Mouse Models for Studying Human Islet Transplantation

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Can a mouse model form an in vivo ‘potency’ assay?
Mouse Models for Assessing Human Islet Function

• Immune-suppressed wild-type mice (e.g. anti-CD4)

• T cell-deficient nude (nu/nu) mice

• Severe-combined immune-deficient (SCID)

• Recombinase activating gene 1,2-deficient (Rag\(^{-/-}\))
Insulin *akita* Mutation

- Missense mutation (Cys96Tyr) in Insulin 2 (Ins 2) gene
- Prevents appropriate folding of pro-insulin
- Autosomal-dominant (chromosome 7)
- Functions as a ‘dominant-negative’
- Durable and irreversible hyperglycemia (>450-500mg/dl)
- Males more severe than females
**Rag1⁻/⁻ akita Blood Glucose**

![Graph showing blood glucose levels for Rag1⁻/⁻ akita](image1)

**Rag1⁻/⁻ akita Weight Change**

![Graph showing weight change for Rag1⁻/⁻ akita](image2)

**SZ Blood Glucose**

![Graph showing blood glucose levels for SZ](image3)

**SZ Weight Change**

![Graph showing weight change for SZ](image4)
Utility of *akita* mice as islet transplant recipients

# Islet Function in C57Bl/6<sup>akita</sup> Mice

<table>
<thead>
<tr>
<th>Donor</th>
<th>n</th>
<th>Graft Function (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ISOGRAFTS</strong></td>
<td>8</td>
<td>&gt; 100 (x8)</td>
</tr>
<tr>
<td>(C57Bl/6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALLOGRAT»</strong></td>
<td>3</td>
<td>9, 9, 12</td>
</tr>
<tr>
<td>(BALB/c)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Islet Transplantation in B6 Rag1-/--akita Mice

Donor Islets

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

• Monitor blood glucose
• Nephrectomy – immunohistochemistry
Correlation between in vitro assays and in vivo function in *Rag1*^-/-*akita* mice

<table>
<thead>
<tr>
<th>Purity</th>
<th>Viability</th>
<th>S.I.</th>
<th>In vivo function (&gt;30 days)</th>
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</thead>
<tbody>
<tr>
<td>60</td>
<td>60</td>
<td>1.6</td>
<td>Yes</td>
</tr>
<tr>
<td>90</td>
<td>80</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>80</td>
<td>75</td>
<td>5.2</td>
<td>Yes</td>
</tr>
<tr>
<td>85</td>
<td>72</td>
<td>2.4</td>
<td>Yes</td>
</tr>
<tr>
<td>90</td>
<td>70</td>
<td>2.4</td>
<td>Yes</td>
</tr>
<tr>
<td>40</td>
<td>60</td>
<td>0.8</td>
<td>No</td>
</tr>
<tr>
<td>60</td>
<td>77</td>
<td>0.2</td>
<td>No</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
<td>0.6</td>
<td>No</td>
</tr>
<tr>
<td>60</td>
<td>60</td>
<td>2.1</td>
<td>No</td>
</tr>
<tr>
<td>75</td>
<td>75</td>
<td>4.0</td>
<td>No</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>1.1</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Isolated Islets Highly Express Proteins Associated with ER-Distress

# Function of Islet Grafts in Rag1-/- Recipients

<table>
<thead>
<tr>
<th>Donor</th>
<th>n</th>
<th>Graft Function (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>8</td>
<td>&gt;100 (x 8)</td>
</tr>
<tr>
<td>Rat (WF)</td>
<td>9</td>
<td>&gt;100 (x 9)</td>
</tr>
<tr>
<td>Porcine</td>
<td>12</td>
<td>&gt;100 (x 12)</td>
</tr>
<tr>
<td>Human</td>
<td>17</td>
<td>47, 65, 74, 91, 94 &gt;100 (x12)</td>
</tr>
</tbody>
</table>
Spontaneous Failure of Human Islets

*Rag1*^-/-*akita* Mice

Blood Glucose (mM)

- Human Islet Tp#1
- Human Islet Tp#2
- Normoglycemia

Day Post Transplantation
Pathology of Failed Human Islets (day 70)

Fibrosis (Tri-Chrome)

Amyloid (Thyoflavin S)
Failure of hIAPP Transgenic Mouse Islets

![Graph showing plasma glucose levels over time for 100 tg+ and 100 tg- groups.](image)

**Plasma Glucose (mg/dl)**

- **Day**

- **100 tg+**
- **100 tg-**

**Legend:**
- STZ
- Tx

- **Failure of hIAPP Transgenic Mouse Islets**
Islet Cell Attrition in Transplantation

1. Mechanical stress from islet isolation, infusion and implantation in ectopic site.
2. Non-immune response (Specific Aim 1)
3. Innate immune response (Specific Aim 2)
4. Adaptive immune response
   a. Autoimmune response
   b. Alloimmune response
5. Islet-toxic immunosuppression
6. Failure of islet revascularization

Figure 1. Factors influencing loss of islet cells following transplantation.
Summary / Conclusions

• Spontaneously diabetic akita mice demonstrate a stable and irreversible model of hyperglycemia

• Diabetic akita mice can be readily maintained for 2-3 months prior to transplantation

• Human islets can reverse diabetes in immune-deficient akita mice (Rag1^-/-akita)

• Human islets can spontaneously fail over time from non-immune factors (metabolic distress?)
Collaborators

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