Beta-Cell Regeneration or Replacement – Hype or Hope?

Jay S. Skyler, MD, MACP

Division of Endocrinology, Diabetes, and Metabolism and Diabetes Research Institute
University of Miami Miller School of Medicine
Ideal Therapeutic Goals in T1D

- Stop Immune Destruction
- Preservation of β-Cell Mass
- β-Cell Replacement or Regeneration
Cellular Replacement Therapy
Beta-Cell Replacement
Pancreas Graft Survival from Deceased Donors
Jan 1, 2000 to Dec 31, 2005

White et al. Lancet 2009; 373:1808-17
Persistence of Insulin Independence & of Graft Function
Islet Alone Recipients Achieving Insulin Independence

Survival Distribution Function

Persistence of Insulin Independence

Persistence of Graft Function (C-peptide Positive)

Months Post First Achieving Insulin Independence

Alejandro et al. Transplantation 2008; 86:1783-8
Islet Transplantation is Improving

Severe Hypoglycemia Post Last Infusion
Islet Alone Recipients with Detectable Fasting C-Peptide

Percent of Recipients

- Pre Inf 1 (N = 57)
- Day 30 (N = 215)
- Month 6 (N = 188)
- Year 1 (N = 162)
- Year 2 (N = 89)
- Year 3 (N = 58)

Severe hypoglycemic episode

Alejandro et al. *Transplantation* 2008; 86:1783-8
Sources of Cells
Possible *in vivo* origins of new $\beta$-cells after birth

- **Replication**
- **Pancreatic stem cell**
- **Neogenesis (budding from ducts)**
- **Transdifferentiation from acinar or alpha cell**
Xenotransplantation
Pig Islets
Pig Islets Reverse Hyperglycemia in Non-human Primates

Days Posttransplant

Blood Glucose [mg/dL]

Exogenous Insulin [U/kg/day]

Days Posttransplant

Blood Glucose

Exogenous Insulin
Reprogramming of Cells
A combination of three transcription factors induces insulin+ cells in adult mouse pancreas in vivo.
β-cell Neogenesis, Proliferation and Apoptosis Can Be Impacted by Various Agents

- Ductal progenitor cells
- Neogenesis
- Proliferation
- Islet
- Apoptosis

Agents:
- Exenatide
- GLP-1
- INGAP Peptide
- HIP2b
- Gastrin
Betatrophin: A Hormone that Controls Pancreatic β Cell Proliferation

Peng Yi,¹ Ji-Sun Park,¹ and Douglas A. Melton¹,*
¹Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Howard Hughes Medical Institute, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138, USA
*Correspondence: dmelton@harvard.edu
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SUMMARY

Replenishing insulin-producing pancreatic β cell mass will benefit both type I and type II diabetics. In adults, pancreatic β cells are generated primarily by self-duplication. We report on a mouse model of insulin resistance that induces dramatic pancreatic β cell proliferation and β cell mass expansion. Using this model, we identify a hormone, betatrophin, that is primarily expressed in liver and fat. Expression of betatrophin correlates with β cell proliferation in other mouse models of insulin resistance and during gestation. Transient expression of betatrophin in diabetics will benefit from treatments that replenish their β cell mass.

Though there is evidence that mouse β cells can be derived from rare adult progenitors under extreme circumstances (Xu et al., 2008), the vast majority of new β cells are generated by simple self-duplication (Dor et al., 2004; Meier et al., 2008; Teta et al., 2007). After a rapid expansion in embryonic and neonatal stages, β cells replicate at an extremely low rate (<0.5% divide per day) in adult rodents (Teta et al., 2005) and in humans (Meier et al., 2008). However, pancreatic β cells retain the capacity to elevate their replication rate in response to physiological challenges, including gestation (Parsons et al., 1992; Rieck et al., 2009), high blood sugar (Alonso et al., 2007), pancreatic injury (Caro et al., 2009; Nis et al., 2007), and enriching in...
Liver

Fat

WAT

BAT

Betatrophin

β cell replication

Pancreatic islet (α, β, δ, PP cells)
Nutrients, Growth Factors, Molecules, Factors, Drugs Suggested to Induce Robust Beta Cell Replication in Rodent or Other Eukaryotic Models

<table>
<thead>
<tr>
<th>Glucose</th>
<th>GPR119 agonists</th>
<th>Gastrin</th>
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<tr>
<td>Free Fatty Acids</td>
<td>CNTF</td>
<td>EGF</td>
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<tr>
<td>Insulin</td>
<td>GCDF</td>
<td>Betacellulin</td>
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<tr>
<td>IGF1</td>
<td>NGF</td>
<td>Reg proteins</td>
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<td>IGF2</td>
<td>GDNF</td>
<td>Ingap</td>
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<td>GH</td>
<td>Ret oncogene</td>
<td>CCK</td>
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<td>GLP-1 (7-36)</td>
<td>Non-gla-Osteocalcins</td>
<td>PDGF</td>
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<tr>
<td>Exendin-4</td>
<td>Myostatin</td>
<td>Adiponectin</td>
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<td>Activin</td>
<td>GABA</td>
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<td>TFF3</td>
<td>Inhibin</td>
<td>Adenosine Kinase inhibitors</td>
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<td>BTC</td>
<td>Ghrelin</td>
<td>Purinergic Receptor Agonists</td>
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<td>PRL</td>
<td>GDNF</td>
<td>Betatrophin</td>
</tr>
<tr>
<td>PL</td>
<td>TMEM27 and BACE2</td>
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<tr>
<td>PTHrP</td>
<td>FoxM1</td>
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<tr>
<td>HGF</td>
<td>HNF4a</td>
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<td>Serotonin</td>
<td>Epigenetic modifiers:</td>
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<tr>
<td>Glucokinase Activators</td>
<td></td>
<td>HDAC-I’s, DNMTs, Ezh2, Bmi1, etc</td>
</tr>
<tr>
<td>Erythropoetin</td>
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</table>
Nutrients, Growth Factors, Molecules, Factors, Drugs Suggested to Induce Robust *Human* Beta Cell Replication
Transdifferentiation of Cells
Transdifferentiation Converts Hepatocytes to Insulin Producing Cells

Subject with Diabetes

Liver cells from biopsy

AdCMV-PDX-1

“self” surrogate liver-β cells
Human Embryonic Stem Cells
The Sequence of Development for Deriving Islets from Stem Cells Is Known

1-2 days 1-2 days 2-4 days 2-4 days 2-3 days 3+ days

ES cells Mesendoderm Definitive endoderm Primitive gut Posterior foregut endoderm Pancreatic endoderm Endocrine precursor Beta cell

D’ Amour et al.  Nature Biotechnology 2006; 24:1392-1401
Transplantation of HESC-derived Pancreatic Cells Makes Functional Islets In Vivo

HESC-derived Graft Implanted 377 days vs. Human Donor Islet Graft Implanted 360 days

- HESC-derived grafts show hallmarks of bonafide human islets
- Express processing enzymes and functional beta cell transcription factors
- Glucose stimulated release of human C-peptide into sera ~ 2 months development of the graft in vivo

O Kelly, ADA, San Diego, June 25, 2011
Encapsulated Pro-islet Grafts Mature in vivo to Functioning Islets

16 weeks post-subcutaneous implant in SCID/Bg mice

<table>
<thead>
<tr>
<th>C-Peptide (pM)</th>
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<tbody>
<tr>
<td>Fasting</td>
<td>792</td>
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<tr>
<td>30 min</td>
<td>4904</td>
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<tr>
<td>60 min</td>
<td>2337</td>
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Continuous Glucose Monitoring Using DexCom Seven CGM in Rats with Viacyte Device

Optimizing Delivery of Cells
The BioHub Concept
Engineering a Multi-functional Device for Insulin Producing Cell Products

Modulating the Local Environment

Co-delivery of “Helper” Cells
Bioactive Surfaces
Localized Drug Delivery
Encapsulation

Multi-functional Platform

Vascular Infiltration
Mechanical Protection

In situ Oxygen Generation
Macroporous Silicone Scaffolds
Fabricating 3-D Scaffolds
Macroporous Silicone Scaffolds
Diabetic large animal model

Omental Pouch

Exogenous Insulin (units/kg/day)

Blood glucose (mg/dL)

25,000 IEQ/kg
Optimization of scaffold fabrication and use of compression molder results in enhanced quality control of finale product and more uniform scaffolds.
Engineering a Multi-functional Device for Insulin Producing Cell Products

Modulating the Local Environment

Co-delivery of “Helper” Cells

Bioactive Surfaces

Localized Drug Delivery

Encapsulation

Vascular Infiltration

Mechanical Protection

In situ Oxygen Generation

Multi-functional Platform
Nano-Scale Encapsulation
Layer-by-Layer Assembly

Thin layer coated directly onto the surface of the islet

- Conducive to intraportal transplantation into liver
- Masking of surface without transport issues
Engineering a Multi-functional Device for Insulin Producing Cell Products

Modulating the Local Environment

Co-delivery of “Helper” Cells

Bioactive Surfaces

Localized Drug Delivery

Encapsulation

Vascular Infiltration

Mechanical Protection

In situ Oxygen Generation

Multi-functional Platform
Bioactive Scaffolds
Incorporating MSC cells + Islets

MSCs (stained with CD90, red) co-cultured with islets (DAPI)
The Facilitating Cell

- CD8⁺
- αβ/γδ TCR⁻
- Distinct from Stem Cell
- 65% resemble tolerogenic plasmacytoid dendritic cells (B220⁺/CD11c⁺/CD116⁻)
- Induce antigen-specific T_{reg}
- Prevent GVHD
- Promote HSC engraftment
Biopsy at 2 years

One year off all immunosuppression
“The pancreas in diabetes is not simply the scarred field of an old battleground, but is the actual field of conflict. It does not submit without a struggle to injury, but endeavors to regenerate”.

Shields Warren, MD
The Pathology of Diabetes Mellitus, 1938
“We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten.”

- Bill Gates, 1997
Report breakthrough in diabetes treatment

New Hope Cures for Diabetes Appear on the Way: Researchers Report

Prospects Include Implant Of an Artificial Pancreas And Transplants of Cells

A BREAKTHROUGH IN DIABETES RESEARCH

The SPEAKER pro tempore, Under a previous order of the House, the gentleman from Texas (Mr. Patman) is recognized for 5 minutes.

Mr. PATMAN. Mr. Speaker, diabetes is a major health problem affecting nearly 5 million Americans of all ages. It has doubled in the past 10 years and is now the seventh leading cause of death from disease and the third most common cause of blindness in the United States. It counts directly for 35,000 annually and is a contribut

Hold out promise of cure for 'juvenile' cases

Transplants offer hope for diabetics

'Artificial Pancreas' Makes Debut

New Machine To Aid Diabetics