β-Cell Preservation and Regeneration After Islet Transplantation

Jyuhn-Huarng Juang, MD

Division of Endocrinology and Metabolism, Department of Internal Medicine, Chang Gung University and Memorial Hospital, TAIWAN
Nature History of Type 1 Diabetes

Genetic Predisposition

Immunologic Abnormalities

Normal insulin release

Progressive impairment in insulin release

Overt diabetes

“Honeymoon” period

Beta-Cell Mass (% of max)

Time (yr)

Birth

0

0 50 100

1. Doctors remove a healthy pancreas from a recently deceased donor. Islet cells make up only 1 to 2 percent of the pancreas.

2. Islet cells and other pancreatic cells, such as acinar cells, are isolated from the organ tissue through the use of a solution of collagenase, an enzyme that breaks down fibrous vessels and ducts. The islet cells are separated from the other pancreatic cells by centrifugal force.

3. The islet cells are then injected into the portal vein of the liver.

4. The islet cells lodge in very small branches of the portal vein within the liver and produce insulin.
Human Islet Transplantation

**Insulin independence: at 1 year**

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893-1998</td>
<td>8%</td>
<td>493 (total)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>11%</td>
<td>237 (type 1)</td>
</tr>
</tbody>
</table>
Human Islet Transplantation

**Insulin independence: at 1 year**

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893-1998</td>
<td>8%</td>
<td>493 (total)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>11%</td>
<td>237 (type 1)</td>
</tr>
<tr>
<td>1992-1998</td>
<td>25% (SIK)</td>
<td>Giessen</td>
</tr>
<tr>
<td></td>
<td>27% (IAK)</td>
<td></td>
</tr>
</tbody>
</table>
## Human Islet Transplantation

**Insulin independence: at 1 year**

<table>
<thead>
<tr>
<th>Year</th>
<th>rate</th>
<th>patient no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893-1998</td>
<td>8%</td>
<td>493 (total)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>11%</td>
<td>237 (type 1)</td>
</tr>
<tr>
<td>1992-1998</td>
<td>25% (SIK)</td>
<td>Giessen</td>
</tr>
<tr>
<td></td>
<td>27% (IAK)</td>
<td></td>
</tr>
<tr>
<td>1999-2000</td>
<td>100% (ITA)</td>
<td>7 (Edmonton)</td>
</tr>
<tr>
<td>2002</td>
<td>85% (ITA)</td>
<td>33 (Edmonton)</td>
</tr>
</tbody>
</table>
# Human Islet Transplantation

## Insulin independence: at 1 year

<table>
<thead>
<tr>
<th>Year</th>
<th>rate</th>
<th>patient no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893-1998</td>
<td>8%</td>
<td>493 (total)</td>
</tr>
<tr>
<td>1990-1999</td>
<td>11%</td>
<td>237 (type 1)</td>
</tr>
<tr>
<td>1992-1998</td>
<td>25% (SIK)</td>
<td>27% (IAK)</td>
</tr>
<tr>
<td>1999-2000</td>
<td>100% (ITA)</td>
<td>7 (Edmonton)</td>
</tr>
<tr>
<td>2002</td>
<td>85% (ITA)</td>
<td>33 (Edmonton)</td>
</tr>
<tr>
<td>2006</td>
<td>44%</td>
<td>36 (9 sites)</td>
</tr>
</tbody>
</table>
Edmonton Protocol


• High quality of human islets

• Glucocorticoid-free immunosuppressive regimen

• Repeat transplants
Human Islet Transplantation

Insulin Independence and Graft Function (Edmonton)

Graft $\beta$-Cell Preservation and Regeneration

- Prevent rejection and autoimmune destruction
- Enhance islet engraftment
- Promote beta-cell regeneration
Prevention of Rejection and Autoimmune Destruction

- Immunosuppression
- Immunomodulation
- Immunoisolation
- Tolerance induction
Approaches to Prevent Rejection and Autoimmune Destruction

- **Microcapsule**
  - Hsu BRS et al. Transplant Proc 1996
  - Cell Transplant 1999

- **CTLA4 Ig**
  - Lu WT et al. Transplant Proc 2001

- **FasL/HO-1 Tg**
  - Juang JH et al. Transplant Proc 2011

- **DCR3 Tg**

- **Rejection**
- **Autoimmune**
Immunoisolation

Microparticle Generator

Alginate-Poly-L-Lysine-Alginate (APA) Microcapsule

Glucose → Islet → Insulin

Immunoglobulin

APA Microencapsuled Rat Islets


DCR3 Transgenetic Islets Prevented Autoimmune Destruction

Overexpression of DCR3 Protected NOD from Insulitis

NOD Mice (12 wks)

DCR3 Transgenetic NOD Mice

DCR3 Transgenetic Islet Transplantation in NOD Mice

<table>
<thead>
<tr>
<th>Donor</th>
<th>PD8 mice</th>
<th>Control mice</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of recipients</td>
<td>20</td>
<td>16</td>
<td>—</td>
</tr>
<tr>
<td>Number of successes</td>
<td>13</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Success rate</td>
<td>65%</td>
<td>38%</td>
<td>—</td>
</tr>
<tr>
<td>Mean survival period (days)</td>
<td>9.1</td>
<td>3.1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Graft $\beta$-Cell Preservation and Regeneration

- Prevent rejection and autoimmune destruction
- Enhance islet engraftment
- Promote beta-cell regeneration
Problems Related to Islet Engraftment

- Hyperglycemia
- Hypoperfusion
- Hypoxia
- Ischemia/Reperfusion
- Nonspecific inflammatory response
Approaches to Enhance the Islet Engraftment

- **Additional Islets**
  - Juang JH et al.
  - Diabetes 1994

- **Insulin**
  - Juang JH et al.
  - Transplant Proc 1998

- **HBO**
  - Juang JH et al.
  - Cell Transplant 2002

- **Pentoxiphylline**
  - Juang JH et al.
  - Transplant Proc 2000

- **NDGA**
  - Hsu BRS et al.
  - Cell Transplant 2001

- **DSG**
  - Juang JH et al.
  - Transplant Proc 2002

- **COPP**
  - Fu SH et al.
  - Transplant Proc 2004

- **Rosiglitazone**
  - Hsu BRS et al.
  - Transplant Proc 2005

Islet Growth and Function

Outcome of Islet Transplantation
Beneficial Influence of Additional Islets on Syngeneic Mouse Islet Transplantation

Juang JH et al., Diabetes 1994;43:1334-9
Beta-Cell Mass and Insulin Content of the Graft

Juang JH et al., Diabetes 1994;43:1334-9
Replication Rate of Islet Grafts

* p < 0.02 vs. other groups in graft removal, and p < 0.04 vs. day 3 in sham operation

Juang JH et al., Diabetes 1994;43:1334-9
Effect of Insulin Treatment on Syngeneic Mouse Islet Transplantation

UT (n=30) vs. NS (n=16)

* P<0.05, ** P<0.01, *** P<0.001 vs. NS

Blood Glucose Changes After Transplantation

- Control (n=16)
- UT-A (n=30)
- UT-B (n=7)
- UT-B+A (n=5)

* P<0.05 vs. NS

Beta-Cell Mass of Mouse Islet Grafts At 4 Weeks After Transplantation

* P<0.05 vs. Control

Graft $\beta$-Cell Preservation and Regeneration

- Prevent rejection and autoimmune destruction
- Enhance islet engraftment
- Promote beta-cell regeneration
Regeneration Therapy in Islet Recipients

- β-cell Mass
- Graft Failure
- Islet Regeneration
- Insulin independence threshold
- Time
- Islet Transplant
Pancreatic Targets for Expansion of $\beta$-Cell Mass

Pancreatic acinus
Gastrin/EGF

Islet of Langerhans

$\beta$-cell
GLP-1R agonists
GIP
DPP-IV inhibitors
TZDs

Pancreatic duct
GLP-1R agonists
DPP-IV inhibitors
Gastrin/EGF

Pancreas

GLP-1 on $\beta$-Cell Mass

- $\beta$-cell proliferation
- $\beta$-cell hypertrophy
- $\beta$-cell regeneration and increased mass
- $\beta$-cell apoptosis
- $\beta$-cell neogenesis

Endocrine Reviews 2007;28:187–218
Exenatide in Clinical Islet Transplantation

1. Exenatide reduces the number of islet infusions to achieve normoglycemia (Am J Transplant 2008;8:1250-61)

2. Exenatide rescues islet recipients with allograft dysfunction (Transplantation 2008;86:36–45)

3. Exenatide improves success rates in recipients with supplemental islet infusions (Transplantation 2008;86:1658–65)
Exendin-4 Improves Outcome of Syngeneic Mouse Islet Transplantation

Blood Glucose

* P<0.05 vs. control

Juang JH et al., Cell Transplant 17:641-7, 2008
Exendin-4 Expands Mouse Graft $\beta$-Cell Mass

Mouse Islet Graft at 6 Weeks

**Insulin Staining**

**Exendin-4**

**Control**

**$\beta$-Cell Mass**

Juang JH et al., Cell Transplant 17:641-7, 2008
Exendin-4 Prevents Mouse Graft $\beta$-Cell Apoptosis and Preserves Graft $\beta$-Cell Mass

Toyoda K et al. Biochem Biophys Res Commun 367:793-9, 2008
Liraglutide Prevents Mouse Graft $\beta$-Cell Apoptosis But Does Not Promote $\beta$-Cell Proliferation

48 hr
Apoptotic $\beta$-cells (%)

2 wk
BrdU+ $\beta$-cells (%)

Sitagliptin Prolongs Mouse Islet Graft Survival

Islets: infected with rAD-TK to allow $[^{18}\text{F}]\text{FHBG}$ PET imaging

Effects of Dipeptidyl Peptidase-4 Inhibition on Syngeneic Mouse Islet Transplantation

Blood Glucose

MK-0431

LAF 237

Effects of Dipeptidyl Peptidase-4 Inhibition on Syngeneic Mouse Islet Transplantation

Body Weight

MK-0431

LAF 237

Effects of Dipeptidyl Peptidase-4 Inhibition on Syngeneic Mouse Islet Transplantation

Insulin Content and $\beta$-Cell Mass

**MK-0431**

**LAF 237**

Islet Transplantation

Graft $\beta$-Cell Preservation and Regeneration

A Cure for Diabetes
CGMH Islet Transplant Team

Grant Support

- National Science Council, Taiwan
- Industrial Technology Research Institute, Taiwan
- Chang Gung Memorial Hospital, Taiwan