The state of affairs of allogenic islet transplantation

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Global epidemiology of Diabetes Mellitus

IDDM     NIDDM
1997  3 700 000  120 300 000
2010  5 000 000  216 000 000

Amos et al. The rising global burden of diabetes and it’s complications: estimates and projections to the year 2010. Diabetic Medicine 1997; 14 (Suppl 5)
Blood Glucose Control with a Functioning Islet Transplant vs. Intensive Insulin Therapy

Fasting Blood Glucose (mg/dL)

Day

Four-year-old child
Transplanted animals

(Rhesus monkeys)

Insulin independence 1 year after pancreas- vs. islet transplantation

~ 80 %

8 %

Bennet, 1999
## Comparison between pancreas and islet allotransplantation

<table>
<thead>
<tr>
<th></th>
<th>Pancreas</th>
<th>Islet</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immunological barrier</strong></td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Autoimmune barrier</strong></td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Immunosuppression</strong></td>
<td>Same</td>
<td>Same</td>
</tr>
<tr>
<td><strong>Transplantation technique</strong></td>
<td>Re-establishment of circulation</td>
<td>Intraportal circulation</td>
</tr>
</tbody>
</table>
Islet Transplantation in Seven Patients with Type 1 Diabetes Mellitus Using a Glucocorticoid-Free Immunosuppressive Regimen

A.M. James Shapiro, M.B., B.S., Jonathan R.T. Lakey, Ph.D., Edmond A. Ryan, M.D.,
Gregory S. Korbutt, Ph.D., Ellen Toth, M.D., Garth L. Warnock, M.D., Norman M. Kneteman, M.D., and Ray V. Rajotte, Ph.D.
Islet Transplant Activity (2000-2005)

>50 Institutions: > 500 patients
One Year Insulin Independence

Completed Transplants (Kaplan-Meier)
EDMONTON – MIAMI – MINNESOTA (n=118)

~ 80% mean overall one-year insulin independence
Five Year Outcomes of Fresh vs Cultured Islets

Insulin Independence

8% CULTURED (n=25)
20% FRESH (n=28)

Time in Months Post First Transplant

Log Rank: 5.52
P= 0.02

A.M. James Shapiro 2004
Allo vs. auto transplantation

Insulin Independence Following Islet Transplantation in Man
A Comparison of Different Recipient Categories

- PIDM-Auto 1990-99 (n=57)∗
- PIDM-Auto 1990-99 (n=21)∗
- Type-1-DM-Allo 1990-99 (n=237)∗

≥ 300,000 IEQ

* only well documented patients
A dose finding study in humans
\[ \approx 10^{-11} \times 10^3 \text{ IEQ} / \text{kg BW} \]
or
\[ \approx 220 \text{ IEQ} / \text{kg BW} \times \text{pre-Tx ins. req.} \]

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M.D., and Ray V. Rajotte, Ph.D.
Single-Donor Marginal-Dose Islet Transplantation Without Immunosuppression

Bernhard J. Jobst
Raja Kandasamy
Jeffrey D. Adamson
Peter M. Elliott
Masahiko Nakano, MD, PhD
Toshiya Sawada
Ippei Matsumoto, MD, PhD
Sung-Hee Ihm, MD
Hui-Jian Zhang, MD
Jamen Parkey, PA-C, MPH
David W. Hunter, MD
David E. R. Sutherland, MD, PhD

≈ 220 IEQ / kg BW x pre-Tx ins. req.

Obtained by matching small recipients & large donors

Objective To assess the safety of a single-donor, marginal-dose islet transplant protocol using potent induction immunotherapy and less diabetogenic maintenance immunosuppression in recipients with type 1 diabetes. A secondary objective was to assess the proportion of islet transplant recipients who achieve insulin independence in the first year after single-donor islet transplantation.

Design, Setting, and Participants Prospective, 1-year follow-up trial conducted July 2001 to August 2003 at a single US center and enrolling 8 women with type 1 diabetes accompanied by recurrent hypoglycemia unawareness or advanced secondary complications.

Interventions Study participants underwent a primary islet allotransplant with 7271 (SD, 1035) islet equivalents/kg prepared from a single cadaver donor pancreas. Induction immunosuppression was with antithymocyte globulin, daclizumab, and etaner...
# The endocrine pancreas

<table>
<thead>
<tr>
<th>Islet diameter (µm)</th>
<th>Number of islets</th>
<th>% of total number of islet</th>
<th>% of total islet volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>782 000</td>
<td>52%</td>
<td>5.4</td>
</tr>
<tr>
<td>50-100</td>
<td>416 000</td>
<td>28%</td>
<td>17</td>
</tr>
<tr>
<td>100-150</td>
<td>203 000</td>
<td>14%</td>
<td>30</td>
</tr>
<tr>
<td>150-200</td>
<td>54 000</td>
<td>3.6%</td>
<td>26</td>
</tr>
<tr>
<td>200-250</td>
<td>20 000</td>
<td>1.3%</td>
<td>15</td>
</tr>
<tr>
<td>&gt; 250</td>
<td>3 000</td>
<td>0.2%</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Total islet volume ≈ 1 ml, 1.5 \(10^6\) islets (> 20 µm)

Islets ≠ IEQ

1.5 \(10^6\) islets ≈ 500 000 IEQ

\(\text{IEQ} = \text{a standardized islet with a diameter of 150 µm}\)
ASSESSMENT OF INTRACELLULAR INSULIN CONTENT DURING ALL STEPS OF HUMAN ISLET ISOLATION PROCEDURE

HEIDE BRANDHORST,1 DANIEL BRANDHORST, MATHIAS D. BRENDEL, BERNHARD J. HERING, AND REINHARD G. BRETZEL
Third Medical Department, Justus Liebig University, Gießen, Germany


Insulin in = Insulin out
Islet isolation improvements?

Almost nothing to gain by spending money and efforts on getting more islets from each pancreas

Quality not numbers!
So why do allogenic islets fail to thrive long term?
ISLET TRANSPLANTATION IN RODENTS

Davalli AM et al,
Diabetes 19:1161-1167,1996

Conclusion from this and other studies is that only about 10-30 % of the transplanted islets survive the first few weeks.
Rapid Publication

Incompatibility Between Human Blood and Isolated Islets of Langerhans

A Finding With Implications for Clinical Intraportal Islet Transplantation?

William Bennet, Berit Sundberg, Carl-Gustav Groth, Mathias D. Brendel, Daniel Brandhorst, Heide Brandhorst, Reinhardt G. Bretzel, Graciela Elgue, Rolf Larsson, Bo Nilsson, and Olle Korsgren

DIABETES, VOL. 48, OCTOBER 1999, 1907-1914
Islet of Langerhans

Vascular Endothelium

© Bennet, 1999
Human islet morphology after 60 min exposure to human blood in vitro

(CD11b, x200)

Bennet, 1999
Clinical islet transplantation

Coagulation/IBMIR

ß cell destruction

Lisa Moberg 2002
No patients with both high C-peptide and TAT levels
Tissue Factor
Normal islets

heparinized islets
Surface heparinized pig islets are protected from IBMIR after intraportal transplantation
Brain Death Significantly Reduces Isolated Pancreatic Islet Yields and Functionality In Vitro and In Vivo After Transplantation in Rats

Juan L. Contreras,¹ Christopher Eckstein,¹ Cheryl A. Smyth,¹ Marty T. Sellers,² Mario Vilatoba,¹ Guadalupe Bilbao,¹ Firoz G. Rahemtulla,³ Carlton J. Young,¹ J. Anthony Thompson,¹ Irshad H. Chaudry,⁴ and Devin E. Eckhoff¹
β cell exhaustion / glucose toxicity
β-Cell Function Following Human Islet Transplantation for Type 1 Diabetes

Michael R. Rickels,¹ Mark H. Schutta,¹ James F. Markmann,² Clyde F. Barker,² Ali Naji,² and Karen L. Teff¹,³

Diabetes 2005, 54: 100-106

Plasma glucose (A) and C-peptide (B) responses to an orally consumed 600-kcal mixed-nutrient meal at t = 0 during the MMT.
Summary

**Allotransplantation**

- Donor management
- Optimized culture conditions (Nic)
- iFVIIa / LMW-DS
- Surface heparinization

**Pancreas** → **Islets** → **IBMIR**

- Acute cellular rejection
- Physiological adaptation
- Glucose toxicity / β cell exhaustion

**Clinical islet transplantation**
Challenges for the future (next 5 years)

A. No special “islet” donor criteria.
B. Improve islet quality, less focus on islet number (donor & isolation)
C. Improve islet culture and shipment
D. Focus on metabolic control, not insulin independence (combine islet tx 1:1 with long acting insulin)
E. More tolerable immunosuppressive regimes (carefully controlled randomized clinical trials)
F. Islet tx can only develop into a treatment for uncomplicated type 1 diabetes if “E” can be achieved (even if an unlimited source of β cells was available)
With the large number of IDDM patients and the lack of donor pancreata the future of islet transplantation is likely to be in xenogenic porcine islet transplantation.
Type 1 Diabetes

- Reserve capacity maintained in healthy persons
- β cell volume required to maintain normal IVGTT
- β cell volume required to obtain insulin independence
Enhanced outcome

• Several (obese) donors
• Small recipients
• Improve islet isolation
• Enhance engraftment
Decay in Islet Function over time

- Undiagnosed acute rejection
- Chronic allograft rejection
- Recurrent Autoimmunity

Failure of islet regeneration

Drug toxicity

β cell exhaustion (glucose toxicity) of an islet-graft just able to maintain normoglycemia

Modified from an original by A.M. James Shapiro 2004
Clinical islet transplantation

Success is dependent on surviving islet mass

- Islet morbidity in during culture
- Loss early after transplantation (inflammation)
- Loss during cellular rejection
- Absence of islet toxic immunosuppressive regimes
Our studies suggest that both human (allogenic) as well as porcine (xenogenic) islets transplanted via the portal vein into the liver will be damaged shortly after transplantation by a strong inflammatory reaction.

This inflammatory reaction has not been described in detail previously and therefore lacks a descriptive name. We have chosen to name it an: *Instant Blood Mediated Inflammatory Reaction* 

"IBMIR"
Islet Cell Allotransplantation in Diabetic Patients

Histologic Findings in Four Adults Simultaneously Receiving Kidney or Liver Transplants

C. E. Sever,* A. J. Demetris,* Y. Zeng,† A. Tzakis,† J. J. Fung,† T. E. Starzl,† and C. Ricordi† From the Department of Pathology,* and the Pittsburgh Transplant Institute†, University of Pittsburgh, Pittsburgh, Pennsylvania

"The liver has emerged as an especially favorable location once the infusate was reduced to such a low volume as to prevent portal hypertension. A significant change of portal vein pressure was not observed in any of the four patients, although islet-cell thrombi could be demonstrated histologically."

"The intense portal inflammation which was seen 2 and 5 days post-transplantation is likely to be a reaction to non-islet cell contaminants such as acinar cells, soft tissue and hematolymphoid elements."

"Mononuclear infiltrates within islet cell clusters such as described in rejection of whole organ pancreas transplant were not seen."

"In summary, the early posttransplant period in diabetic patients receiving a combined kidney-islet allograft is characterized by focal portal inflammation consisting of lymphocytes, macrophages, and occasional eosinophils, which probably represents clean-up of decaying nonendocrine allograft components."

Refined maneuvers requiring less infusate resulting in minimal ex vivo damage to islet cells and biliary ducts was subsequently found in other patients. After 3 weeks, all four patients were transplanted, with histologic and functional results similar to those reported elsewhere. Informed consent was obtained from all patients prior to transplantation. At our institution, treatment with the powerful immunosuppressive agent FK506 has contributed to successful islet cell transplantation in patients requiring insulin injection.
Disseminated intravascular coagulation and portal hypertension following pancreatic islet autotransplantation

Acute portal hypertension and disseminated intravascular coagulation following pancreatic islet autotransplantation after subtotal pancreatectomy

Portal vein thrombosis after transplantation of partially purified pancreatic islets in a combined human liver/islet allograft.

Fatal disseminated intravascular coagulation after autologous islet transplantation
Induced expression of inflammatory mediators in human islets

• Diseased donor
• Brain death
• Ischemia
• Islet isolation
• Culture conditions
Expression of inflammation-related genes in human islets

- TF induce coagulation & inflammation
- MCP-1 powerful chemoattractant for leukocytes

U Johansson et al BBRC
Five Year Kaplan-Meier Survival Curves
(Insulin Independence from time of first transplant)

Survival (%) vs Time in Months Post First Transplant

Fresh (N=25) vs Cultured (N=22)

Log Rank Statistic: 1.6
P-Value: 0.2

A.M. James Shapiro 2004
Islet activated coagulation

Tissue Factor on the islets activates the coagulation cascade via FVII
Human islet morphology after 5 min exposure to human blood in vitro

Before

(H&E, x400)

IBMIR

(CD41, x200)

(CD11b, x200)

(P-selectin, x200)

Bennet, 1999
Isolated Islets of Langerhans Trigger an Instant Blood Mediated Inflammatory Reaction

A Finding with Implications for Intraportal Islet Transplantation

William Bennet

Stockholm 2000
β-Cell Function Following Human Islet Transplantation for Type 1 Diabetes

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