Future Therapies in the Treatment of Diabetes: Islet Transplantation

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Pancreatic islets of Langerhans

~ 1 million islets comprise 2-3% of the total pancreatic mass

Red = β-cells, stained for insulin
Green = α-cells, stained for glucagon
Islet cell responses defend against hypoglycemia

↓ Plasma Glucose → Islet Cell Responses → ↓ Insulin Secretion → ↑ Hepatic Glucose Production → ↑ Plasma Glucose

↑ Glucagon Secretion

↑ Hepatic Glucose Production
Case - continuous glucose monitoring
Pancreas transplantation

Larsen. Endocrine Reviews 25: 919, 2004
Glycemic control in pancreas transplantation

B

Glucose concentration (mg/dL)

Time

12:00 AM  4:00 AM  8:00 AM  12:00 PM  4:00 PM  8:00 PM  12:00 AM

Kessler et al. Diabetes Care 25: 2256, 2002
β-cell secretory capacity in pancreas transplantation

![Graph showing insulin levels over time for different groups.

- PANCREAS-KIDNEY TRANSPLANT
- KIDNEY TRANSPLANT
- KIDNEY DONOR

ARGinine (5 g) 230 mg/dl clamp 340 mg/dl clamp

MINUTES

Rickels et al. J Clin Endocrinol Metab 95: 1238, 2010
Islet cell responses to hypoglycemia in pancreas transplantation

β-cell response

Insulin and variable glucose i.v.

α-cell response

Insulin and variable glucose i.v.


C

MINUTES

MINTUS

PG PEPTIDE (nmol/L)

GLUCAGON (ng/L)
Islet transplantation

Deceased Donor
no diabetes

Recipient
type 1 diabetes
NIH Clinical Islet Transplantation (CIT) Consortium

T1D & Severe Hypoglycemia

CIT07 (N=11/48)
Thymoglobulin
Etanercept
Heparin
Tacrolimus
Sirolimus

T1D & Kidney Allograft

CIT06 (N=2/24)
Thymoglobulin
Etanercept
Heparin
Tacrolimus
MMF

Islet Transplantation #1

Insulin-Independence at day 75

Islet Transplantation #2

Primary Endpoint: HbA1c < 7% and free from severe hypoglycemic episodes at one year following the initial transplant

www.citisletstudy.org
Clinical endpoint – HbA₁c <7.0% w/o hypoglycemia

<table>
<thead>
<tr>
<th>Consortium</th>
<th>IE/kg</th>
<th>HbA₁c Pre</th>
<th>HbA₁c 1 Year</th>
<th>HbA₁c 2 Years</th>
<th>A₁c &lt;7% No SH 1 Year</th>
<th>A₁c &lt;7% No SH 2 Years</th>
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</thead>
<tbody>
<tr>
<td>Australian¹</td>
<td>15,366</td>
<td>8.3%</td>
<td>6.5%</td>
<td>N.D.</td>
<td>82%</td>
<td>N.D.</td>
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<td>n = 17</td>
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<td>UK²</td>
<td>8,770</td>
<td>8.0%</td>
<td>6.3%</td>
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<td>GRAGIL³</td>
<td>9,716</td>
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<td>6.2%</td>
<td>N.D.</td>
<td>83%</td>
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</table>

¹ O’ Connell ….Kay Am J Transplant 13: 1850, 2013
³ Lablanche et al. Diabetes Care in press, 2015
⁴ [www.citisletstudy.org](http://www.citisletstudy.org)
Long term metabolic control with CIT07 at Penn

Glycemic control

Insulin use

Updated from Rickels et al. Diabetes 64: 1713, 2015
Glycemic control in islet transplantation
β-cell secretory capacity in islet transplantation

Updated from Rickels et al. *Diabetes* 62: 2890, 2013
Islet cell responses to hypoglycemia in islet transplantation

**β-cell response**

- Normal Hypoglycemia
- Normal Euglycemia
- T1D Post-Transplant Hypoglycemia
- T1D Post-Transplant Euglycemia

**α-cell response**

- T1D Pre-Transplant Hypoglycemia
- T1D Post-Transplant Hypoglycemia
- Normal Hypoglycemia

Updated from Rickels et al. *Diabetes* 64: 1713, 2015
Islet replacement restores defense against hypoglycemia

- Islet Transplantation
  - ↓ Plasma Glucose → Islet Cell Responses
  - ↓ Insulin Secretion
  - ↑ Glucagon Secretion
  - ↑ Hepatic Glucose Production
  - ↑ Plasma Glucose
Summary

- Intrahepatic transplantation of purified islets isolated from a deceased donor pancreas offers an alternative to whole pancreas transplantation that can restore physiologic insulin delivery and islet function, thus stabilizing glycemic control with protection against hypoglycemia.

- The primary endpoint for evaluation of clinical islet transplantation is a HbA1c < 7.0% without severe hypoglycemia episodes.

- Current protocols may result in recovery of sufficient β-cell secretory capacity to afford durable graft survival that resists metabolic exhaustion.

- The benefits of islet transplantation on long-term improvement in glycemic control, especially amelioration of glycemic instability and problematic hypoglycemia, must be balanced against the risks for procedural complications and of the immunosuppressive drug therapy.
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