Islet Cell Allo-Transplantation

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Special thanks to Melena Bellin, MD at The University of Minnesota who provided content for this presentation.

Disclosure

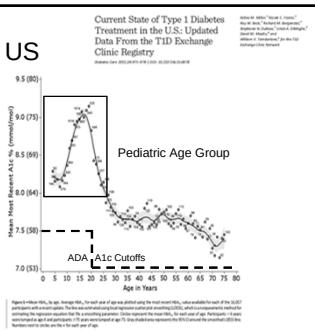
- No direct conflicts of interest regarding islet transplantation.
- Dr. Forlenza is a consultant for Abbott Diabetes Care and conducts research sponsored by Medtronic, Animas, Dexcom, Tandem, Bigfoot, Insulet, and Novo Nordisk.

Objectives

- Define Islet Allo-Transplantation
- Describe specific indications for Islet Allo-Transplantation and recent evidence on outcomes.
- Discuss the limitations to islet Allo-Transplantation and the future directions of research
- Audience Discussion: questions asked by patients and families, how we address them and how we may wish to address them differently

Current T1D Control in the US

- Despite >20 years of knowledge of the importance of tight control, patients are still poorly controlled.
  - Evidence from the Type 1 Diabetes Exchange Registry from 2015.
  - Average A1c by age group is too high at all ages and much too high in adolescents.



Islet Transplantation: Definition

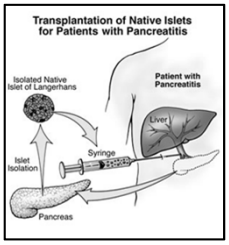
- Transplantation of the pancreatic islets **to *treat* or *prevent* diabetes mellitus**
- Performed for:
  - Labile type 1 diabetes mellitus **(“*treat*”)**
  - Prevention of surgical diabetes when pancreas is removed to treat pancreatitis **(“*prevent*”)**

Islet Transplants for Pancreatic Disease

- ***Auto*logous islet transplantation (TP-IAT)**:
  - patient’s own islets, **for treatment of pancreatitis**
  - no risk of rejection
  - no immunosuppression
  - An excellent **research model** for both forms of islet tx!
- ***Allo*genic islet transplantation**:
  - cadaveric donor islets, **for treatment of Type 1 DM**
  - risk of rejection and autoimmunity (from T1D)
  - requires immunosuppression
  - Performed under a FDA IND (for the islet product) in U.S.
- ***Xeno*genic islet transplantation:**
  - Use of non-human (e.g. porcine) islets as a source
  - Essentially pre-clinical only and has more issues than allogenic transplant

Background: TPIAT with Auto Transplantation

- Total Pancreatectomy (TP) is successful for improving pain and quality of life.
- Islet auto-transplantation (IAT) may prevent or minimize diabetes.

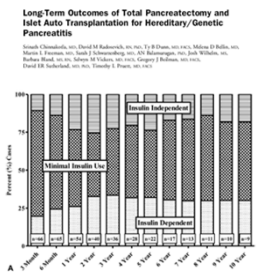


Background: Islet Engraftment from Auto Transplantation

- After transplant, islets are at high risk for loss.
  - Hyperglycemia causes islet overstimulation in a post-transplant anoxic environment.
- Animal models have demonstrated that hyperglycemia increases beta-cell apoptosis.[14-19]
  - Maintenance of narrow-range euglycemia reduces the islets necessary to prevent post-surgical diabetes.
  - Retrospective cohort analysis from UMN supports these findings in humans.

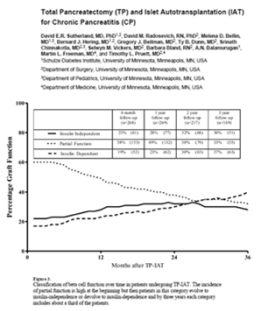
Auto Transplantation Success

- These results from UMN show that long-term insulin independence can occur in ~25% of patients.
- Insulin dependence can occur in ~ 25% of patients.
- Over 50% of patients have "minimal insulin use"



Auto Transplantation Success

- Larger cohort from UMN of adults and children.
- Shows that over time the rate of insulin independence rises up to 2 years post transplant.
- Also shows that the rate of partial function falls with time.
  - As does insulin independence after 2 years.



Total Pancreatectomy (TP) and Islet Autotransplantation (IAT) for Chronic Pancreatitis (CP)

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Figure 2
Classification of beta cell function over time in patients undergoing TP-IAT. The incidence of partial function is high at the beginning but then patients in this category evolve to insulin-independence or devolve to insulin-dependence and by three years each category includes about a third of the patients.

Improved Success with use of AP?

- Better BG control after transplant with use of AP.
- In the CL group AP use allowed for significant islet cell rest and thus a lack of variation based on islet cell yield.
- In the control group, islets were not rested and thus avg BG varied with islet yield.

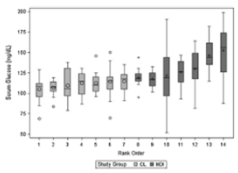

Figure 2: Serum glucose values by patient and study group. Large circle denotes mean, box denotes 25th percentile, median and 75th percentile and small circles denote outliers. CL, closed loop; MDI, multiple daily injections.

American Journal of Transplantation 2015; 00: 1–6
Wiley Periodicals Inc.

doi: 10.1111/ajt.13609

Successful Application of Closed-Loop Artificial Pancreas Therapy After Islet Autotransplantation

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Received 17 August 2015, revised 13 September 2015 and accepted for publication 18 September 2015

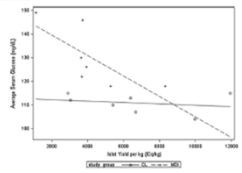


Figure 3: Multiple least-squares linear regression analysis for effect modification. CL, closed loop; MDI, multiple daily injections.

Differences between Auto and Allo Transplant

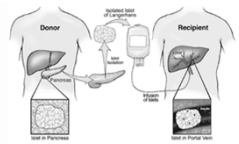
- Makes Success Less Likely (auto vs. allo)
  - Auto islets are likely to be damaged from the underlying disease state (chronic pancreatitis).
  - Auto islets are less purified making portal infusion more challenging.
  - Allo islets may come from multiple donor sources to increase their number.
- Makes Success More Likely (auto vs. allo)
  - Auto islets undergo less cold ischemia time.
  - Auto islets are less purified and thus may have more islet stem cell mass.
  - Auto islets don't require immune suppression and patients don't have underlying auto immunity.

Indications for Islet Allo-Transplantation

- Islet Allo-Transplantation is still under FDA phase 3 clinical trials.
- FDA Recommended Inclusion Criteria:
  - Established T1D for at least 5 years
  - Severe metabolic instability with multiple episodes of severe hypoglycemia, often with hypoglycemia unawareness.
  - Instability has persisted for at least 6 months with intensive management from a qualified diabetes team.
  - Adults (18+ years old).
- FDA Recommended Exclusion Criteria:
  - Subjects with extremes of BMI
  - Subjects with high baseline insulin requirements (>1 U/kg/day)
  - Subjects with complications of chronic hyperglylcemia.
  - HbA1c >12%
  - Conditions which place them at risk from immune suppression.

What does an islet allo transplant involve?

- Detailed pre-transplant evaluation
- Eligible participants listed with UNOS (waitlist time ~1y)
- Hospitalized x 5 days
- Minor surgery: percutaneous or minilaparotomy
- Immunosuppression & infection prophylaxis
  - ATG, tacrolimus, and sirolimus/ MMF
- Insulin weaned off *gradually* after transplant
- Cost is ~$75,000 just for the islets!



Edmonton Protocol

- Published in 2000 (NEJM), it shifted the focus to glucocorticoid-free immunosuppression.
  - Instituted immunosuppression immediately before transplantation with sirolimus (T-cell inhibitor), low-dose tacrolimus (inhibits T-cell activation), daclizumab (IL-2 inhibitor) and avoidance of glucocorticoids.
- Showed that 100% (7 of 7) of allo-islet transplant patients achieved insulin independence.
- Used multiple (2-4) donors to increase islet mass to >5,000 IEQ/kg.

Edmonton Protocol Follow Up Data

- At 2 years post transplant the overall rate of insulin independence is ~30%.
  - Though more recent data puts the rate at almost 50%.
- Rates of insulin independence continue to decline out to 8 years post-transplant.
  - Most (>70%) of patients are still C-Peptide positive with hypoglycemia protection.

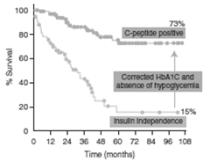


Figure 3. Nine-year insulin independence and C-peptide islet graft function rates with the original Edmonton Protocol immunosuppression. (Data from the University of Alberta.)

Cold Spring Harb Perspect Med 2012;2:a007823

Wider Scale Transplantation

- Clinical trials at multiple sites using the Edmonton protocol has been tested via the Immune Tolerance Network.
- Found that there was significant variation in success between sites.
  - Likely due to site-specific experience with islet preparation and possibly dosing of sirolimus.

Wider Scale Transplantation

- Studies have reported improved success with larger islet masses (>11,000 IEQ/kg) over multiple infusions.
  - This limits the total number of potential recipients.
- Exposure to islets from multiple recipients results in sensitization to more HLA antigens.
  - Argument for single donor over multiple pooled donors.

Success is Improving

- Better successes in each era studied.
- Collaborative Islet Transplant Registry (CITR) data from 1999-2010

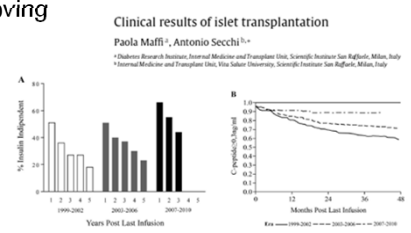


Fig. 1. A. Rates of insulin independence after allogeneic islet infusion (islet transplant alone and IAK), annually after last infusion by era (P = 0.02). B. Durability of graft function (basal C-peptide >0.3 ng/mL) after the last infusion, by era (P < 0.001). The immediate drop at time 0 is occurrences of primary non-function (i.e., C-peptide never>0.3 ng/mL). Modified from: Barton F et al., Improvement in Outcomes of Clinical Islet Transplantation: 1999–2010 Diabetes Care, 2012.

DIABETES CARE, VOLUME 35, JULY 2012

Improved Immunosuppressive Protocol

- Corticosteroids are incredibly islet-toxic. Their removal in the Edmonton Protocol revolutionized islet transplantation.
- Sirolimus and tacrolimus have been used instead, though they are also somewhat islet-toxic.
- Mycophenolate mofeti has been shown to be less islet-toxic.

Improved Immunosuppressive Protocol

- Bellin, et. all showed the benefit of alternative immunosuppression in single donor allo transplants:
  - Induction with antithymocyte globulin (ATG) plus etanercept (TNF-alpha blocker).
  - Maintenance with cyclosporine and everolimus or mycophenolate mofeti.
  - Found that 5 of 6 recipients with T1D were insulin-independent at 1 year post transplant and 4 were insulin independent at >3 years post-transplant.
- The addition of exenatide and etanercept to the Edmonton protocol has also improved outcomes.

New Immunosuppressive Agents

- Abatacept and belatacept (block T-cell interaction with CD80/CD86) have shown early promise to improve single donor outcomes when combined with ATG.

Future Research: Site Selection

- Islets are traditionally infused into the portal vein to engraft in liver sinusoids.
- Benefits of this site include
  - relative ease of access,
  - good oxygenation and blood flow,
  - physiologic sensing and insulin diffusion environment.
- Drawbacks include
  - instant blood mediated inflammatory reaction after transplant with cell loss,
  - high concentration of immunosuppressive agents due to first pass metabolism,
  - loss of counter regulation compared alternative sites,
  - difficulty in obtaining tissue to assess rejection

Future Research: Site Selection

- Placement in the an omental pouch shows promise in animal models to provide a rich blood supply with limited IBMIR.
- Other commonly proposed sites include skeletal muscle and the kidney capsule.

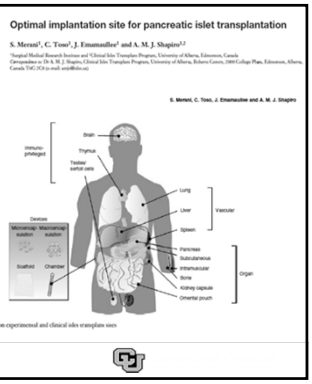


Fig. 1 Common experimented and clinical islet transplant sites

Islet Encapsulation

- The concept of providing a secure oxygen and nutrient-rich environment for islets while affording a degree of immune isolation.
  - Idea dates back to 1977.
- **This concept is gaining widespread public awareness.**
- Patients often ask about this at clinic visits and occasionally during our “new onset” talks.

Macroencapsulation

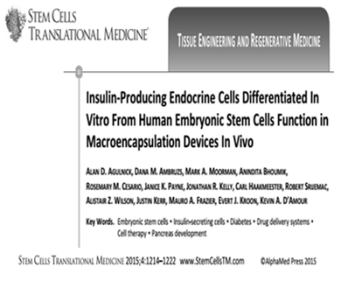
- Macrocapsules contain a large number of islets within the device.
  - Device may be intravascular or extravascular.
  - Intravascular devices associated with clotting and embolization.
- Most popular design has been a planar device with two composite membranes and a loading port.

Macroencapsulation

- Original planar device the TheraCyte Implant showed promise in the late 1990’s and early 2000’s in pig and monkey models.
  - Original Patent has lapsed.
- New focus on use of a planar macroencapsulation device for use with human embryonic stem cell-derived islets.
  - The macroencapsulation protects the body against possible teratomas formed from the stem cells.
  - Device is also easily retrievalable.

Macroencapsulation

- ViaCyte is a commercialization effort of embryonic stem cells and planar macroencapsulation technology
  - It has received a lot of coverage in the non-medical literature and is a frequent source of questions for me from families.
- Mouse model study of success of function of human embryonic stem cells in macroencapsulation device.



STEM CELLS TRANSLATIONAL MEDICINE

TISSUE ENGINEERING AND REGENERATIVE MEDICINE

Insulin-Producing Endocrine Cells Differentiated In Vitro From Human Embryonic Stem Cells Function in Macroencapsulation Devices In Vivo

ALAN D. AGULNICK, DANA M. AMBRUZS, MARK A. MOORMAN, ANINDITA BHOUMIK, ROSEMARY M. CESARO, JANICE K. PAYNE, JONATHAN R. KELLY, CARL HAAKMEESTER, ROBERT SUDMAC, ALISTAIR Z. WILSON, JUSTIN KERR, MAURO A. FRAZER, EVERT J. KROON, KEVIN A. D'AMOUR

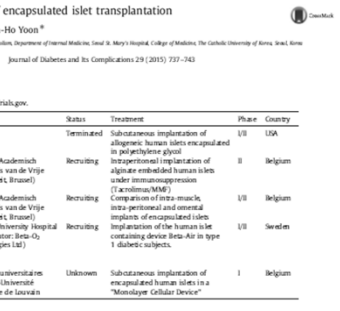
Key Words. Embryonic stem cells • Insulin-secreting cells • Diabetes • Drug delivery systems • Cell therapy • Pancreas development

STEM CELLS TRANSLATIONAL MEDICINE 2015;4:1214–1222 www.StemCellsTM.com

Macroencapsulation

- Pre-clinical trial results showed success reversing hyperglycemia in small animal models.
- ViaCyte has begun Phase 1 clinical trials as of August 2014.
  - https://clinicaltrials.gov/ct2/show/NCT02239354
  - Current sites are UC San Diego and University of Alberta.
  - Enrolling patients 18-55 years old with T1D for 3+ years
  - Single arm, open label, non-randomized trial with an estimated enrollment of 40 patients and an outcome assessment of August 2017.

Other Encapsulation Trials



Current status of encapsulated islet transplantation

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Journal of Diabetes and Its Complications 29 (2015) 737–743

Table 1
Clinical trials on encapsulated allogeneic islet transplantation registered at ClinicalTrials.gov.

Official title	Identifier	Sponsor	Status	Treatment	Phase	Country
A Single-Center Phase I/II Study of Peg-Encapsulated Islet Allografts Implanted In Patients With Type 1 Diabetes	NCT00260234	Novocell	Terminated	Subcutaneous implantation of allogeneic human islets encapsulated in polyethylene glycol	I/II	USA
Functional Survival of Beta Cell Allografts After Transplantation in the Peritoneal Cavity of Non-uremic Type 1 Diabetic Patients	NCT01379729	AZ-VUB (Academisch Ziekenhuis van de Vrije Universiteit, Brussel)	Recruiting	Intraperitoneal implantation of alginate embedded human islets under immunosuppression (Tacrolimus/MMF)	II	Belgium
Long-term Function of Beta Cell Allografts in Non-uremic Type 1 Diabetic Patients	NCT00798785	AZ-VUB (Academisch Ziekenhuis van de Vrije Universiteit, Brussel)	Recruiting	Comparison of intra-muscle, intra-peritoneal and omental implants of encapsulated islets	I/II	Belgium
An Open Label, Pilot Investigation, to Assess the Safety and Efficacy of Transplantation of Macro-encapsulated Human Islets Within the Beautificial Pancreas Beta-Air in Patients With Type 1 Diabetes Mellitus	NCT02064309	Uppsala University Hospital (Collaborator: Beta-O_2 Technologies Ltd)	Recruiting	Implantation of the human islet containing device Beta-Air in type 1 diabetic subjects.	I/II	Sweden
A Monocentre Phase 1 Trial to Assess a Monolayer Cellular Device in the Treatment of Type 1 Diabetes	NCT00790257	Cliniques universitaires Saint-Luc-Université Catholique de Louvain	Unknown	Subcutaneous implantation of encapsulated human islets in a "Monolayer Cellular Device"	1	Belgium

Islet Transplantation: What is Success?

- Traditionally defined as insulin independence.
  - Major current indication for experimental allotransplant, however, is hypoglycemia unawareness.
  - Should improvement in severe hypoglycemic events be the measure?
- Many patients achieve what I call chronic honeymoon state whereby they require some small amounts of insulin but control is better (and easier) than prior to transplant.
  - Should presence of C-peptide be the measure?

Islet Transplantation: Discussion

- What questions do your patients ask?
- How do you respond?
  - How may you respond differently after the information discussed today?
- How do you balance providing hope with tempering expectations?
- How broadly would you define “cure?”
- How would you discuss the risks and benefits of islet transplantation?
- At what cost point would you say it would be widely accessable?