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Transplantation of islets of Langerhans: new developments

T. Berney[a, b], L. Bühler[a, c], A. Caulfield[b], J. Oberholzer[a], Ch. Toso[a], R. Alejandro[b], D. K. C. Cooper[c], C. Ricordi[b], Ph. Morel[a]

[a] Clinique de Chirurgie Digestive, Hôpital Cantonal Universitaire de Genève, Switzerland
[b] Diabetes Research Institute, University of Miami School of Medicine, Miami, Florida, USA
[c] Transplantation Biology Research Center, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts, USA

Summary

The clinical results recently reported by the Edmonton group in recipients of allogeneic islet grafts, all of whom achieved at least temporary insulin independence, has rekindled interest in transplantation of islets of Langerhans as a means to cure diabetes. Long-term islet graft survival has been achieved in a non-human primate pre-clinical model with a protocol of T-cell signaling-blockade using a new monoclonal antibody. Islet xenotransplantation (namely the use of animal islets, with the aim of transplanting them into humans), or stem cell technology (the controlled differentiation of stem cells to obtain specialised cells for the treatment of diabetes) are other procedures currently being evaluated in animal models. The recent clinical success suggests that, in the near future, diabetes might be treated by islet transplantation early in the clinical course of the disease before the development of complications, and without the risks associated with conventional immunosuppression.

Key words: diabetes; islets of Langerhans; transplantation; xenotransplantation

Introduction

The spectacular results recently reported by the Edmonton group in a series of 12 consecutive recipients of allogeneic islet grafts, all of whom achieved at least temporary insulin independence, has rekindled interest in transplantation of islets of Langerhans as a cure for diabetes [1, 2]. In parallel, long-term islet graft survival has been achieved in a non-human primate pre-clinical model with a protocol of T-cell signaling-blockade using a monoclonal antibody [3, 4]. These seminal observations suggest that, in the near future, diabetes might be reversible by islet cell transplantation early in the clinical course of the disease before the occurrence of complications, but without the hazards associated with long-term conventional immunosuppression. The enthusiasm thus generated is best illustrated by the high priority accorded to the field of islet transplantation by the recently established Immune Tolerance Network (ITN) in the United States, a collaborative effort supported by major funding organisations with the mandate to advance clinical application of effective tolerogenic therapies [5].

Abbreviations
Gal = galactose α1-3 galactose
IE = islet equivalent
ITN = immune tolerance network
mAb = monoclonal antibody
PERV = porcine endogenous retrovirus
TNF = tumour necrosis factor

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Rationale for islet transplantation in type 1 diabetes

When exogenous insulin therapy became available, it proved to be a life-preserving advance for patients suffering from type 1 diabetes mellitus. However, it uncovered the devastating long-term complications associated with micro- and macroangiopathy, which may lead to end-stage renal failure, lower limb ischaemia or blindness [6]. The Diabetes Control and Complications Trial demonstrated that tight control of blood glucose levels achieved by intensive insulin therapy could significantly delay the occurrence of the long-term complications of type 1 diabetes [7], and was cost-effective in terms of health care expenditure [8]. Even though intensive insulin therapy does not sustain normal blood glucose levels throughout the day and is accompanied by an increased frequency of severe hypoglycaemic events, the Diabetes Control and Complications Trial results are a proof of principle of the benefits of strict metabolic control [9]. The further observation that pancreas transplantation could reverse lesions of diabetic nephropathy [10] supported the notion that endocrine tissue replacement might be the only procedure to consistently achieve physiological control of blood glucose levels. Indeed, islets function for a lifetime, producing and releasing insulin in response to an intrinsic real-time "glucose sensor" detecting increases or decreases in blood glucose levels [11]. Whole organ pancreas transplantation leads to sustained euglycaemia and insulin-independence in the vast majority of recipients, with graft survival rates as high as 78% at 5 years [12]. However, despite significant progress, pancreas transplantation is still associated with peri-operative mortality and significant morbidity [13, 14].

In contrast, islet cell transplantation offers the advantage of being able to be performed as a minimally invasive procedure, in which islets can be infused percutaneously into the liver via the portal vein [15–18] (fig. 1). As most successful clinical islet transplantation currently requires 2–4 human donors per recipient [1], the shortage of organ donors might prevent most eligible diabetic patients from receiving a graft. Islet cell availability could become unlimited when strategies such as the use of xenogeneic islets, engineered beta-cell lines, and in vitro or in vivo islet expansion reach the stage of clinical applicability [19–23]. Further, islet grafts might be maintained without chronic immunosuppression if the induction of donor-specific tolerance [19, 24] or immuno-isolation in biological capsules emerge as viable clinical strategies [25].

Islet donation and purification

Since the late eighties, islet isolation has been performed by an automated method, which has proved a major breakthrough for the feasibility of large-scale islet transplantation in the clinical setting [26] and has allowed, for the first time, recovery of a sufficient number of islets from a single donor for successful transplantation in a diabetic recipient [27]. The principle of the method lies in the continuous digestion of the pancreas loaded in a chamber and fully immersed in warm enzyme (collagenase) solution. The solution circulates in a closed circuit through a 450 μm mesh, which allows the islets that are progressively released to be saved from further digestion, while retaining larger chunks of pancreatic tissue. The chamber is shaken vigorously throughout the digestion

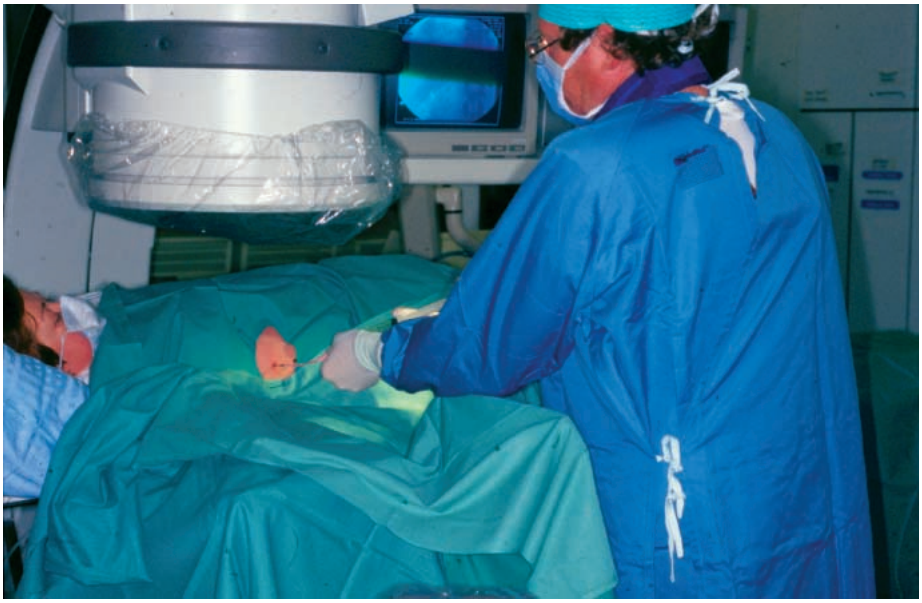


Figure 1

Transhepatic percutaneous injection of islets of Langerhans is a minimally-invasive procedure. The injection is performed under local anaesthesia using interventional radiology techniques. The portal vein is accessed under angiographic guidance (figure 3), and the purified islet suspension is slowly infused into the vein with continuous monitoring of the intraportal hydrostatic pressure.

process, which adds a mechanical component to the enzymatic action.

Freed islets are then purified from the exocrine tissue by centrifugation of the dispersed suspension in density gradients, using a computerised centrifuge [28]. The small difference in density between endocrine and exocrine tissue makes it difficult to obtain ultra-pure islet preparations and necessitates a compromise between purity and yield (fig. 2). The recent availability of highly-purified enzyme blends, notably by the elimination of endotoxin contaminants, has further allowed improvement in the yields and reproducibility of islet tissue isolation [29].

Islet implantation

Islet transplantation is still an experimental procedure and is mainly offered to type-1 diabetes patients with end-stage renal failure, with the aim of achieving control of glucose metabolism and insulin-independence. It is performed either as a simultaneous islet-kidney or solitarily as an islet-after-kidney transplant procedure. Islet transplantation alone in patients with functioning kidneys is proposed in cases of "brittle" type-1 diabetes. Solitary islet transplantation in order to prevent the development of diabetic complications, is not yet considered a reasonable option, because of the need for chronic immunosuppressive therapy and its various side-effects [16].

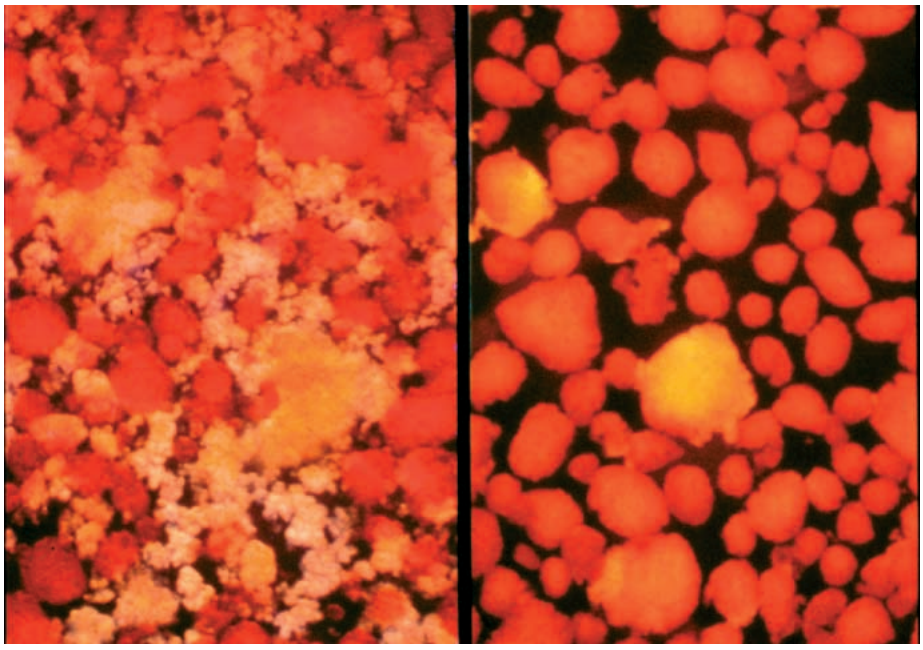
Currently, the most favoured site for islet graft implantation is the liver, in which the islets are implanted by infusion into the portal vein. When simultaneous islet-kidney transplantation is performed, islets are infused into the portal system, usually by catheterisation of a colic vein, during the open surgical procedure [16]. A minimally-invasive procedure, requiring interventional radiology technology, is used in cases of islet-after-kidney or solitary islet transplantation (fig. 1). In these patients, the portal vein is reached by a transhepatic percutaneous approach under angiographic guidance (fig. 3). The purified islet suspension is slowly infused with continuous monitoring of the intraportal hydrostatic pressure [18].

Obstacles to islet engraftment

A majority of islets are lost early after transplantation [30]. The early events leading to graft loss are collectively termed primary non-function, and are not related to immune phenomena. Rather, they result from poor intrinsic quality of the islet preparation or from interaction of the islets with inflammatory elements of the hepatic microenvironment in which they are implanted. Direct islet damage provoked by cytokines and nitric oxide released by activated Kupffer cells and sinusoidal endothelial cells in response to the islet implantation has been clearly demonstrated [31, 32]. Another reason for early islet graft loss might reside in an inflammatory reaction elicited by the interaction between the implanted islets and components of the blood stream, such as complement and mononuclear cells [33, 34]. Early islet loss might also be attributed to relatively low oxygen

Figure 2

Isolated human islets of Langerhans.
(A) Unpurified islets, stained in red by dithizone (x100), are surrounded by exocrine tissue.
(B) Purified islets of over 90% purity.



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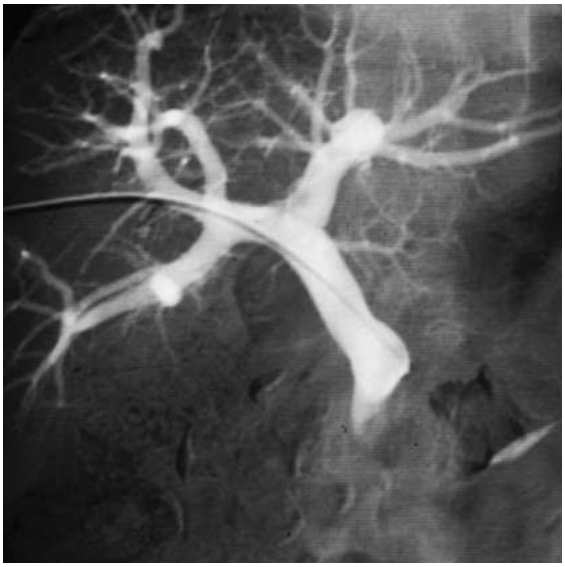

Figure 3

Transhepatic portal venogram. The catheter has been placed in the main portal vein prior to injection of islets.

tension in the portal vein, as recently demonstrated in a rodent model [35]. Additionally, islets are an essentially avascular graft, which renders them particularly prone to hypoxia, at least during the few days it takes before neovessels revascularise the transplant [36].

A second set of problems arises from the high metabolic demand imposed on the islet graft, which results from several factors [17]. A normal pancreas consists in approximately 1 million islets, a figure that is far from being matched with the threshold of 6'000 islets equivalents per kilogram (IE/kg) considered necessary for graft function. Bearing in mind the significant number of transplanted islets lost to the noxious inflammatory stimuli described above, it is clear that most of the time the engrafted islet mass only marginally fulfils its demands for insulin-release. Furthermore, until recently, islet transplantation necessitated conventional immunosuppression, based on a combination of several drugs, comprising calcineurin inhibitors (cyclosporin or tacrolimus) and steroids. All 3 drugs have long been known to have diabetogenic effects, further increasing the metabolic load on the islets [37].

Finally, islet grafts are prone to destruction by recurrence of autoimmunity in addition to allorejection [17]. Recurrence of autoimmunity in transplanted islet tissue was clearly demonstrated by the recurrence of insulitis in recipients of segmental pancreatic grafts from an identical twin and receiving no immunosuppression. However, the autoimmune process was rarely observed in recipients of whole organ pancreatic allografts receiving immunosuppression [38]. Although immune rejection and recurrence of autoimmunity are exceedingly difficult to distinguish, there is evidence that the latter mechanism participates in long-term islet graft loss despite adequate conventional immunosuppression. In this regard, a significantly lower 1-year islet graft survival was demonstrated in recipients positive for anti-islet-cell autoantibodies [39].

Results of clinical islet transplantation

Through December 2000, a total of 493 islet allografts have been performed worldwide, including 394 since 1990, a relative increase in numbers related to the introduction of the automated method of islet isolation [40]. Cumulative one-year patient and graft survivals of 96% and 41%, respectively, were obtained in the 237 fully documented C-peptide-negative, type-1 diabetic patients who received islet transplants between 1990 and 1999. The persistence of graft function can be assessed by measurable levels of basal serum C-peptide, at a threshold of 0.5 ng/ml. The observation that 27% of recipients lost graft function within 1 month of transplantation (and 40% within 3 months) indicates that primary non-function has been a major cause of islet graft loss [40].

While the evidence of measurable C-peptide in the serum indicates unequivocal survival of at least some of the islet grafts, durable insulin-independence has unfortunately frequently not been achieved. However, it must be emphasised that islet graft function in the absence of full insulin-independence may still be associated with markedly improved glucose regulation [41, 42].

Analysis of data reported to the international Islet Transplant Registry has identified 4 features associated with persisting graft function at 1 year. The four criteria that now form the basis for state-of-the-art islet allotransplantation are: (1) transplantation of an islet mass ≥6000 IE/kg body weight; (2) cold ischaemia time of the pancreas (≤8 hours); (3) induction of immunosuppression with antilymphocyte/antithymocyte globulins or anti-IL2-receptor monoclonal antibodies, as opposed to OKT3 or no specific induction therapy, and (4) the liver as the site of islet graft implantation, as opposed to the spleen or the omentum. A significant beneficial effect is obtained particularly when all 4 criteria are fulfilled.

The University of Miami experience has demonstrated long-term allogeneic islet function in 6 of 8 patients for more than 60 days, including 2 patients in whom C-peptide secretion was achieved for over 9 years [41, 43]. Although all recipients had elevated levels of glycosylated haemoglobin (HbA_{1c}) despite intensive insulin therapy and recurrent episodes of moderate-to-severe hypoglycaemia prior to transplantation, insulin requirements and HbA_{1c} levels were significantly reduced in all 6 patients with evidence of graft function. In addition, neither patient with long-term graft function has experienced hypoglycaemic episodes.

Improved results were reported by the Giessen group by the implementation of new strategies aimed at promoting islet engraftment and survival. The Giessen protocol was based on the fulfilment of the 4 criteria defined by the Islet Transplant Registry, refined by strategies such as use of endotoxin-free reagents, use of antioxidant agents (nicotinamide, pentoxifylline, vitamin E), and the administration of intravenous insulin starting 2–3 days prior to transplant in order to diminish metabolic demand on the graft. With this protocol, insulin-independence was achieved in approximately 25% of 50 patients transplanted between 1992 and 1997 [40, 44, 45].

In a recent publication, the group at Geneva University Hospital implemented peritransplant management along the same lines and reported graft function for 3 months to 5 years in all of 13 consecutive type 1 diabetic recipients of islet allografts [46]. These results led to the creation of a multicenter islet transplantation program in a network consisting of Geneva and 4 institutions in France. Pancreata procured in any of the collaborating centers were shipped to the core laboratory in Geneva and processed with ischaemic times less than 8 hours. Isolated islets were then transplanted to diabetic patients at these institutions. Again, immediate function was observed in all 10 patients transplanted between March 1999 and June 2000 [47]. At one year, 2 patients were insulin-independent (each with islets isolated from a single pancreas), 3 patients were insulin-dependent but had persistent C-peptide secretion, and 5 patients had lost all graft function [47].

The report in 2000 by the Edmonton group of a consecutive series of 7 type 1 diabetic recipients of islet allografts with persistent insulin-independence was received as a new level of achievement by the islet transplantation community [1]. These results were obtained in recipients of islet grafts in the absence of severe nephropathy and kidney transplantation. The Edmonton protocol uniquely combined several strategies designed to address specifically the various obstacles encountered in the isolation-transplantation-immunosuppression sequence [17]. First, pancreatic cold ischaemia time was kept to a minimum prior to isolation (1.5–13 hours, mean 4.8 hours), and emphasis was put on obtaining high-purity islet preparations. Second, in order to achieve a total transplanted islet mass of at least 10,000 IE/kg, all patients received at least two islet transplants. Finally, an improved non-diabetogenic immunosuppressive protocol was used, consisting of low-dose tacrolimus, rapamycin (sirolimus) and anti-IL2-receptor monoclonal antibody (daclizumab) induction, in the absence of steroids. Tacrolimus can be administered in low doses thanks to its synergism with rapamycin, and this association has been shown to be extremely potent in the prevention of acute rejection in a mixed series of liver, pancreas and kidney transplant recipients [48].

In a recent update of the Edmonton protocol results, it appears that ten of twelve patients remained insulin-independent with a median follow-up of 10 months. A compelling improvement of blood glucose control was achieved, as demonstrated by a marked reduction of mean amplitude of glycaemic excursions and HbA_{1c} levels. None of the patients experienced hypoglycaemic episodes, and oral glucose tolerance tests were normal in 4 patients, showed impaired glucose tolerance in 5 patients, and fulfilled criteria for a diagnosis of diabetes in 3 patients [2]. In spite of the need for 2–4 donors per recipient, the Edmonton immunosuppression protocol has been a considerable achievement in the field.

Novel strategies in current islet transplantation trials

Islet cell transplantation is regarded as an ideal model for the implementation of novel cytoprotective/immunosuppressive/tolerogenic protocols for several reasons: (i) the need for improved results is still considerable; (ii) loss of islet graft due to a failure of the implemented strategy is not life-threatening; (iii) retransplantation is technically easy and is associated with low morbidity; and (iv) tolerance induction is of particular interest in islet transplantation, because both allogeneic and autoimmune barriers have to be overcome.

Inflammatory events mediated by activated macrophages and endothelial cells can be antagonised by compounds neutralising the effects of inflammatory cytokines, notably tumour necrosis factor-α (TNF). The newly-available agents infliximab (an anti-TNF monoclonal antibody) and etanercept (a fusion protein of soluble TNF-receptors linked to human immunoglobulin), which have been tested in clinical trials in patients with rheumatoid arthritis or Crohn's disease, have shown potent anti-inflammatory activity and mild adverse effects [49] and could be a valuable addition to the armamentarium. The University of Miami has recently carried out islet transplantation in 6 patients with islets isolated each time from a single pancreas, using a protocol comprising a single injection of infliximab at the time of transplant, a tacrolimus/rapamycin immunosuppressive regimen, and donor bone marrow cell infusion to promote microchimerism and donor-specific tolerance. All patients have functioning grafts after a median follow-up of 4 months, significantly reduced insulin requirements and markedly improved metabolic control [50].

Immunosuppressive regimens are likely to undergo significant improvements thanks to the advent of a number of novel agents aimed at preventing delivery of signals of T-cell activation, some of which have already reached clinical application. T-cell-antigen interaction can be targeted by humanised anti-CD3 monoclonal antibodies (mAb) lacking Fc-receptor-binding properties (and thus avoiding massive cytokine release by cross-linked macrophages) and with reduced immunogenicity [51]. The University of Minnesota has recently reported 3 insulin-independent patients with a median follow-up of 95 days after islet allotransplantation, using a protocol comprising induction with the new generation anti-CD3 mAb, and a tacrolimus/rapamycin immunosuppressive regimen [52].

Blockade of co-stimulatory signals of T-cell activation has been efficiently obtained with a humanised mAb targeting the CD154 molecule [53], with excellent graft survival (>200 days) reported in models of islet allotransplantation in surgically-induced diabetic primates [3, 4]. These results prompted the launching in 1999 of a clinical trial of the humanised anti-CD154 mAb as an immunosuppressive monotherapy in recipients of solitary islet transplants. Unfortunately, reports of unusual rates of thromboembolic complications in another trial of kidney transplant recipients receiving the mAb led to a complete halt of all clinical trials. The thrombotic issue will have to be resolved if this promising immunomodulatory strategy is to reach the clinical setting again [54, 55].

The Immune Tolerance Network (ITN), a collaborative effort supported by major funding administrations such as the Juvenile Diabetes Foundation International and the National Institute of Diabetes and Digestive and Kidney Diseases, was established in 1999 with the mandate to advance the clinical application of effective tolerogenic therapies for a broad range of immune-related conditions, including transplantation and autoimmune diseases [5]. For islet transplantation, the ITN is committed to supporting clinical research focusing on the following points: (i) novel immunotherapeutic strategies aiming at early withdrawal of immunosuppression, and (ii) therapeutic establishment of haematopoietic chimerism, with emphasis on depletion- and irradiation-free conditioning protocols [5]. The nature of the ITN – research subgroups composed of authorities in their fields, with financial support to match their ambitions – will undoubtedly give a significant boost to clinical islet transplantation. Before the launching of tolerance induction trials, the ITN has selected 10 centers worldwide, including the groups at the Universities of Geneva, Miami, and Harvard, with the aim of reproducing the results of the Edmonton protocol.

Shortage of human organs: Will xenotransplantation or stem cell technology solve the problem?

If islet cell allotransplantation were to become fully successful, the availability of human pancreatic tissue would rapidly become insufficient in view of the large number of potential recipients and also the number of islets required for each patient. Some research is, therefore, now orientated towards the use of other sources of islets. Islet xenotransplantation, namely the use of animal islets, with the aim of transplanting them into humans, is a possible approach. Stem cell technology, the controlled differentiation of stem cells to obtain specialised cells for the treatment of diseases, is a second approach.

Islet xenotransplantation

Interest in xenotransplantation has increased in recent years, due to the serious shortage of human organ donors. Although nonhuman primates are genetically closer to humans, the pig appears to be the most suitable source of organs for humans [56]. The metabolic function of pig insulin would certainly be adequate as for many years it has been used to treat diabetic patients, and its structure differs from human insulin in only one amino acid residue. However, the implantation of xenogeneic tissue has provoked ethical and epidemiological controversies [57]. Transmission of porcine endogenous retroviruses (PERV) from porcine cell lines or endothelial cells to human cells has been demonstrated in vitro [58, 59]. However, using the same in vitro conditions that allowed infection of human cells [58], it has not been possible to achieve viral transmission from cells from selected strains of miniature swine (C. Patience, personal communication). Although the theoretical possibility of cross-species transmission of PERV has been verified in vivo after transplantation of porcine islet or fetal pancreatic tissue into immunodeficient strains of mice [60, 61], PERV transmission into humans has never been observed. It has not been possible to demonstrate any viral transmission, let alone clinical infection or disease, in patients who had been exposed to living porcine tissues [62, 63].

The major obstacle to successful xenotransplantation is the immunological incompatibility between pigs and humans. The major xenoantigen responsible for rejection of porcine grafts in humans has been identified as the carbohydrate epitope, galactose α1-3galactose (Gal) [64]. All mammals, except humans, apes and Old World monkeys, express this oligosaccharide on the surface of their vascular endothelial cells. Primates that do not synthesise this carbohydrate begin to produce antibodies directed against it during neonatal life, as they do to ABO blood type antigens. These natural antibodies initiate the hyperacute rejection of xenotransplanted organs by activating complement and coagulation and inducing thrombosis and haemorrhage in the graft [65].

Xenotransplantation of islets presents some possible advantages over that of a whole organ. With non-vascularised grafts, such as islets, the absence of immediate vascularisation prevents contact between the recipient's circulating natural preexisting antibodies and the endothelial cells of the islets. Until recently, cellular immunity was believed to be predominant in the rejection of tissue xenografts [66–69], but the exact mechanism remains incompletely understood. Long-term survival of pig [66, 67] and human [68, 69] pancreatic islets in athymic nude mice suggests a T cell-mediated process, in which CD4+ T cells have been shown to play a major role [70, 71]. However, the use of conventional immunosuppressive agents that block the T cell response in immunocompetent recipients allows only a modest prolongation of survival of xenografted islets [72]. Recently, high titers of anti-Gal antibodies have been shown to accelerate rejection of Gal-positive islets in (1, 3-galactosyltransferase – knockout mice, indicating that humoral responses participate in the rejection process [73]. Most studies of islet xenograft transplantation were performed in rodents, and experiments in the relevant pig-to-nonhuman primate model have been uncommon [74–76].

Korsgren's group has reported its experience with fetal porcine islet-like cell clusters transplanted into cynomolgus monkeys [74]. Fetal porcine cells were transplanted under the kidney capsule of non-diabetic monkeys that were either non-immunosuppressed or receiving cyclosporine and 15-deoxyspergualin. In the non-immunosuppressed animals, islet biopsies revealed a progressive and strong cellular infiltrate over 6 days, mainly composed of macrophages, CD8+ T cells and a few B cells. In the immunosuppressed animals, the cellular infiltrate was slightly delayed, but by day 12 the islet xenografts were completely infiltrated with macrophages and T cells. No deposits of antibody or complement were detected.

The Minneapolis group recently presented its experience with adult porcine intraportal islet transplantation into rhesus monkeys, treated with T cell-directed immunosuppression that included anti-thymocyte globulin, an anti-IL2-receptor mAb, tacrolimus and rapamycin [75]. Porcine C-peptide was detectable for up to 22 days and histological examination showed insulin-positive cells in the liver biopsies also for up to 22 days. Cellular infiltrates, composed of macrophages and T cells, were progressively detected in the xenografts. In contrast to the findings of Korsgren et al., some porcine islets stained positive for IgG, IgM, and complement, suggesting a humoral element in the rejection process.

In a recent study [76], we have transplanted porcine islets intraportally to baboons receiving either conventional triple drug immunosuppressive therapy, or a more intensive regimen, including depletion of T cells and complement, removal of anti-Gal antibodies by immuno-adsorption and the use of an anti-CD154 mAb. In the first group, porcine C-peptide was detected only transiently after porcine islet injection and histological examination of liver biopsies taken between days 2–19 did not reveal viable islets. In the second group, porcine C-peptide was detected up to 5 days after transplantation. Biopsies showed viable islets up to day 14, but not thereafter, with a progressive mononuclear cell and macrophage infiltration. These results suggest that powerful immune responses are involved in rejection of discordant xenogeneic islets and that adequate immunosuppressive regimens still need to be developed.

The first clinical experience of porcine islet xenotransplantation into human patients was reported by the Swedish group headed by Groth [77]. This surgical team transplanted a total of 10 diabetic patients with porcine islets, but no reduction in insulin requirement was observed in any of them [20]. However, the trial indicated that some xenogeneic islet cells do not appear to be acutely rejected if the patient is receiving pharmacological immunosuppressive therapy. Furthermore, xenotransplantation of porcine fetal pancreatic tissue into the human can be carried out without morbidity.

Encapsulation of islets has been proposed for preventing rejection of both allo and xeno islets. The principle is that permeability of the capsule membrane is sufficient to allow nutrients and oxygen to reach the islets and for insulin to be released into the bloodstream, but restrictive enough to exclude immune cells and antibodies. Such encapsulation can be achieved using alginate-polylysine-alginate capsules. Functional in vitro tests of microencapsulated islets have shown that insulin-release profiles following glucose stimulation are similar to those of free islets. Microencapsulated islet allo- and xenografts have been implanted successfully in rodents, reversing chemically-induced diabetes [25, 78, 79]. Porcine encapsulated islets have been reported to induce normoglycaemia in a spontaneously diabetic cynomolgus monkey (without immunosuppressive therapy) for more than 800 days [80]. Insulin-independence has also been reported for >9 months in an immunosuppressed type 1 diabetic patient transplanted intraperitoneally with encapsulated allogeneic islets,

demonstrating the temporary viability of encapsulated islets [81]. Long-term islet viability is, however, compromised by the fibrosis (induced by the capsule material) that takes place around the capsules and leads to a progressive loss of islet cells. Research in this field is devoted to the development of new materials that do not induce such fibrosis.

Stem cell technology

Stem cells are self-renewing progenitor cells that can differentiate into one or more specialised cell types. Traditionally, pluripotent stem cells were thought to be only found in embryos. Recently, several studies have shown that adult organ-specific stem cells can differentiate into cells of other organs. For example, it has been shown that bone marrow-derived cells can differentiate into muscle [82], liver [83], cartilage or fat tissue [84, 85]. Ductal cells of the adult pancreas contain stem cells able to differentiate into islets of Langerhans [23, 86]. Ramiya et al. [23] cultured in vitro pancreatic ductal epithelial cells obtained from adult mice and could obtain functioning islets containing α, β and δ cells. These islets responded in vitro to glucose stimulation and could reverse insulin-dependent diabetes after transplantation into diabetic mice. The enormous potential of stem cell technology would be to provide a source of functional islets without the need of fetal, allogeneic or xenogeneic tissues. However, research in this field is still at a very early stage and clinical application remains in the relatively distant future.

Conclusions

Numerous significant advances in research and clinical islet allotransplantation have been achieved recently. New immunosuppressive agents, such as bioengineered monoclonal antibodies, may be available in the near future and should allow further clinical improvements. Other research developments in islet xenotransplantation or stem cell technology could provide unlimited sources of functional islets for transplantation. These elements give hope that diabetes might be treated by islet cell transplantation early in the clinical course before occurrence of complications, and without the risks associated with long-term conventional immunosuppression.

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Correspondence:
L. Bühler, MD
Department of Surgery
University Hospital of Geneva
CH-1211 Geneva 14
E-Mail: leo.buhler@hcuge.ch

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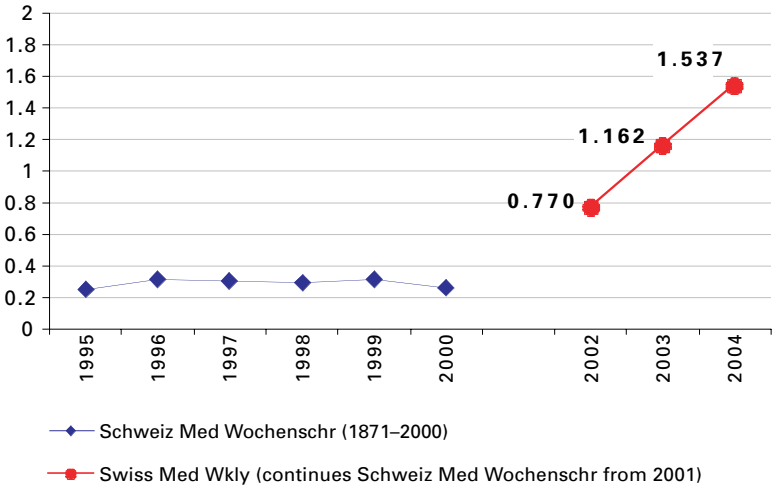

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