We Will Cure Diabetes
(but we underestimated the opponent)!

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Disclosures / Conflicts of Interest

- No financial conflicts / disclosures
First: What is Type 1 Diabetes?

**Immunological disease**

↓

**Metabolic disease**
What is a ‘cure’ for diabetes?

**Beta cell replacement / Artificial Pancreas**

- Reversal at disease onset
- Primary disease prevention
The Barrier of Autoimmunity
Normal Healthy Islet
Islet Undergoing Autoimmune Attack (NOD mouse model)
“Patchy” distribution of insulitis (CD45 staining) in a recent onset type 1 diabetic patient

Courtesy of Prof. Noel G. Morgan (Peninsula Medical School, UK)
Islet Transplantation as a Biological ‘Prosthesis’
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%)
Beta Cell Replacement: Towards a ‘Cure’

Durable Transplant without
immunosuppression (cure)

Transplant with more benign
immunosuppression

Transplant with chronic
immunosuppression
The ‘smoking gun’ of autoimmunity: Disease Recurrence in Transplantation


Sutherland, DE et al.
Disease Recurrence in NOD Mice

(NOD_{scid} \rightarrow \text{NOD})

Days Post Transplant

% Grafts Functioning

- Spontaneously Diabetic NOD (n = 8)
- SZ-Young NOD (n = 5)
NOD Disease Recurrence – β cell selective destruction
Transplantation of Donor Islets

Donor Pancreas

Islet in Pancreas

Islet Isolation

Syringe

Isolated Islet of Langerhans

Recipient

Portal Vein

Pancreas

Islet in Portal Vein
<10% of Islet Recipients Ever Achieved Insulin Independence
“The Edmonton Protocol”:

- Tacrolimus 3-6 ng/ml
- Rapamycin 12-15 ng/ml
- Daclizumab 1 mg/kg x 5

Day 0 14 28 42 56 90

Transplant #1  Transplant #2

**Pre-transplant**

**Post-transplant**

![Graph showing blood glucose levels over time](image-url)
Patient 1: pretransplant

Sensor Modal Day

MiniMed Solutions: CGMS Sensor
MMT-7310 3.0B

Legend

<table>
<thead>
<tr>
<th>Monday</th>
<th>Tuesday</th>
<th>Thursday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb</td>
<td></td>
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</tbody>
</table>
Patient 1: 9 months following transplant

Alleviation of Hypoglycemia
Sensor Modal Day

Patient 3: pretransplant

MiniMed Solutions: CGMS Sensor
MMT-7310 3.0A

Legend

Sunday  Tuesday  Thursday  Saturday
Monday   Wednesday  Friday

Gottlieb
Report Printed: 23-Jan-06  10:23 AM
Patient 3: 1 month following transplant

Sensor Modal Day

Glucose - mg/dL

Time Of Day

Legend

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

Report Printed: 23-Jan-06 10:24 AM
Patient 4: 4 months following transplant
Islet Recipient HbA1c

Days Post Infusion

Transplant #1
743,241 IEQ

Transplant #2
572,689 IEQ

%
Longer-Term Follow-up:
Gradual Attrition of Islet Function
At 5 years, C-peptide secretion preserved but <10% maintain insulin independence.

Diabetes 2005; 54:2060
Current multi-center demonstration trial for:

- Islet Transplant alone
- Islet-After Kidney

http://www.CITIsletStudy.org
http://www.isletstudy.org
New Therapies

T lymphocyte depletion strategies: University of Minnesota (Bernhard Hering)
Achievement and Retention of Insulin Independence

**Achievement**

- **UMN-TCD**
- **CITR-TCD**
- **CITR-NTCD**

**Retention**

- **UMN-TCD**
- **CITR-TCD**
- **CITR-NTCD**

*p=0.02*

*p<0.01*
With TCD induction, 5-yr insulin independence rates in ITA are comparable with those seen in PTA.

Of the 43% of UMN-TCD ITA on insulin at 5-yr follow up, 29% show partial islet allograft function (17% of CITR-TCD).

<table>
<thead>
<tr>
<th>Years post Last Infusion</th>
<th>PTA-UNOS/SRTR (N=132, 2001)</th>
<th>ITA-UMN T-Cell Depleting (N=20)</th>
<th>ITA-CITR T-Cell Depleting (N=100)</th>
<th>ITA-CITR-Other Induction (N=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>59</td>
<td>34</td>
<td>29</td>
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<td>3</td>
<td>52</td>
<td>57</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>0.02</td>
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CITR 04/2010
The Elephant in the Living Room:

We don’t yet *have* a robust means of inducing immune ‘tolerance’ in man
‘Reality Check’

- We still chronically immune suppress in clinical transplantation

- Long-term solid organ allograft survival has only modestly improved over many years
**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>
</tr>
</thead>
<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>
</tr>
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Disease reversal at onset:
The testing ground for ‘tolerogenic’ agents
Targeting the Immune Response

**CD20**

- B cells are not required for type 1 diabetes
- Autoantibodies mark type 1 diabetes but are not pathogenic
- β-cells are actively involved in their own demise

**CD3**

- Effector T cells are resistant to suppression by T_{Reg} cells in type 1 diabetes
- T_{Reg} cells are less suppressive in type 1 diabetes
- Impaired maturation of APCs in type 1 diabetes
- CTLs kill β-cells
- MHC class I
- MHC class II
- TCR
- Islet antigen
- Islet β-cell
- Apoptotic β-cell
Major Therapeutic Targets

CD3 (T cells)

Herold, KC et al
346:1692, 2002

CD20 (B cells)

Pescovitz, MD et al
361:2143, 2009
Possible Reasons for Islet Graft Failure

- Insufficient islet mass
- Poor quality of islets
- Engraftment loss
- Metabolic stress
- Toxicity of anti-rejection drugs
- Allograft rejection
- Autoimmunity
- Alternative Tissue Sources
No lack of current and proposed targets for modifying allograft rejection / autoimmunity
New Generation Therapeutics

Key Direction

Combinational Therapies
Targets of Antibody Therapy for Promoting Islet Allograft and Xenograft Acceptance / Tolerance

- CD8 - Co-receptor
- CD4 - Co-receptor
- LFA-1 (CD11a) - Adhesion
- CD40L (CD154) - Co-stimulation
- CD45RB - T cell activation
- B7.1/B7.1 (CD80/86) - Co-stimulation
- CD3 - Signal 1/ Activation
Targets of Antibody Therapy for Promoting Islet Allograft and Xenograft Acceptance / Tolerance

- CD2 - T cell activation
- CD3 - Signal 1/ Activation
- CD8 - Co-receptor
- CD4 - Co-receptor
- LFA-1 (CD11a) - Adhesion
- CD40L (CD154) - Co-stimulation
- CD45RB - T cell activation
- B7.1/B7.1 (CD80/86) - Co-stimulation
Efficacy of Combined Anti-CD154 + Anti-LFA-1 Combination Therapy

- Anti-CD154 (MR1) n=20
- Anti-LFA-1 (KBA) n = 13
- Anti-CD154 + Anti-LFA-1 n = 16
Spontaneous Failure of Human Islets in *Rag1^-/-akita* Mice

Blood Glucose (mM)

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

Day Post Transplantation

Fibrosis (Tri-Chrome)

Amyloid (Thyoflavin S)
Goal:

Continue to identify key *barriers* to successful transplant outcome and develop/test therapeutic agents

- Basic Studies
- Clinical Issues
Can Bone Marrow from *Non*-Disease Prone Donors *Dominantly* Protect From Disease?

- **NOD marrow**
- **B6.H-2g7-*gfp***
- **[NOD + B6.H-2g7-*gfp]**

γ-irradiate recipient to eliminate host hematopoietic cells (2 x 450R)

Monitor BM Engraftment and Disease
Disease Incidence

% diabetic

Weeks Post Bone Marrow Transplant

- NOD (n=31/33)
- mixture (n=3/27)
- B6.g7(gfp) (n=0/26)
What is a ‘cure’ for diabetes?

Beta cell replacement / Artificial Pancreas

Reversal at disease onset

Primary disease prevention
Collaborators

Basic Studies:
Joshua Beilke
Mark Nicolls
Marilyne Coulombe
Andrew Diamond
Jon Buhrman
Tinalyn Kupfer
Megan Crawford
Cisco Ramirez

Clinical Studies:
Alex Wiseman
Peter Gottlieb
Brian Freed