Published in final edited form as:

Curr Opin Organ Transplant. 2011 December ; 16(6): 627–631. doi:10.1097/MOT.0b013e32834cfb84.

Strategies Towards Single-Donor Islets of Langerhans Transplantation

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Abstract

Purpose of Review—The current review addresses a critical need in clinical islet transplantation, namely the routine transition from the requirement of 2 to 4 donors down to 1 donor per recipient. The ability to achieve single donor islet transplantation will provide many more islet grafts for treatment of an ever-expanding patient base with type 1 diabetes with poor glycemic control. Avoiding exposure of recipients to multiple different donor HLA-antigens is critical if risk of donor-sensitization is to be avoided. This is important as further islet or pancreas transplants in the remote future, or the potential future need for a solid organ kidney transplant may become prohibitive if the recipient is sensitized.

Recent Findings—This review systematically addresses all areas which contribute to the success or failure of single-donor islet engraftment, beginning with donor related factors, optimizing islet isolation and culture conditions, and describes a series of strategies in the treatment of the recipient to prevent inflammation, apoptosis, islet thrombosis, and improve metabolic functional outcome, all of which will lead to improved single donor engraftment success.

Summary—If single donor islet transplantation can be routinely achieved, therapy will become more widely available, more accepted by the transplant community (currently pancreas transplantation requires only a single donor), and this will have a major impact overall as an effective treatment option in type 1 diabetes.

Keywords

Single-Donor Islets; Langerhans Transplantation; type 1 diabetes

1. Introduction

Clinical islet transplantation is being offered currently to a subset of approximately 15% of patients with type 1 diabetes (T1DM) with refractory hypoglycemia or marked glycemic lability, that cannot be corrected by other means including intensive insulin, improved monitoring, insulin pump therapies, or continuous glucose monitoring systems (CGMS). Objective selection criteria include a Clark Score of ≥ 4 , HYPO score ≥ 1000 , Lability Index ≥ 400 , or a combination of these variables. With over 750 islet transplants performed in over 30 international centres, this therapy is steadily transferring from research to a standard recognized clinical therapy. Islet transplantation is also being offered after kidney

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Conflict of Interest

None to declare

transplantation, where justification is simpler as the patients already require lifelong immunosuppression, and the intraportal islet implantation procedure is a simple non-surgical intervention with relatively low risk. Currently, islet transplantation offers a highly effective means to restore endogenous, regulated insulin secretion thereby stabilizing glycemic control, preventing hypoglycemia and corrects hemoglobin A1C (HbA1C) to a level predicted to prevent and reverse chronic, secondary complications of diabetes. The trade-off in terms of lifelong need for immunosuppressive therapies can readily be justified in this setting, but not for patients with otherwise good glycemic control, and not routinely for children at this time.

Islet transplantation will only transition further from therapy for few to a cure for all with T1DM once islet transplantation becomes more readily available, means to expand the islet donor supply through expansion of existing islets, stem cell approaches or xenotransplant sources become available, but the remaining challenge of inducing immunological tolerance, preventing islet destruction from recurrence of autoimmunity or alloimmune rejection, and avoiding all potential side effects from immunosuppressive therapies will all need to be addressed to further this transition.

The current review addresses a number of strategies that may improve single donor islet transplantation success. With the initial reports of the Edmonton Protocol in 2000[1] it is clear that islets were needed from 2 and up to 4 donors to treat each recipient in order to achieve the state of complete insulin independence. Our own centre has treated 145 patients with over 300 separate intraportal islet infusions over the past 10 years, representing the most active clinical site worldwide. Despite remarkable progress in both short and long-term outcomes with insulin independent success, it has still been remarkably difficult to achieve routine single donor islet engraftment in our hands. The ratio of number of pancreas donors required to treat one recipient markedly underestimates the true need for pancreas donors, as the current process for islet extraction is only associated with a 50% conversion rate to clinical transplantation, and reflects the complex isolation and purification process. Achieving routine single donor islet engraftment would clearly allow many more patients to be treated worldwide, and would allow islet transplantation to match or exceed activity in whole pancreas transplantation, which now exceeds 30,000 cases worldwide. Single-donor islet engraftment is especially important in islet transplantation as it avoids exposing the recipient to poly-human leukocyte associated (HLA) antigens. HLA-sensitization places not only the islet transplant itself at risk, but may preclude successful future islet, whole pancreas, kidney or other solid organ transplantation if needed, an especially important issue for patients with underlying diabetes. This review will therefore discuss a number of different strategies that are collectively anticipated to improve single donor islet transplantation success. It seems unlikely that any single factor will secure single-donor success, but rather a multi-modal approach will routinely be required to achieve this.

2. Improving Access to Human Pancreas Donors

The starting material for any clinical islet transplant procedure is a pancreas retrieved from either a heart-beating, brain dead organ donor, or a donor that has succumbed after cardiac death (Deceased Cardiac Death; DCD). The use of more marginal pancreas donors is associated with less successful islet yield and potency, but unfortunately, the majority of available organ donors fall into the marginal category. Nonetheless, several groups have made remarkable progress with the use of marginal pancreas donors, and notably the Philadelphia and other groups have had success with single-donor engraftment with DCD pancreas organs.[2] Living-donor islet transplant has been promoted by the Kyoto group by distal pancreatectomy from mother to daughter, and interestingly a half pancreas islet preparation was sufficient to achieve a sustained period of insulin independence and

excellent glycemic control in the recipient.[3] The potential downside is that the donor must face a major surgical intervention, and even if completed laparoscopically, there are risks of surgical diabetes in the donor, and potential risks from pancreatic fistula or infection, making this an unpalatable approach for many recipients.

3. Improving Islet Isolation Success

Extracting large numbers of viable, potent human islets from a donor organ pancreas is a challenging and intensive process that requires considerable expertise, access to unique reagents, including unstable and variable preparations of collagenase enzymes, and access to an ultra-clean room facilities that comply with Good Manufacturing Practice (cGMP). The pancreatic duct is cannulated, and collagenase enzyme solutions are perfused to the pancreatic islet-acinar interface to help cleave the islets from their exocrine pancreatic bed. The pancreas is then chopped placed within a Ricordi Chamber, and enzyme solution is circulated as the pancreatic fragments are shaken against a 500 μm screen and marbles. This system was developed by Dr. Camillo Ricordi, and despite being developed over 20 years ago, remains the established technique for clinical islet isolation.[4] Conversion rates from pancreas processing to clinical transplantation are variable, but most transplant approximately 50%, while discarding preparations that fail to provide sufficient yield to meet a 5,000 Islet Equivalents (IEQ) per kilogram, based on the recipient weight. It is anticipated that the total islet mass required may decrease over time, if some of the innovations discussed below prove to be effective. If the threshold for clinical transplantation were reduced to 2,000 IEQ/kg then this would immediately improve the isolation to transplant ratio from 50% up to 90% or more, which would have a dramatic impact in clinical transplantation activity.

One of the challenges for approval of islet transplantation as a routine treatment is the lack of a reliable and predictive potency assay. It is well recognized that the insulin Stimulation Index (SI) represents only a crude demonstration of a particular islet product to secrete insulin, that the membrane integrity dye exclusion methods are insensitive, and alternative approaches including calcium flux analysis, oxygen consumption rate, and other innovative approaches are being developed.[5] The Food and Drug Administration (FDA) have indicated to the islet transplant community that a simple and reliable predictive potency assay remains one of the highest priorities if islet transplantation moves forward from research to clinical approval and Biological Licensure in the US.

Innovations during islet culture including additives such as insulin-like growth factor 2 (IGF-2), and improving oxygen delivery to islets during culture with breathable membranes may further protect islets from damage.[6]

4. Improving Islet Engraftment in the Recipient

Achieving single-donor islet engraftment success requires a critical interaction between final implanted islet mass and several recipient factors, including recipient insulin requirement and sensitivity. Typically, single-donor islet engraftment success is easier to achieve in recipients with low baseline insulin requirements (<0.5 U/kg/day insulin). Currently, the intrahepatic portal venous site is the only site that has routinely resulted in insulin independence in the clinic. Development of future, alternative islet implantation sites, may allow other sites to achieve or further improve on islet engraftment if engineered appropriately. The degree of activation of the recipient's autoimmune and alloimmune systems may create potent and occasionally insurmountable barriers to successful islet engraftment and early survival. We will now review a series of different approaches in the recipient's treatment that may favour islet potency, survival and function leading to improved single donor success.

i. Anti-inflammatory

When islets are embolized into the portal system, islets become trapped in the terminal portal venous radical branches, become coated with blood clot and through process of healing, undergo revascularization from the recipient hepatic arterial system. Prior to successful angiogenesis, islets remain ischemic, inflamed, and are subject to apoptosis and necrosis. Several strategies are being developed to suppress inflammation, facilitate neovascularization, and improve single-donor success. Hering *et al* defined a series of strategies that improved single-donor islet transplant success at their centre, including careful donor and recipient selection, potent T-cell depletion with thymoglobulin or a non-depleting OKT3-ala-ala antibody.[7,8] Koh *et al* in Edmonton investigated the impact of peritransplant insulin and heparin, and in our own experience found that single-donor islet transplant success rate rose from 10% to 40%.[9] This paper is one of the first clinical papers to support an extensive scientific contribution by Korsgren and the Uppsala Group to address means of preventing the instant blood mediated inflammatory response (IBMIR). [10]

Tumor Necrosis Factor-Alpha (TNF- α) represents one of the most dominant targets in acute inflammatory injury of islets. Farney *et al* initially demonstrated the potential benefit of TNF- α blockade in islet transplantation in mice.[11] Hering *et al* incorporated this TNF- α strategy using etanercept in their single-donor centre experience, with the first dose given intravenously (50 mg) before transplant and repeated subcutaneously 25 mg on days 3, 7 and 10.[8,9] Unraveling the secrets of single-donor success, especially in terms of understanding the contributions of various factors represents a considerable challenge.[12]

Other novel anti-inflammatory targets include Anakinra, which is an interleukin-1-receptor antagonist (IL1-Ra). Matsumoto *et al* have had limited clinical experience in 3 patients using the IL1-Ra antibody suggesting that this might confer additional benefit.[13] We have investigated the combination of anti-TNF- α and IL1-Ra blockade with both Etanercept and Anakinra in marginal mass islet transplant models of human islets in immunodeficient mice, and found this combination to be synergistic in promoting engraftment.

ii. Anti-Apoptosis and anti-IBMIR strategies

We have extensively investigated strategies to switch off the apoptosis pathways in transplanted human, mouse, and pig islets as a means to promote single-donor islet transplantation success since apoptosis appears to be one of the most dominant targets for modifiable survival of islets after transplantation. Emamaullee *et al* first showed that engineering of human islets with viral vectors targeting XIAP and showed that XIAP could substantially improve islet survival in mice.[14] We recognized that the use of an adenoviral vector was not a palatable approach for safe clinical application, and searched for molecular drug targets that might serve to block the pan-caspase. We recently investigated a compound IDN6556 (Conatus Pharmaceuticals Inc., San Diego) which led to marked improvement in marginal mass engraftment.[15] We further tested IDN6556 in a large animal pig autograft model and found similar findings. The addition of a pan-caspase inhibitor led to routine reversal of the diabetic state with marginal mass transplantation of between 10%–30% of the usual minimal islet transplant mass required to reverse diabetes. If the mouse and pig findings extrapolate to the clinic, we anticipate that this approach will substantially lower the required basal islet transplant mass needed to secure full insulin independence, will improve metabolic reserve, reduce risk of donor-related sensitization from dying islets, and may facilitate the induction of immunological tolerance.

Korsgren's team from Uppsala have developed a substantial body of pre-clinical data to suggest that IBMIR is a major potential target to reduce inflammation and improve islet

survival after transplantation. High expression of tissue factor on the surface of human islets leads to platelet aggregation, activation and islet injury. This group has developed several potential targets to therapeutically manipulate the IBMIR response, including the use of dextran sulphate, or surface binding of heparin to the islets to abrogate IBMIR.[16,17]

iii. Metabolic and Growth Stimulation Strategies

The use of glucagon-like-peptide-1 (GLP1) analogs currently used in the management of patients with T2DM have shown remarkable promise in the setting of single-donor clinical islet transplantation. The Universities of Illinois, Miami and British Columbia have all demonstrated that the short-acting GLP-1 analogue, exenatide, can facilitate single-donor islet engraftment.[18,19,20,21] While the addition of exenatide can improve metabolic function, administration is associated with intolerable nausea in 30%. We have explored a related compound, Liraglutide (NovoNordisk, Denmark), a long-acting GLP-1 analogue, with substantially reduced risk of nausea. We found that Liraglutide could promote single-donor islet engraftment in mice, improved early engraftment, and enhanced survival of human islets in culture.[22,23,24] Potential alternative strategies using dipeptidylpeptidase-4 (DPP-4) inhibitors such as Sitagliptin in islet transplantation are also being explored in separate trials. Again, it seems unlikely that these strategies alone will not result in routine single donor islet transplant engraftment but rather will require a multi-modal approach to maximize the potential engraftment and expansion of a limited initial islet mass.

iv. Recipient immunosuppression strategies to facilitate single-donor engraftment

Effective control of both autoimmune and alloimmune pathways remain an essential prerequisite for transplant success. Unfortunately, many of the compounds used to prevent rejection and control autoimmunity are also locally toxic to the islet graft.[25,26] Elimination of tacrolimus may facilitate metabolic function, but also increases risk of rejection. More recently, use of T-depletional immunosuppression can substantially improve long-term islet graft survival. Up to 5 clinical islet transplant groups including our own, the University of Geneva, Lille, Minnesota, San Francisco, and other groups have now routinely achieved rates of up to 50% insulin independence beyond 5 years after transplantation in islet-alone grafts, results which now match the results of pancreas-alone transplantation, at least within the international pancreas transplant registry for pancreas-alone grafts. In Edmonton, we have been exploring Alemtuzumab, an anti-CD52 antibody that potently depletes T-cells, and found robust, durable insulin independence beyond 5 years, in a cohort of almost 30 subjects, and that this approach ameliorates both allo and autoimmune reactivity. We have combined this therapy with tacrolimus and CellCept, but have not been able to achieve high rates of single-donor islet engraftment success with that approach alone, to date.

A number of exciting and novel immunosuppressive targets are emerging with direct clinical application that may facilitate elimination of tacrolimus from the immunosuppressive regimen. The combination of potent T-depletion with sirolimus and CellCept is one option, but may not provide sufficient maintenance chronic immunosuppression to prevent immune destruction. The use of co-stimulation blockade, using Belatacept which blocks costimulation signaling through the CD80-CD86 pathways has shown considerable promise in clinical renal transplantation, and is presently being explored in Emory and Edmonton (CIT/NIH trial). It remains to be seen whether co-stimulation blockade alone, and calcineurin-inhibitor free maintenance will be sufficient to prevent rejection events. Recently, the University of San Francisco group reported on remarkable successful outcomes when Belatacept costimulation blockade is combined with thymoglobulin T-cell depletion.[27] This strategy has allowed for a calcineurin-inhibitor free maintenance strategy and has markedly improved single-donor islet engraftment success in selected cases.

Additionally, this group has studied the potential benefit of an anti-LFA-1 antibody called efalizumab in clinical islet transplantation. When combined with thymoglobulin, again this has allowed for tacrolimus-free maintenance immunosuppression and good clinical outcome, but unfortunately, the antibody is on clinical hold due to small but increased risk of progressive multifocal leukoencephalopathy (PML).

6. Summary

Remarkable progress has occurred in clinical islet transplantation over the last 12 years. Before this time, routine insulin independence was almost impossible to achieve. The Edmonton Protocol promoted by our group in 2000 brought unparalleled attention as all 7 of the first treated subjects achieved and maintained insulin independence at the time of the report. We subsequently found evanescent rates of insulin independence dwindling to around 10% at five years. This has subsequently improved considerably with the use of T-depletional induction therapies and more potent maintenance immunosuppressive strategies based upon use of tacrolimus, and currently at least 5 centres report rates of insulin independence at 5 or more years after transplant exceeding 50%, rates that currently match the registry data of pancreas-alone transplantation. Routine attainment of single-donor islet transplant success remains an achievable and extremely important goal in islet transplantation. This would allow for many more subjects to be treated with islets, and would reduce the potential risk of donor HLA-sensitization by avoiding a need to expose recipients to multiple donors. At the present time in our own centre and in most other international centres (with the exception of Minnesota, San Francisco, and the University of Illinois, Chicago), at least 2 islet infusions are required to maintain insulin independence. Moving from multiple donor to single donor success will require a multimodal approach, including optimization of donor pancreas organs, protection of islets from cold and warm ischemic injury and the injurious process of islet isolation, requires access to effective, stable and consistent human compatible collagenase enzyme blends for digestion, and several multimodal strategies for treatment of the recipient to suppress immunological, inflammatory and thrombosis pathways, while at the same time stimulating neovascularization and metabolic function of the islet graft. Such a multimodal approach will no doubt transform short and long-term islet transplantation success and will continue to facilitate the rapid transition from research to routine clinical care for this exciting and effective cellular treatment therapy for diabetes.

Acknowledgments

AMJS is supported through a Senior Scholarship from Alberta Innovates Health Care Solutions, and through grant support from the Clinical Islet Transplant Consortium, National Institutes of Allergy, Immunology, and Diabetes (NIAID), and the National Institute of Diabetes, Digestive Diseases and Kidney (NIDDK), through the National Institutes of Health (NIH). AMJS also receives grant support through the Juvenile Diabetes Research Foundation (JDRF) and through the Diabetes Research Institute Foundation of Canada (DRIFCan). AMJS is a member of the Alberta Diabetes Institute.

Abbreviations

T1DM	Type 1 diabetes mellitus
CGMS	continuous glucose monitoring system
LI	Lability Index
HbA1C	Hemoglobin A1C
HLA	poly-human Leukocyte associated antigens

IBMR	instant blood mediated inflammatory response
DCD	Deceased Cardiac Death
cGMP	Good Manufacturing Practice
UW	University of Wisconsin solution
HTK	Histidine Tryptophan Ketoglutarate solution
TLM	Two-Layer Method
IEQ	Islet equivalents
MTF	Mammalian-Tissue free
SI	Stimulation Index
FDA	Food and Drug Administration
BMI	Body mass index
T2DM	type 2 diabetes mellitus
IGF-2	Insulin-like growth factor 2
TNF-α	Tumor Necrosis Factor – Alpha
ILN-Ra	Interleukin receptor antagonist
TAT	Thrombin-antithrombin complex
CIT	Clinical Islet Transplant Consortium
GLP1	glucagon-like-peptide-1
DPP-4	Dipeptidyl peptidase-4
PML	progressive multifocal leukoencephalopathy
MSC	mesenchymal stem cells

References

1. Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*. 2000; 343(4):230–238. [PubMed: 10911004]
2. Saidi F, Bradley J, Greer D, et al. Changing pattern of organ donation at a single center: are potential brain dead donors being lost to donation after cardiac death? *Am J Transplant*. 2010; 10(11):2390–2391. [PubMed: 20977630]
3. Matsumoto S, Okitsu T, Iwanaga Y, et al. Insulin independence after living donor distal pancreatectomy and islet allotransplantation. *Lancet*. 2005; 365(9471):1642–1644. [PubMed: 15889479]
4. Ricordi C, Lacy PE, Finke EH, et al. Automated method for isolation of human pancreatic islets. *Diabetes*. 1988; 37(4):413–420. [PubMed: 3288530]
5. Papas KK, Colton CK, Nelson RA, et al. Human islet oxygen consumption rate and DNA measurements predict diabetes reversal in nude mice. *Am J Transplant*. 2007; 7(3):707–713. [PubMed: 17229069]
6. Papas KK, Avgoustiniatos ES, Tempelman LA, et al. High-density culture of human islets on top of silicone rubber membranes. *Transplant Proc*. 2005; 37(8):3412–3414. [PubMed: 16298611]
7. Hering BJ, Kandaswamy R, Ansie JD, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA*. 2005; 293(7):830–835. [PubMed: 15713772]

8. Hering BJ. Repurification: rescue rather than routine remedy. *Am J Transplant*. 2005; 5(1):1–2. [PubMed: 15636604]
- 9**. Koh A, Senior P, Salam A, et al. Insulin-heparin infusions peritransplant substantially improve single-donor clinical islet transplant success. *Transplantation*. 2010; 89(4):465–471. This article demonstrates that single donor islet transplant success can increase from 10% to 40% with the addition of therapeutic heparin and high-dose insulin in the peritransplant period, and illustrates that prevention of IBMIR may be of clinical benefit. [PubMed: 20177350]
10. Johansson H, Lukinius A, Moberg L, 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(6):1755. [PubMed: 15919797]
11. Xenos ES, Farney AC, Widner MB, et al. Effect of tumor necrosis factor alpha and of the soluble tumor necrosis factor receptor on insulin secretion of isolated islets of Langerhans. *Transplant Proc*. 1992; 24(6):2863–2864. [PubMed: 1334599]
12. Shapiro AM, Ricordi C. Unraveling the secrets of single donor success in islet transplantation. *Am J Transplant*. 2004; 4(3):295–298. [PubMed: 14961980]
- 13**. Matsumoto S, Takita M, Chaussabel D, et al. Improving efficacy of clinical islet transplantation with Iodixanol based islet purification, thymoglobulin induction and blockage of IL-1-beta and TNF-alpha. *Cell Transplant*. 2011 Published ahead of print. This article discusses the combined use of IL-1 beta receptor blockade with anti-TNF-alpha blockade in clinical islet transplantation. 10.3723/096368910X564058
14. Emamaullee J, Rajotte RV, Liston P, et al. XIAP overexpression in human islets prevents early post-transplant apoptosis and reduces the islet mass needed to treat diabetes. *Diabetes*. 2005; 54:2541–2548. [PubMed: 16123341]
- 15**. McCall M, Toso C, Emamaullee J, et al. The caspase inhibitor IDN-6556 (PF3491390) improves marginal mass engraftment after islet transplantation in mice. *Surgery*. 2011; 150:48–55. This article demonstrates that a potent pan-caspase inhibitor, IDN6556 can substantially improve marginal mass islet engraftment of human islets transplanted in to immunodeficient mice, and forms the basis of a planned clinical trial by the Edmonton Group. [PubMed: 21596412]
16. Cabric S, Eich T, Sanchez J, et al. A new method for incorporating functional heparin onto the surface of islets of Langerhans. *Tissue Eng Part C Methods*. 2008; 14(2):141.147. [PubMed: 18544029]
17. Schmidt P, Magnusson C, Lundrgren T, et al. Low molecular weight dextran sulfate is well tolerated in humans and increases endogenous expression of islet protective hepatocyte growth factor. *Transplantation*. 2008; 86(11):1523–1530. [PubMed: 19077884]
18. Cechin SR, Perez-Alvarez I, Fenjves E, et al. Anti-inflammatory properties of exenatide in human pancreatic islets. *Cell Transplant*. 2011 e-published ahead of print. 10.3727/09638911X576027
19. Faradji RN, Froud T, Messinger S, et al. Long-term metabolic and hormonal effects of exenatide on islet transplant recipients with allograft dysfunction. *Cell Transplant*. 2009; 18(10):1247–1259. [PubMed: 20003758]
20. Ghofaili KA, Fug M, Ao Z, et al. Effect of exenatide on beta cell function after islet transplantation in type 1 diabetes. *Transplantation*. 2007; 83:24–28. [PubMed: 17220786]
21. Gangemi A, Salehi P, Hatipoglu B, et al. Islet transplantation for brittle type 1 diabetes: The UIC protocol. *Am J Transplant*. 2008; 8:1250–1261. [PubMed: 18444920]
22. Merani S, Truong W, Emamaullee JA, et al. Liraglutide, a long-acting human glucagon-like-peptide 1 analogue, improves glucose hemostasis in marginal mass islet transplantation in mice. *Endocrinology*. 2008; 149(9):4322–4328. [PubMed: 18511515]
23. Emamaullee JA, Merani S, Toso C, et al. Porcine marginal mass islet autografts resist metabolic failure over time and are enhanced by early treatment with Liraglutide. *Endocrinology*. 2009; 150(5):2145–2152. [PubMed: 19131571]
24. Toso C, McCall M, Emamaullee J, et al. Liraglutide, a long-acting human glucagon-like peptide 1 analogue, improves human islet survival in culture. *Transpl Int*. 2010; 23(3):259–265. [PubMed: 19821955]

25. Suarez-Pinzon WL, Lakey JR, Rabinovitch A. Combination therapy with glucagon-like peptide-1 and gastrin induces beta-cell neogenesis from pancreatic duct cells in human islets transplanted in immunodeficient diabetic mice. *Cell Transplant*. 2008; 17(6):631–640. [PubMed: 18819251]
26. Nir T, Melton DA, Dor Y. Recovery from diabetes in mice by beta cell regeneration. *J Clin Invest*. 2007; 117(9):2553–2561. [PubMed: 17786244]
27. Posselt AM, Szot GL, Frassetto LA, 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(12):1595–1601. [PubMed: 20978464]

key-points

- Islet transplantation has now come of age, and over 750 transplants have been completed worldwide.
- Single donor transplant success will be a key element of continued success, and will require innovations in islet manufacture, suppression of inflammation, thrombosis and apoptosis to become routine.
- This article discusses a series of strategies currently in clinical trial testing to promote single donor transplant success.