REVIEW

Islet transplant: an option for childhood diabetes?

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Careful assessment of the safety and efficacy of islet transplantation should guide the selection process of a small number of children with type 1 diabetes who may be eligible for the procedure—some of whom are already receiving immunosuppression because of a previous transplant, others who are scheduled to receive de novo islet alone transplantation because of a life threatening risk of hypoglycemia. The outcomes of these initial investigations are predicted to shape the future boundaries of islet transplantation, diabetes, and transplantation.

Development of the Edmonton Protocol,[1] a surgery-free, steroid-free regimen for transplanting insulin producing islet cells generated enthusiasm towards a procedure that is simple and relatively non-invasive, restoring endogenous insulin production to levels allowing the majority of treated subjects with type 1 diabetes to discontinue insulin therapy.[2 3] Insulin independence in these patients has been associated with normalisation of HbA1c and near perfect glycaemic control.[4] The hope is for islet cell, like pancreas, transplantation to provide lifelong insulin independence, and if applied early, to prevent, stabilise, or reverse diabetic complications, while avoiding the surgical, metabolic, and immunological risks of whole pancreas transplantation. Given the recent success of the Edmonton protocol and variants thereof, is islet transplantation a viable treatment option for children with type 1 diabetes?

There is a worldwide increase in the incidence of type 1 diabetes mellitus, especially in young children.[5] Approximately 1.3 and 1.4 million individuals are affected with type 1 diabetes mellitus in Europe and the United States, respectively.[6 7] Current treatment modalities of home blood glucose monitoring and insulin regimens remain suboptimal, as evidenced by persistent significant morbidity and mortality.[8] The physical and financial cost of diabetes is attributable to short term events such as hypoglycemia, hyperglycemia, and diabetic ketoacidosis,[9] as well as long term debilitating and frequently fatal complications.[10 11] Children have the greatest potential risk for serious morbidity, and earlier than expected mortality, because of microvascular and macrovascular complications of type 1 diabetes.[12] A clear cut link between early tight glycaemic control and decreased frequency of long term complications in type 1 diabetes has been established.[13 14] Intensive glycaemic control is currently based on frequent self monitoring of capillary blood glucose, four or more times each day, using skin puncture sampling and analysis with a portable glucose meter.[13 14] Daily blood glucose values are used to adjust insulin dosages for subcutaneous interrupted or continuous administration (multiple injections of one or more types of insulin versus insulin pump therapy, respectively).

The main drawback of such intensive glycaemic control, as tested in the US Diabetes Control and Complications Trial,[14] was a threefold increase in the occurrence of severe hypoglycaemia, despite four or more blood glucose tests per day.[10 11] The risks of fatal hypoglycaemia, cognitive or behavioural impairment,[14–17] the tendency for hypoglycaemia to enhance and mask future hypoglycaemia,[18 19] and the impact of hypoglycaemia on brain development,[20 21] are most relevant in children with intensively managed type 1 diabetes.[22–24] Overfeeding, weight gain, and avoidance of exercise because of parental fear of hypoglycaemia, coupled with quality of life concerns about the need for even more frequent skin puncture sampling, have placed children with diabetes, and their care providers, at a particular disadvantage. Moreover, inaccuracy of children's techniques during use of conventional blood glucose monitors can lead to erroneous blood glucose test results further compromising good control.[25] Perhaps the greatest limitation of intensive control in children, is that it is required of all children with type 1 diabetes and their families, and thus disregards potential severe obstacles to assuming such a disciplined regimen of life in particular high risk groups. The limitations of current intensive control, including lack of sleep related, postprandial,[26] and around the clock glycaemic data, highlighted the need for alternatives to current management of type 1 diabetes. In children, these alternatives have been generally reactive or adaptive, such as development of alternative site (non-finger pricking) glucose monitoring devices, and adjunctive means for continuous glucose monitoring, as well as attempts at identifying children at risk for diabetes and development of prevention strategies. Serious limitations have recently been identified to all of the above approaches.[27] Transition into adolescence often heightens these challenges, as the need to preserve a "normal" self image among peers frequently translates to poor compliance with intensive diabetes regimens at this time.

Efforts towards a cure for type 1 diabetes have generally been preferentially tried in adults, on the assumption that risks of such therapy in children outweigh risks of type 1 diabetes and the inconvenience necessitated for its control. On heightened realisation of paediatric specific significant risks of type 1 diabetes, this trend has just recently shifted. Clinical trials, aimed at treating type 1 diabetes using non-risk-free immunemodulatory therapy in children and adolescents,

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are now underway in both North America and Europe.[28]

Standardised mortality rates are higher in children with type 1 diabetes mellitus.[29] Moreover, severe asymptomatic nocturnal hypoglycaemia (mean blood glucose 1.9 mmol/l, range 1.6–2.3, duration 30–630 minutes) was detected by overnight venous sampling in 45% of children with type 1 diabetes treated by a split mixed insulin regimen, and in 60% of children on multiple daily injections.[30]

Excluding non-compliance with intensive diabetes management, the above data highlight the need for identification of a small category of compliant high risk children in whom the side effects of a steroid-free immunosuppressive regimen can be justified. Identification of such patients will be extremely difficult and should focus on one of the following criteria:

(1) Recurrent unexplained severe hypoglycaemia with potentially damaging CNS effects (blood glucose below 2.2 mmol/l, often presenting with seizures, hemiparesis, or coma), despite dietary manipulation and prophylactic insulin adjustment.

(2) Presence of incipient progressive vascular complications, especially retinopathy and nephropathy, onset of which in childhood or adolescence carries the potential of severe disability in early or mid-adulthood.

(3) Concurrent immunosuppressive medications for a comorbidity which can be safely treated with a steroid-free immunosuppressive regimen.

Whole pancreas transplantation can effectively restore endogenous insulin secretion in type 1 diabetes, and prevent, retard, or reverse diabetic complications.[31] However, the procedure carries risk of perioperative morbidity related to the exocrine pancreas, limiting the broader application of this major intervention in children with type 1 diabetes, and has not been carried out in children with diabetes to date. The process requires use of potent immunosuppressive medications including glucocorticoids (steroids), the diabetogenicity and growth suppressive properties of which further dampen enthusiasm for pancreas alone transplants for children with diabetes. Newer, more targeted immunosuppressive regimens that do not require steroid or high dose calcineurin inhibitors, with complete avoidance of surgical site or exocrine related complications, make islet transplantation a far more attractive potential transplant option in children. The potential for in vitro islet graft manipulation to reduce immunogenicity, and the recent development of tolerance promoting strategies in small and large animal models, may offer the potential to further reduce the longer term risks of islet transplant therapy.

Islet transplantation has been investigated in the past as a treatment for type 1 diabetes mellitus in selected adult patients with inadequate glucose control despite insulin therapy. However, the perennial hope that such an approach would result in long term freedom from the need for exogenous insulin, with prevention of the secondary complications of diabetes, failed to materialise in practice. Of the 267 allografts transplanted since 1990 (up to 1998), only 12.4% have resulted in insulin independence for periods of more than one week, and only 8.2% have done so for periods of more than one year.[32 33] In the majority of these procedures, the regimen of immunosuppression consisted of antibody induction with an antilymphocyte globulin combined with cyclosporine, azathioprine, and glucocorticoids.

The published observations from Edmonton, Canada[1] from a series of seven adult consecutive subjects with type 1 diabetes, were the first indication that islet transplantation can result in insulin independence with excellent metabolic control when glucocorticoid-free immunosuppression is combined with the infusion of an adequate islet mass.[1] In that series, all seven subjects quickly attained and sustained insulin independence after percutaneous transhepatic portal vein transplantation of islets. Adult recipients required islets from two donor pancreases, and one required a third transplant from two donors to achieve sustained insulin independence. Nearly all donor pancreases were previously rejected as suitable for whole organ transplantation before being subject to the islet isolation procedures. There was no recurrence of hypoglycaemic coma following transplantation. Complications were minor, and there were no significant increases in lipid concentrations during follow up. In an update to this published report, a total of 34 patients received islet infusions at the University of Alberta, Edmonton, Canada; 85% remain insulin free at one year, and three of four patients remain insulin free beyond three years. Immunosuppression for these patients was achieved using a glucocorticoid-free immunosuppressive protocol that included sirolimus,[34] low dose tacrolimus,[35] and a monoclonal antibody against the interleukin 2 receptor (daclizumab).[36] The success of the Edmonton Protocol regimen is currently being replicated across nine centres in an international trial funded by the US National Institutes of Health. In the United Kingdom, a further 10 centres plan to replicate the procedure in trials supported and coordinated through Diabetes UK.

Currently, islet-alone transplants are performed in highly selected adults with type 1 diabetes, with careful consideration to the risk-benefit ratio in every case. Indications for islet transplantation in adults are hypoglycaemic unawareness, severe metabolic instability, and the existence of secondary diabetic complications. Concerns about islet transplantation using the Edmonton protocol relate to some known risks of the procedure and medications, as well as unknown elements inherent to any new immunosuppressant modality.

Side effects of the Edmonton protocol include bleeding, portal vein thrombosis, renal toxicity in pre-existing compromised renal function, mucosal ulcers, hypercholesterolaemia, and in adults, antihypertensive interactions. Theoretical risks include hypersensitisation to donor antigens compromising potential future transplants,[37] life threatening infection, immunosuppression related cancer, and post-transplantation lymphoproliferative disorders.[38] To date, the Edmonton protocol has been very well tolerated, with no mortality, in contrast to at least three documented deaths from hypoglycaemia in patients wait listed for the procedure.

The concept of moving forward to consider the option for islet transplantation in children with type 1 diabetes cannot be undertaken lightly. It is recognised that for the vast majority of children with diabetes, judicious split mixed or basal/bolus insulin therapy provides an excellent treatment option, minimising the acute risks of hypoglycaemia and ketoacidosis and stabilising glycaemic control to within acceptable standards.[39 40] The short term risk of secondary diabetic complications would be extremely unusual in the paediatric population, since the tissue damage caused by advanced glycation end products for example, takes many years to evolve. Therefore the potential risks attendant to immunosuppression cannot be justified currently for virtually all children with diabetes.

However, there are two exceptional circumstances where the risk-benefit equipoise could potentially favour islet transplantation in the paediatric population. Firstly, where a child with type 1 diabetes is already facing the risks of immunosuppression in order to sustain a previous solid organ allograft (for example, previous liver, kidney, heart transplant). Secondly, in extremely exceptional circumstances, there are very few children with type 1 diabetes that face significant risk from hypoglycaemia, despite compliance with an optimal insulin and monitoring regimen. If high risk children could be identified prospectively, a pre-emptive islet transplant could avoid the neurological consequences of intractable hypoglycaemia.

In the situation where a diabetic child is already receiving immunosuppression, the decision to consider islet transplantation is relatively straightforward, since the procedural risks

of portal access are considered to be low, provided only purer layer islets are infused.[41] The decision process is clearly more complex, however, when a child is being considered for islet alone transplantation. The onus is on the transplant programme to be sure that all other options have been explored in the child's care, that a final decision to proceed with transplantation should be based on an independent expert opinion from a paediatric diabetologist, and that the child and family members clearly understand the material risks and benefits of the procedure and long term risks of the medications. Failure to comply with an intensive insulin and monitoring regimen is considered to be a contraindication for islet transplantation, as poor compliance with immunosuppressive or islet graft monitoring would likely place the graft or child at higher risk for poor outcome.

While the risks of immunosuppression are not to be underestimated, it should be recognised that there are thousands of children that have undergone organ transplantation (liver, kidney, heart) and are able to lead normal or near normal lives.[42–44] The short and longer term risks of immunosuppression are diminishing with the evolution of more specific, more targeted therapies. In the "Edmonton Protocol" the complete avoidance of glucocorticoids and the use of low doses of the calcineurin inhibitor tacrolimus (one third or less of the dose used typically in other transplant situations) is likely to be better tolerated in the paediatric population.[45] Complete steroid avoidance is predicted to minimise the negative impact on growth and development observed previously in transplantation. The risks of cytomegalovirus transmission, post-transplant lymphoproliferative disorder, malignancy, or life threatening infections have not yet been encountered in adult islet alone recipients treated to date. The risk of recipient sensitisation to donor antigen also appears to be very low.

Islet transplantation in children also raises a number of key, pertinent scientific questions:

(1) Will islets prepared from a single donor be successful in securing sustained insulin independence in a low weight recipient (the likelihood of a successful islet preparation exceeding 12 000 IE/kg will be considerably higher in a low weight paediatric recipient). This may prove to be a critical question as islet transplantation continues to evolve; if fewer islets are required to reverse diabetes in a child, perhaps one cadaveric pancreas donor organ could be used to treat two or more paediatric recipients. Furthermore, the option for living donor distal pancreatectomy (perhaps by laparoscopic removal) could potentially become an additional approach to overcome a limited cadaveric organ supply. In the latter option, and with a higher degree of HLA matching, immunosuppression may be successfully reduced to a minimal risk level.

(2) Will the islet mass be sufficient over time as the child grows—that is, will the child outgrow the finite implanted islet mass as the body weight increases over time, or will the islet mass actually expand in response to the milieu of growth factors during growth and development?

(3) What impact will a successful islet transplant have on quality of life and compliance with therapy during the period of adolescence? It is well recognised that diabetes can be extremely challenging to manage during adolescence, and compliance with minimal maintenance lower dose immunosuppression may facilitate the transition to adulthood.

(4) Will islet transplantation succeed in the paediatric population, or will the more recent autoimmune memory response to islet autoantigens be more difficult to control with the "Edmonton Protocol" immunosuppression regimen? Moreover, will the relatively limited capacity of the paediatric portal circulation increase the risk of portal vein thrombosis?

(5) If immunosuppression is tapered or completely discontinued at a remote timepoint after islet transplantation, will any islet grafts continue to function?

An ethical concern of using the Edmonton protocol for islet transplantation in children and adolescents is its teratogenic potential that has yet to be defined. The current recommendation is that patients taking sirolimus should not become pregnant. More precise quantification of this risk will likely emerge over time, probably from patients undergoing kidney or other solid organ transplantation. This might deter many children and their parents from considering islet transplantation as a therapeutic option. A few options exist however, that might allow successful pregnancy to be considered at a remote time point after islet transplantation:

(1) The sirolimus/tacrolimus combination could be switched to either tacrolimus monotherapy or tacrolimus/cellcept—a combination that has been used during successful pregnancies in over 100 cases with only small added risk of teratogenicity.

(2) The original combination containing sirolimus could be continued during pregnancy—as long as additional supportive data proving minimal risk to the mother and fetus, could be obtained from the International Transplant Registry database at that time.

(3) All immunosuppression could be weaned and completely discontinued during pregnancy—to lessen the risk to the fetus. In this situation, it is possible that the islet graft would be rejected, with the patient returning to insulin.

It is also possible that during the pregnant state, the mother would develop "tolerance" to the islet allograft. This might provide enormous insight towards the future development of tolerogenic regimens in transplantation.

The robust hope, which the Edmonton protocol has provided for 175 million children and adults with diabetes, expands as insight is gained into future advances currently underway in the field of islet transplantation.[46] These include progress at induction of central and peripheral tolerance, in vitro islet manipulation, and development of alternate islet sources including living donors,[47] intra- and extra-pancreatic stem cells,[48 49] bioengineered cells,[50] and xenografts.[51]

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REFERENCES

1 **Shapiro AM**, Lakey JR, 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**:230–8.
2 **Shapiro AM**, Ryan EA, Lakey JR. Diabetes. Islet cell transplantation. *Lancet* 2001;**358**(suppl):S21.
3 **Shapiro AM**, Ryan EA, Lakey JR. Clinical islet transplant—state of the art. *Transplant Proc* 2001;**33**:3502–3.
4 **Ryan EA**, Lakey JR, Paty BW, *et al.* Successful islet transplantation: continued insulin reserve provides long-term glycemic control. *Diabetes* 2002;**51**:2148–57.
5 **Hodges C**. Diabetes. Childhood incidence. *Nurs Times* 1997;**93**:40–2.
6 http://www.who.dk.
7 **Fain JA**. National trends in diabetes. An epidemiologic perspective. *Nurs Clin North Am* 1993;**28**:1–7.
8 **Muhlhauser I**, Overmann H, Bender R, *et al.* Predictors of mortality and end-stage diabetic complications in patients with type 1 diabetes mellitus on intensified insulin therapy. *Diabet Med* 2000;**17**:727–34.
9 **Basile F**. The increasing prevalence of diabetes and its economic burden. *Am J Manag Care* 2000;**6**(21 suppl):S1077–81.
10 **Skyler JS**. The economic burden of diabetes and the benefits of improved glycemic control: the potential role of a continuous glucose monitoring system. *Diabetes Technol Ther* 2000;**2**(suppl 1):S7–12.
11 **Epidemiology of Diabetes Interventions and Complications (EDIC)**. Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care* 1999;**22**:99–111.
12 **Halimi S**. [Benefits of blood glucose self-monitoring in the management of insulin-dependent (IDDM) and non-insulin-dependent diabetes

(NIDDM). Analysis of the literature: mixed results]. *Diabetes Metab* 1998;**24**(suppl 3):35–41.
13 **Chase HP**, Lockspeiser T, Peery B, *et al*. The impact of the diabetes control and complications trial and humalog insulin on glycohemoglobin levels and severe hypoglycemia in type 1 diabetes. *Diabetes Care* 2001;**24**:430–4.
14 **The Diabetes Control and Complications Trial Research Group**. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;**329**:977–86.
15 **Sanders NM**, Ritter S. Repeated 2-deoxy-D-glucose-induced glucoprivation attenuates Fos expression and glucoregulatory responses during subsequent glucoprivation. *Diabetes* 2000;**49**:1865–74.
16 **Patrick AW**, Campbell IW. Fatal hypoglycaemia in insulin-treated diabetes mellitus: clinical features and neuropathological changes. *Diabet Med* 1990;**7**:349–54.
17 **Gonder-Frederick LA**, Clarke WL, Cox DJ. The emotional, social, and behavioral implications of insulin-induced hypoglycemia. *Semin Clin Neuropsychiatry* 1997;**2**:57–65.
18 **Vannucci RC**, Vannucci SJ. Glucose metabolism in the developing brain. *Semin Perinatol* 2000;**24**:107–15.
19 **Bolli GB**. Counterregulatory mechanisms to insulin-induced hypoglycemia in humans: relevance to the problem of intensive treatment of IDDM. *J Pediatr Endocrinol Metab* 1998;**11**(suppl 1):103–15.
20 **Duvanel CB**, Fawer CL, Cotting J, *et al*. Long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational-age preterm infants. *J Pediatr* 1999;**134**:492–8.
21 **Rapaport R**, Sills IN. Implications of the DCCT for children and adolescents with IDDM. *N J Med* 1994;**91**:227–8.
22 **Perwien AR**, Johnson SB, Dymtrow D, *et al*. Blood glucose monitoring skills in children with type I diabetes. *Clin Pediatr (Phila)* 2000;**39**:351–7.
23 **Matyka KA**, Wigg L, Pramming S, *et al*. Cognitive function and mood after profound nocturnal hypoglycaemia in prepubertal children with conventional insulin treatment for diabetes. *Arch Dis Child* 1999;**81**:138–42.
24 **Matyka KA**, Crawford C, Wiggs L, *et al*. Alterations in sleep physiology in young children with insulin-dependent diabetes mellitus: relationship to nocturnal hypoglycemia. *J Pediatr* 2000;**137**:233–8.
25 **Buse JB**, Hroscikoski M. The case for a role for postprandial glucose monitoring in diabetes management. *J Fam Pract* 1998;**47**(5 suppl):S29–36.
26 **Bode BW**, Hirsch IB. Using the continuous glucose monitoring system to improve the management of type 1 diabetes. *Diabetes Technol Ther* 2000;**2**(suppl 1):S43–8.
27 **Scheen AJ**, Philips JC. [Info-congress. Insulin therapy for preventing type 1 diabetes in high-risk relatives: negative results of the "Diabetes Prevention Trial-Type 1"]. *Rev Med Liege* 2001;**56**:536–8.
28 **Herold KC**, Hagopian W, Auger JA, *et al*. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. *N Engl J Med* 2002;**346**:1692–8.
29 **Edge JA**, Hawkins MM, Winter DL, *et al*. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child* 2001;**85**:16–22.
30 **Dunger DB**. Use of continuous glucose monitoring to investigate nocturnal hypoglycaemia prevalence in relation to insulin regimen and exercise. *Diabetes* 2002;**51**(suppl 2):A2.
31 **Odorico JS**, Sollinger HW. Technical and immunosuppressive advances in transplantation for insulin-dependent diabetes mellitus. *World J Surg* 2002;**26**:194–211.
32 **Brendel MHB**, Schultz A, Bretzel R. *International islet transplant registry report*. University of Giessen, Germany, 1999:1.
33 **Brendel MHB**, Schultz A, Bretzel R. *International islet transplant registry report*. University of Giessen, Germany, 2001.
34 **Sehgal SN**. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action; immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 1998;**31**:335–40.
35 **Land W**, Malaise J, Sandberg J, *et al*. Tacrolimus versus cyclosporine in primary simultaneous pancreas-kidney transplantation: preliminary results at 1 year of a large multicenter trial. *Transplant Proc* 2002;**34**:1911.
36 **Vincenti F**, Kirkman R, Light S, *et al*. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. *N Engl J Med* 1998;**338**:161–5.
37 **McAlister VC**, Gao Z, Peltekian K, *et al*. Sirolimus-tacrolimus combination immunosuppression. *Lancet* 2000;**355**:376–7.
38 **Green M**, Reyes J, Webber S, *et al*. The role of antiviral and immunoglobin therapy in the prevention of Epstein-Barr virus infection and post-transplant lymphoproliferative disease following solid organ transplantation. *Transpl Infect Dis* 2001;**3**:97–103.
39 **Dorchy H**. Insulin regimens and insulin adjustments in diabetic children, adolescents and young adults: personal experience. *Diabetes Metab* 2000;**26**:500–7.
40 **Ludvigsson J**, Bolli GB. Intensive insulin treatment in diabetic children. *Diabetes Nutr Metab* 2001;**14**:292–304.
41 **Brandhorst H**, Brandhorst D, Brendel MD, *et al*. Assessment of intracellular insulin content during all steps of human islet isolation procedure. *Cell Transplant* 1998;**7**:489–95.
42 **Wallot MA**, Mathot M, Janssen M, *et al*. Long-term survival and late graft loss in pediatric liver transplant recipients—a 15-year single-center experience. *Liver Transpl* 2002;**8**:615–22.
43 **Gjertson DW**, Cecka JM. Determinants of long-term survival of pediatric kidney grafts reported to the United Network for Organ Sharing kidney transplant registry. *Pediatr Transplant* 2001;**5**:5–15.
44 **Fortuna RS**, Chinnock RE, Bailey LL. Heart transplantation among 233 infants during the first six months of life: the Loma Linda experience. Loma Linda Pediatric Heart Transplant Group. *Clin Transpl* 1999:263–72.
45 **van Mourik ID**, Kelly DA. Immunosuppressive drugs in paediatric liver transplantation. *Paediatr Drugs* 2001;**3**:43–60.
46 **Shapiro AM**, Lakey JR. Future trends in islet cell transplantation. *Diabetes Technol Ther* 2000;**2**:449–52.
47 **Robertson RP**, Lanz KJ, Sutherland DE, *et al*. Relationship between diabetes and obesity 9 to 18 years after hemipancreatectomy and transplantation in donors and recipients. *Transplantation* 2002;**73**:736–41.
48 **Bonner-Weir S**, Sharma A. Pancreatic stem cells. *J Pathol* 2002;**197**:519–26.
49 **Soria B**, Skoudy A, Martin F. From stem cells to beta cells: new strategies in cell therapy of diabetes mellitus. *Diabetologia* 2001;**44**:407–15.
50 **Wang MY**, Shimabukuro M, Lee Y, *et al*. Adenovirus-mediated overexpression of uncoupling protein-2 in pancreatic islets of Zucker diabetic rats increases oxidative activity and improves beta-cell function. *Diabetes* 1999;**48**:1020–5.
51 **Gorczynski RM**, Hu J, Chen Z, *et al*. A CD200FC immunoadhesin prolongs rat islet xenograft survival in mice. *Transplantation* 2002;**73**:1948–53.