Clinical magnetic resonance imaging of islet grafts using nanoparticle labeling

Christian Toso, MD
University of Alberta, Edmonton, Canada
Islet Transplant Center

Islet Cell Resource Center Consortium
4th Annual Islet Workshop
Islet graft monitoring

Five Year Islet Function - University of Alberta

C-peptide positive 82%

Corrected HbA1C and absence of hypoglycemia

Insulin Independence 11%
Islet mass

100%

50%

Insulin requirement

Time after transplant (years)

Poor primary engraftment: damage during isolation and transplant, IBMIR, non-specific inflammatory activation

Progressive islet loss: allo-, auto-immunity activation

The ideal monitoring technique:

- Non invasive
- Non harmful to the graft
- Enable a repeated and accurate assessment
- Early detection of graft damages to allow treatment
Islet graft monitoring

Two types of monitoring:

- Monitoring of islet mass
- Monitoring of harmful events to the graft (rejection, autoimmunity)
Islet graft monitoring

Islet monitoring:

• Metabolic tests
  • IVGTT
  • Arginine test
  • Mixed meal...

• Blood tests
  • PCR for insulin or Granzyme B mRNA
  • Donor HLA DNA
  • Flow-cytometry

• Biopsy

• Imaging
  • PET (FDG, DTBZ labeling)
  • MRI (SPIO labeling)
### Table 1  Islet Graft Function Monitoring

<table>
<thead>
<tr>
<th>Overall function</th>
<th>Serum glucose</th>
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<tbody>
<tr>
<td></td>
<td>Serum insulin</td>
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<td>Serum C peptide</td>
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<tr>
<td></td>
<td>HbA1c, fructosamine</td>
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<td></td>
<td>Insulin requirement (U/Kg)</td>
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<tr>
<td></td>
<td>Number of hypoglycemias</td>
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<td></td>
<td>Secretory Unit of Islet Transplant Objects (SUITO)</td>
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<tr>
<td></td>
<td>Beta score</td>
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<tr>
<td>Glucose stability</td>
<td>Mean Amplitude of Glycemic Excursions (MAGE)</td>
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<td></td>
<td>Lability index</td>
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<tr>
<td></td>
<td>Continuous Glucose Monitoring Systems (CGMS)</td>
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<tr>
<td>Hypoglycemic events</td>
<td>HYPO score</td>
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<tr>
<td></td>
<td>Continuous Glucose Monitoring Systems (CGMS)</td>
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<tr>
<td>Stimulation tests</td>
<td>Arginine stimulation test</td>
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<tr>
<td></td>
<td>Glucagon test</td>
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<tr>
<td></td>
<td>Mixed meal stimulation test</td>
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<tr>
<td></td>
<td>Oral Glucose Tolerance Test (OGTT)</td>
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<tr>
<td></td>
<td>IV Glucose Tolerance Test (IVGTT)</td>
</tr>
</tbody>
</table>

Detection of circulating insulin mRNA in the blood after islet transplantation
Detection of Insulin mRNA in the Peripheral Blood after Human Islet Transplantation Predicts Deterioration of Metabolic Control

Berney et al, AJT, 2006
Sensitivity: 85%; Specificity: 73%

For negative metabolic events:
- Kidney rejection (simultaneous islet kidney transplant)
- Doubling of insulin requirements
- Start insulin
- Increase of HbA1c (over 0.7%)

Berney et al, AJT, 2006
Assessment of Cytotoxic Lymphocyte Gene Expression in the Peripheral Blood of Human Islet Allograft Recipients

Elevation Precedes Clinical Evidence of Rejection

Dongmei Han,¹ Xiumin Xu,¹ David Baidal,¹ Jenifer Leith,¹ Camillo Ricordi,¹,²,³ Rodolfo Alejandro,¹,² and Norma S. Kenyon¹,²,³

RT-PCR for
- Granzyme B
- Perforine
- Fas ligand

Han et al, Diabetes, 2004
Biopsy
Islet graft monitoring
Islet graft monitoring

Liver

Islets
Islets in 7/16 needle biopsies (44%)
Islet imaging:

- Positron-Emission Tomography (PET)
  - Ex vivo labelling: FDG
  - In situ labelling: DTBZ
- Magnetic Resonance Imaging (MRI)
$^{18}$F Fluoro-deoxyglucose (FDG) :
Islet graft monitoring

Fluoro-deoxy-glucose (FDG)

Toso et al, Transplantation, 2005
- short **half-life** of the tracer (FDG: 110min)
- rapid **release** of the tracer from the cells

Toso et al, Transplantation, 2005
[¹¹C]Dihydrotetrabenazine (DTBZ) :

[¹¹C]CH₃O

CH₃O

CH₂CH(CH₃)₂

OH

Souza et al, JCI, 2005
Islet graft monitoring

BB rats

Souza et al, JCI, 2006
DTBZ-PET scans in rats

% of injected dose/ g of tissue

- Control kidney (n: 5)
- 2000 islets (n: 3)

p = 0.86
Islet imaging:

• Positron-Emission Tomography (PET)
  • Ex vivo labelling: FDG
  • In situ labelling: DTBZ
• Magnetic Resonance Imaging (MRI)
Islet graft monitoring

Rat islet transplantation:

Syngeneic

Allogeneic

Jirak et al Magn Reson Med 2004
Berkova et al Transplant Proc 2005
Kriz et al Transplantation 2005
Evgenov et al Nat Med 2006
Feasibility and safety in human?
Islet graft monitoring

Transplantation of 10,000IEQ/Kg in rats

Pre-transplantation

Resovist loaded Islets

Endorem loaded Islets
Static incubations (from 7 human islet isolations):

- Insulin concentration

- Stimulation index

**p=NS**
Transplantation in NUDE mice:

Islet graft monitoring

- % of mice with high blood glucose (≥11 mmol/l)
  - HI Resovist
  - HI control
  - p=0.9

Time since transplantation (days)
Islet graft monitoring

Case reports:

- 7 labeled islet infusions in 4 patients with type I diabetes
- female/male: 1/3
- 47 to 56 year-old
- incubations with iron nanoparticles (Resovist) for 24 to 48 hours
- MRI pre- and at various time points post transplant

Toso et al, AJT, 2008
<table>
<thead>
<tr>
<th>Patient</th>
<th>Nb (IEQ)</th>
<th>Purity (%)</th>
<th>Viability (%)</th>
<th>Nb (IEQ)</th>
<th>Nb/Kg (IEQ/Kg)</th>
<th>Purity (%)</th>
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<tbody>
<tr>
<td></td>
<td>93</td>
<td>284</td>
<td>999</td>
<td>5439</td>
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<td>50,000</td>
<td>80</td>
<td>90</td>
<td>294</td>
<td>55,56</td>
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<td>100</td>
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<td>354</td>
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<td>80</td>
<td>330</td>
<td>111</td>
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<td>287</td>
<td>166</td>
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<td>468</td>
<td>58,60</td>
<td>66</td>
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<td>306</td>
<td>250</td>
<td>80</td>
<td>422</td>
<td>51,03</td>
<td>43</td>
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<td>Mean</td>
<td>172</td>
<td>205</td>
<td>83</td>
<td>371</td>
<td>62,59</td>
<td>54</td>
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<tr>
<td>SD ±</td>
<td>144,690</td>
<td>±3</td>
<td>±4</td>
<td>100,640</td>
<td>±14,42</td>
<td>±16</td>
</tr>
</tbody>
</table>

Islet graft monitoring

Toso et al, AJT, 2008

39 ±26 %
Islet graft monitoring

Patient 2

Toso et al, AJT, 2008
Iron overload (hemosiderosis) is a contraindication to MR imaging of islets grafts.

Toso et al, AJT, 2008
Islet graft monitoring

Pre-transplant

5 weeks after first infusion, 6 days after second infusion

Toso et al, AJT, 2008
Islet graft monitoring

Pre-transplant

6 weeks

Patient 1

Toso et al, AJT, 2008
Islet graft monitoring

Toso et al, AJT, 2008
Islet graft monitoring

Patient 1

Pre-transplant

6 weeks

8 months

Toso et al, AJT, 2008
This study demonstrates the feasibility and safety of MRI-based islet graft monitoring in clinical practice.

Iron overload (spontaneous or induced) represents the major obstacle to the technique.

Toso et al, AJT, 2008
Future developments:

• Quantifying the spots within the liver

• Increase the number of patients to assess whether rejection can be detected in a timely fashion
Islet monitoring of tomorrow

- Metabolic tests
  - Detection of immune markers in the peripheral blood:
    - Insulin/granzyme B mRNA
    - Donor DNA
    - Flow-cytometry
  - If suspect

- Islet graft imaging:
  - MRI
  - PET
  - If suspect

- Liver biopsy
  - If suspect

- Treatment
  - +
University of Geneva, Switzerland

University of Alberta, Edmonton, Canada

FS Chia Scholarship
Thank you!