Ending Diabetes with Islet Transplantation

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UCSF Diabetes Center
Islet transplantation cures diabetes
Challenges in islet transplantation

- Works best in patient with low BMI
- 50% patients require 2\textsuperscript{nd} infusion
- insulin independence ~50%

• Rejection?
• Recurrent autoimmunity?
• Toxicity of immunosuppressive drugs?
• Islet graft failure?
Impact of immunosuppression on islet function

One-Year Insulin Independence by ERA
C-Peptide Negative Type-1 Diabetic Recipients; 1990-1999; n=237*

- Red: 1990-93 (n=82)
- Blue: 1994-97 (n=118)
- Green: 1998-99 (n=37)

* Only well documented cases

Steroid avoidance
## Choice of immunosuppression

<table>
<thead>
<tr>
<th>B. Maintenance</th>
<th>Annual Follow-Up post Tx1</th>
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<tbody>
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<td><strong>CalcInh/MPDHInh</strong></td>
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<tr>
<td><strong>CalcInh/MPDHInh/mTORInh</strong></td>
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<tr>
<td><strong>CalcInh/mTORInh</strong></td>
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<td><strong>IMPDHInh</strong></td>
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</table>
Calcineurin inhibitors impair islet physiology

LETTERS

Calcineurin/NFAT signalling regulates pancreatic β-cell growth and function

Jeremy J. Heit¹, Åsa A. Apelqvist¹ †, Xueying Gu¹, Monte M. Winslow², Joel R. Neilson³, Gerald R. Crabtree¹,⁴ & Seung K. Kim¹,⁵
Targeting the immune system

CTLA4Ig = Belatacept

Efalizumab
Immunosuppressive regimen for Bela and EFA studies

Efalizumab or Belatacept

-2d 0 90d 1yr 3yr 5yr

Solumetrol

ATG

Sirolimus
Target 8-12ng/L trough, substitute MMF if not tolerated

Efalizumab
n=5
or
Belatacept
n=5

1mg/kg/wk 0.5 mg/kg/wk
10mg/kg/mo 5 mg/kg/mo 5 mg/kg/2 mos

Withdrawn in May 2009
duration 1.3-2.5 yrs

Slide from Drs. Peter Stock and Andrew Posselt
Insulin needs of Bela and EFA studies

- BELA-1
- BELA-2
- BELA-3
- BELA-4
- BELA-5
- EFA-1
- EFA-2
- EFA-3
- EFA-4
- EFA-5

Time from initial transplant (days)

- Insulin Independent
- Partial Use
- Full Use

Pancreas Txp
Dramatic rise of Tregs in all EFA patients

Belatacept

Efalizumab

Slide from Drs. Peter Stock and Andy Posselt
Global immunosuppression by EFA

<table>
<thead>
<tr>
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<th>Anti-donor</th>
<th>Anti-CD3+anti-CD28</th>
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<td>CD8</td>
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<tr>
<td></td>
<td>CD4</td>
<td>CD8</td>
</tr>
</tbody>
</table>

- Anti-donor
  - CD4
  - CD8

- Anti-CD3+anti-CD28
  - CD4
  - CD8

Graphical representation showing the percentage of CD4 and CD8 cells before (Pre-Tx) and after treatment with EFA for 1 year and more than 5 months off EFA.
Insulin independence without immunosuppression

- Single islet transplant, insulin independent for 8+ years
- on EFA for 15 months, maintained on Sirolimus after EFA cessation
- Tregs increased to 70% one month after transplant
- No detectable T cell response while on EFA
- Patient stopped taking all drugs on Sep 2012 due to PTLD
- Remains insulin independent today

Cure and Tolerance!
More challenges in islet transplantation

1.2 million type 1 diabetics in the US
25 million type 2 diabetes
<10,000 donors/year

~200,000 islets should be enough
~500,000 islets is often not enough

donor shortage

graft dysfunction

immunosuppression

A sure path to eliminate immunosuppression?
Unlimited source of beta cells from stem cells

Slide from Drs. Holger Russ and Matthias Hebrok
Overcoming challenges in islet transplantation

~200,000 islets should be enough
~500,000 islets is often not enough

A sure path to eliminate immunosuppression?
Islet death after transplant

d0

d7
Hypoxia and nutrient deprivation kill islets

Reducing pO2

Reducing nutrients

Islet death (%) vs. hours

Islet viability (%) vs. hours

159mmHg  15mmHg
Hypoxia and nutrient deprivation kill islets
Hypoxia and nutrient deprivation kill islets
Preconditioning prevents islet death in hypoxia

Atmospheric oxygen tension

Physiological oxygen tension

Differentiation

Transplant

Oxygen tension (%)

days

%P1+ cells

CTRL 1% O₂ High density High density +1% O₂

21% O₂ 5% O₂

ns * ** ***

0 20 40 60 80 100

0 5 10 15 20 25 30
Screening for nutrients to sustain islets

% islet cell death

- Nutrient replete
- Nutrient deprived

Bar chart showing the percentage of islet cell death for different supplements and nutrient states.
Nanorod delivery of nutrients

In collaboration with Desai Lab
Overcoming challenges in islet transplantation

A sure path to eliminate immunosuppression?
Immune protection by encapsulation - a diffusion device

Polycaprolactone (PCL)
Polymer

In collaboration with Desai Lab
Immune protection by encapsulation - a convective device

In collaboration with Roy Lab
Islet transplantation tolerance using Tregs

Lee et al Am J Transpl 2014
How to end diabetes with islet transplantation

preconditioning

Supplement

Belatacept
Efalizumab

in vitro

by

nutrients
oxygen

immune

cells

thin-film device

Device

Artery

Graft connection

Convective flow refreshes nutrients

Autologous polyclonal Tregs

beta-cells
UCSF basic and translational research team

Stem cell biology
- Matthias Hebrok
- Holger Russ

Transplant surgery
- Gaetano Faleo
- Vinh Nguyen
- Steve Wisel

Bioengineering
- Tejal Desai
- Ryan Chang
- Shuvo Roy

Immunology
- Shang Song
- Jeff Bluestone
- Karim Lee
The UCSF Clinical Islet transplant team

- Andrew Posselt, Peter Stock
- Greg Szot, Florinna Dekovic, Vinh Nguyen, Vi Dang,
- Umesh Masharani, Lynda Frassetto, Kristina Johnson, Bob Kerlin, Joan McElroy, Debbie Ramos, Tara Rojas, Mehdi Tavakol,