Advances in pancreatic islet transplantation in humans

Sulaiman A. Nanji and A. M. James Shapiro

Department of Surgery, University of Alberta, Edmonton, Alberta, Canada

With recent advances in methods of islet isolation and the introduction of more potent and less diabetogenic immunosuppressive therapies, islet transplantation has progressed from research to clinical reality. Presently, several international centres have demonstrated successful clinical outcomes with high rates of insulin independence after islet transplantation. Ongoing refinements in donor pancreas procurement and processing, developments in islet isolation and purification technology, and advances in novel immunological conditioning and induction therapies have led to the acceptance of islet transplantation as a safe and effective therapy for patients with type 1 diabetes. This review provides a historical perspective of islet transplantation, outlines the recent advances and current clinical outcomes, and addresses the present challenges and future directions in clinical islet transplantation.

Introduction

Diabetes affects more than 200 million people worldwide, representing the third most common disease and forth leading cause of death in North America [1]. There are currently 30 000 new type 1 diabetics annually in North America [2,3]. The incidence of type 2 diabetes in particular is increasing rapidly and accounts for the major impact of this disease. Diabetes (and mainly type 2) poses a colossal financial burden to our global society, comprising nine to 15% of healthcare expenses in developed countries. The mainstay treatment for type 1 diabetic patients is chronic insulin injection. While exogenous insulin therapy has dramatically reduced mortality from diabetes, patients often succumb to the long-term sequelae of diabetic angiopathy, either in the form of nephropathy, neuropathy or retinopathy. Maintaining rigorous glycaemic control with intensive insulin therapy has been shown to delay and sometimes prevent the progression of these complications [4], but patients are at risk of severe and sometimes fatal hypoglycaemic events [5,6]. Although insulin pumps and implantable insulin-secreting devices are a promising approach to improved glucose homeostasis, the development of reliable and accurate glucose sensor technology has been a limiting factor. A more physiologic approach to correct the diabetic state is the transplantation of insulin-producing tissue.

At present, vascularized pancreas transplantation reliably restores normoglycaemia and maintains long-term glucose homeostasis. It has been shown to improve quality of life [7,8] and even reverse some secondary complications of diabetes [9]. Simultaneous pancreas and kidney transplantation are presently considered the standard of care for selected patients with type 1 diabetes with end-stage renal failure [10]. Although pancreas transplantation achieves insulin-independence in greater than 80% of patients beyond 1 year [11], it remains a significant surgical procedure with substantial

Correspondence:
A.M. James Shapiro MD, PhD FRCS(Eng) FRCSC, Roberts Centre, University of Alberta, 2000 College Plaza, 8215 112 St, Edmonton, AB, Canada T6G 2C8.
**E-mail:**
shapiro@islet.ca

morbidity and occasional mortality [12]. Numerous studies have reported on the beneficial effects on survival, quality of life and impact in stabilization and even reversal of secondary diabetic complications when a pancreas is transplanted into a patient with end-stage renal failure in addition to a kidney [13–15]. A recent controversial report by Venstrom and colleagues has raised the possibility that patient survival could be compromised after pancreas transplant alone or pancreas after kidney transplant, compared with patients awaiting this procedure in the USA [16]. This study has recently been brought in to question, as it excluded patients with modestly impaired renal function – the group that might be expected to have an increased risk of mortality on the waiting list.

In view of the risks associated with surgery and long-term immunosuppressive drug therapy, pancreas transplantation is largely reserved for patients with diabetes with clinically significant complications, where the severity of their disease justifies accepting the risks of the procedure and immunosuppression. Therefore, with the exception of rare patients with severe, labile forms of diabetes, pancreas transplantation is not a practical option for young patients with diabetes who have not yet developed complications.

A promising alternative is the transplantation of islet cells isolated from donor pancreata and embolized into the recipient liver via the portal vein (figure 1). Compared to pancreas transplantation, islet transplantation is technically much simpler (although there are still
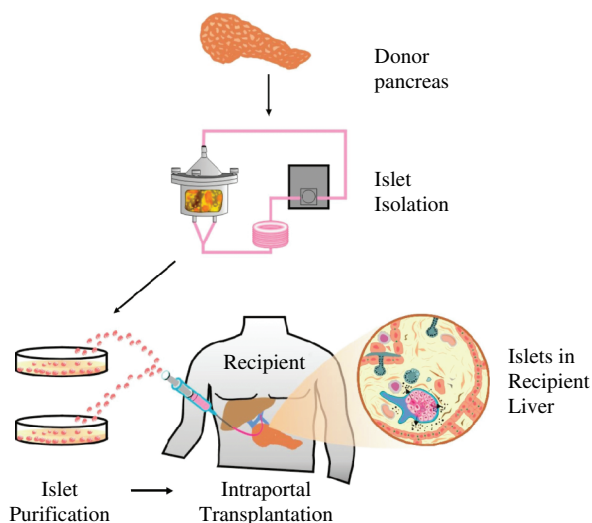
Fig. 1 Islet transplantation – steps involved in the preparation of islets from donor pancreas organs through to implantation into the portal vein of patients with type 1 diabetes.
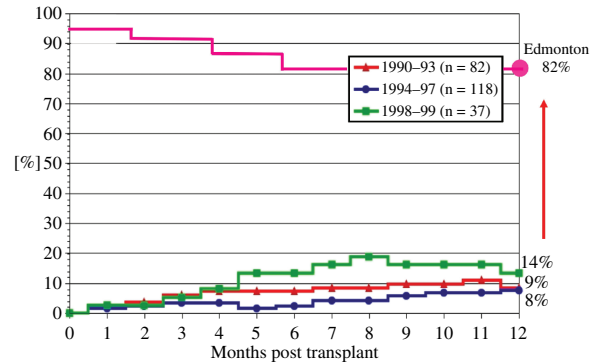
Fig. 2 Improvements in clinical outcome with high rates of insulin independence with patients treated in the Edmonton Protocol, compared to previous reports in the international Islet Transplant Registry.

potential risks), has low morbidity and offers the opportunity for storage of the islet graft in tissue culture or cryopreservation for banking. Moreover, the fact that islets can be kept in culture provides a unique opportunity to immunologically manipulate the islet graft, as well as optimize recipient conditioning prior to transplantation, thereby facilitating tolerance induction. The low morbidity of the procedure and the potential for tolerance induction make islet transplantation a promising strategy for correcting diabetes in young patients, including children [17], prior to the establishment of secondary complications.

While enthusiasm for clinical islet transplantation began in the early 1970s, its application was significantly limited, largely because of poor quality, low-yield islet preparations and ineffective immunosuppression. Recently, however, clinical outcomes in islet transplantation have improved dramatically, making it an effective therapy for selected patients with type 1 diabetes.

Islet Transplantation: Early Efforts to Present Success

The connection between pancreas and diabetes was first described in 1889 by von Mering and Minkowski, who observed that pancreatectomized dogs developed hyperglycaemia and glycosuria [18]. Five years later, Dr Watson-Williams at the Bristol Infirmary in England performed the first clinical pancreatic tissue transplant by implanting three pieces of freshly slaughtered sheep's pancreas into the subcutaneous tissues of a young boy dying from diabetic ketoacidosis [19]. Although the boy died 3 days after the procedure, he demonstrated an improvement in glucosuria before his death. In 1916, Pybus of Newcastle-on-Tyne

reported a mild reduction in glucose excretion in one of two diabetic patients transplanted with fragments of human cadaveric pancreatic tissue [20]. Four years later, at the University of Toronto, Frederick Banting discovered that ligation of the pancreatic duct in dogs led to enhanced recovery of the 'internal secretions' of the pancreas [21]. Subsequent studies by Banting, Best, Collip and MacLeod led to the discovery of insulin [22,23], and its rapid introduction into clinical practice revolutionized the treatment of diabetes.

While mortality from diabetes was radically reduced with exogenous insulin therapy, the development of secondary complications became strikingly apparent as patients lived longer with their disease [24–26]. Research in pancreatic tissue transplantation was revived when it was evident that insulin could not prevent these potentially fatal complications. In 1966, Kelly and Lillehei at the University of Minnesota performed the first vascularized pancreas transplant [27]. Initial series were associated with dismal morbidity and mortality [28], and the concept of transplanting just the islets instead of the whole pancreas was viewed as an attractive alternative.

Progress in rodent models in the early 1970s with improvements in the islet isolation procedure [29], and subsequent reports of successful reversal of chemical diabetes in rodents receiving islet isografts [30–32], generated excitement in the clinical application of this approach. However, early attempts at replicating rodent studies in large animal models were disappointing, largely because of the inability to isolate sufficient quantities of optimal islets for transplantation. As a result, researchers attempted to transplant pancreatic fragments instead of isolated islets in order to deliver a sufficient islet mass to achieve insulin independence. On the basis of the initial success in dogs [33,34], clinical trials were attempted, culminating in the first series of clinical islet allotransplants by Najarian and colleagues in 1977 at the University of Minnesota [35]. Initial clinical studies were disappointing as implantation of pancreatic tissue fragments into the peritoneal cavity or embolized to the liver was essentially ineffective. None of the patients were rendered insulin independent and only some had reduced insulin requirements for limited periods [35]. Moreover, although the liver appeared to be the optimal site for islet transplantation, the injection of larger volumes of tissue was associated with significant complications including portal vein thrombosis, portal hypertension and even mortality [36,37]. It was clear that more purified islet preparations would be required in order to improve safety for islet transplantation to become a clinical reality.

Several advances, such as the Ricordi digestion chamber [38], the COBE continuous purification system [39], controlled pancreatic distension with the digestive enzyme collagenase [40] and purified enzyme blends with low endotoxin levels [41], all contributed to improvements in obtaining higher-yield, better-quality islet preparations. Nevertheless, clinical outcomes remained disappointingly poor. Between 1974 and 1999, over 450 cases of islet allotransplantation for the treatment of type 1 diabetes were reported to the Islet Transplant Registry, with less than 10% of patients achieving insulin independence for longer than 1 year; although 28% had sustained C-peptide secretion [42–44]. The lack of clinical success was attributed to several factors, including inadequate islet transplant mass, ineffective prophylaxis against allograft rejection and autoimmune recurrence, and continued use of toxic, diabetogenic immunosuppressive agents such as cyclosporin and glucocorticoids [45–47]. In consideration of these limitations, a new protocol was implemented in Edmonton, Canada in 1999 that radically changed the face of clinical islet transplantation. The initial series of seven type 1 diabetic patients all achieved and maintained insulin independence beyond 1 year, demonstrating for the first time that islet transplantation could be as effective at achieving insulin independence as whole pancreas transplantation (figure 2) [48]. The success of the 'Edmonton Protocol' has been attributed to two key modifications from previous clinical trials. First, patients received an adequate number of high-grade islets prepared from an average of two donor organs. Second, more potent but less diabetogenic, steroid-free antirejection therapy was achieved using a novel combination of sirolimus, low-dose tacrolimus and an anti-interleukin-2 receptor monoclonal antibody (anti-IL-2R mAb). Since the release of the early Edmonton results, considerably more experience has been accrued both in Edmonton and at other centres worldwide. At the University of Alberta, a total of 66 patients have now received islet-alone transplants. Most patients continue to require two islet infusions in order to provide adequate engraft mass (approximately 12 000 IE/kg islet mass, based on the recipient body weight). Of patients undergoing completed islet transplants, 82% remain insulin free by the end of 1 year. There is some fall off in insulin independence, with 70% remaining insulin-free at 2 years and 50% free at 3 years post-transplant. Most patients that return to insulin continue to secrete endogenous insulin (and C-peptide) in sufficient amounts to continue to stabilize risk of hypoglycaemic reactions or of glycaemic liability, and 88% of patients continue to demonstrate islet function out to 5 years post-transplant. Islet trans

plantation has proven to be remarkably successful in stabilizing glucose control to a degree that is vastly superior to even intensive insulin therapy, and patients typically demonstrate normalization of HbA1C [49]. An international multicentre trial of the Edmonton Protocol was recently completed by the Immune Tolerance Network in nine sites, and this study demonstrated that the original Edmonton findings could be replicated at times to a very high level of success, depending on the experience of the site [50]. Worldwide, there have now been over 350 patients treated since 1999, and increasing momentum and focus on the remaining challenges of islet isolation, alternative insulin-secreting regulated sources and better immunosuppression with less side-effects, and the possibility of immunological tolerance continue to drive the field forward.

Recent Advances in Islet Transplantation

Pancreas Procurement and Islet Isolation

Over the past few years, there has been tremendous progress in clinical islet transplantation, from refinements of the Edmonton Protocol to novel strategies for improved islet isolation, implantation and recipient immunosuppression. One of the most critical areas of research is the islet isolation procedure, which remains highly labour intensive, expensive and relatively inconsistent. Even the highest-grade preparations only recover about 20–50% of the potential islet mass [51]. Moreover, rates for successful islet isolation at leading centres vary from 25 to 75%, depending largely on the quality of the pancreas, the amount of cold storage and the heterogeneity of collagenase preparations. To address these concerns, several strategies have evolved to enhance islet yields and ensure reproducibility of the procedure.

The quality of the donor pancreas depends largely on donor factors, such as age, body mass index, serum glucose levels and haemodynamic stability [52]. However, principles in pancreas procurement such as atraumatic manipulation of the pancreas, immediate *in situ* cooling of the pancreas and rapid transport of the organ to the islet isolation laboratory have been shown to minimize both warm and cold ischaemic injury, stabilize endogenous enzyme activity, and lead to significantly improved islet yields and viability [53]. A further concern that has a significant impact on islet isolation yield is the duration of cold ischaemia [54–56], given that the donor pancreas typically requires to be transported over long distances to centralized islet isolation centres. There have been no reports of successful single-donor islet transplants with cold storage times in excess of 10 h

[44], and others have demonstrated that longer cold ischaemic times reduce post-transplant islet function [57]. One of the most remarkable advances to overcome this concern has been the introduction of a 'two-layer' cold storage method using perfluorocarbons (PFCs) and standard University of Wisconsin preservation solution [57–59]. PFCs have an extremely high affinity for oxygen, which diffuses into the preserved pancreas, thereby maintaining membrane integrity and reducing ischaemic cell swelling [60,61]. The two-layer method has been shown to reverse the damaging effects of warm ischaemia, increase islet yields and improve islet engraftment [62–65]. This method also has the potential to expand the donor pool by salvaging pancreata that would otherwise be unusable [66].

Although patients in the initial Edmonton series were transplanted with islets immediately after isolation, some centres are currently maintaining islets in culture prior to transplantation. Culturing islets does not appear to have detrimental effects on viability and function [67] and provides opportunities for pretransplant conditioning of the recipient, immunological manipulation of the islet graft to promote engraftment and prevent rejection, and for identifying the best matched recipients. In addition, through the development of specific culturing conditions, the Miami group has demonstrated that islets can be shipped to remote transplant centres without compromising viability [68]. Moreover, maintaining islets in culture enhances islet purity, which in turn improves engraftment and safety while reducing graft immunogenicity [69–71]. However, others have argued that islets still attached to acinar tissue, so called mantle islets, are superior to completely pure islet preparations. This is based on the observation that exocrine tissue can exert trophic effects on precursor cells in the ductal epithelium of a less pure sample, thereby promoting neogenesis of β cells [72,73].

Islet Engraftment

The loss of viable islets is a significant concern not only during the isolation and purification process [74] but also when embolized into the portal vein of the recipient liver. Based on metabolic tests in post-transplant recipients, it is estimated that only 25–50% of the implanted islet mass actually engrafts in the patient [49]. Recently, the Uppsala group in Sweden have shown that human islets exposed to ABO-compatible blood triggers an instant blood-mediated inflammatory reaction (IBMIR), characterized by activation of platelets and the coagulation and complement systems, leading to islet damage by clot formation and leucocyte infiltration [75]. Further

investigation into the mechanisms of this phenomenon revealed that tissue factor and thrombin play critical roles in mediating IBMIR, indicating that strategies to block binding of these factors may have considerable therapeutic potential in islet transplantation [76,77]. Furthermore, in recent years, several experimental strategies have been developed to enhance islet engraftment. For instance, anti-inflammatory treatment with TNF–α-receptor antibody in a marginal mass islet model in mice [78], as well as antioxidant therapy with nicotinamide [79,80], vitamin D3 [81,82], pentoxiphylline [83] or cholesterol-lowering agents pravastatin or simvastatin [84,85], have all demonstrated positive impact in the preclinical setting and suggest a potential role in future clinical trials designed to improve islet engraftment.
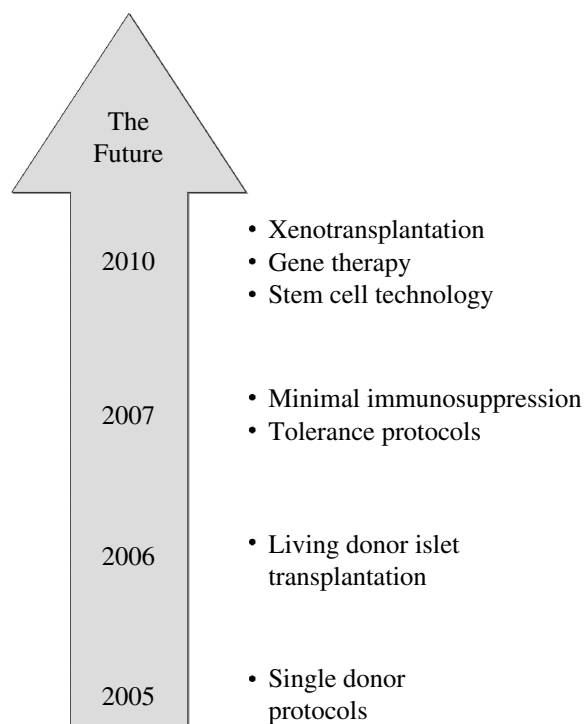
Recipient Immunosuppression

Perhaps the most critical area for further investigation in islet transplantation is immunosuppression. The antirejection regimen in the Edmonton Protocol is arguably one of the most important recent developments in making islet transplantation a clinical reality. The minimization of diabetogenic agents, while maintaining adequate potency to contend with both allograft rejection and autoimmune recurrence, is a matter of tremendous importance as less toxic and more specific drugs enter the clinical arena. While the drug sirolimus has facilitated clinical islet transplant success through provision of effective immunosuppression to contend with both auto- and alloimmunity, the agent is also responsible for many of the side-effects encountered after islet transplantation. It has also been suggested that sirolimus could still have a detrimental effect on islet engraftment and neovascularization, as well as potential detrimental direct toxicity to islets [86]. On balance, however, this agent has proven to be advantageous compared to former steroid and high-dose calcineurin-inhibitor based therapies. Recently, the steroid-free sirolimus and low-dose tacrolimus-based protocol in the Edmonton experience has been shown to be highly effective in patients undergoing islet after kidney transplantation [87]. In addition, the Minnesota group has implemented novel immunosuppressive protocols in their recent series of islet recipients, which has resulted in an unprecedented level of insulin independence after single-donor islet infusions [88]. The first series of patients received inductive treatment with a T–cell-depleting antibody, hOKT3γ_1-Ala-Ala, which has been shown to impede the progression of diabetes and improve metabolic control in children treated at the time of their diagnosis [89]. The second series of patients received thymoglobulin induction, an anti–TNF-receptor

drug (etanercept), and maintenance immunosupression with mycophenolate mofetil and sirolimus. While the rates of single-donor islet transplant success have been impressive, major biasing factors have included use of only perfect-grade, high body-weight pancreas donors, coupled with selection of low body weight and insulin sensitive recipients.

Future Challenges

Single Donor Grafts

As islet transplantation moves forward, one of the first challenges is to reliably achieve insulin independence with single-donor grafts (figure 3). Based on experience with islet autotransplantation after total pancreatectomy, an minimum of 300 000 islets are necessary to achieve insulin independence in 70% of recipients [90]. This is in stark contrast to the 850 000 islets required in the Edmonton series of patients, suggesting that factors such as the presence of autoimmunity, diabetogenic immunosuppression, and brain death of the donor may have detrimental effects on islet engraftment and function. Cadaveric brain-dead organ donors are often haemodynamically unstable, require high doses of inotropic support and circulating brain-derived inflammatory peptides can

Fig. 3 Future milestones in clinical islet transplantation.

The Future

2010
- Xenotransplantation
- Gene therapy
- Stem cell technology

2007
- Minimal immunosuppression
- Tolerance protocols

2006
- Living donor islet transplantation

2005
- Single donor protocols

have direct toxic effects on the pancreas prior to retrieval [91]. Advances in procurement techniques from cadaveric donors and improvements with less toxic and more potent immunosuppression will progressively lead to lower islet requirements to achieve normoglycaemia.

Limited Donor Supply

Even if single-donor islet transplantation becomes consistently successful, the tremendous shortfall in the number of cadaveric pancreata would drastically limit the number of diabetic patients that could benefit from this procedure. Therefore, uncovering alternate sources of islet cells or the development of islet-cell surrogates are critically important challenges before islet transplantation can broadly be applied in the treatment of diabetes. Recently, the University of Pennsylvania has demonstrated successful reversal of diabetes with single-donor islet transplants using organs procured from non–heart-beating donors [92]. At the other end of the spectrum, living donation of a segmental pancreas graft may also be an attractive alternative source for islets. Initial experience in living donor segmental pancreas transplants at the University of Minnesota revealed an increased risk to the donor of procedural complications and impaired glucose tolerance; however, more careful selection of donors has essentially eliminated these risks [28,93–95]. On the basis of this experience, segmental pancreas grafts could be procured from living donors and subsequently used for islet transplantation instead of a segmental pancreas transplant, thereby reducing the surgical risks to the patient. However, ensuring that an adequate islet mass can be obtained from a segment of pancreas in order to secure insulin independence will be a significant challenge in bringing this strategy closer to the clinic.

Xenotransplantation is another area of tremendous potential as an unlimited source of islet cells. The development of transgenic pigs expressing human complement-regulatory proteins to surmount immune destructive pathways has been encouraging [96]; however, the ongoing requirement of heavy immunosuppression and concerns regarding zoonotic viral transmission are ongoing obstacles. Recently, controversy in xenotransplantation has achieved a new height with the report by Valdes [97] regarding improved glucose homeostasis by cotransplantation of pig sertoli cells and neonatal porcine islets in diabetic children. While this preliminary report demonstrates great potential, the replication of these results in primates and a larger cohort of children will be required before definitive conclusions can be drawn [98].

While additional sources of islet cells are being investigated, the development of islet surrogates that are insulin-producing and glucose-responsive would completely eliminate the problem of supply and demand. Research in the area of stem cells has demonstrated considerable promise in recent years based on evidence of pancreatic stem-cell proliferation using neogenesis peptides such as INGAP [99], hepatocyte growth factor, epidermal growth factor and gastrin. The opportunity for trans-differentiation of ductal elements into insulin-producing cells also provides another exciting opportunity for β-cell expansion [100]. Substantial progress has also been made in genetic engineering, such as the transformation of hepatocytes to secrete a single-chain insulin analogue [101], and the alteration of intestinal mucosal K-cells to secrete insulin in response to hyperglycaemia [102]. While these strategies seem promising, concerns regarding imprecise physiological glucose homeostasis, potential transmission of malignancy and cellular rejection all need to be addressed as these approaches are further developed.

Tolerance Induction

The ultimate goal of islet transplantation is to completely restore glucose homeostasis and prevent long-term diabetic complications without the need for maintenance immunosuppressive therapy. At present, the risks of malignancy and life-threatening infection have been very low. However, fears of these complications as well as medication side-effects, such mouth ulceration, hypercholesterolaemia, renal dysfunction and hypertension [49], have limited broader application in patients with less severe diabetes. It should be noted that unlike other solid organ transplants, islet transplantation is disadvantaged because there is a lack of an effective predictive marker of early rejection – and for this reason the immunosuppressive regimens used in islet transplantation currently err on the side of over-immunosuppression. If the degree of systemic immunosuppression could be reduced, ultimately towards inducing a permanent state of unresponsiveness to the allograft (tolerance), islet transplantation could be applied in the earliest stages of diabetes, including transplantation in children.

Several experimental approaches have been shown to induce tolerance in islet transplantation. One strategy that has demonstrated significant promise in preclinical models is the blockade of critical costimulatory molecules on the surface of T cells. Blocking signalling through these molecules effectively prevents the activation and clonal expansion of T cells, forcing them to anergy and apoptosis [103,104]. In a primate model of

islet transplantation, the blockade of CD154 costimulation with the specific mAb hu5C8, can induce long-term insulin independence following intraportal islet transplantation [105,106]. Similarly, blockade of CD28 signalling using LEA29Y, in combination with sirolimus and an anti-IL-2R mAb, can also facilitate indefinite islet allograft survival in monkeys [107]. In addition to the blockade of costimulation, T-cell depletion at the time of transplantation using potent lymphocyte-depleting agents is an effective strategy for facilitating tolerance. For example, an anti-CD3 diphtheria-based immunotoxin has been shown to facilitate long-term survival of islet xenografts [108,109] and allografts [110] in primate models. Moreover, the agent Campath-1H (Alemtuzumab), a humanized antibody specific for CD52 determinants on the surface of T cells, has demonstrated considerable success in maintaining function of renal allografts in patients [111,112] and is currently being explored in clinical islet transplantation [113]. Initial trials with Campath-1H and sirolimus in a small number of islet recipients in Edmonton did not show superior outcome to standard tacrolimus-sirolimus based therapy. The challenges involved with further refinement in optimal immunosuppression for islet transplantation are significant, as the relatively small numbers of procedures carried out at any single centre limits the potential power of analysis. Therefore, leading islet transplant centres are collaborating closely and are moving forward with multisite trials with the goal being to systematically explore novel therapeutic approaches in a coordinated manner.

One strategy that has proven clinical success in establishing tolerance is the induction of mixed haematopoeitic chimerism through donor-specific bone-marrow transplantation. Reports of bone marrow transplant recipients with established donor chimerism, who have been able to accept a renal transplant from the same donor without immunosuppression, indicate that robust tolerance is achievable in the clinic [114–116]. Unfortunately, concerns regarding toxicities with recipient preconditioning and the threat of graft-vs.-host disease have precluded clinical application of this strategy. For islet transplantation, less toxic preconditioning strategies are absolutely essential before the risks associated with bone marrow transplantation can be justified in a patient whose disease is controlled with insulin therapy. Using agents that block costimulation or deplete lymphocytes, as described above, clinical non-myeloablative strategies are in development, and trials of donor bone marrow infusion combined with solid organ or islet transplantation are rapidly evolving [117].

Another area of active research towards the avoidance of immunosuppression is the encapsulation of islets in immunoprotective devices prior to implantation. Several immunoisolation systems have been extensively studied and have been shown to enhance the survival of both allogeneic and xenogeneic islets [118]. However, the clinical application of these devices has been impeded by many important concerns, including adequate access of the encapsulated islets to blood supply and oxygen for survival, triggering of nonspecific foreign body reactions to the biomaterials resulting in their destruction, practical concerns regarding the volume of infusion of an encapsulated preparation and graft loss from cytokine-mediated immunological responses. While the concept of protecting islets is enticing, developments in polymer biology are definitely required before this approach can be applied to patients.

It has been suggested that islet transplantation could serve as a primary test bed for novel tolerance protocols because failure to achieve tolerance would result in the patient's return to insulin therapy rather than potential death in the case of losing a life-sustaining heart or liver transplant. Nevertheless, limitations such as the need to overcome both alloimmune and autoimmune barriers, as well the lack of specific serological markers to detect allograft rejection, may prove to be significant challenges as new tolerance strategies are tested in islet transplantation.

Summary and Conclusions

Although the concept of transplanting islets for the treatment of diabetes has existed for over a century, several technical and biological barriers have impeded clinical application of this approach in the past. However, in recent years, landmark advances in islet isolation and less diabetogenic immunosuppression have moved islet transplantation forward from research to clinical reality. With the introduction of the Edmonton Protocol and ongoing developments, islet transplantation has now been accepted as a safe and effective therapy for select patients with type 1 diabetes. At present, because patients receiving islet allografts must exchange insulin for lifelong immunosuppressive therapy, the procedure can only be justified in patients with very unstable forms of diabetes. Development of novel immunosuppressive protocols using more specific and less toxic drugs, ultimately towards inducing tolerance, is an important step in applying islet transplantation earlier in the course of the disease, including transplantation in children. Moreover, advances in identifying other sources of islet cells, together with progress in better understanding the

biology of diabetes, will help increase the limited supply of islets through gene therapy, stem-cell biology techniques or xenotransplantation. It is anticipated that continued international collaboration will further stimulate excitement in the field, as innovative solutions are created to meet the remarkable challenges that lie ahead.

Acknowledgements

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