

Recent Progress in Clinical Islet Transplantation

Jae Berm Park, Sung Joo Kim

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Allo-islet transplantation is believed to be a promising treatment for normalizing blood glucose levels without hypoglycemic episodes in patients with type 1 diabetes mellitus (T1DM). In 2000, a pioneering study by the Edmonton group showed that allo-islet transplantation could achieve insulin independence for at least 1 year post-transplantation in all seven consecutive patients. This breakthrough study excited numerous researchers, clinicians, and patients. Although longer follow-up studies did not have the same success as the first study, substantial efforts to establish successful islet transplantation have been made in the last decade. Several leading centers of islet transplantation have reported success rates of nearly 50% insulin independence at 5 years post-transplantation. However, recent advancements in transplant outcomes are limited to only a few centers and select patients; thus, we are still confronted with numerous hurdles against long-term successful islet transplantation. Herein, we review the recent advances and challenges for allo-islet transplantation to be accepted as a standard therapy for patients with T1DM.

Key Words: Diabetes Mellitus; Type 1 Diabetes; Islet of Langerhans Transplantation; Insulin Independence

Correspondence to: Sung Joo Kim
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3476
Fax: +82-2-3410-0040
E-mail: kmhyj111@gmail.com

Received 9 September 2014
Revised 22 September 2014
Accepted 7 October 2014

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a disease that is mainly presented in childhood and is caused by the irreversible destruction of insulin-producing beta cells in the pancreatic islets by an autoimmune mechanism. Patients with T1DM suffer from acute serious metabolic crises such as hyperglycemia, diabetic ketoacidosis and hypoglycemia, and chronic diabetic complications. These chronic complications can include diabetic nephropathy, retinopathy, and neuropathy, in addition to diabetic foot. Receiving an exogenous insulin supply is the only way to maintain an appropriate glycemic state. Accordingly, intensive insulin therapy, including frequent glucose monitoring and exogenous insulin injections, is the recommended treatment for preventing hyperglycemic episodes and halting progressive diabetic complications [1]. However, intensive insulin therapy frequently causes hypoglycemic episodes; moreover, it often cannot prevent life-threatening acute metabolic crises or the progression of chronic complications. Furthermore,

despite the importance of intensive glycemic control, a proportion of patients with T1DM fail to maintain effective intensive insulin therapy. As a treatment modality in patients with T1DM, transplantation of insulin-producing pancreatic islets or the pancreas organ itself has been considered to be an ideal therapeutic choice. Transplantation of the pancreas as a vascularized solid organ was first performed first by Kelly and Lillehei at the University of Minnesota in 1966. In the early days of pancreas transplantation, the success rate was very low. Since 1966, more than 42,000 pancreas transplants worldwide have been reported to the International Pancreas Transplant Registry (IPTR). With the development of improved operating techniques, better post-transplant management, and novel immunosuppressants, 1-year and 5-year pancreas transplantation success rates have risen to > 95% and 88%, respectively (patient survival), 85% and > 60%, respectively (graft survival), and 89% and 71%, respectively (graft survival for simultaneous pancreas-kidney transplantations). These success rates are comparable to those of kidney or liver transplants [2].

Transplantation of insulin-producing pancreatic islets has been also considered as a therapeutic alternative in patients with T1DM. The first report of this technique to yield successful glycemic control in rodents was published by Reckard in 1973 [3], followed by the first clinical report of successful islet transplantation in a patient with T1DM by Najarian in 1977. Islet transplantation has several advantages over pancreas transplantation. First of all, the morbidity and mortality rates of islet transplantation are lower; moreover, the procedure is less of a burden compared with pancreas transplantation. Furthermore, the repeated transplantation of islets can be performed with relative technical ease. If the xenogeneic immunologic barrier can be controlled, the islet source can be expanded until it is essentially unlimited. Despite these potential advantages over pancreas transplants, islet transplantation remains an experimental approach for T1DM treatment. Herein, we introduce recent advances in clinical islet transplantation and summarize the hurdles and future directions for successful islet transplantation.

BRIEF HISTORY OF ISLET TRANSPLANTATION

The first attempted islet transplantation was described by Williams in 1884, and consisted of the subcutaneous implantation of pieces of sheep pancreas into a 15-year-old boy with diabetic ketoacidosis. This attempt was earlier than the discovery of insulin by Banting in 1921. The modern era of islet transplantation began in the 1960s and 1970s. Pioneering experiments in rodent islet transplantation by Lacy [4,5] demonstrated the potential of islet transplantation to control hyperglycemia. Since this work, critical advances have been achieved regarding an improved route of islet administration [6] and the development of an automated method to isolate human islets [7]. The application of this improved collagenase enzyme mixture and automated method resulted in the acquisition of a sufficient number of islets for transplantation, thus overcoming the previous hurdle of achieving efficient islet isolation and purification. Moreover, the development of novel immunosuppressants was accompanied by increased long-term survival rates of human patients receiving islet grafts [8]. However, despite these advances in islet transplantation, only 11% of the 237 recipients who received islet transplantations between 1990 and 1999 could maintain insulin independence for more than 12 months [9].

ISLET TRANSPLANTATION WITH THE EDMONTON PROTOCOL

A study by Shapiro et al. (University of Alberta) in 2000 reported the evolutionary islet transplantation outcomes after using the so-called Edmonton protocol. All 7 consecutive patients with T1DM achieved insulin independence over a median follow-up period of 11.9 months [10]. The patients received a mean islet count of 13,000 IEq/kg over at least two islet transplantations, and also received a steroid-free immunosuppression regimen including induction of anti-IL2-Rc antibodies and a combination of an mTOR inhibitor and a low dose of tacrolimus. Islet culture was not performed prior to transplantation. However, data from longer follow-up period revealed a progressive loss of islet function over time [11]. In an attempt to reproduce this evolutionary Edmonton outcome, an international trial at 9 academic centers in North America and Europe was conducted using a single common protocol. Only 16 (44%) of the 36 patients (comprising 77 total islet infusions) remained insulin-independent at 1 year (1 insulin-independent subject at 3 years). And, only 10 patients (28%) had partial graft function at 1 year (11 at 3 years) [12]. Despite these disappointing results regarding insulin independence, persistent islet function even without insulin independence was found to provide protection from severe hypoglycemia and to result in improved levels of glycated hemoglobin. Therefore, even in the absence of insulin independence, islet transplantation can be beneficial for maintaining residual islet function, i.e. restoring C-peptide production [13].

The Clinical Islet Transplant Program at the University of Alberta continues to achieve successful islet transplantation, and has performed over 300 islet infusions using a modified approach.

ISLET TRANSPLANTATION ADVANCES IN THE 2000s

A study by Hering et al. (University of Minnesota) reported that 5 out of 8 patients who had received a single islet infusion (7,271 IEq/kg) remained insulin-independent for more than 1 year [14]. In this study, patients received an immunosuppression regimen including induction therapy with anti-thymocyte globulin, anti-IL-2 receptor antibodies, blockage of tumor necrosis factor (TNF), and a single-dose steroid. Patients were also maintained on a mammalian target of rapamycin (mTOR) inhibitor and a low dose of tacrolimus, and were given anti-coagulation therapy with intravenous heparin for 48 hours and low molecular weight heparin for 7

days. A study by Froud et al. (University of Miami) reported that 14 out of 16 patients achieved insulin independence with one or two islet infusions after *in vitro* islet culture. Of these, 11/14 (79%) were insulin-independent at 1 year, and 6/14 (43%) were insulin-independent at 18 months [15].

In this study, a steroid-free immunosuppressive regimen consisting of a reduced dose of tacrolimus that was suitable for islet transplantation, with less diabetogenic and less toxic effects, was applied.

Since the initial Edmonton trial, many efforts have been put forth to achieve insulin independence. The Clinical Islet Transplantation (CIT) Consortium, which consists of 13 academic centers, was established in 2004. The CIT is supported by the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA), and currently conducts islet-alone transplantation in patients with type I diabetes and severe hypoglycemia unawareness (CIT-06; NCT00468117), in addition to islet-after-kidney transplantation (CIT-07; NCT00434811).

A group in Uppsala has carried out *in vitro* and animal studies aimed at elucidating the mechanisms of islet cell damage and graft loss, otherwise known as the instant blood-mediated inflammatory response (IBMIR), which can occur immediately after islet cell infusion through the portal vein [16-18]. Chemical additives such as low molecular weight dextran sulfate or nicotinamide, which can be added at the time of islet culture to reduce the expression of the tissue factor MCP-1 or islet heparinization factors on the surface, have been proposed as one strategy for overcoming IBMIR [19,20].

CURRENT STATUS OF ISLET TRANSPLANTATION

Between 1999 and 2009, 453 patients with T1DM received at least

one allo-islet infusion in North America; 203 patients received at least one infusion in a European or Australian Juvenile Diabetes Research Foundation (JDRF) center. In total, 862 infusions were performed in North America and 379 infusions were performed in Europe and Australia at a JDRF center [21].

The annual numbers of allograft islet recipients and infusions in North American and European/Australian JDRF centers are shown in Fig. 1.

In addition to increased numbers of islet transplantation recipients and infusions, the transplant outcomes of islet transplantation have also improved over the last decade. According to the Collaborative Islet Transplant Registry (CITR), the insulin independence rate was 44% at 3 years post-islet infusion (final infusion) in patients whose first islet infusion had taken place between 2007 and 2010. In contrast, the insulin independence rate was only 27% in patients whose first islet infusion had occurred between 1999 and 2002 [21].

The Edmonton group at the University of Alberta reported that 109 (79%) of 138 total recipients displayed either full 48 (34.8%) or partial graft function, whereas 29 (21%) recipients lacked all islet function [22]. A report by O'Connell et al. described the results of a multicenter Australian trial, in which 7 of 9 recipients (78%) were found to be insulin-independent for more than 2 years [23]. Members of the Lille group reported insulin independence rates at 1 year of 71% after islet transplantation alone (ITA) and 54% after islet-after-kidney transplantation (IAK) [24]. Overall, recent transplant outcomes have become more successful in several centers, mainly CIT centers that operate at high standards of excellence (San Francisco, Minnesota, Edmonton, the Swiss-French GRAGIL network, and so on). Several leading centers have reported insulin independence rates of approximately 50% at 5 years post-transplantation [24,25]. However, transplant outcomes do vary according to the

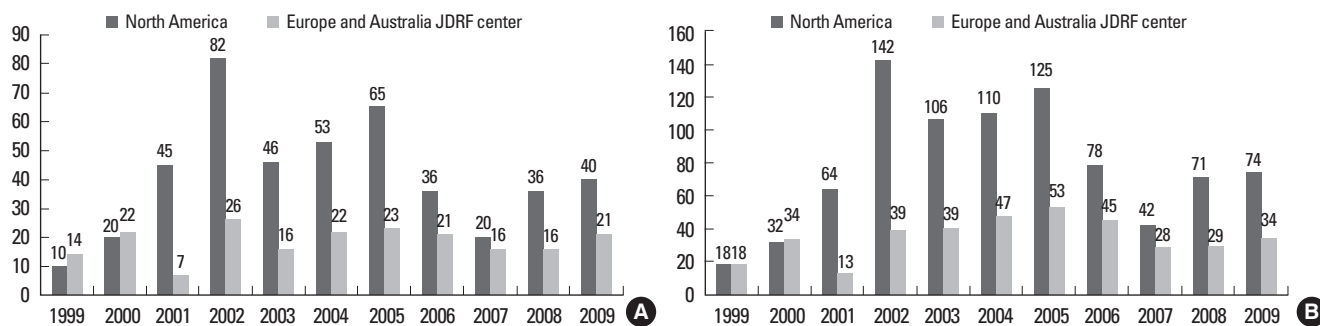


Fig. 1. Allograft islet transplantation by year. (A) Number of allograft islet recipients by year of first islet infusion. (B) Number of allograft islet infusions by year.

transplant center at which they are performed.

RECENT CHALLENGES TO SUCCESSFUL ISLET TRANSPLANTATION

Despite recent improvements in clinical outcomes, islet trans-

plantation remains an experimental modality. Many hurdles must be overcome before successful islet transplantation becomes routine (Fig. 2). The clinical trials that are currently in progress are listed in Table 1.

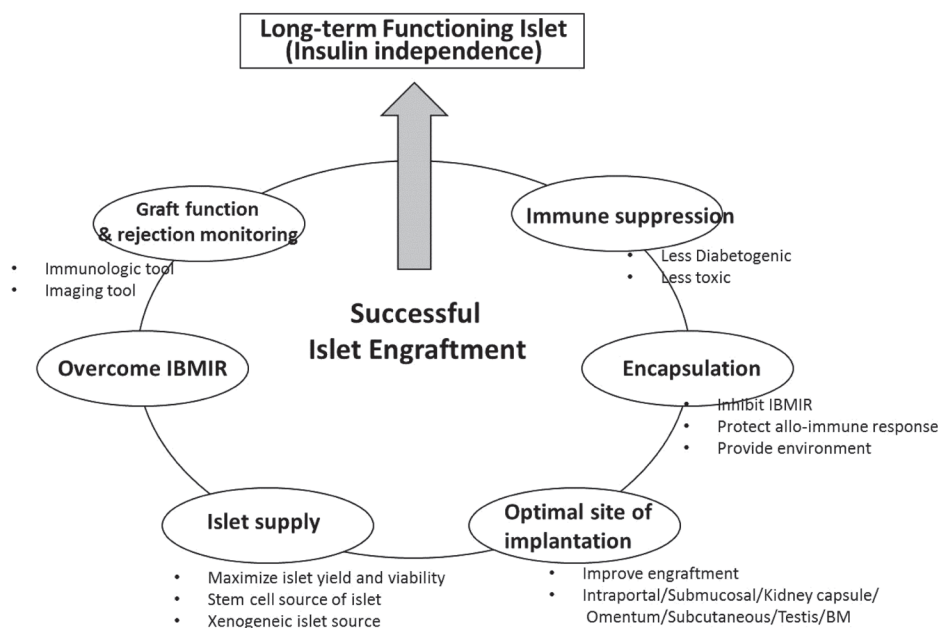


Fig. 2. Strategies for successful islet transplantation.

Table 1. Current clinical trials in allo-islet transplantation

	Title	Institute
General trials		
NCT00468117	Efficacy of Islet After Kidney Transplantation	Clinical Islet Transplantation (CIT) Consortium
NCT01705899	Islet Allograft Transplantation in Type 1 Diabetes	Ohio State University
NCT00784966	Islet After Kidney Transplant for Type 1 Diabetes	Virginia Commonwealth University
NCT01123187	Islet Cell Transplantation in Patients With Type 1 Diabetes With Previous Kidney Transplantation	University Hospital, Lille
NCT00853424	A Comparison of Islet Cell Transplantation With Medical Therapy for the Treatment of Diabetic Eye Disease	University of British Columbia
NCT01148680	Trial Comparing Metabolic Efficiency of Islet Graft to Intensive Insulin Therapy for Type 1 Diabetes's Treatment	University Hospital, Grenoble
NCT00679042	Islet Transplantation in Type 1 Diabetic Patients Using the University of Illinois at Chicago Protocol	University of Illinois
NCT01241864	Islet Transplantation in Type 1 Diabetic Kidney Allograft	University of Chicago
NCT01630850	Islet Transplantation in Patients With Brittle Type 1 Diabetes	University of Chicago
NCT01379729	Bet Cell Therapy in Diabetes Type 1	AZ-VUB
NCT01897688	A Phase 3 Single Center Study of Islet Transplantation in Non-uremic Diabetic Patients	Northwestern University, Chicago
NCT00530686	Pancreatic Islet Cell Transplantation - A Novel Approach to Improve Islet Quality and Engraftment	Baylor Research Institute
Trials for enhancing engraftment		
NCT01653899	Caspase Inhibition in Islet Transplantation	University of Alberta
NCT01817959	Study to Assess Efficacy and Safety of Reparixin in Pancreatic Islet Transplantation	Dompé s.p.a.
NCT00789308	Safety and Effectiveness of Low Molecular Weight Sulfated Dextran in Islet Transplantation	National Institute of Allergy and Infectious Diseases
NCT00853944	Effect of Sitagliptin on Graft Function Following Islet Transplantation	University of British Columbia
NCT00646724	Cotransplantation of Islet and Mesenchymal Stem Cell in Type 1 Diabetic Patients Fuzhou General Hospital	Fuzhou General Hospital

IMMUNOSUPPRESSION REGIMEN

Since the Edmonton protocol was established, immunosuppression regimens across various centers have mainly consisted of a combination of tacrolimus, an m-TOR inhibitor, avoidance of steroids, and induction of anti-IL-2 R α antibodies. However, no consensus has yet been reached regarding how to make these regimens less diabetogenic and less toxic. Some centers have reported good transplant outcomes by depleting antibody induction [25]. Tacrolimus is well known to have a diabetogenic effect; thus, efforts to develop regimens lacking tacrolimus have also been emphasized [26,27]. On the other hand, mTOR inhibitors such as sirolimus have been reported to be associated with reduced islet engraftment and impaired beta-cell function [28]. No consensus has yet been reached regarding the optimal immunosuppression regimen in clinical allo-islet transplantation, although immunosuppression regimens with novel agents have been evaluated in the non-human primate islet transplantation model [29].

EFFORTS TO IMPROVE ISLET YIELD AND ENGRAFTMENT

The development of methods for automated islet purification and isolation by Ricordi and colleagues [7], coupled with advances in digestion enzymes, has greatly improved both the yield and viability of isolated islet cells. However, since the number of islet cells transplanted is a major factor in successful transplantation, continued efforts have been directed at improving islet yield and maintaining islet function prior to transplantation. Takita et al. [30] reported that pancreatic ductal perfusion at the time of pancreas procurement enhanced islet yield in human islet isolations. Mesenchymal stem cells (MSCs) can also provide a supporting environment to protect islet cells or improve engraftment. Lu et al. [31] demonstrated that the cotransplantation of MSCs increased islet survival by reducing oxidative damage. Moreover, coculture with MSCs, which secrete various trophic factors, enhanced islet survival [32].

GRAFT MONITORING

In recent years, pancreatic islets have been imaged with various tools. Initial islet engraftments have been successfully documented with positron emission tomography imaging (PET) and computed tomography (CT) [33]. Attempts to quantify islets in an ani-

mal model while simultaneously maintaining islet function have employed infiltration of magnetic nanoparticles into islet cells, followed by magnetic resonance imaging [34]. However, these monitoring tools required the *in vitro* manipulation of islets and were also limited by the short half-life of labeling materials. In a recent advance, Pattou et al. reported a successful glucagon-like peptide (GLP)-1-receptor scanning strategy to monitor human islets transplanted into muscle [35]. These tools will be helpful for future comparative studies, since they will enable the evaluation of efforts to improve islet engraftment as well as the diagnosis of rejections in clinical situations.

ENCAPSULATION OR COTRANSPLANTATION

Studies to improve islet engraftment have also focused on aspects related to tissue engineering. Many efforts have been made to encapsulate pancreatic islet cells so that they are not exposed to the blood, thus triggering the IBMIR [36-38].

Macroencapsulation and microencapsulation have also been proposed as solutions for supplying oxygen or growth hormones, as well as enhancing engraftment, thus avoiding an allo-immune response. Clinical trials of islet encapsulation that are currently in progress are listed in Table 1.

Recent investigations have also focused on strategies to prevent an allo-immune reaction *via* regulatory T-cell coating [39] or to enhance engraftment by coencapsulation with MSCs [40]. Mesenchymal stem cells are well known to generate a microenvironment favorable for engraftment by secreting various trophic factors, reducing oxidative damage, enhancing angiogenesis, and modulating immune functions. Thus, cotransplantation as well as coculture with MSCs may enhance the success of islet transplantation strategies [41,42]. Numerous studies are currently in progress to test this hypothesis; however, many more studies will be required to fully understand the relationship between MSCs and engraftment.

ALTERNATIVE ISLET TRANSPLANTATION SITES

The main route of transplantation is currently islet infusion at the portal vein *via* a percutaneous transhepatic approach, even though this route often results in low oxygen tension and activation of the IBMIR. Many studies have investigated alternative sites for islet transplantation, such as the submucosa of the stomach *via* endoscopy [43], intramuscular sites [35], or the subcutaneous layer.

In a recent pilot study in humans, bone marrow was used as the site of islet transplantation, although this was in a case of auto-islet transplantation [44]. Bone marrow is a potential alternative site for successful islet engraftment because it provides a well-vascularized and immune-privileged environment. The kidney subcapsule, testis, anterior chamber of the eye, peritoneum, and omentum were also all evaluated as suitable sites for islet transplantation in an animal model.

IMMUNOLOGIC PROBLEMS AFTER REPEATED ISLET INFUSION (SENSITIZATION)

Patients with T1DM usually require multiple infusions of islet cells to acquire or maintain insulin independence. However, multiple islet infusions are often accompanied by sensitization, which is a major concern. In a recent study, pretransplant HLA antibodies were found to be associated with reduced graft survival [45]. Further studies should focus on patients undergoing islet transplantation who have previously had a kidney transplantation, patients who require a kidney transplantation and who have previously undergone islet transplantation, and patients who require repeated islet infusions.

XENO-ISLET TRANSPLANTATION

Results from xeno-islet transplantation studies may be applicable to the development of successful allo-islet transplantation approaches. Clinical applications of xeno-islet transplantation are also in process.

The α 1,3-galactosyltransferase transgenic knockout (GTKO) pig has been an important tool for understanding how to enhance islet function, overcome the xenogeneic immunologic barrier, overcome acute humoral xenograft rejection, inhibit complement pathway activation, and prevent intravascular thrombosis. Thus, this knockout pig has greatly helped clinicians overcome the barrier of hyperacute rejection (HAR). Multiple transgenic pigs have been put forth, including the GTKO pig, which express human complement regulatory proteins (hCRPs) or human tissue factor pathway inhibitors (TFPIs) for reducing complement activation, thrombus formation, and the requirement for exogenous immune suppression [46-48]. Additional genetic modifications aimed at preventing early graft loss and/or enhancing the engraftment process (*via* anti-apoptotic, anti-oxidative, or anti-inflammatory properties)

are under development. Various immunosuppression strategies, including a costimulatory blockade, have been used to block xenogeneic cellular mechanisms in a non-human primate model [46,49]. Two of the main strategies used for successful xeno-islet transplantation are islet encapsulation and allo-islet transplantation. Encapsulation of xenogeneic islets can reduce the immune response to the islets, consequently preventing an inappropriate inflammatory response. Thus, the bidirectional diffusion of glucose, oxygen, and other nutrients can occur. Alternative sites of pancreatic islet implantation, including the omentum, subcutaneous tissue, and the submucosal layer, are also promising for optimizing islet engraftment and function and reducing the necessary implantation mass. The subcutaneous layer is an especially promising site for islet transplantation because it is readily accessible with a layered device, which may enhance islet survival in xeno-islet transplantations.

CONCLUSIONS

Islet transplantation is a promising, cutting edge therapy for treating patients with T1DM. However, many obstacles must be overcome before successful clinical islet transplantation is a reality. Currently, the success rates of islet transplantations vary according to the particular transplant center. Most recipients require islets from more than one donor organ to achieve insulin independence, which is a challenge in the current era of donor organ shortage. The most effective immunosuppression regimen in islet transplantation is still unknown; moreover, better ways of monitoring islet graft survival are also needed. Additional efforts should also focus on determining the optimal site for transplantation, and on testing whether MSC-based strategies or encapsulation approaches can enable successful islet transplantation. Moreover, we have still not identified the key factors for successful islet transplantation. Despite these numerous questions, islet transplantation has great potential to be a highly beneficial treatment strategy for patients with T1DM in the near future.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-86.
2. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. *Nat Rev Endocrinol* 2013;9:555-62.
3. Reckard CR, Ziegler MM, Barker CF. Physiological and immunological

- consequences of transplanting isolated pancreatic islets. *Surgery* 1973;74:91-9.
4. Ballinger WF, Lacy PE. Transplantation of intact pancreatic islets in rats. *Surgery* 1972;72:175-86.
 5. Lacy PE, Kostianovsky M. Method for the isolation of intact islets of Langerhans from the rat pancreas. *Diabetes* 1967;16:35-9.
 6. Kemp CB, Knight MJ, Scharp DW, Lacy PE, Ballinger WF. Transplantation of isolated pancreatic islets into the portal vein of diabetic rats. *Nature* 1973;244:447.
 7. Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. *Diabetes* 1988;37:413-20.
 8. Tzakis AG, Ricordi C, Alejandro R, Zeng Y, Fung JJ, Todo S, et al. Pancreatic islet transplantation after upper abdominal exenteration and liver replacement. *Lancet* 1990;336:402-5.
 9. Bretzel RG, Hering BJ, Schultz AO, Geier C, Federlin K. International islet transplant registry report. Yearbook of Cell and Tissue Transplantation 1996-1997: Springer; 1996:153-60.
 10. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000;343:230-8.
 11. Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, et al. Five-year follow-up after clinical islet transplantation. *Diabetes* 2005;54:2060-9.
 12. Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, et al. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med* 2006;355:1318-30.
 13. Ryan EA, Shandro T, Green K, Paty BW, Senior PA, Bigam D, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. *Diabetes* 2004;53:955-62.
 14. Hering BJ, Kandaswamy R, Ansite JD, Eckman PM, Nakano M, Sawada T, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA* 2005;293:830-5.
 15. Froud T, Ricordi C, Baidal DA, Hafiz MM, Ponte G, Cure P, et al. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: MIAMI experience. *Am J Transplant* 2005;5:2037-46.
 16. Moberg L, Johansson H, Lukinius A, Berne C, Foss A, Kallen R, et al. Production of tissue factor by pancreatic islet cells as a trigger of detrimental thrombotic reactions in clinical islet transplantation. *Lancet* 2002;360:2039-45.
 17. Johansson H, Lukinius A, Moberg L, Lundgren T, Berne C, Foss A, et al. Tissue factor produced by the endocrine cells of the islets of Langerhans is associated with a negative outcome of clinical islet transplantation. *Diabetes* 2005;54:1755-62.
 18. Johansson H, Goto M, Dufrane D, Siegbahn A, Elgue G, Gianello P, et al. Low molecular weight dextran sulfate: a strong candidate drug to block IBMIR in clinical islet transplantation. *Am J Transplant* 2006;6:305-12.
 19. Moberg L, Olsson A, Berne C, Felldin M, Foss A, Kallen R, et al. Nicotinamide inhibits tissue factor expression in isolated human pancreatic islets: implications for clinical islet transplantation. *Transplantation* 2003;76:1285-8.
 20. Cabric S, Sanchez J, Lundgren T, Foss A, Felldin M, Kallen R, et al. Islet surface heparinization prevents the instant blood-mediated inflammatory reaction in islet transplantation. *Diabetes* 2007;56:2008-15.
 21. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, et al. Improvement in outcomes of clinical islet transplantation: 1999-2010. *Diabetes Care* 2012;35:1436-45.
 22. Senior PA, Kin T, Shapiro J, Koh A. Islet Transplantation at the University of Alberta: status update and review of progress over the last decade. *Can J Diabetes* 2012;36:32-7.
 23. O'Connell PJ, Holmes-Walker DJ, Goodman D, Hawthorne WJ, Loudovaris T, Gunton JE, et al. Multicenter Australian trial of islet transplantation: improving accessibility and outcomes. *Am J Transplant* 2013;13:1850-8.
 24. Vantyghem MC, Kerr-Conte J, Arnalsteen L, Sergeant G, Defrance F, Gmyr V, et al. Primary graft function, metabolic control, and graft survival after islet transplantation. *Diabetes Care* 2009;32:1473-8.
 25. Bellin MD, Kandaswamy R, Parkey J, Zhang HJ, Liu B, Ihm SH, et al. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. *Am J Transplant* 2008;8:2463-70.
 26. Posselt AM, Szot GL, Frassetto LA, Masharani U, Tavakol M, Amin R, et al. Islet transplantation in type 1 diabetic patients using calcineurin inhibitor-free immunosuppressive protocols based on T-cell adhesion or costimulation blockade. *Transplantation* 2010;90:1595-601.
 27. Posselt AM, Bellin MD, Tavakol M, Szot GL, Frassetto LA, Masharani U, et al. Islet transplantation in type 1 diabetes using an immunosuppressive protocol based on the anti-LFA-1 antibody efalizumab. *Am J Transplant* 2010;10:1870-80.
 28. Zhang N, Su D, Qu S, Tse T, Bottino R, Balamurugan AN, et al. Sirolimus is associated with reduced islet engraftment and impaired beta-cell function. *Diabetes* 2006;55:2429-36.
 29. Lowe MC, Badell IR, Turner AP, Thompson PW, Leopardi FV, Strobert EA, et al. Belatacept and sirolimus prolong nonhuman primate islet allograft survival: adverse consequences of concomitant alefacept therapy. *Am J Transplant* 2013;13:312-9.
 30. Takita M, Itoh T, Shimoda M, Kanak MA, Shahbazov R, Kunnathodi F, et al. Pancreatic Ductal Perfusion at Organ Procurement Enhances Islet Yield in Human Islet Isolation. *Pancreas* 2014;43:1249-55.
 31. Lu Y, Jin X, Chen Y, Li S, Yuan Y, Mai G, et al. Mesenchymal stem cells protect islets from hypoxia/reoxygenation-induced injury. *Cell Biochem Funct* 2010;28:637-43.
 32. 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;89:509-17.
 33. Eich T, Eriksson O, Lundgren T, Nordic Network for Clinical Islet T. Visualization of early engraftment in clinical islet transplantation by positron-emission tomography. *N Engl J Med* 2007;356:2754-5.
 34. Borot S, Crowe LA, Parnaud G, Ris F, Meier R, Giovannoni L, et al. Quantification of islet loss and graft functionality during immune rejection by 3-tesla MRI in a rat model. *Transplantation* 2013;96:438-44.
 35. Pattou F, Kerr-Conte J, Wild D. GLP-1-receptor scanning for imaging of human beta cells transplanted in muscle. *N Engl J Med* 2010;363:1289-90.
 36. Ludwig B, Rotem A, Schmid J, Weir GC, Colton CK, Brendel MD, et al. Improvement of islet function in a bioartificial pancreas by enhanced oxygen supply and growth hormone releasing hormone agonist. *Proc Natl Acad Sci U S A* 2012;109:5022-7.
 37. Pedraza E, Coronel MM, Fraker CA, Ricordi C, Stabler CL. Preventing hypoxia-induced cell death in beta cells and islets via hydrolytically activated, oxygen-generating biomaterials. *Proc Natl Acad Sci U S A* 2012;109:4245-50.
 38. Im BH, Jeong JH, Haque MR, Lee DY, Ahn CH, Kim JE, et al. The effects of 8-arm-PEG-catechol/heparin shielding system and immunosuppressive drug, FK506 on the survival of intraportally allotransplanted islets. *Biomaterials* 2013;34:2098-106.
 39. Marek N, Krzystyniak A, Ergenc I, Cochet O, Misawa R, Wang LJ, et al. Coating human pancreatic islets with CD4(+)CD25(high)CD127(-) reg-

- ulatory T cells as a novel approach for the local immunoprotection. *Ann Surg* 2011;254:512-8; discussion 8-9.
40. Veriter S, Gianello P, Igarashi Y, Beaurin G, Ghyselinck A, Aouassar N, et al. Improvement of Subcutaneous Bioartificial Pancreas Vascularization and Function by Co-Encapsulation of Pig Islets and Mesenchymal Stem Cells in Primates. *Cell Transplant* 2014;23:1349-64.
 41. Ito T, Itakura S, Todorov I, Rawson J, Asari S, Shintaku J, et al. Mesenchymal stem cell and islet co-transplantation promotes graft revascularization and function. *Transplantation* 2010;89:1438-45.
 42. Solari MG, Srinivasan S, Boumaza I, Unadkat J, Harb G, Garcia-Ocana A, et al. Marginal mass islet transplantation with autologous mesenchymal stem cells promotes long-term islet allograft survival and sustained normoglycemia. *J Autoimmun* 2009;32:116-24.
 43. Echeverri GJ, McGrath K, Bottino R, Hara H, Dons EM, van der Windt DJ, et al. Endoscopic gastric submucosal transplantation of islets (ENDO-STI): technique and initial results in diabetic pigs. *Am J Transplant* 2009;9:2485-96.
 44. Maffi P, Balzano G, Ponzoni M, Nano R, Sordi V, Melzi R, et al. Autologous pancreatic islet transplantation in human bone marrow. *Diabetes* 2013;62:3523-31.
 45. Campbell PM, Salam A, Ryan EA, Senior P, Paty BW, Bigam D, et al. Pre-transplant HLA antibodies are associated with reduced graft survival after clinical islet transplantation. *Am J Transplant* 2007;7:1242-8.
 46. Thompson P, Badell IR, Lowe M, Cano J, Song M, Leopardi F, et al. Islet xenotransplantation using gal-deficient neonatal donors improves engraftment and function. *Am J Transplant* 2011;11:2593-602.
 47. van der Windt DJ, Bottino R, Kumar G, Wijkstrom M, Hara H, Ezzelarab M, et al. Clinical islet xenotransplantation: how close are we? *Diabetes* 2012;61:3046-55.
 48. Chen Y, Stewart JM, Gunthart M, Hawthorne WJ, Salvaris EJ, O'Connell PJ, et al. Xenoantibody response to porcine islet cell transplantation using GTKO, CD55, CD59, and fucosyltransferase multiple transgenic donors. *Xenotransplantation* 2014;21:244-53.
 49. Lowe M, Badell IR, Thompson P, Martin B, Leopardi F, Strobert E, et al. A novel monoclonal antibody to CD40 prolongs islet allograft survival. *Am J Transplant* 2012;12:2079-87.