Is Islet Transplantation a Realistic Therapy for the Treatment of Type 1 Diabetes in the Near Future?

R. Brian Stevens, MD, PhD, Shinichi Matsumoto, MD, PhD, and Christopher L. Marsh, MD, FACS

Since Banting and Best’s discovery of insulin in 1921, the administration of exogenous insulin has been the primary treatment for type 1 diabetes. Although this therapy has enabled millions to survive and lead fairly normal lives, it has fallen short of a cure. Type 1 diabetes affects millions of individuals and is associated with multiple medical problems, including renal failure and a reduced life expectancy. Tight control of blood glucose levels, achieved with intensive insulin therapy, reduces the secondary complications of diabetes. Unfortunately, such tight control often results in frequent episodes of hypoglycemia.

In contrast to the results achieved with intensive insulin therapy, pancreas transplantation usually results in independence from exogenous insulin, normal glucose levels (both fasting and postprandially), normal HbA1c levels, and freedom from hypoglycemia. Pancreas transplantation is now widely accepted as a reasonable therapeutic option for many individuals with diabetes and either rapidly progressive or significant end-organ disease (e.g., renal failure) or severe metabolic instability (e.g., hypoglycemic unawareness). Nevertheless, whether one performs a pancreas transplant with systemic or portal venous drainage, both have significant morbidity and mortality rates. Thus, most individuals with type 1 diabetes are not candidates for pancreas transplantation.

What has been needed is a less morbid alternative for individuals who have the medical need for a pancreas transplant, but who are not surgical candidates for this operation. Islet transplantation may now meet this need. This article will review the current state of islet transplantation, with a particular focus on the reasons for the recent success of the Edmonton protocol, and will discuss challenges to the widespread use of islet transplantation in the treatment of type 1 diabetes.

Historical Perspective of Islet Transplantation

Before the Edmonton protocol, human allogeneic islet transplantation was rarely successful. Since the initial observations of Lacy and Kostianovsky in 1967, islet transplantation has reversed hyperglycemia in both large and small animal models of diabetes. However, multiple investigators have reported early or only partial success with human islet transplantation.

Gores et al. reported two successful instances of islet transplantation (out of six attempts) in type 1 diabetic recipients who received a simultaneous cadaveric kidney transplant. These patients, while euglycemic, had mildly elevated HbA1c levels.

Although many islet transplant recipients are not insulin-independent, they often have reduced exogenous insulin requirements and decreased HbA1c levels typically unattainable with intensive insulin therapy. In these patients with reduced insulin requirements, fewer episodes of hypoglycemic unawareness have been noted. Unfortunately, in humans, persistent euglycemia has been the exception rather than the rule.

Recently, reports of greater success in allogeneic islet transplantation have renewed interest in islet transplantation as a possible therapeutic option for some patients with diabetes. A close analysis of the successes and failures in both autologous and allogeneic islet transplantation shed light on the reasons for the unprecedented success of the Edmonton experience.

Autologous Islet Transplantation

A study of autologous islet transplantation foreshadowed the recent success in allogeneic islet transplantation. The low cure rates associated with allogeneic islet transplantation were in stark contrast to the success reported with autologous islet transplantation (8 vs. 75% insulin independence at 1 year). In fact, autologous islet recipients transplanted with >250,000 islets achieved a persistent euglycemic state (70–80%) and normal HbA1c levels.
With refined islet isolation and purification methods becoming widely applicable, a considerable increase in the number of clinical allogeneic islet transplants has occurred. The 1999 Islet Transplant Registry (ITR) report concluded that establishment of insulin independence after islet transplantation was associated with the following factors: 1) pancreatic preservation times ≤ 8 h, 2) islet mass transplanted is adjusted to body weight (≥6,000 islet equivalents per kilogram of body weight [IE/kg]), 3) intrahepatic transplantation, and 4) induction with monoclonal or polyclonal T-cell antibodies.

In the ITR report, one-third of islet allograft recipients with type 1 diabetes who were C-peptide–negative before transplant met all of these characteristics. Forty-eight percent of these patients showed basal C-peptide levels of 0.5 mg/ml; 73% had HbA1c levels ≤ 8%; and 22% were insulin-independent at 1 year’s follow-up. Insulin-independent and -dependent recipients did not differ in age, body mass index, duration of diabetes, pre-transplant HbA1c level or insulin requirements, or age of the cadaveric pancreas donor.

Factors Affecting Allogeneic Islets Transplanted From Cadaveric Donors
Why have transplanted allogeneic islets—isolated from cadaveric donors—in the past rarely cured patients with diabetes? Cadaveric islets are injured during the procurement, preservation, and isolation process (Table 1). Moreover, islets obtained from cadaveric donors may have increased immunogenicity as compared to noncadaveric islets, potentially heightening damage to the islets by the recipient’s immune system. In addition, immunosuppressive agents, most of which are toxic to islets, must be used in recipients of cadaveric islets. Thus, allogeneic islet grafts likely failed because of the use of toxic immunosuppressive agents and because of immunological mediators of inflammation and antigen-specific immunity.

Persistent euglycemia after islet transplantation is clearly dependent on factors that affect the viability of the islet preparation. In addition, the inflammatory and immunological challenges the islet graft faces in the post-transplant period significantly affect the success of the transplant.

Table 1. Reasons for Islet Allograft Failures in the Past

<table>
<thead>
<tr>
<th>Organ procurement and preservation methods</th>
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<tr>
<td>Injury during procurement</td>
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<tr>
<td>Venous hypertension via UW flush</td>
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<td>Poor cooling of pancreases</td>
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<th>Pancreatic processing &amp; islet purification</th>
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<td>Unreliable collagenase activity</td>
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<tr>
<td>Poor pancreatic distension with collagenase</td>
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<td>Discontinuous ficoll gradient</td>
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<tr>
<th>Islet injury due to immunosuppressive agents</th>
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<tr>
<td>High-dose steroids</td>
<td></td>
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<tr>
<td>High-dose calcineurins</td>
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<tr>
<td>(cyclosporine or tacrolimus)</td>
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<tr>
<th>Transplantation of inadequate islet mass</th>
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Although sirolimus is less nephrotoxic than FK506, it is associated with an increased incidence of thrombocytopenia and leukopenia and may be toxic to islets in high doses, also. Recent work by Dr. Breay Paty in Dr. R. Paul Robertson’s lab evaluated the toxicity of immunosuppressive drugs on β-cell function. This study revealed a significant inhibition of insulin secretion in HIT T-15 cells and Wister rat islets by sirolimus, methylprednisolone (Solumedrol), cyclosporine, and tacrolimus. These results confirm the aforementioned hypothesis that low-dose immunosuppression protocols will be especially important in preventing islet toxicity and exhaustion. Nevertheless, sirolimus seems to enhance islet allograft survival without a substantial metabolic impact on islet function.

Therapies designed to deplete or inactivate T-cells may harm islets because they induce the release of cytokines from T-cells. This therapy, termed “induction” when given at the time of transplantation, uses preparations such as antithymocyte globulin (ATG [Thymoglobulin]) or OKT3 (Muromonab). ATG is associated with less cytokine release than OKT3 and with reduced rejection rates in cadaveric renal transplantation. ATG modulates the T-cells for the long term and may account for this beneficial effect on acute rejection rates.

Newer induction agents are available that block the IL-2 receptor pathway by binding to the IL-2 receptor. The two drugs in this new class are humanized murine monoclonal antibody preparations called basilixamab (Simulect) and daclizumab (Zenepax). In clinical trials, these agents have been shown to reduce early rejection rates. Anti-IL-2 receptor antibody therapy may be particularly useful in islet transplantation because it does not induce the release of large amounts of cytokines.
Impact of Cytokine Release on Islet Survival

Cytokines influence multiple cellular processes, from cell maturation to cytotoxicity. In fact, increased cytokine expression is associated with rejection, graft-versus-host disease, and immunemediated islet injury.

Macrophage products (IL-1, IL-6, TNF-α, and nitric oxide) are primary mediators of transplanted islet dysfunction. During islet cell isolation procedures and subsequent implantation, cytokines (IL-1, IFN-α and IFN-γ, and TNF-α) are released by passenger leukocytes and Kupffer cells within the liver. Many of these cytokines (IL-1, IFN-γ, IL-6, and TNF-α) are deleterious, either directly or indirectly, to islet function and engraftment. In fact, IL-β, IL-6, TNF-α, and C-reactive protein have been shown to be elevated after intraportal islet transplantation.

Release of TNF-α is associated with inflammation and rejection and is toxic to islets. Furthermore, TNF-α potentiates the activity of other cytokines with regard to islet cytotoxicity. As mentioned above, standard T-cell cytolytic immunosuppression is associated with a “cytokine storm” phenomenon.

For example, OKT3 induced mRNA expression of several cytokines in human peripheral blood mononuclear cells. In addition, elevated levels of IL-1, IL-2, IL-3, IFN-γ, TNF-α, IL-6, IL-10, and GM-CSF were observed at various time points after OKT3 administration. For these reasons, blocking TNF-α may limit damage to islets, especially when transplanting a low number of islets or when there are donor or isolation factors present that could upregulate TNF-α release.

TNFR:Fc (Enbrel) is a recombinant human p75 TNF receptor (dimeric):Fc fusion protein linked to IgG1. TNFR:Fc binds to and inhibits the bioactivity of TNF-α and lymphotoxin (LT) in human and animal studies. Its theoretical benefit is supported by its use in rodent models of islet transplantation.

In a recent study of renal allograft recipients receiving OKT3 for acute rejection, pretreatment with TNFR:Fc lowered the bioactivity of serum TNF-α and attenuated the symptoms of OKT3 treatment. At our center, we have utilized TNFR:Fc routinely to block cytokine release and more recently instituted “steroid-free/calcineurin-sparing” immunosuppressive protocols in kidney transplant recipients and have seen a significant reduction in rejection rates (<5%). Our early experience supports the safety of these strategies for kidney (and islets) transplants.

Factors Associated With Success of the Edmonton Protocol

The Edmonton protocol addresses many of the barriers discussed above (Table 2). In this trial, pre-uremic diabetic patients were transplanted with allogeneic islets. All achieved a euglycemic state (average follow-up: 11.9 months; range: 4.4–14.9 months).

These results were associated with use of a steroid-free and calcineurin-sparing immunosuppression protocol.

Induction involved use of IL-2 receptor antibodies. In addition, rapid processing and transplantation of a predetermined minimal islet mass (11,547 ± 1,604 IE/kg) diminished pancreatic preservation injury. Thus, Shapiro and colleagues have clearly demonstrated that a less “islet toxic” immunosuppression protocol, in conjunction with rapid transplantation of a sufficient islet mass, can result in achievement of a persistent euglycemic state in diabetic recipients.

However, in the Edmonton protocol, for every patient cured, two to three unsuccessful isolations from pancreas donors were required. In contrast, pancreas transplantation requires only one donor. If islet cell transplantation could be accomplished using one donor alone, this procedure would surely replace pancreas transplantation. While there are approximately 1 million islets per pancreas, current pancreas preservation and islet isolation techniques enable us to recover fewer than half.

Many simultaneous and sequential steps will need to be taken to expand

<table>
<thead>
<tr>
<th>Table 2. Reasons for the Success of the Edmonton Protocol</th>
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<tr>
<td><strong>Improved organ procurement</strong></td>
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<tr>
<td>• Dedicated procurement team</td>
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<td>• Standard procurement procedure</td>
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<tr>
<td>-avoids overperfusion with UW</td>
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<td>-pancreas removed before liver and kidneys</td>
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<td>-minimal manipulation</td>
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<td><strong>Minimized organ preservation injury</strong></td>
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<td>• Process pancreas &lt;8 h from cross clamp</td>
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<td><strong>Improved pancreatic islet cell processing</strong></td>
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<tr>
<td>• Modification of the Ricordi method</td>
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<td>• More reliable collagenase solution (liberase)</td>
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<td>• Liberase loaded into pancreatic duct using a controlled perfusion technique</td>
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<tr>
<td><strong>Improved pancreatic islet cell purification</strong></td>
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<td>• Continuous gradient elutriation (COBE 2991 cell processor)</td>
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<td><strong>Reduced immunosuppressive injury to islets</strong></td>
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<tr>
<td>• Elimination of steroids</td>
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<td>• Reduction of calcineurin dose</td>
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<tr>
<td>• Sirolimus (minimal islet toxicity)</td>
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<td>• Use of IL-2 receptor blocking agent for induction</td>
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<td>-Elimination of “cytokine storm”</td>
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<td><strong>Transplantation of an adequate islet mass</strong></td>
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<td>• Intraportal transplantation of &gt;10,000 IE/kg body weight (multiple donors)</td>
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what has been accomplished from the Edmonton experience and apply it to developing programs (Table 3). Two short-term and critical steps to enhancing this field are: 1) standardizing and expediting the allocation of cadaveric pancreases to either solid-organ pancreas transplant or islet processing centers for transplantation; and 2) improving the preservation of pancreases that may be considered “marginal” to allow for shipping and utilization at these centers, thus expanding the islet donor pool.

**Improved Pancreas Preservation: the Two-Layer Method**

One technique that may help obviate this problem is preservation of pancreases after retrieval from the organ donor but before islet isolation via the two-layer method (TLM) (Figure 1). This technique provides for continued oxygenation of the pancreas by floating the organ on the interface of two fluid layers of differing density. The more-dense fluid layer, perfluorocarbon, carries oxygen in solution. The less-dense layer, University of Wisconsin (UW) preservation solution (Viaspan), is currently used for preservation of solid organs.

When pancreases are preserved by the TLM before islet isolation, yields are increased when compared to storage in conventional UW solution in both canine and human 24-h preservation models. Use of the TLM extends the acceptable preservation time of pancreases to 24 h and can approximately double islet yield (Unpublished observations, S. Matsumoto, I. Sweet, C. Marsh, Y. Kuroda, R.B. Stevens).

Adenosine triphosphate (ATP) levels in pancreatic tissue measured after storage using the TLM appear to correlate with eventual islet yields (Figure 1B). Our data suggest that ATP levels measured after TLM preservation may predict low islet yields before processing begins, thus reducing the number of failed pancreas processing events and in turn reducing the total cost of processing pancreases for clinical transplantation.

**Islet Transplantation: Current Status**

The Edmonton protocol has resulted in unprecedented success in which 100% of patients remain euglycemic. However, this protocol has been applied to a select, relatively healthy group of patients receiving islets from a select group of donors. The Immune Tolerance Network (ITN), supported by the National Institutes of Health’s National Institute of Diabetes and Digestive and Kidney Diseases and National Institute of Allergy and Infectious Diseases and by the Juvenile Diabetes Research Foundation International, will attempt to replicate these findings on a national scale.

This widespread implementation of the Edmonton protocol is already driving the standardization of islet processing techniques and will further reveal the toxicity (or lack thereof) of the immunosuppressive strategy. But are the subjects of the ITN effort the most appropriate patients to receive this elaborate and expensive therapy? Is it appropriate to subject healthier diabetic patients to the risks of long-term immunosuppression (nephrotoxicity, infections, malignancy, teratogenicity) in an attempt to prevent end-organ damage from diabetes? Or, should this limited resource be reserved for uremic patients in whom diabetic control is very important, but who have already sustained irreversible damage to some systems?

Typically, patients who are candidates for pancreas or islet transplantation have progressive peripheral complications of diabetes, with proteinuria and/or deteriorating renal function or severe hypoglycemic unawareness. The Edmonton trial was successful in “pre-uremic”

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**Table 3. Requirements for Expanded Application of the Edmonton Protocol (Short-Term)**

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
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| Improved organ procurement | • Standard method for the pancreas to be used for islets  
  • Standardize criteria of islet donors among organ procurement organizations (OPOs)  
  • Develop expedited system of organ placement to islet processing centers |
| Increased organ preservation time | • Institute two-layer method (TLM) of pancreas preservation (Figure 1A)  
  • Standardize shipping to processing centers |
| Improved pancreatic processing | • Decreased variability between liberase lots  
  • Improved efficiency of Edmonton [Ricordi] method  
  • Develop assays to predict which pancreases to process |
| Improved islet purification | • Increased islet/nonislet ratio and variability  
  • Continuous osmolality and density gradient histidine lactobionate nicotinamide (HLN) and iodixanol |
| Sponsor regional processing centers linked to multiple OPOs | • Encourage cost-effective management of national resource  
  • Develop islet banks  
  • Develop simple standard quality control assays |
| Multicenter trials with standardized islet preparations | • Reproduce the findings of the Edmonton protocol (in process)  
  • Transition to single-donor cure protocols  
  • Develop a consensus on best groups that can benefit  
  • Compare long-term results of solid-organ pancreas to islet transplantation  
  • Test new (less toxic, pro-tolerance) immunosuppressive strategies |
patients, but it remains to be seen whether a variation of this strategy can be applied to the most common group transplanted in the International Transplant Registry, namely those requiring a kidney transplant or those who have had a previous kidney transplant.

Clearly, we will need a better understanding of the potential success rates in these groups, the long-term outcomes, the risk/benefit ratio of this therapy, and how it compares to pancreas transplantation or intensive insulin management before the therapy expands out of clinical trials.

Future Directions
Despite the aforementioned limitations, we are on the verge of a new era in islet transplantation that can be likened to the expansion of liver transplantation in the early 1980s. If the Edmonton trial is replicated on a large-scale basis and the same level of success is found to apply to patients needing a kidney transplant, then the demand for islet transplantation will be exponential. Table 4 outlines the requirements that will be necessary for a major expansion of islet transplantation.

Considering the human organ shortage in comparison to the incidence of diabetes, an inexhaustible source of islets will be required. Certainly, we will need islets from either human β-cell lines generated from progenitor stem cells or other species (xenotransplantation).

Xenotransplantation will most likely require unique protocols to induce tolerance to the foreign tissue or encapsulation of islets to provide a barrier against the allo- or autoimmune attack.58–60 This is unless, of course, other technologies provide a nontoxic solution, such as gene transfection of insulin-producing genes or the development of microcomputers with real-time biosensing integrated into insulin pumps that provide minute-to-minute control of insulin release for glucose control.61–63 These topics are beyond the scope of this review, nevertheless we cannot overemphasize the importance of investigating these strategies while at the same
Table 4. Requirements for Islet Transplantation to Become the Preferred Treatment for Type 1 Diabetes

**Reduced or eliminated need for immunosuppressive agents**
- Induce donor MHC-specific hyporeactivity or tolerance
  - co-stimulation blockade
  - donor bone marrow-deprived stem cells (co-transplantation)
- Immunological barriers (e.g., encapsulation)

**Increased islet masses available for transplantation**
- β-cell expansion
- Xenotransplantation
- Genetically engineered β-cell lines

Co-Stimulatory Blockade

Briefly, antigens are processed by APCs and presented to host T-cells in context with the major histocompatibility complex (MHC), and this is considered signal one. More recently, CD28 was found to be a pivotal co-stimulatory molecule that provides a necessary “second signal” for the stimulation of T-cells when presented with antigen. Such co-stimulation promotes the production of the cytokine IL-2, a major determinant of the size and tempo of immune responses.

CD28 binds the ligands B7-1 (CD80) or B7-2 (CD86) expressed on activated APCs. T-cells also express a B7 ligand, termed cytotoxic T-lymphocyte antigen 4 (CTLA4). Most intriguing have been the efforts on the part of many researchers, it remains unclear whether strategies aimed toward creating chimerism will promote tolerance and allow for the reduction of chronic immunosuppression.

Although controversial, the tolerizing effect may be derived from the interaction of antigen-presenting cells (APCs [donor dendritic cells, T-cells, or B-cells]) with donor-reactive T-cells, resulting in apoptosis (direct deletion) or stimulation of regulatory or suppressor T-cells. Others speculate that chimerism is a two-edged sword that may promote rejection or tolerance, depending on the antigenic disparities present and the maturational state of the host T-cell. Notwithstanding, many investigators feel that chimerism is not necessary for development of tolerance.

Tolerance Protocols

Establishing tolerance (specific hyporeactivity of the immune system to donor tissue but not to other foreign antigens) is particularly important in islet transplantation given the direct toxic effect of many immunosuppressants on islets. The following is a brief review of tolerance strategies and their implications for future islet transplantation.

Even before solid-organ transplantation became a clinical reality, Billingham, Brent, and Medawar observed that Freemartin cattle sharing a common placenta displayed red blood cell chimerism. They hypothesized that hematopoetic chimerism may lead to tolerance and acceptance of skin grafts. This idea gained renewed popularity when Starzl and others noted that some patients with long-term functioning liver grafts had circulating dendritic cells at distant sites.

Trials with bone marrow transplantation to augment solid-organ transplants have been performed but with only minimal enhancement of donor-specific hyporeactivity. Despite significant efforts on the part of many researchers, it remains unclear whether strategies aimed toward creating chimerism will promote tolerance and allow for the reduction of chronic immunosuppression.

Although controversial, the tolerizing effect may be derived from the interaction of antigen-presenting cells (APCs [donor dendritic cells, T-cells, or B-cells]) with donor-reactive T-cells, resulting in apoptosis (direct deletion) or stimulation of regulatory or suppressor T-cells. Others speculate that chimerism is a two-edged sword that may promote rejection or tolerance, depending on the antigenic disparities present and the maturational state of the host T-cell. Notwithstanding, many investigators feel that chimerism is not necessary for development of tolerance.

Can co-stimulatory blockade, which has shown such promise in primate models, work in humans? Unfortunately, despite the success in primate models, early human trials are needed and have yet to be reported.

Interestingly, several investigators have shown that standard immunosuppression agents actually block the immune system’s inherent tolerance mechanisms, which are designed to prevent problems such as food allergies. For instance, cyclosporine inhibits cell-mediated clonal deletion, a key mechanism through which the immune system regulates the number of activated T-cells.

Fortuitously, sirolimus, one of the newer immunosuppressive medications, may not block some of these endogenous regulatory mechanisms. Sirolimus inhibits IL-2 receptor signaling and cell cycle progression of antigen-activated T-cells. T-cells activated by antigen in the presence of sirolimus or CD28 blockade cannot proceed through the cell cycle and therefore become unresponsive to antigenic stimulation.

This property of sirolimus and CD28 blockade (provided through induction therapy with anti-thymocyte globulin) might explain why some immunosuppression strategies without steroids are, to date, so successful. Moreover, islet transplants in NOD mice given rapamycin with donor-specific transfusions and co-stimulatory blockade molecules produced long-lasting tolerance.

These clues suggest a regimen to test that could provide “near or partial toler-
ance” with single- and low-dose mainte-
nance immunosuppression. This strate-
gy, if applied to islet transplantation, 
should have minimal side effects and 
and making it reasonable for any dia-
abetic patient failing medical manage-
ment, such as intensive insulin therapy.

Organ Donors and Allocation
Another obstacle to islet transplantation 
is recognition of this therapy by organ 
procurement agencies, transplant pro-
grams, and the Health Care Financing 
Administration. Furthermore, there is a 
limited supply of human cadaveric 
donors that can potentially be used for 
pancreas retrieval and islet processing. 
The UNOS OPTN 2000 annual report 
reveals that, for 1999, there were 1,627 
pancreas donors. There were 2,025 
patients waiting for a pancreas trans-
plant, and 1,674 kidney/pancreas trans-
plants were performed in 1995. 
However, if older or more marginal 
donors can be used for islet processing 
(as compared to the strict criteria typi-
cally used for solid-organ pancreas 
donors), then the donor numbers could 
expand to equal the number of liver 
donors, which was 4,954.97 Herein, the 
TLM will be vital for using these mar-
ginal donors. We anticipate that a 
national consensus will need to be 
developed using an algorithm for expe-
dited organ allocation to islet processing 
centers and financial incentives to 
induce pancreas procurement for islets.

Implications for Type 1 Diabetes
For most patients and physicians, all of 
this provides a new thread of hope. 
Unfortunately, only a few patients will 
benefit from the ITN or future trials, and 
many questions have been raised regard-
ing which patients will benefit most 
from islet transplantation.

Nevertheless, the most exciting point 
is that this therapy is and must be suc-
cessful. The efforts of researchers and 
patients, who have donated money 
toward research, have made a significant 
impact. However, the questions of the 
risks of immunosuppression remain and 
signal the need for safe tolerance proto-
cols that minimize the risks of long-term 
immunosuppression.

Conclusion
Islet cell transplantation is a true suc-
cess, but it is not a panacea for most 
patients. We propose that the next step 
for islet transplantation is the implemen-
tation of standardized procurement and 
expedited allocation and shipping sys-
tems for pancreases, including using the 
TLM of preservation, while concurrently 
refining islet processing techniques. 
The latter may require not only grants, 
but also inducements aimed at industry 
to apply venture capital and research 
and development efforts in this area. 
Simultaneously, we need to forge ahead 
with our clinical trials with different immuno-
suppressive/tolerance strategies and 
patient groups to further define success 
and identify the benefits of this unique 
benchmark cellular therapy.

REFERENCES
1 The DCCT Research Group: The effect of 
intensive treatment of diabetes on the 
development and progression of long-term complications of 
independent-dependent diabetes mellitus. N Engl J 
2 Robertson RP, Sutherland DE, Kendall DM, 
Teuscher AU, Gruessner RW, Gruessner A: Meta-
bolic characterization of long-term successful 
pancreas transplants in type I diabetes. J Invest 
Med 44:549–555, 1996
3 Sutherland D, Gruessner A, Bland B: Inter-
Minneapolis, Minn., University of Minnesota, 
2000
4 Gaber AO, Shokouh Amiri H, Grewal HP, 
Britt LG: A technique for portal pancreatic trans-
plantation with enteric drainage. Surg Gynecol 
Obstet 177:417–419, 1993
5 Sutherland DE, Gores PF, Farney AC, 
Wahoff DC, Matas AJ, Dunn DL, Gruessner RW, 
Najarian JS: Evolution of kidney, pancreas, and 
islet transplantation for patients with diabetes at 
the University of Minnesota. Am J Surg 
166:456–491, 1993
6 Lacy P, Kostianovsky M: Method for the iso-
lation of intact islets of Langerhans from the rat 
7 Warnock G, Kneteman N, Ryan E, Seelis R, 
Rabinovich A, Rajotte R: Normoglycemia after 
transplantation of freshly isolated and cryopre-
served pancreatic islets in type 1 (insulin-dependent) 
diabetes mellitus. Diabetologia 34:55–58, 
1991
8 Najarian JS: Evolution of kidney, pancreas, and 
autonomic symptoms after intraportal islet 
transplantation in two cases of insulin-independence under 
protocols for islet transplantation is the implemen-
tation of unpurified islets from single donor with 
9 Meyer C, Hering BJ, Grossmann R, Brand-
horst H, Brandhorst D, Gerich J, Fedeline K, 
Bretzel RG: Improved glucose counterregulation 
and autonomic symptoms after intraportal islet 
transplants alone in patients with long-standing type I diabetes mellitus. Transplantation 
10 Hering B, Brendel M, Schultz A, Schultz B, 
Bretzel R: International Islet Transplant Registry 
Newsletter. Giessen, Germany, Justus-Liebig Uni-
versity of Giessen, 1999
11 Shapirow AM, Lakey JR, Ryan EA, Korbutt 
GS, Toth E, Warnock GL, Kneteman NM, Rajotte 
RV: Islet transplantation in seven patients with 
type 1 diabetes mellitus using a glucocorticoid-
free immunosuppressive regimen. N Engl J Med 
343:230–238, 2000
12 Najarian JS: Cold storage preservation of islet 
1997
13 Keymeulen B, Ling Z, Gorus FK, Delvaux 
G, Bouwens L, Grouping A, Hendriexx C, 
Pipeliers-Marichal M, Van Schravendijk C, 
Salmela K, Pipeliers DG: Implantation of stan-
dardized beta-cell grafts in a liver segment of 
IDDM patients: graft and recipient characteris-
tics in two cases of insulin independence under 
mental immunosuppression for prior kidney 
14 Farney A, Najarian J, Nakhlhe R: Autotrans-
plantation of dispersed pancreatic islet tissue 
combined with total or near total pancreatopathy 
for treatment of chronic pancreatitis. Surgery 
15 Pyzdrowski KL, Kendall DM, Halber JB, 
Nakhlhe RE, Sutherland DE, Robertson RP: Pre-
served insulin secretion and insulin independence in 
recipients of islet autografts. N Engl J Med 
327:220–226, 1992
16 Sutherland DE, Morrow CE, Florack G, 
Kretschmer OJ, Baumgartner D, Matas AJ, 
Najarian JS: Cold storage preservation of islet 
and pancreas grafts as assessed by in vivo func-
tion after transplantation to diabetic hosts. Cry-
obioiogy 20:138–150, 1983
17 Kneteman N, Lakey J, Kizilisik L, Ao Z, 
Warnock G, Rajotte R: Cadaver pancreas recover-
y technique: impact on islet recovery and in vivo 
18 Takada M, Nadeau K, Hancock W, Macken-
zeo H, Shaw G, Waaga A, Chandraker A, Sayegh 
M, Tinley N: Effects of explosive brain death on 

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83Powell JD, Lerner CG, Schwartz RH: Inhibition of cell cycle progression by rapamycin induces T cell clonal anergy even in the presence of costimulation. *J Immunol* 162:2775–2784, 1999


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