Islet Transplants: Is it a Reality?

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‘Practical Ways to Achieve Targets in Diabetes Care’
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George Eisenbarth, M.D, Ph.D.

1947 - 2012
What is Type 1 Diabetes?

*Immunological* response

*Metabolic* disease
Where does the blind immunologist fit in?
What is an islet transplant?
Pancreatic Islets within Pancreas

- Duodenum
- Pancreas
- Exocrine tissue
- Acinar cells
- Pancreatic Islet

- $\alpha$-cells (10-20%)
- $\beta$-cells (60-80%)
- $\delta$-cells (~5%)
- PP-cells (<1%)
Transplantation of Donor Islets

Donor

Pancreas

Islet in Pancreas

Recipient

Islet Isolation

Syringe

Isolated Islet of Langerhans

Portal Vein

Islet in Portal Vein

Pancreas
Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis

David ER Sutherland, MD, PhD, FACS, David M Radosevich, RN, PhD, Melena D Bellin, MD, Bernard J Hering, MD, Gregory J Beilman, MD, FACS, Ty B Dunn, MD, FACS, Srinath Chinnakotla, MD, Selwyn M Vickers, MD, FACS, Barbara Bland, RN, MS, AN Balamurugan, PhD, Martin L Freeman, MD, Timothy L Pruett, MD, FACS


<table>
<thead>
<tr>
<th>Era</th>
<th>Pediatric</th>
<th>Adult</th>
<th>Total</th>
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<tr>
<td>1977 to 1995</td>
<td>1</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>1996 to 2005</td>
<td>19</td>
<td>91</td>
<td>110</td>
</tr>
<tr>
<td>2006 to 2011</td>
<td>33</td>
<td>217</td>
<td>250</td>
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Figure 1. Annual number of total pancreatectomy with intraportal islet autotransplantation cases since the inception of the program in 1977. More than half the cases have been in era 3.
Progress in Islet Transplantation: ‘Edmonton Protocol’ and Beyond
“The Edmonton Protocol”

The New England Journal of Medicine

VOLUME 343
JULY 27, 2000
NUMBER 4

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. Korbut, Ph.D., Ellen Toth, M.D., Garth L. Warnock, M.D., Norman M. Kneteman, M.D., and Ray V. Rajotte, Ph.D.

Tacrolimus 3-6 ng/ml // 3-6 ng/ml
Rapamycin 12-15 ng/ml // 7-10 ng/ml

Daclizumab (anti-CD25) 1 mg/kg x 5

Day 0 14 28 42 56 90

Transplant #1 Transplant #2
Blood glucose (mg/dl) vs. Time of day for Pre- and Post-transplant periods.

Pre-transplant

Shapiro et al.
N Engl J Med
2000;
343:230-238

Post-transplant

Time of day

Blood glucose (mg/dl)
International Trial of the Edmonton Protocol for Islet Transplantation

A.M. James Shapiro, M.D., Ph.D., Camillo Ricordi, M.D., Bernhard J. Hering, M.D., Hugh Auchincloss, M.D., Robert Lindblad, M.D., R. Paul Robertson, M.D., Antonio Secchi, M.D., Mathias D. Brendel, M.D., Thierry Berney, M.D., Daniel C. Brennan, M.D., Enrico Cagliero, M.D., Rodolfo Alejandro, M.D., Edmond A. Ryan, M.D., Barbara DiMercurio, R.N., Philippe Morel, M.D., Kenneth S. Polonsky, M.D., Jo-Anna Reems, Ph.D., Reinhard G. Bretzel, M.D., Federico Bertuzzi, M.D., Tatiana Froud, M.D., Raja Kandaswamy, M.D., David E.R. Sutherland, M.D., Ph.D., George Eisenbarth, M.D., Ph.D., Miriam Segal, Ph.D., Jutta Preiksaitis, M.D., Gregory S. Korbutt, Ph.D., Franca B. Barton, M.S., Lisa Viviano, R.N., Vicki Seyfert-Margolis, Ph.D., Jeffrey Bluestone, Ph.D., and Jonathan R.T. Lakey, Ph.D.

NEJM 355:1318, 2006

Persistent islet function even without insulin independence provides both protection from severe hypoglycemia and improved levels of glycated hemoglobin. (ClinicalTrials.gov number, NCT00014911.)
Patient 1: pretransplant

Sensor Modal Day

MiniMed Solutions: CGMS Sensor
MMT-7310 3.0B

![Graph showing glucose levels over time with specific time points and days marked.]

- **Legend**
  - Sunday
  - Monday
  - Tuesday
  - Wednesday
  - Thursday
  - Friday
  - Saturday

Gottlieb
Patient 1: 9 months following transplant

Alleviation of Hypoglycemia
Patient 3: pretransplant
Patient 3: 1 month following transplant
Islet Recipient HbA1c

Days Post Infusion

Transplant #1
743,241 IEQ

Transplant #2
572,689 IEQ

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<tr>
<th>Days Post Infusion</th>
<th>HbA1c</th>
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<tbody>
<tr>
<td>0</td>
<td>6.6</td>
</tr>
<tr>
<td>7</td>
<td>6.5</td>
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<tr>
<td>14</td>
<td>6.3</td>
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<tr>
<td>21</td>
<td>5.9</td>
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<tr>
<td>28</td>
<td>5.7</td>
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<td>35</td>
<td>5.2</td>
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<td>112</td>
<td>4.8</td>
</tr>
<tr>
<td>119</td>
<td>4.8</td>
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</table>
What’s the Problem?
At 5 years, C-peptide secretion preserved but <10% maintain insulin independence.

Diabetes 2005; 54:2060
Continued Improvements

Diabetes Care Symposium
ORIGINAL ARTICLE

Improvement in Outcomes of Clinical Islet Transplantation: 1999–2010

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- A.M. James Shapiro, MD, PhD¹³

Diabetes Care 35:1436, 2012
Steady Improvement in Graft Survival
Research *Does* Make Difference!
Current multi-center demonstration trial for:

• *Islet Transplant alone*
• *Islet-After Kidney*

http://www.CITIsletStudy.org
http://www.isletstudy.org
Where do we go from here?
Goal: Connect the Silos
Barriers to Successful Islet Transplantation

- Insufficient islet mass
- Poor quality of islets
- Failure to implant
- Toxicity of anti-rejection drugs
- Transplant rejection
- Autoimmunity
- Metabolic Distress
Immunotherapies: A work in progress

The Elephant in the Living Room:

We don’t yet have a robust means of inducing immune ‘tolerance’ in man
Example: 5 Yr Pancreas Transplant Survival
(National Registry Data 2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>Pancreas Alone</th>
<th>Pancreas after Kidney</th>
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<tbody>
<tr>
<td>1994</td>
<td>43%</td>
<td>47%</td>
</tr>
<tr>
<td>1997</td>
<td>40%</td>
<td>46%</td>
</tr>
<tr>
<td>2000</td>
<td>52%</td>
<td>53%</td>
</tr>
<tr>
<td>2003</td>
<td>43%</td>
<td>48%</td>
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</tbody>
</table>
Interface between immunity and metabolism:
Did we forget about diabetes?
At 5 years, C-peptide secretion preserved but <10% maintain insulin independence.

Rejection or ‘Decay’

Diabetes 2005; 54:2060
Islet Graft Attrition:

Non-immune islet dysfunction
(where Type 1 and Type 2 diabetes may converge)
Islet Transplantation in B6 Rag1⁻/⁻-akita Mice

Donor Islets

Transplant 500-2000 IEQ under the kidney capsule of B6 Rag1⁻/⁻-akita

- Monitor blood glucose
- Nephrectomy – immunohistochemistry
Spontaneous Failure of Human Islets in \textit{Rag1}^{-/-}\textit{-akita} Mice

![Graph showing blood glucose levels over day post transplantation for Human Islets Tp#1 and Tp#2, relative to Normoglycemia.]
Pathology of Failed Human Islets (day 70)

**Fibrosis**
(Tri-Chrome)

**Amyloid**
(Thyoflavin S)
Widespread Amyloid Deposition in Transplanted Human Pancreatic Islets

Islet associated inflammation (e.g. IL-1) associated with Type 2 diabetes.

Prospects: Understand the interplay amongst differing pathways of islet injury

Non-Antigen-Specific Inflammation → Islet Response / Metabolic Stress

Antigen-Specific (Adaptive) Immunity
Beta Cell Replacement: Towards a ‘Cure’

*Durable Transplant without immunosuppression (cure)*

*Transplant with more benign immunosuppression*

*Transplant with chronic immunosuppression*
Conclusions

• *Islet Transplant Remains a Viable Treatment for T1D*

• *Results Continue to Improve Over Time*

• *Ongoing need to treat multiple features of islet graft failure (‘immune’ and ‘non-immune’)*