Chen X, Liang J, Stabler CL. Local release of dexamethasone from macroporous scaffolds accelerates islet transplant engraftment by promotion of anti-inflammatory M2 macrophages. *Biomaterials*. 2017;114:71-81.
- Barkai U, Weir GC, Colton CK, et al. Enhanced oxygen supply improves islet viability in a new bioartificial pancreas. *Cell Transplant*. 2013;22(8):1463-1476.
- Agulnick AD, Ambruzs DM, Moorman MA, et al. Insulin-producing endocrine cells differentiated in vitro from human embryonic stem cells function in macroencapsulation devices in vivo. *Stem Cells Transl Med*. 2015;4(10):1214-1222.
- Ludwig B, Ludwig S, Steffen A, et al. Favorable outcome of experimental islet xenotransplantation without immunosuppression in a nonhuman primate model of diabetes. *Proc Natl Acad Sci USA*. 2017;114(44):11745-11750.
- Kirk K, Hao E, Lahmy R, Itkin-Ansari P. Human embryonic stem cell derived islet progenitors mature inside an encapsulation device without evidence of increased biomass or cell escape. *Stem Cell Res*. 2014;12(3):807-814.
- Smink AM, Li S, Hertsig DT, et al. The efficacy of a prevascularized, retrievable poly(D, L-lactide-co-epsilon-caprolactone) subcutaneous scaffold as transplantation site for pancreatic islets. *Transplantation*. 2017;101(4):e112-e119.
- Buitinga M, Assen F, Hanegraaf M, et al. Micro-fabricated scaffolds lead to efficient remission of diabetes in mice. *Biomaterials*. 2017;135:10-22.
- Lembert N, Wesche J, Petersen P, et al. Encapsulation of islets in rough surface, hydroxymethylated polysulfone capillaries stimulates VEGF release and promotes vascularization after transplantation. *Cell Transplant*. 2005;14(2-3):97-108.
- Coronel MM, Geusz R, Stabler CL. Mitigating hypoxic stress on pancreatic islets via in situ oxygen generating biomaterial. *Biomaterials*. 2017;129:139-151.
- Ceccarelli J, Putnam AJ. Sculpting the blank slate: how fibrin's support of vascularization can inspire biomaterial design. *Acta Biomater*. 2014;10(4):1515-1523.
- Perteghella S, Viganò B, Mastracci L, et al. Stromal vascular fraction loaded silk fibroin mats effectively support the survival of diabetic mice after pancreatic islet transplantation. *Macromol Biosci*. 2017;17(9):1700131.
- Mao D, Zhu M, Zhang X, et al. A macroporous heparin-releasing silk fibroin scaffold improves islet transplantation outcome by promoting islet revascularisation and survival. *Acta Biomater*. 2017;59:210-220.
- Hamilton DC, Shih HH, Schubert RA, et al. A silk-based encapsulation platform for pancreatic islet transplantation improves islet function in vivo. *J Tissue Eng Regen Med*. 2017;11(3):887-895.

25. Kriz J, Vilck G, Mazzuca DM, Toleikis PM, Foster PJ, White DJ. A novel technique for the transplantation of pancreatic islets within a vascularized device into the greater omentum to achieve insulin independence. *Am J Surg*. 2012;203(6):793-797.
26. Abualhassan N, Sapozhnikov L, Pawlick RL, et al. Lung-derived microcavities facilitate diabetes reversal after mouse and human intraperitoneal islet transplantation. *PLoS ONE*. 2016;11(5):e0156053.
27. Wang X, Wang K, Zhang W, Qiang M, Luo Y. A bilaminated decellularized scaffold for islet transplantation: structure, properties and functions in diabetic mice. *Biomaterials*. 2017;138:80-90.
28. Kasoju N, Kubies D, Fabryova E, et al. In vivo vascularization of anisotropic channeled porous polylactide-based capsules for islet transplantation: the effects of scaffold architecture and implantation site. *Physiol Res*. 2015;64(suppl 1):S75-S84.
29. Pepper AR, Gala-Lopez B, Pawlick R, Merani S, Kin T, Shapiro AM. A prevascularized subcutaneous device-less site for islet and cellular transplantation. *Nat Biotechnol*. 2015;33(5):518-523.
30. Gala-Lopez BL, Pepper AR, Dinyari P, et al. Subcutaneous clinical islet transplantation in a prevascularized subcutaneous pouch – preliminary experience. *CellR4*. 2016;4:e2132.
31. Pepper AR, Pawlick R, Bruni A, et al. Harnessing the foreign body reaction in marginal mass device-less subcutaneous islet transplantation in mice. *Transplantation*. 2016;100(7):1474-1479.
32. Pepper AR, Pawlick R, Gala-Lopez B, et al. Diabetes is reversed in a murine model by marginal mass syngeneic islet transplantation using a subcutaneous cell pouch device. *Transplantation*. 2015;99(11):2294-2300.
33. Ludwig B, Reichel A, Steffen A, et al. Transplantation of human islets without immunosuppression. *Proc Natl Acad Sci USA*. 2013;110(47):19054-19058.
34. Schulz TC. Concise review: manufacturing of pancreatic endoderm cells for clinical trials in type 1 diabetes. *Stem Cells Transl Med*. 2015;4(8):927-931.
35. Basta G, Montanucci P, Calafiore R. Islet transplantation versus stem cells for the cell therapy of type 1 diabetes mellitus. *Minerva Endocrinol*. 2015;40(4):267-282.
36. Fujikawa T, Oh SH, Pi L, Hatch HM, Shupe T, Petersen BE. Teratoma formation leads to failure of treatment for type I diabetes using embryonic stem cell-derived insulin-producing cells. *Am J Pathol*. 2005;166(6):1781-1791.
37. Mimeault M, Batra SK. Recent progress on normal and malignant pancreatic stem/progenitor cell research: therapeutic implications for the treatment of type 1 or 2 diabetes mellitus and aggressive pancreatic cancer. *Gut*. 2008;57(10):1456-1468.
38. Saxena P, Heng BC, Bai P, Folcher M, Zulewski H, Fussenegger M. A programmable synthetic lineage-control network that differentiates human iPSCs into glucose-sensitive insulin-secreting beta-like cells. *Nat Commun*. 2016;7:11247.
39. Cuthbertson RA, Mandel TE. A comparison of portal versus systemic venous drainage in murine foetal pancreatic islet transplantation. *Aust J Exp Biol Med Sci*. 1986;64(Pt 2):175-184.
40. Kim HI, Yu JE, Park CG, Kim SJ. Comparison of four pancreatic islet implantation sites. *J Korean Med Sci*. 2010;25(2):203-210.
41. Pedraza E, Brady AC, Fraker CA, Stabler CL. Synthesis of macroporous poly(dimethylsiloxane) scaffolds for tissue engineering applications. *J Biomater Sci Polym Ed*. 2013;24(9):1041-1056.
42. Montazeri L, Hojjati-Emami S, Bonakdar S, et al. Improvement of islet engrafts by enhanced angiogenesis and microparticle-mediated oxygenation. *Biomaterials*. 2016;89:157-165.
43. Chen X, Zhang X, Larson C, Chen F, Kissler H, Kaufman DB. The epididymal fat pad as a transplant site for minimal islet mass. *Transplantation*. 2007;84(1):122-125.
44. Gibly RF, Zhang X, Lowe WL Jr, Shea LD. Porous scaffolds support extrahepatic human islet transplantation, engraftment, and function in mice. *Cell Transplant*. 2013;22(5):811-819.
45. Hlavaty KA, Gibly RF, Zhang X, et al. Enhancing human islet transplantation by localized release of trophic factors from PLG scaffolds. *Am J Transplant*. 2014;14(7):1523-1532.
46. de Vos P, Hillebrands JL, de Haan BJ, Strubbe JH, van Schilfgaarde R. Efficacy of a prevascularized expanded polytetrafluoroethylene solid support system as a transplantation site for pancreatic islets. *Transplantation*. 1997;63(6):824-830.
47. Chang R, Faleo G, Russ HA, et al. Nanoporous immunoprotective device for stem-cell-derived beta-cell replacement therapy. *ACS Nano*. 2017;11(8):7747-7757.
48. Stendahl JC, Kaufman DB, Stupp SI. Extracellular matrix in pancreatic islets: relevance to scaffold design and transplantation. *Cell Transplant*. 2009;18(1):1-12.
49. Carlsson PO, Espes D, Sedigh A, et al. Transplantation of macroencapsulated human islets within the bioartificial pancreas betaAir to patients with type 1 diabetes mellitus. *Am J Transplant*. 2017. <https://doi.org/10.1111/ajt.14642>
50. Pileggi A, Molano RD, Ricordi C, et al. Reversal of diabetes by pancreatic islet transplantation into a subcutaneous, neovascularized device. *Transplantation*. 2006;81(9):1318-1324.
51. Cunha JP, Leuckx G, Sterkendries P, et al. Human multipotent adult progenitor cells enhance islet function and revascularisation when co-transplanted as a composite pellet in a mouse model of diabetes. *Diabetologia*. 2017;60(1):134-142.
52. Summerfield A, Meurens F, Ricklin ME. The immunology of the porcine skin and its value as a model for human skin. *Mol Immunol*. 2015;66(1):14-21.

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