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Review

Stem Cell Strategies to Promote Islet Transplantation Outcomes

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Abstract:

Pancreas or islet transplantation is the only reliable cure for Type 1 Diabetes. However, shortage of donor tissue supply, longitudinal graft attrition due to innate and adaptive immunity and the recurrence of autoimmunity, as well as the harmful side-effects of chronic immunosuppressive therapy limit the wide-spread acceptance of islet transplantation as a mainstream cure for autoimmune diabetes. Herein, preclinical and clinical stem-cells-based research approaches aimed at obtaining large quantities of islets for transplantation, overcoming islet graft loss and dysfunction post-transplantation, discovering alternate transplant sites to improve graft survival, and understanding the concepts of immunogenicity and autoimmunity to auto-antigens expressed by autologous stem cells-derived β−cells are discussed in depth.

Keywords

Stem cells; islet transplantation; type 1 diabetes

1. Introduction

Type 1 diabetes (T1D) is caused by the progressive autoimmune attack of insulin producing cells in the pancreas, resulting eventually in the complete loss of glycometabolic control. To date, pancreas or islet transplantation remains the most reliable cure for T1D [1-4]. However, hurdles such as inadequate donor tissue supply, graft rejection, recurrence of autoimmunity, and the deleterious side effects associated with chronic immunosuppression have prevented islet transplantation from being accepted as a mainstream cure. To circumvent these obstacles and improve longitudinal islet graft survival outcomes, preclinical and clinical studies have focused on exploring alternate β−cell sources and sites for transplantation [5-10], novel immunosuppressives [3, 11-16] and other protective measures such as graft encapsulation [17-19]. The data obtained from these studies have definitively demonstrated the significant potential of stem cell-based strategies in improving experimental and clinical islet transplantation outcomes.

2. Stem Cell-Based Approaches to Overcome Limitations of Islet Transplantation

The advantages of stem cell-based strategies are two-fold: stem cells can not only differentiate into a self-replenishing supply of glucose-responsive insulin-producing cells for transplantation, but they can also improve transplantation outcomes on account of their proangiogenic, anti-apoptotic and immune-modulatory properties [6]. Stem cells from a variety of sources, for instance, embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), pancreas-derived multipotent precursor cells, pancreatic β−cell progenitors residing within the ductal epithelium, exocrine tissue or the islet proper, neural progenitor cells, amniotic fluid-derived stem cells, as well as facultative β−cell progenitors from the spleen, liver and the endometrium have all been tested for their β−cell-regenerative potential [6].

The use of pluripotent stem cells for deriving functional β−cells addresses some pertinent limitations that are incurred in the transplantation process, such as donor pancreas shortage as well as expensive, labor intensive organ procurement and islet isolation processes. Since pluripotent stem cells can be cryopreserved, they are also readily available for directed differentiation into β−like cells which is an added bonus [20, 21]. For instance, ESCs obtained from donated, in vitro fertilized ova can be propagated indefinitely to provide sufficient cells for virtually all medical applications [22, 23]. However, drawbacks do exist, as the embryonic nature of ESCs itself poses a major ethical problem and their allogenecity necessitates protection from immune attack.

The revolutionary discovery of iPSCs, somatic cells that can be reprogrammed to pluripotency, circumvents both the use of embryonic cells and allogeneic rejection [23-26]. Prior to iPSCs, the only autologous source of pluripotent stem cells was the prospective banking of umbilical cord blood. Currently, iPSC technology has progressed to a point where the possibility of using patient-specific iPSCs as a renewable source of autologous cells for cellular therapy without the concern of immune rejection led by major histocompatibility complex restriction, is a viable consideration [26-28]. Diabetic-patient iPSCs coupled with precision genome editing for gene correction could eventually permit a truly personalized approach to β−cell regeneration [29-32].

The immunomodulatory properties of stem cells can also be exploited to prevent, arrest or reverse autoimmune diabetes, ameliorate innate/alloimmune graft rejection, as well as prevent

recurrence of the disease. Numerous studies have demonstrated that co-transplantation of beneficial stem cells or accessory non-islet cells with islets can improve islet transplantation outcomes [10]. For instance, umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs), adipose tissue-derived MSCs (ASCs), bone-marrow derived MSCs (BM-MSCs) and hematopoietic stem cells (BM-HSCs) have all been shown to arrest β−cell destruction, preserve residual β−cell mass, facilitate endogenous β−cell regeneration, and ameliorate islet graft rejection [6]. These stem cells with their considerable immunomodulatory properties, alone or in combination with β−cell replacement strategies have been successful in reversing hyperglycemia in T1D [6]. In fact, autologous MSC infusion has been shown to arrest disease progression and preserve−cell function in patients with new-onset T1D [33].

3. Stem Cell-Based Strategies for Preventing Islet Graft Loss and Dysfunction Post-Transplantation

In the peri-transplant period following clinical intra-portal islet transplantation, a β−cell loss ranging from 5 to 47% has been estimated, based on plasma glutamic acid decarboxylase 65 [34]. Stress incurred by islets during the harvesting and transplantation processes such as the instant blood-mediated inflammatory reaction and the harmful effects of proinflammatory cytokines and hypoxia are major contributors to this initial loss [3]. The disrupted, impaired vascularization associated with the isolation process exposes islets to hypoxia and nutrient deprivation that continues until vascularization and inervation is reestablished in the liver [35, 36]. Additionally, alloimmune rejection and recurrence or persistence of autoimmunity [3], toxicity associated with requisite immuno-suppressive regimens [3, 37] as well as the gluco- and lipotoxicity [38, 39], amyloid formation [40] and liver ischemia [41] further compound the islet loss incurred following transplantation. Several studies to improve engraftment with cell therapy are currently ongoing (Clinical Trial.gov registration no. NCT00646724, NCT02384018).

3.1 Overcoming Loss of Transplanted Islet Mass

A comparison of stem cells from different sources clearly highlights the significant clinical potential of ESCs to generate large quantities of functional β−cells for transplantation [6, 42-45]. Cell encapsulation is an ingenuous technique that primarily offers the transplanted insulin-producing cells physical protection from immune attack, thus allowing the cells to survive without chronic immunosuppression. Additionally, this technology prevents tumor dissemination, another serious drawback associated with the use of ESCs that limits its therapeutic usage. Several encapsulation technologies are currently at different stages of being perfected for clinical application that would ultimately enable insulin-producing cells to survive and function following transplantation [9, 46, 47]. Currently, a Phase I/II trial (clinical trials identifier: NCT02239354) is being conducted by Viacyte Inc in which human ESCs at the early differentiation stage of endocrine progenitors are encased in a macroencapsulation device and implanted subcutaneously [44, 48-50]. Although these cells mature and are functional after transplantation, the encapsulation device itself prevents glucose-responsive insulin secretion by acting as a diffusion barrier [51-53]. IND approval has now been obtained by Viacyte Inc for a new encapsulation product that will enable the ESC−derived insulin-producing β−cells graft to be vascularized, however this will once again resurrect the problem of providing requisite immunosuppression [54].

An active, open label, interventional clinical trial is being conducted in patients with T1D at the Uppsala University Hospital Sweden to assess the safety and efficacy of transplanting macro-encapsulated human islets contained within a bioartificial pancreas β-Air device. The trial will investigate if this method improves glycaemic control and reduces incidences of hypoglycaemic episodes (Clinical trial.gov identifier NCT02064309) [17]. Very recently, Farina et al. even demonstrated the efficacy of a 3D-printed vascularized device for subcutaneous transplantation of human islets. However, pericapsular fibrotic overgrowth was often observed associated with poor survival of encapsulated islets [55]. Co-encapsulation or cotransplantation of MSCs with encapsulated islets has been shown to reduce the pericapsular fibrotic overgrowth and improve the functional outcome of allotransplants [56].

The Boston Autologous Islet Replacement Program (BAIRT) aims to differentiate autologous iPSCs to β−like cells for autologous transplantation into patients with clinical diabetes arising post-pancreatectomy for chronic pancreatitis. One of the benefits of iPSC derived β−cell grafts is that they can be scaled to generate the requisite large quantities of autologous β−cells for transplantation to ensure that insulin secretory capacity may be fully restored to healthy levels and the graft not be subjected to longitudinal attrition [57].

Researchers at Cornell University have recently developed an implantable, removable device: an ionized calcium-releasing, nano-porous polymer “thread” dubbed TRAFFIC ((Thread-Reinforced Alginate Fiber For Islets enCapsulation) to implant attached islets that are protected by a thin, hydrogel coating [58]. This technique allows the coated cells to be removed or replaced easily when they have outlived their usefulness. The hydrogel cover for the thread also prevents gaps between the capsules that may contribute to scar tissue development. Minimal invasive laparoscopic surgery would be required to implant the hydrogel-coated thread into the peritoneal cavity. With the help of Danish pharmaceutical collaborator Novo Nordisk, TRAFFIC has now received patent protection.

3.2 Overcoming Islet Dysfunction Following Transplantation

MSCs have been shown to improve islet function and survival following cotransplantation, owing to their anti-apoptotic, pro-angiogenic [59, 60] and graft-supporting immunomodulatory effects [61-63]. Interestingly, the pro-angiogenic effects of MSCs are augmented by hypoxia, thereby improving graft revascularization [64]. MSCs can also differentiate into perivascular smooth muscle cells (pericytes), thus promoting vessel stabilization [65, 66]. The immunomodulatory activities of MSCs include diminishing the activation and proliferation of various immune-competent cells such as natural killer cells, dendritic cells (DCs) and cytotoxic T cells and B cells; modulating the function, differentiation and chemotaxis of neutrophils and B cells, as well as the generation of regulatory T cells (Tregs) [10, 67-76]. They also protect grafted islets via their secretion of anti-inflammatory cytokines and growth factors such as hepatocyte growth factor (HGF) [59, 60, 77]. A recent in vitro study demonstrated reduction of hypoxia-induced damage in human islets with the use of MSC-preconditioned medium, indicating that MSCs produce factors that improve survival of islets undergoing hypoxia [78]. Transplantation of heterospheroids consisting of rat islet cells and human BM-MSCs also demonstrated effective angiogenesis and anti-apoptosis [59]. The islet/MSC heterospheroid transplantation not only insured that islets and BM-MSCs were located in the same area of the liver after intra-portal vein

transplantation, but also maintained higher insulin production levels when compared to the group in which islet cell clusters were transplanted alone [59]. Similarly, in nonobese diabetic (NOD) mice, successful omental engraftment of "Neo-Islets" accompanied with long-term euglycemia and the absence of hypoglycemia was observed even without chronic immunosuppression. The "Neo-Islets" were generated by ex vivo coaggregation of allogeneic islet cells with large numbers of MSCs [79]. Cotransplantation of MSCs with neonatal porcine islets also improved graft function in diabetic mice, with significantly earlier return to normoglycemia and revascularization, improved glucose tolerance and increased insulin content [80]. Nakamura et al have introduced a novel cell transplantation platform (CellSaic) consisting of human MSCs and petaloid pieces of recombinant peptide that can prevent cell death by arranging the cells in a mosaic [81]. When human MSC CellSaics were subcutaneously implanted with islets into diabetic mice, islet cell death was prevented, angiogenesis in the graft accelerated and glucose tolerance improved.

While their ready accessibility from the adipose tissue present in discarded lipoasperates makes ASCs an eminently attractive source of stem cells with regards to autologous transplantation, their functional similarity to BM-MSCs, such as their ability to increase secretion of angiogeneic growth factors on exposure to hypoxia and to promote neovascularization by overexpressing vascular endothelial growth factor-A, enhances their clinical applicability [82-88]. A very recent study demonstrated that when ASCs from the adipose tissue of chronic pancreatitis patients were cotransplanted with mouse or human islets, both longitudinal survival and function of islets were improved [89]. Secretion of IGF-1, promotion of angiogenesis and inhibition of inflammatory processes by ASCs were contributory factors for this positive effect.

A single arm, open-label, single-center pilot study to assess the safety, feasibility, and efficacy of Stem Cell Educator therapy for the treatment of patients with T1D is ongoing (ClinicalTrials.gov Identifier: NCT02624804). Briefly, the apparatus basically consists of a closed-loop system wherein the patient's blood is circulated through a blood cell separator, following which the separated lymphocytes are cocultured briefly with adherent human cord blood-derived multipotent stem cells (CB-SCs) in vitro. The "educated" lymphocytes are now introduced to the patient's circulation wherein they induce immune modulations that result in restoration of immune homeostasis as demonstrated by both preclinical and clinical data. Safety and ethical concerns generally associated with conventional stem cell-based approaches are a non-issue with this procedure [90].

Cotransplantation of neural crest stem cells (NCSCs) with islets has also been shown to promote insulin release and β−cell proliferation in the islet graft [91, 92]. Surface coating of pancreatic islets with NCSCs improved engraftment and function after intraportal transplantation [93]. More importantly, NSCSs have significant therapeutic potential since they can be retrieved from adult tissues such as skin, thus harboring the potential for autologous use [94]. Several preclinical studies have described the beneficial effects endothelial progenitor cells (EPCs) on islet graft survival when islets are co-transplanted with EPCs [95-98]. A syngeneic islet intraportal transplantation study demonstrated that granulocyte-macrophage colony stimulating factor was able to mobilize recipient bone marrow-derived EPCs peripherally, wherein they enhanced revascularization of the grafted islets and promoted graft survival [99]. EPC-derived effects include direct differentiation into new vessels and pericytes, enhanced insulin secretion and coordinated β−cell function [96, 98, 99]. EPCs also release microvesicles that carry proangiogenic microRNAs which enhance syngeneic islet graft function, survival and vascularization [10, 100]. Human multipotent adult progenitor cells also secrete large amounts of angiogenic growth factors, and

cotransplantation of mouse pancreatic islets with these cells was shown to enhance graft vascularization and subsequent islet graft function [101].

Apart from stem cells, co-transplantation of islets with tolerogenic cells such as myeloid-derived suppressor cells (MDSCs) has also been shown to prolong islet allograft survival though iNOS-mediated T-cell inhibition in immunocompetent diabetic mice [102]. MDSCs suppress T cell function and proliferation and promote the development of regulatory T cells (Tregs) through the costimulatory molecule B7-H1 [103-105]. In fact, intra-portal transplantation of co-aggregates composed of mouse Tregs with allogeneic mouse islet cells was shown to support longitudinal islet graft survival in the absence of any immunosuppression [106]. Similarly, adoptive transfer of in vitro expanded human Tregs into recipient humanized immunocompetent diabetic mice was shown to delay human islet graft rejection [107]. Currently at the Cell Transplantation and Gene Therapy Institute in China, an open label interventional clinical trial is enrolling for a study wherein neonatal porcine islets will be xenotransplanted in diabetic patients that will simultaneously receive autologous T regulatory cells to induce specific immune tolerance for porcine islets grafts along with immunosuppression (ClinicalTrials.gov Identifier: NCT03162237). Mouse islet co-transplantation with hepatic stellate cells (HepSCs) also induces immune tolerance towards islet allografts in mouse via the recruitment of MDSCs [108, 109]. HepSCs display immunosuppressive properties by promoting Treg induction, inducing T-cell apoptosis and inhibiting cytotoxic CD8+ T cells. Several studies also indicate the role of DCs in promoting permanent islet allograft acceptance [110-112].

3.3 Alternate Transplantation Sites

There are several disadvantages of using the liver as the transplantation site, such as the instant blood-mediated inflammatory reaction, relative hypoxia, as well as the potential complications of portal hypertension, bleeding, portal vein thrombosis and hepatic ischaemia [113, 114]. Infusion into the liver restricts the transplantable islet tissue volume since increased volume is associated with portal hypertension and acute thrombosis [115]. To circumvent these problems, clinical trials are being conducted using extrahepatic sites for islet transplantation. The outcomes of trials using the omentum (ClinicalTrials.gov id NCT02213003, NCT02803905), subcutaneous tissue (NCT01652911), gastric submucosa (NCT02402439), intramuscular (NCT02872571, NCT01967186), bone marrow [116], and the anterior chamber of the eye (NCT02916680, NCT02846571) amongst other transplant sites, may yield new insights towards improving transplantation outcomes in the future.

3.4 Immunogenicity and Autoimmunity to Autoantigens Expressed by Autologous Stem Cell Derived –Cells

A final point to consider is the possibility that reprogramming, differentiation, the types of cells generated, as well as the implant site may render iPSCs and their derivatives more or less susceptible to immune rejection [117]. Genetic and epigenetic defects appear directly or indirectly associated to the immunogenicity of the iPSC derivatives. Although this immunogenicity may be weaker in comparison to that of allografts, they can elicit serious rejection of the transplanted tissue [117]. Therefore, it is absolutely imperative to carry out extensive genetic/epigenetic screening of iPSCs in order to ensure their clinical safety, along with stringent evaluation of the

immunogenicity of cells that have been derived from patient-specific iPSCs, prior to their clinical usage. However, regarding immunogenicity, several recent studies have reported negligible or limited immunogenicity of the transplanted iPSC-derived cells [118, 119]. In fact, to the contrary, autologous iPSC-derived cell grafts have been shown to induce self-tolerant immune mechanisms [120], This indicates that despite differences in antigenic expression that exist between somatic cells and iPSC-derived cells, the differentiation of iPSCs itself may be responsible for the observed loss of immunogenicity and induction of tolerance. While it is apparent from these studies that iPSC-derived cells are eminently suitable candidates for cell replacement therapy, it is important to keep in mind that the type of cells that are generated from iPSCs may influence their immune susceptibility.

Last but not least, the possibility of the immune system mounting an attack against the autologous stem cell-derived β cells should not be overlooked. There is always the threat that prior exposure to autologous islet antigens may trigger the immune system to reject the iPSC-derived β−cells expressing autoantigens such as GAD65 (glutamic acid decarboxylase), ZnT8 (zinc transporter 8), Tspan7 (tetraspannin 7), and IA-2 (insulinoma antigen 2) [117]. To overcome the risk of autoimmunity when using β−cells derived from diabetic-patient iPSCs for transplantation, precision genome editing for gene correction is a possible strategy for consideration [121].

4. Conclusions

Stem cell-based strategies for providing a potentially limitless source of β−cells for transplantation as well as for promoting islet graft survival, is a rapidly expanding field of research that is hampered by limitations such as immune recognition of these cells by the host and their subsequent destruction. Although the development of novel biomaterials for encapsulation and ingenious encapsulation techniques demonstrate significant potential in circumventing the need for toxic and chronic immunosuppressive therapy and for promoting engraftment, several challenges remain. Therefore, studies aimed at identifying safe, reliable and scalable tissue sources, at refining islet and stem cell isolation and culture protocols, and at improving longitudinal graft survival need to be ramped up in order to make permanent islet graft acceptance and insulin independence following transplantation a reality.

Author Contributions

Dr. Preeti Chhabra contributed to writing and proof-reading this article. Dr. Kenneth L. Brayman contributed to writing and proof-reading this article.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Chhabra P, Brayman KL. Overcoming barriers in clinical islet transplantation: current limitations and future prospects. Curr Prob Surg. 2014; 51: 49-86.
2. Ramesh A, Chhabra P, Brayman KL. Pancreatic islet transplantation in type 1 diabetes mellitus: an update on recent developments. Curr Diabetes Rev. 2013; 9: 294-311.

3. Chhabra P, Brayman KL. Current status of immunomodulatory and cellular therapies in preclinical and clinical islet transplantation. J Transplant. 2011; 2011: 637692.
4. Huang X, Moore DJ, Ketchum RJ, Nunemaker CS, Kovatchev B, Mccall AL, et al. Resolving the conundrum of islet transplantation by linking metabolic dysregulation, inflammation, and immune regulation. Endocr Rev. 2008; 29: 603-630.
5. Schuetz C, Anazawa T, Cross SE, Labriola L, Rph M, Scholz H, et al. β cell replacement therapy: the next 10 years. Transplantation. 2018; 102: 215-229.
6. Preeti C, Brayman KL. Stem cell therapy to cure type 1 diabetes: from hype to hope. Stem Cells Transl Med. 2013; 2: 328-336.
7. Chhabra P, Brayman KL. The use of stem cells in kidney disease. Curr Opin Organ Transplant. 2009; 14: 72-78.
8. Chhabra P, Mirmira RG, Brayman KL. Regenerative medicine and tissue engineering: contribution of stem cells in organ transplantation. Curr Opin Organ Transplant. 2009; 14: 46-50.
9. Lysy PA, Weir GC, Susan BW. Concise veview: pancreas regeneration: recent advances and perspectives. Stem Cells Transl Med. 2012; 1: 150-159.
10. Staels W, De GS, Heremans Y, Coppens V, Van GN, Leuckx G, et al. Accessory cells for β-cell transplantation. Diabetes Obes Metab. 2016; 18: 115-124.
11. Chhabra P, Schlegel K, Okusa MD, Lobo PI, Brayman KL. Naturally occurring immunoglobulin M (nIgM) autoantibodies prevent autoimmune diabetes and mitigate inflammation after transplantation. Ann Surg. 2012; 256: 634-641.
12. Bowers PCD. Anti-inflammatory interventional strategies to promote islet transplantation outcomes. Surg Curr Res. 2014; 4: e116.
13. Chhabra P, Linden J, Lobo P, Okusa MD, Brayman KL. The immunosuppressive role of adenosine A2A receptors in ischemia reperfusion injury and islet transplantation. Curr Diabetes Rev. 2012; 8: 419-433.
14. Chhabra P, Wang K, Zeng Q, Jecmenica M, Langman L, Linden J, et al. Adenosine A(2A) agonist administration improves islet transplant outcome: evidence for the role of innate immunity in islet graft rejection. Cell Transplant. 2010; 19: 597-612.
15. Sharma AK, Kinsey GR, Chhabra P, Brayman KL, French BA, Glover DK, et al. Anti-inflammatory and immunosuppressive actions of adenosine A2A receptor in ischemia-reperfusion injury after organ transplantation. In “Adenosine receptors: pharmacology, fnctions and terapeutic apects” 1 ed. Warrick K, editor. New York, USA: NOVA Science Publishers; 2015. Chapter 1, p.1-35.
16. Chhabra P, Kensinger CD, Moore DJ, Brayman KL. Present accomplishments and future prospects of cell-based therapies for type 1 diabetes mellitus. In: Type 1 gabetes – pthogenesis, gnetics and imunotherapy 1 ed. Wagner D, editor. Croatia: InTech; 2011. Chapter14, p. 295-336.
17. Carlsson PO, Espes D, Sedigh A, Rotem A, Zimermann B, Grinberg H, et al. Transplantation of macroencapsulated human islets within the bioartificial pancreas βAir to patients with type 1 diabetes mellitus. Am J Transplant. 2017; DOI: 10.1111/ajt.14642.
18. Bowers DT, Olingy CE, Chhabra P, Langman L, Merrill PH, Linhart RS, et al. An engineered macroencapsulation membrane releasing FTY720 to precondition pancreatic islet transplantation. J Biomed Mater Res B Appl Biomater. 2018; 106: 555-568.

19. Bowers DT, Chhabra P, Langman L, Botchwey EA, Brayman KL. FTY720-loaded poly(DL-lactide-co-glycolide) electrospun scaffold significantly increases microvessel density over 7 days in streptozotocin-induced diabetic C57b16/J mice: preliminary results. Transplant Proc. 2011; 43: 3285-3287.
20. Crook JM, Tomaskovic-Crook E, Ludwig TE, Crook JM, Tomaskovic-Crook E, Ludwig TE, et al. Cryobanking pluripotent stem cells. Methods Mol Biol. 2017; 1590: 151-164.
21. Pavón A, Beloqui I, Salcedo JM, Martin AG. Cryobanking mesenchymal stem cells. Methods Mol Biol. 2017; 1590: 191-196.
22. Ilic D, Ogilvie C. Human embryonic stem cells-What have we done? What are we doing? Where are we going? Stem Cells. 2017; 35: 17-25.
23. Martello G, Smith A. The nature of embryonic stem cells. Annu Cell Dev Biol. 2014; 30: 647-675.
24. Volarevic V, Markovic BS, Gazdic M, Volarevic A, Jovicic N, Arsenijevic N, et al. Ethical and safety issues of stem cell-based therapy. Int J Med Sci. 2018; 15: 36-45.
25. Kooreman NG, de Almeida PE, Stack JP, Nelakanti RV, Diecke S, Shao NY, et al. Alloimmune responses of humanized mice to human pluripotent stem cell therapeutics. Cell Rep. 2017; 20: 1978-1990.
26. Liu X, Li W, Fu X, Xu Y. The immunogenicity and immune tolerance of pluripotent stem cell derivatives. Front Immunol. 2017; 8: 645.
27. Hossain MK, Dayem AA, Han J, Saha SK, Yang GM, Choi HY, et al. Recent advances in disease modeling and drug discovery for diabetes mellitus using induced pluripotent stem cells. Int J Mol Sci. 2016; 17: 256.
28. Jin X, Lin T, Xu Y. Stem cell therapy and immunological rejection in animal models. Curr Mol Pharmacol. 2016; 9: 284-288.
29. Millman JR, Xie C, Dervort AV, Gürtler M, Pagliuca FW, Melton DA. Generation of stem cell-derived β-cells from patients with type 1 diabetes. Nat Commun. 2016; 7: 11463.
30. Chang CY, Ting HC, Su HL, Jeng JR. Combining induced pluripotent stem cells and genome editing technologies for clinical applications. Cell Transplant. 2017. DOI: 10.3727/096368917X695119.
31. Hockemeyer D, Jaenisch R. Induced pluripotent stem cells meet genome editing. Cell Stem Cell. 2016; 18: 573-586.
32. Hamazaki T, Rouby NE, Fredette NC, Santostefano KE, Terada N. Concise review: induced pluripotent stem cell research in the era of precision medicine. Stem Cells. 2017; 35: 545-550.
33. Carlsson PO, Schwarcz E, Korsgren O, Le BK. Preserved β-cell function in type 1 diabetes by mesenchymal stromal cells. Diabetes. 2015; 64: 587-592.
34. Zhidong L, Pieter DP, Rui M, Pieter G, Hampe CS, Martens GA, et al. Plasma GAD65, a marker for early β-cell loss after intraportal islet cell transplantation in diabetic patients. J Clin Endocrinol Metab. 2015; 100: 2314-2321.
35. Linn T, Schmitz J, Hauck-Schmalenberger I, Lai Y, Bretzel RG, Brandhorst H, et al. Ischaemia is linked to inflammation and induction of angiogenesis in pancreatic islets. Clin Exp Immunol. 2006; 144: 179-187.
36. Korsgren O, Jansson L, Andersson A, Sundler F. Reinnervation of transplanted pancreatic islets: a comparison between islets implanted into the kidney, spleen, or liver. Transplantation. 1993; 56: 138-143.

37. Desai NM, Goss JA, Deng S, Wolf BA, Markmann E, Palanjian M, et al. Elevated portal vein drug levels of sirolimus and tacrolimus in islet transplant recipients: local immunosuppression or islet toxicity? Transplantation. 2003; 76: 1623-1625.
38. Leitão CB, Bernetti K, Tharavanij T, Cure P, Lauriola V, Berggren PO, et al. Lipotoxicity and decreased islet graft survival. Diabetes Care. 2010; 33: 658-660.
39. Ngo A, Sutherland DER, Beilman GJ, Bellin MD. Deterioration of glycemic control after corticosteroid administration in islet autotransplant recipients: a cautionary tale. Acta Diabetol. 2014; 51: 141-145.
40. Westermark GT, Westermark P, Berne C, Korsgren O. Widespread amyloid deposition in transplanted human pancreatic islets. N Engl J Med. 2008; 359: 977-979.
41. Yin D, Ding JJ, Ma L, Hara M, Chong AS. Liver ischemia contributes to early islet failure following intraportal transplantation: benefits of liver ischemic-preconditioning. Am J Transplant. 2006; 6: 60–68.
42. Weir GC, Caveltiweder C, Bonnerweir S. Stem cell approaches for diabetes: towards beta cell replacement. Genome Med. 2011; 3: 1-9.
43. Kunjom MJ, Chen B, Sui L, Karen S, Luc B. Recent advances and prospects in the differentiation of pancreatic cells from human embryonic stem cells. Diabetes. 2010; 59: 2094-2101.
44. Kroon E, Martinson LA, Kadoya K, Bang AG, Kelly OG, Eliazer S, et al. Pancreatic endoderm derived from human embryonic stem cells generates glucose-responsive insulin-secreting cells in vivo. Nat Biotechnol. 2008; 26: 443-452.
45. Bose B, Shenoy SP, Konda S, Wangikar P. Human embryonic stem cell differentiation into insulin secreting β-cells for diabetes. Cell Biol Int. 2012; 36: 1013-1020.
46. O'Sullivan ES, Vegas A, Anderson DG, Weir GC. Islets transplanted in immunoisolation devices: a review of the progress and the challenges that remain. Endocr Rev. 2011; 32: 827-844.
47. Tuch BE, Hughes TC, Evans MD. Encapsulated pancreatic progenitors derived from human embryonic stem cells as a therapy for insulin-dependent diabetes. Diabetes Metab Res Rev. 2011; 27: 928-932.
48. Bruin JE, Rezania A, Xu J, Narayan K, Fox JK, O'Neil JJ, et al. Maturation and function of human embryonic stem cell-derived pancreatic progenitors in macroencapsulation devices following transplant into mice. Diabetologia. 2013; 56: 1987-1998.
49. Agulnick AD, Ambruzs DM, Moorman MA, Bhoumik A, Cesario RM, Payne JK, 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: 1214-1222.
50. Motté E, Szepessy E, Suenens K, Stangé G, Bomans M, Jacobstulleneersthevissen D, et al. Composition and function of macroencapsulated human embryonic stem cell-derived implants: comparison with clinical human islet cell grafts. Am J Physiol Endocrinol Metab. 2014; 307: E838-E846.
51. Johnson JD. The quest to make fully functional human pancreatic beta cells from embryonic stem cells: climbing a mountain in the clouds. Diabetologia. 2016; 59: 2047-2057.
52. Korsgren E, Korsgren O. Glucose effectiveness: the mouse trap in the development of novel ß-cell replacement therapies. Transplantation. 2016; 100: 111-115.

53. Trivedi N, Keegan M, Steil GM, Hollisterlock J, Hasenkamp WM, Colton CK, et al. Islets in alginate macrobeads reverse diabetes despite minimal acute insulin secretory responses. Transplantation. 2001; 71: 203-211.
54. ViaCyte. ViaCyte receives IND allowance from FDA and clearance from Health Canada to commence international clinical trial of PEC-direct cell therapy for high-risk type 1 diabetes. http://viacyte.com/press-releases/viacyte-receives-ind-allowance-from-fda-and-clearance-from-health-canada-to-commence-international-clinical-trial-of-pec-direct-cell-therapy-for-high-risk-type-1-diabetes/. Published May 22, 2017.
55. Farina M, Ballerini A, Fraga DW, Nicolov E, Hogan M, Demarchi D, et al. 3D printed vascularized device for subcutaneous transplantation of human islets. Biotechnol J. 2017; 12: 1700268.
56. Vaithilingam V, Evans M, Lewy DM, Bean PA, Bal S, Tuch BE. Co-encapsulation and co-transplantation of mesenchymal stem cells reduces pericapsular fibrosis and improves encapsulated islet survival and function when allografted. Sci Rep. 2017; 7: 10059.
57. Pagliuca FW, Millman JR, Gürtler M, Segel M, Dervort AV, Ryu JH, et al. Generation of functional human pancreatic β cells in vitro. Cell. 2014; 159: 428-439.
58. An D, Chiu A, Flanders JA, Song W, Shou D, Lu YC, et al. Designing a retrievable and scalable cell encapsulation device for potential treatment of type 1 diabetes. Proc Natl Acad Sci U S A. 2018; 115: E263-E272.
59. Shin JY, Jeong JH, Han J, Bhang SH, Jeong GJ, Haque MR, et al. Transplantation of heterospheroids of islet cells and mesenchymal stem cells for effective angiogenesis and antiapoptosis. Tissue Eng Part A. 2015; 21: 1024-1035.
60. Fabryova E, Jirak D, Girman P, Zacharovova K, Galisova A, Saudek F, et al. Effect of mesenchymal stem cells on the vascularization of the artificial site for islet transplantation in rats. Transplant Proc. 2014; 46: 1963-1966.
61. English K. Mesenchymal stem cells to promote islet transplant survival. Curr Opin Organ Transplant. 2016; 21: 568-573.
62. Davis NE, Hamilton D, Fontaine MJ. Harnessing the immunomodulatory and tissue repair properties of mesenchymal stem cells to restore β cell function. Curr Diabetes Rep. 2012; 12: 612-622.
63. Park KS, Kim YS, Kim JH, Choi B, Kim SH, Tan AH, et al. Trophic molecules derived from human mesenchymal stem cells enhance survival, function, and angiogenesis of isolated islets after transplantation. Transplantation. 2010; 89: 509-517.
64. Schive SW, Mirlashari MR, Hasvold G, Wang M, Josefsen D, Gullestad HP, et al. Human adipose-derived mesenchymal stem cells respond to short-term hypoxia by secreting factors beneficial for human islets in vitro and potentiate antidiabetic effect in vivo. Cell Med. 2017; 9: 103-116.
65. Wong SP, Rowley JE, Redpath AN, Tilman JD, Fellous TG, Johnson JR. Pericytes, mesenchymal stem cells and their contributions to tissue repair. Pharmacol Ther. 2015; 151: 107-120.
66. Ahmed TA, Elbadri N. Pericytes: The role of multipotent stem cells in vascular maintenance and regenerative medicine. Adv Exp Med Biol. 2017. DOI: 10.1007/5584_2017_138.
67. Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. Stem Cells. 2006; 24: 74–85.

68. Chen L, Zhang W, Yue H, Han Q, Chen B, Shi M, et al. Effects of human mesenchymal stem cells on the differentiation of dendritic cells from CD34+ cells. Stem Cells Dev. 2007; 16: 719-731.
69. Jiang XX, Zhang Y, Liu B, Zhang SX, Wu Y, Yu XD, et al. Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. Blood. 2005; 105: 4120-4126.
70. Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood. 2005; 105: 1815-1822.
71. Casiraghi F, Azzollini N, Cassis P, Imberti B, Morigi M, Cugini D, et al. Pretransplant infusion of mesenchymal stem cells prolongs the survival of a semiallogeneic heart transplant through the generation of regulatory T cells. J Immunol. 2008; 181: 3933-3946.
72. Sato K, Ozaki K, Oh I, Meguro A, Hatanaka K, Nagai T, et al. Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. Blood. 2007; 109: 228-234.
73. Selmani Z, Naji A, Zidi I, Favier B, Gaiffe E, Obert L, et al. Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4+CD25highFOXP3+ regulatory T cells. Stem Cells. 2008; 26: 212-222.
74. Engela AU, Baan CC, Peeters AM, Weimar W, Hoogduijn MJ. Interaction between adipose tissue-derived mesenchymal stem cells and regulatory T-cells. Cell Transplant. 2013; 22: 41-54.
75. Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, Cazzanti F, et al. Human mesenchymal stem cells modulate B-cell functions. Blood. 2006; 107: 367-372.
76. Raffaghello L, Bianchi G, Bertolotto M, Montecucco F, Busca A, Dallegri F, et al. Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche. Stem Cells. 2008; 26: 151-162.
77. Yeung TY, Seeberger KL, Kin T, Adesida A, Jomha N, Shapiro AMJ, et al. Human mesenchymal stem cells protect human islets from pro-inflammatory cytokines. Plos One. 2012; 7: e38189.
78. Brandhorst D, Brandhorst H, Acreman S, Schive SW, Bjørnson HS, Johnson P. Hypoxia-induced damage in human islets is reduced with the use of mesenchymal stem cell-preconditioned medium. Transplant Proc. 2017; 49: 2330-2332.
79. Westenfelder C, Gooch A, Hu Z, Ahlstrom J, Zhang P. Durable control of autoimmune diabetes in mice achieved by intraperitoneal transplantation of “Neo-Islets,” three-dimensional aggregates of allogeneic islet and “Mesenchymal Stem Cells”. Stem Cells Transl Med. 2017; 6: 1631-1643.
80. Hayward JA, Ellis CE, Seeberger K, Lee T, Salama B, Muletsierra A, et al. Co-transplantation of mesenchymal stem cells with neonatal porcine islets improve graft function in diabetic mice. Diabetes. 2017; 66: 1312-1321.
81. Nakamura K, Iwazawa R, Yoshioka Y. Introduction to a new cell transplantation platform via recombinant peptide petaloid pieces and its application to islet transplantation with mesenchymal stem cells. Transpl Int. 2016; 29: 1039-1050.
82. Tang W, Zeve D, Suh JM, Bosnakovski D, Kyba M, Hammer RE, et al. White fat progenitor cells reside in the adipose vasculature. Science. 2008; 322: 583-586.
83. Mizuno H. Adipose-derived stem cells for tissue repair and regeneration: ten years of research and a literature review. J Nippon Med Sch. 2009; 76: 56-66.

84. Rehman J, Traktuev D, Li J, Merfeldclauss S, Temmgrove CJ, Bovenkerk JE, et al. Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. Circulation. 2004; 109: 1292-1298.
85. Kuo YR, Wang CT, Cheng JT, Kao GS, Chiang YC, Wang CJ. Adipose-derived stem cells accelerate diabetic wound healing through the induction of autocrine and paracrine effects. Cell Transplant. 2016; 25: 71-81.
86. Fumimoto Y, Matsuyama A, Komoda H, Okura H, Lee CM, Nagao A, et al. Creation of a rich subcutaneous vascular network with implanted adipose tissue-derived stromal cells and adipose tissue enhances subcutaneous grafting of islets in diabetic mice. Tissue Eng Part C Methods. 2009; 15: 437-444.
87. Bhang SH, Min JJ, Shin JY, La WG, Yong HH, Min JK, et al. Mutual effect of subcutaneously transplanted human adipose-derived stem cells and pancreatic islets within fibrin gel. Biomaterials. 2013; 34: 7247-7256.
88. Cavallari G, Olivi E, Bianchi F, Neri F, Foroni L, Valente S, et al. Mesenchymal stem cells and islet cotransplantation in diabetic rats: improved islet graft revascularization and function by human adipose tissue-derived stem cells preconditioned with natural molecules. Cell Transplant. 2012; 21: 2771-2781.
89. Song L, Sun Z, Kim DS, Gou W, Strange C, Dong H, et al. Adipose stem cells from chronic pancreatitis patients improve mouse and human islet survival and function. Stem Cell Res Ther. 2017; 8: 192.
90. Zhao Y, Jiang Z, Zhao T, Ye M, Hu C, Yin Z, et al. Reversal of type 1 diabetes via islet β cell regeneration following immune modulation by cord blood-derived multipotent stem cells. BMC Med. 2012; 10: 3.
91. Olerud J, Kanaykina N, Vasylovska S, Vasilovska S, King D, Sandberg M, et al. Neural crest stem cells increase beta cell proliferation and improve islet function in co-transplanted murine pancreatic islets. Diabetologia. 2009; 52: 2594-2601.
92. Grapensparr L, Vasylovska S, Li Z, Olerud J, Jansson L, Kozlova E, et al. Co-transplantation of human pancreatic islets with post-migratory neural crest stem cells increases β-cell proliferation and vascular and neural regrowth. J Clin Endocrinol Metab. 2015; 100: E583-E590.
93. Lau J, Vasylovska S, Kozlova E, Carlsson PO. Surface-coating of pancreatic islets with neural crest stem cells improves engraftment and function after intraportal transplantation. Cell Transplant. 2015; 24: 2263-2272.
94. Yang R, Xu X. Isolation and culture of neural crest stem cells from human hair follicles. J Vis Exp. 2013; 6: e3194.
95. Kim JH, Oh BJ, Lee HN, Park HS, Park SG, Park KS. Endothelial colony-forming cell coating of pig islets prevents xenogeneic instant blood-mediated inflammatory reaction. Cell Transplant. 2011; 20: 1805-1815.
96. Kang S, Park HS, Jo A, Hong SH, Han NL, Lee YY, et al. Endothelial progenitor cell cotransplantation enhances islet engraftment by rapid revascularization. Diabetes. 2012; 61: 866-876.
97. Oh BJ, Oh SH, Jin SM, Suh S, Bae JC, Park CG, et al. Co-transplantation of bone marrow-derived endothelial progenitor cells improves revascularization and organization in islet grafts. Am J Transplant. 2013; 13: 1429-1440.

98. Penko D, Rojascanales D, Mohanasundaram D, Peiris HS, Sun WY, Drogemuller CJ, et al. Endothelial progenitor cells enhance islet engraftment, influence β-cell function, and modulate islet connexin 36 expression. Cell Transplant. 2015; 24: 37-48.
99. Contreras JL, Smyth CA, Eckstein C, Bilbao G, Thompson JA, Young CJ, et al. Peripheral mobilization of recipient bone marrow-derived endothelial progenitor cells enhances pancreatic islet revascularization and engraftment after intraportal transplantation. Surgery. 2003; 134: 390-398.
100. Cantaluppi V, Gatti S, Medica D, Figliolini F, Bruno S, Deregibus MC, et al. Microvesicles derived from endothelial progenitor cells protect the kidney from ischemia|[ndash]|reperfusion injury by microRNA-dependent reprogramming of resident renal cells. Kidney Int. 2012; 82: 412-427.
101. Cunha JP, Leuckx G, Sterkendries P, Korf H, Bomfimferreira G, Overbergh L, 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: 134-142.
102. Arakawa Y, Qin J, Chou HS, Bhatt S, Wang L, Stuehr D, et al. Co-transplantation with myeloid-derived suppressor cells protects cell transplants: a crucial role of inducible nitric oxide synthase. Transplantation. 2014; 97: 740-747.
103. Chou HS, Hsieh CC, Charles R, Wang L, Wagner T, Fung JJ, et al. Myeloid-derived suppressor cells protect islet transplants by B7-H1 mediated enhancement of T regulatory cells. Transplantation. 2012; 93: 272-282.
104. Yin B, Ma G, Yen CY, Zhou Z, Wang GX, Divino CM, et al. Myeloid-derived suppressor cells prevent type 1 diabetes in murine models. J Immunol. 2010; 185: 5828-5834.
105. Zhang W, Li J, Qi G, Tu G, Yang C, Xu M. Myeloid-derived suppressor cells in transplantation: the dawn of cell therapy. J Transl Med. 2018; 16: 19.
106. Takemoto N, Konagaya S, Kuwabara R, Iwata H. Coaggregates of regulatory T cells and islet cells allow long-term graft survival in liver without immunosuppression. Transplantation. 2015; 99: 942-947.
107. Xiao F, Ma L, Zhao M, Huang G, Mirenda V, Dorling A, et al. Ex vivo expanded human regulatory T cells delay islet allograft rejection via inhibiting islet-derived monocyte chemoattractant protein-1 production in CD34+ stem cells-reconstituted NOD-scid IL2rγnull mice. Plos One. 2014; 9: e90387.
108. Zhang ZY, Zhou ZQ, Song KB, Kim SC, Zhou GW. Hepatic stellate cells induce immunotolerance of islet allografts. Transplant Proc. 2014; 46: 1594-1600.
109. Chou HS, Hsieh CC, Yang HR, Wang L, Arakawa Y, Brown K, et al. Hepatic stellate cells regulate immune response by way of induction of myeloid suppressor cells in mice. Hepatology. 2011; 53: 1007–1019.
110. Baas MC, Kuhn C, Valette F, Mangez C, Duarte MS, Hill M, et al. Combining autologous dendritic cell therapy with CD3 antibodies promotes regulatory T cells and permanent islet allograft acceptance. J Immunol. 2014; 193: 4696-4703.
111. Sun G, Shan J, Li Y, Zhou Y, Guo Y, Wu W, et al. Adoptive infusion of tolerogenic dendritic cells prolongs the survival of pancreatic islet allografts: a systematic review of 13 mouse and rat studies. Plos One. 2012; 7: e52096.

112. Thomas DC, Wong FS, Zaccone P, Green EA, Wållberg M. Protection of islet grafts through transforming growth factor-β–induced tolerogenic dendritic cells. Diabetes. 2013; 62: 3132-3142.
113. Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, et al. Five-year follow-up after clinical islet transplantation. Diabetes. 2005; 54: 2060-2069.
114. Stokes RA, Cheng K, Lalwani A, Swarbrick MM, Thomas HE, Loudovaris T, et al. Transplantation sites for human and murine islets. Diabetologia. 2017; 60: 1961-1971.
115. Wilhelm JJ, Bellin MD, Dunn TB, Balamurugan AN, Pruett TL, Radosevich DM, et al. Proposed thresholds for pancreatic tissue volume for safe intraportal islet autotransplantation after total pancreatectomy. Am J Transplant. 2013; 13: 3183–3191.
116. Maffi P, Balzano G, Ponzoni M, Nano R, Sordi V, Melzi R, et al. Autologous pancreatic islet transplantation in human bone marrow. Diabetes. 2013; 62: 3523-3531.
117. Sordi V, Pellegrini S, Piemonti L. Immunological issues after stem cell-based β cell replacement. Curr Diabetes Rep. 2017; 17: 68.
118. Araki R, Uda M, Hoki Y, Sunayama M, Nakamura M, Ando S, et al. Negligible immunogenicity of terminally differentiated cells derived from induced pluripotent or embryonic stem cells. Nature. 2013; 494: 100-104.
119. Guha P, Morgan J, Mostoslavsky G, Rodrigues N, Boyd A. Lack of immune response to differentiated cells derived from syngeneic induced pluripotent stem cells. Cell Stem Cell. 2013; 12: 407-412.
120. de Almeida PE, Meyer EH, Kooreman NG, Diecke S, Dey D, Sanchezfreire V, et al. Transplanted terminally differentiated induced pluripotent stem cells are accepted by immune mechanisms similar to self-tolerance. Nat Commun. 2014; 5: 3903.
121. Kieffer TJ, Woltjen K, Osafune K, Yabe D, Inagaki N. Beta-cell replacement strategies for diabetes. J Diabetes Investig. 2017. DOI: 10.1111/jdi.12758.