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 sheds 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 transplantation met all of these characteristics. Forty-eight percent of these patients showed basal C-peptide levels of 0.5 ng/ml; 73% had HbA1c levels ≤ 7%; 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>
<th>• Injury during procurement</th>
<th>• Venous hypertension via UW flush</th>
<th>• Poor cooling of pancreases</th>
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</thead>
<tbody>
<tr>
<td>Pancreatic processing &amp; islet purification</td>
<td>• Unreliable collagenase activity</td>
<td>• Poor pancreatic distension with collagenase</td>
<td>• Discontinuous ficoll gradient</td>
</tr>
<tr>
<td>Islet injury due to immunosuppressive agents</td>
<td>• High-dose steroids</td>
<td>• High-dose calcineurins (cyclosporine or tacrolimus)</td>
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</table>

With the development of new induction agents, therapy for patients with type 1 diabetes is becoming more successful. The new induction agents are so effective that these centers have been able to recommend the use of improved immunosuppression protocols and pharmacological impact on islet function. The term “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.

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 Wistar 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.

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 the 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 the use of islet transplantation.

Table 2. Reasons for the Success of the Edmonton Protocol

<table>
<thead>
<tr>
<th>Improved organ procurement</th>
<th>Minimized organ preservation injury</th>
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</thead>
<tbody>
<tr>
<td>• Dedicated procurement team</td>
<td>• Process pancreas &lt;8 h from cross clamp</td>
</tr>
<tr>
<td>• Standard procurement procedure</td>
<td>• Avoids overperfusion with UW</td>
</tr>
<tr>
<td>- avoids overperfusion with UW</td>
<td>• pancreas removed before liver and kidneys</td>
</tr>
<tr>
<td>- pancreas removed before liver and kidneys</td>
<td>• minimal manipulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improved islet cell processing</th>
<th>Reduced immunosuppressive injury to islets</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Modification of the Ricordi method</td>
<td>• Elimination of steroids</td>
</tr>
<tr>
<td>• More reliable collagenase solution (liberase)</td>
<td>• Reduction of calcineurin dose</td>
</tr>
<tr>
<td>• Liberase loaded into pancreatic duct using a controlled perfusion technique</td>
<td>• Sirolimus (minimal islet toxicity)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improved islet cell purification</th>
<th>Transplantation of an adequate islet mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continuous gradient elutriation (COBE 2991 cell processor)</td>
<td>• Intraportal transplantation of &gt;10,000 IE/kg body weight (multiple donors)</td>
</tr>
</tbody>
</table>

CLINICAL DIABETES • Volume 19, Number 2, 2001
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 to 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 hyperglycemic 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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<tbody>
<tr>
<td>Improved organ procurement</td>
<td>• Standard method for the pancreas to be used for islets</td>
</tr>
<tr>
<td></td>
<td>• Standardize criteria of islet donors among organ procurement organizations (OPOs)</td>
</tr>
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<td></td>
<td>• Develop expedited system of organ placement to islet processing centers</td>
</tr>
<tr>
<td>Increased organ preservation time</td>
<td>• Institute two-layer method (TLM) of pancreas preservation (Figure 1A)</td>
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<tr>
<td></td>
<td>• Standardize shipping to processing centers</td>
</tr>
<tr>
<td>Improved pancreatic processing</td>
<td>• Decreased variability between liberase lots</td>
</tr>
<tr>
<td></td>
<td>• Improved efficiency of Edmonton [Ricordi] method</td>
</tr>
<tr>
<td></td>
<td>• Develop assays to predict which pancreases to process</td>
</tr>
<tr>
<td>Improved islet purification</td>
<td>• Increased islet/nonislet ratio and variability</td>
</tr>
<tr>
<td></td>
<td>• Continuous osmolality and density gradient histidine lactobionate nicotinamide (HLN) and iodixanol</td>
</tr>
<tr>
<td>Sponsor regional processing centers linked to multiple OPOs</td>
<td>• Encourage cost-effective management of national resource</td>
</tr>
<tr>
<td></td>
<td>• Develop islet banks</td>
</tr>
<tr>
<td></td>
<td>• Develop simple standard quality control assays</td>
</tr>
<tr>
<td>Multicenter trials with standardized islet preparations</td>
<td>• Reproduce the findings of the Edmonton protocol (in process)</td>
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<tr>
<td></td>
<td>• Transition to single-donor cure protocols</td>
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<tr>
<td></td>
<td>• Develop a consensus on best groups that can benefit</td>
</tr>
<tr>
<td></td>
<td>• Compare long-term results of solid-organ pancreas to islet transplantation</td>
</tr>
<tr>
<td></td>
<td>• Test new (less toxic, pro-tolerance) immunosuppressive strategies</td>
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</table>
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. 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.

These topics are beyond the scope of this review, nevertheless we cannot over-emphasize the importance of investigating these strategies while at the same

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**Figure 1.**

A. Islet isolations from human cadaveric pancreases stored for prolonged periods. Islet yield, purity, and viability was determined in pancreases (n = 9) stored in UW solution (UW) for an average of 13.3 ± 3.3 h. After this initial UW storage, the pancreases were split into halves, with each half preserved by either TLM or UW for an additional 22.3 ± 2.3 h (total cold ischemic time = 35.6 ± 3.0 h). Islet purity and viability are substantially improved with TLM versus UW preservation.

B. Pancreatic ATP levels after TLM preservation correlate with islet yield. We obtained biopsies before islet isolation from 15 pancreases preserved by the TLM. We then divided the isolation results into three groups: High Yield (>6,000 EI/g), Average Yield (3,000–6,000 IE/g), and Low Yield (<3,000 IE/g).
time assuring safety to the patient.

To make islet transplantation available for most patients with diabetes, a large source of islets and less toxic immunosuppression strategies (possibly even less toxic than in the Edmonton trial or that employed for kidney transplants) will be required. We envision a safe regimen that induces “partial tolerance” and that can be maintained with minimal immunosuppression.

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.

Tolerance 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 may 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 may help 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-

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Table 4. Requirements for Islet Transplantation to Become the Preferred Treatment for Type 1 Diabetes

<table>
<thead>
<tr>
<th>Reduced or eliminated need for immunosuppressive agents</th>
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<tbody>
<tr>
<td>• Induce donor MHC-specific hyporeactivity or tolerance</td>
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<tr>
<td>- co-stimulation blockade</td>
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<tr>
<td>- donor bone marrow-deprived stem cells (co-transplantation)</td>
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<tr>
<td>• Immunological barriers (e.g., encapsulation)</td>
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<tr>
<th>Increased islet masses available for transplantation</th>
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<tbody>
<tr>
<td>• β-cell expansion</td>
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<tr>
<td>• Xenotransplantation</td>
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<tr>
<td>• Genetically engineered β-cell lines</td>
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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 regarding which patients will benefit most from islet transplantation.

Nevertheless, the most exciting point is that this therapy is and must be successful. 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 protocols that minimize the risks of long-term immunosuppression.

Conclusion

Islet cell transplantation is a true success, but it is not a panacea for most patients. We propose that the next step for islet transplantation is the implementation of standardized procurement and expedited allocation and shipping systems 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 in clinical trials with different immunosuppressive/tolerance strategies and patient groups to further define success and identify the benefits of this unique benchmark cellular therapy.

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