Cleveland Clinic

Klinik Adacık **Hücre Transplantasyonu: 2015 Güncelleme**

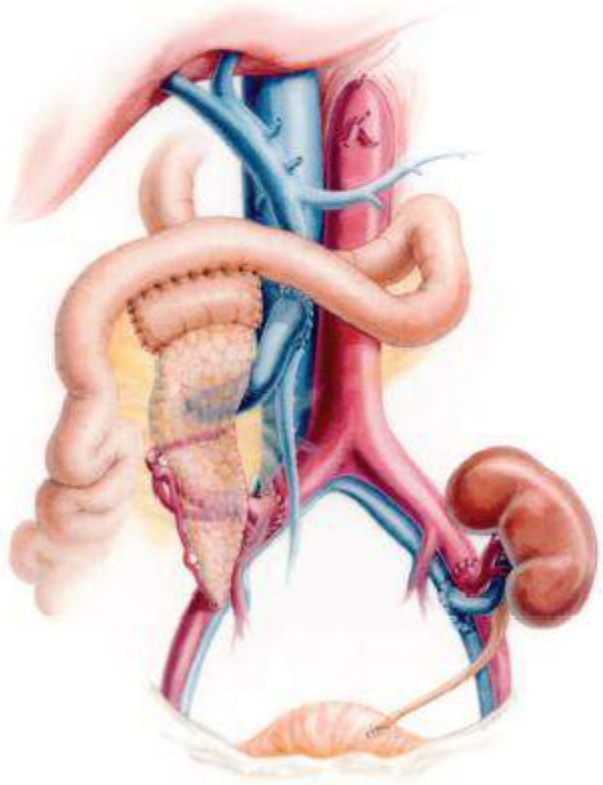
Doc. Dr. Betul Hatipoglu

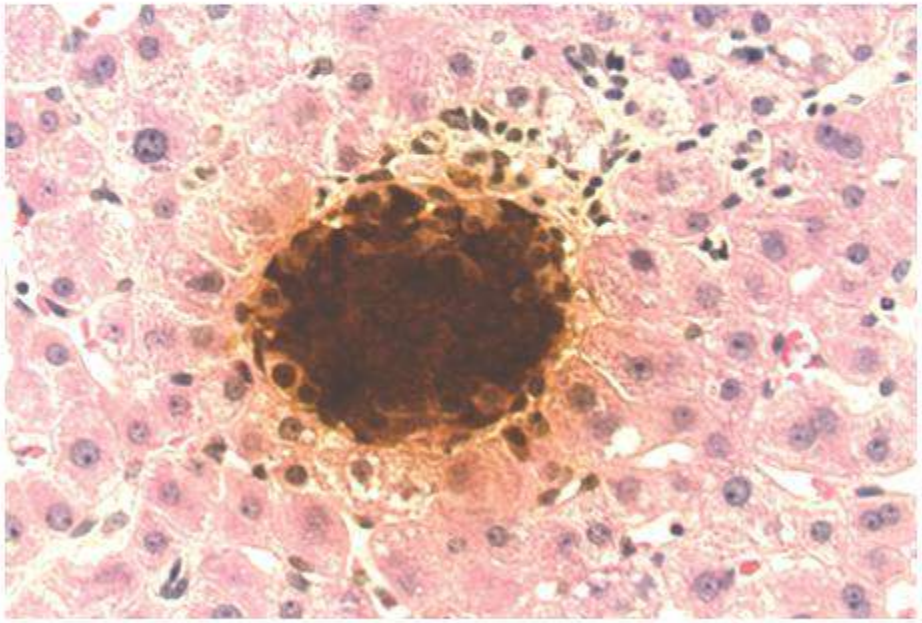
Departments of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, OH USA

Cleveland Clinic

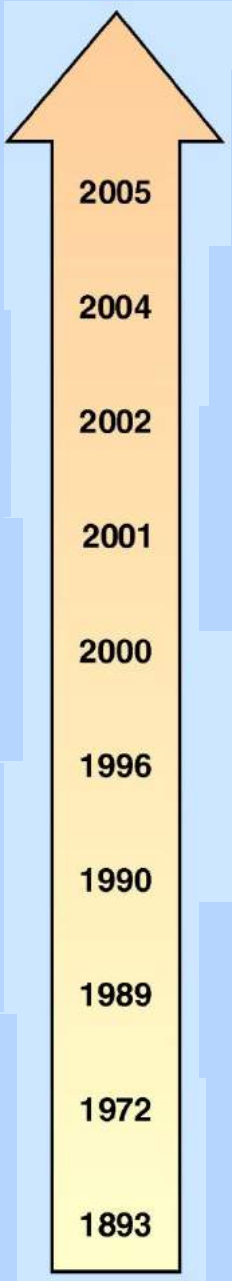
Cleveland Clinic

Cleveland Clinic





Islet Milestones



The New England
Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

A.M. JAMES SHAPIRO, M.B., B.S., JONATHAN R.T. LAKEY, PH.D., EDMOND A. RYAN, M.D., GREGORY S. KORBUTT, PH.D., ELLEN TOTH, M.D., GARTH L. WARNOCK, M.D., NORMAN M. KNETEMAN, M.D., AND RAY V. RAJOTTE, PH.D.

Edmonton Protokolu

- Kaliteli adacik secimi
- Hasta secimi
- Immunosuppresif ilac secimi

Wolters Kluwer Health | Lippincott Williams & Wilkins

Transplantation

THE OFFICIAL JOURNAL OF THE TRANSPLANTATION SOCIETY

2008 Update From the Collaborative Islet Transplant Registry

The University of Alberta Edmonton, Alberta, Canada

The University of Miami, Miami, FL

The University of Minnesota, Minneapolis, MN

Lille University Hospital, Lille Cedex, France

The University of Pennsylvania, Philadelphia, PA

Baylor College of Medicine/The Methodist Hospital, Houston, TX

Center for Islet Transplantation at Harvard Medical School, Boston, MA

Southern California Islet Consortium (SCIC), Duarte, CA

The University of Chicago, Chicago, IL

University of Illinois at Chicago, Chicago, IL

Emory Transplant Center, Atlanta, GA

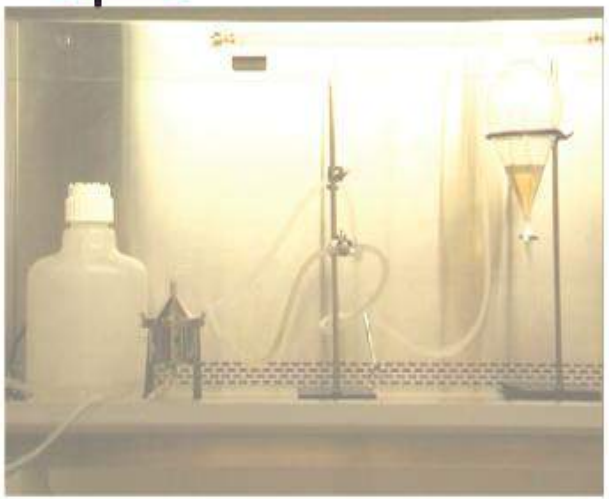
Geneva/GRAGIL Network

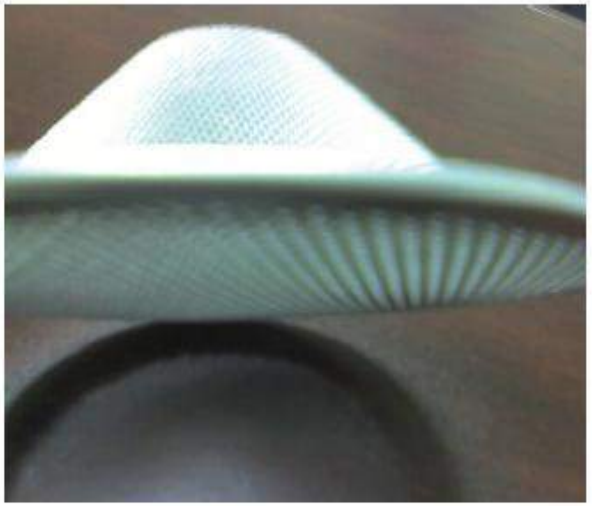
University of Wisconsin, Madison, WI

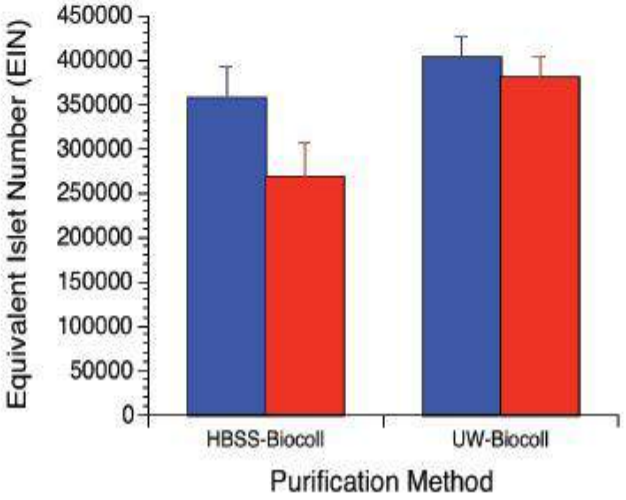
Introduction - UIC islet transplantation

UIC UNIVERSITY OF ILLINOIS AT CHICAGO

Methods - Islet Isolation



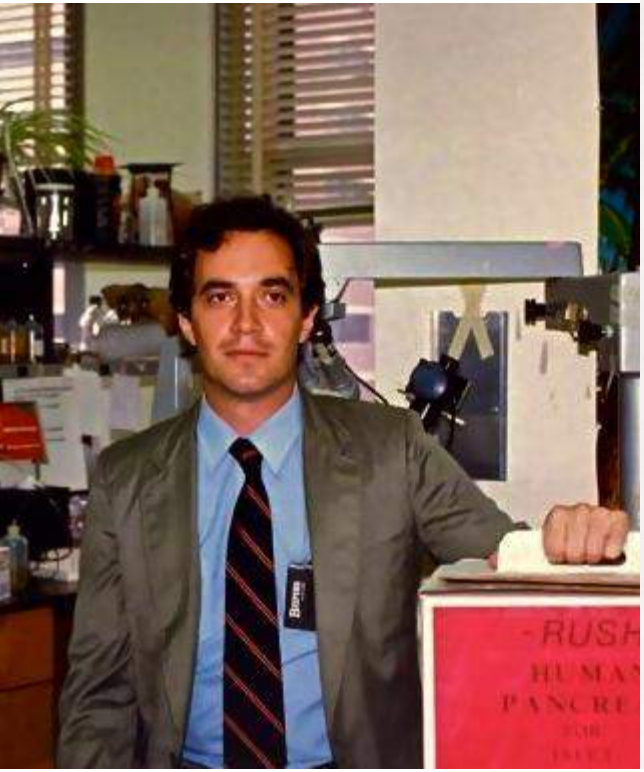


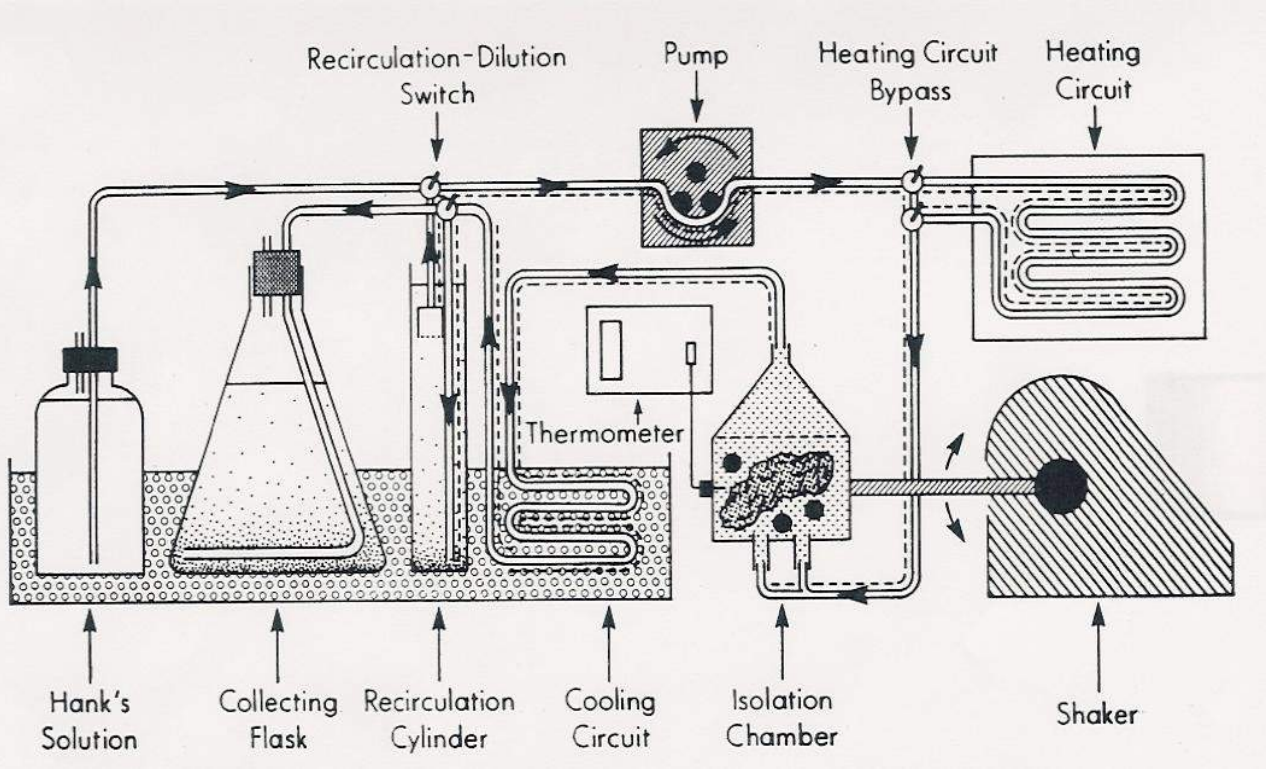


Reprinted from DIABETES, VOL. 37, NO. 4, APRIL 1988

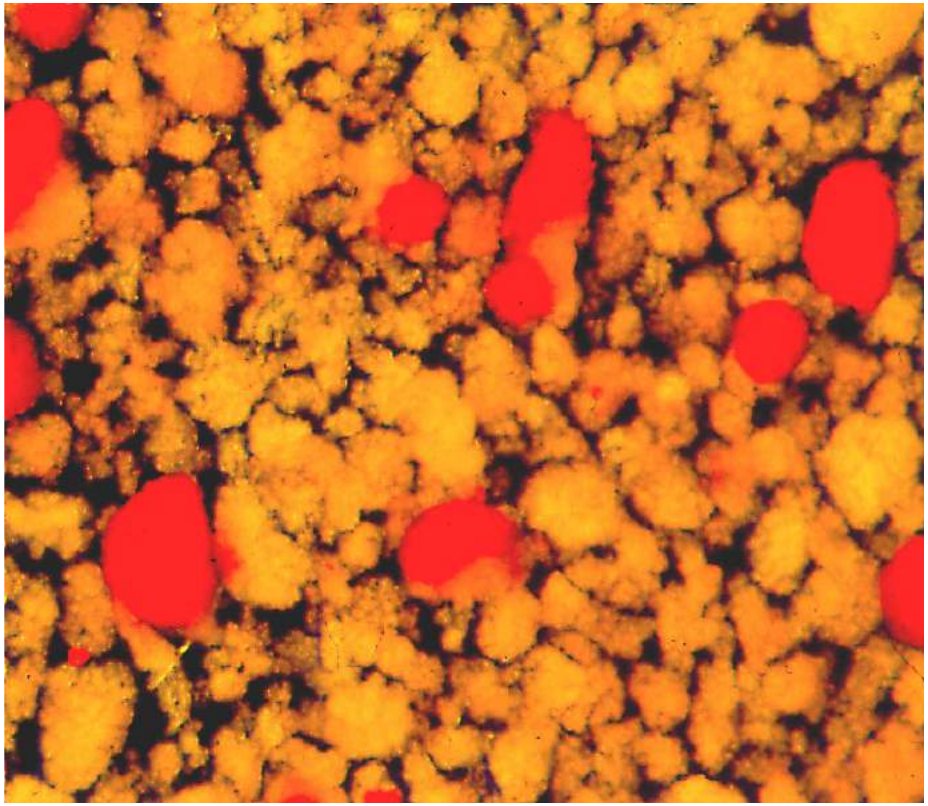
Automated Method for Isolation of Human Pancreatic Islets

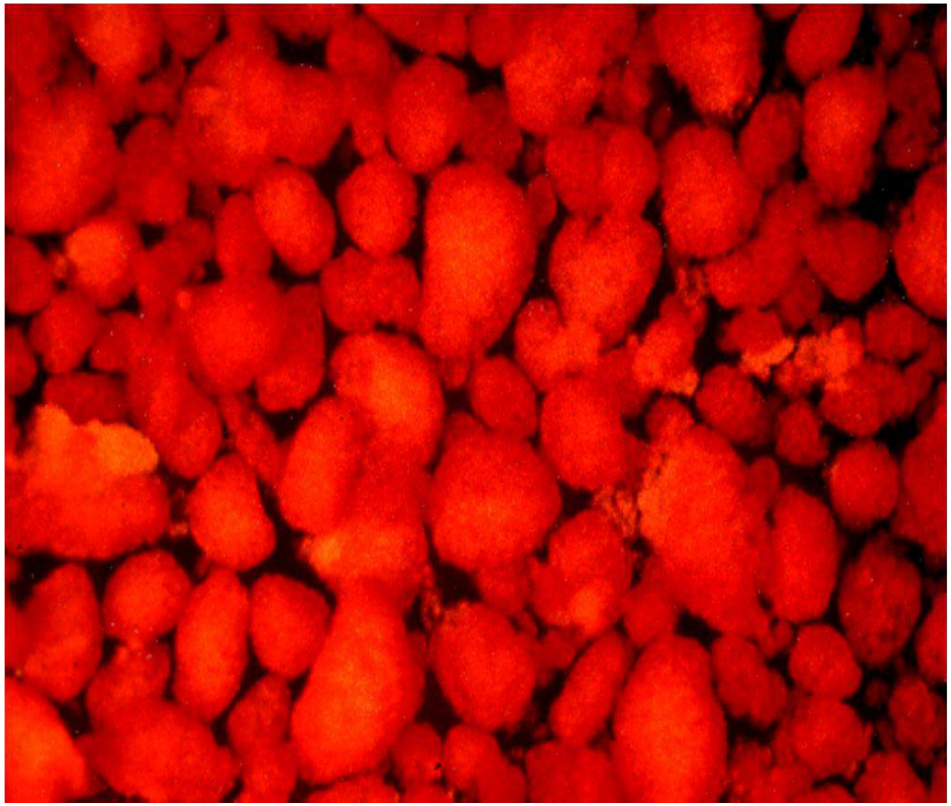
CAMILLO RICORDI, PAUL E. LACY, EDWARD H. FINKE, BARBARA J. OLACK, AND DAVID W. SCHARP





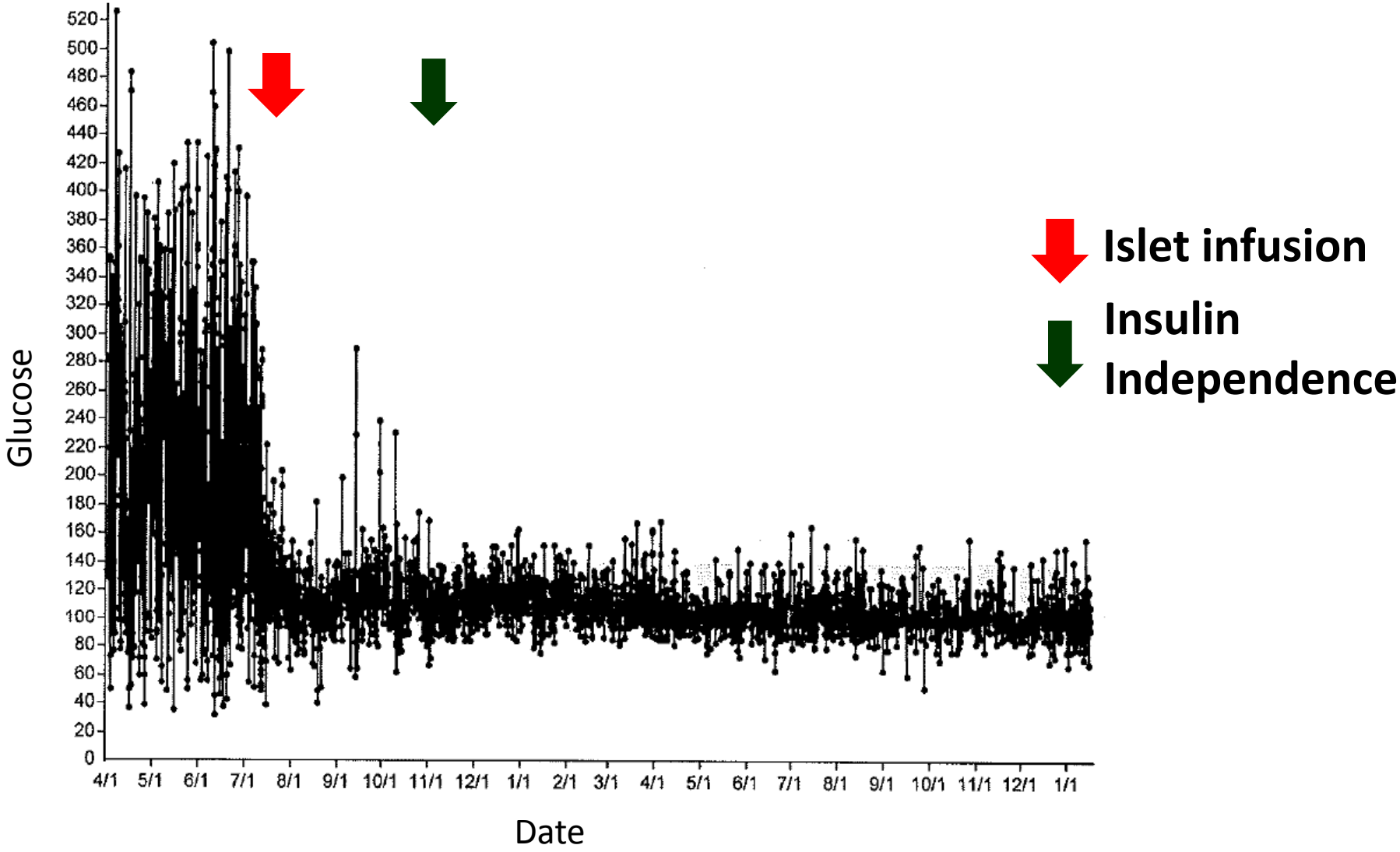
Purification of pancreatic islets for allotransplantation



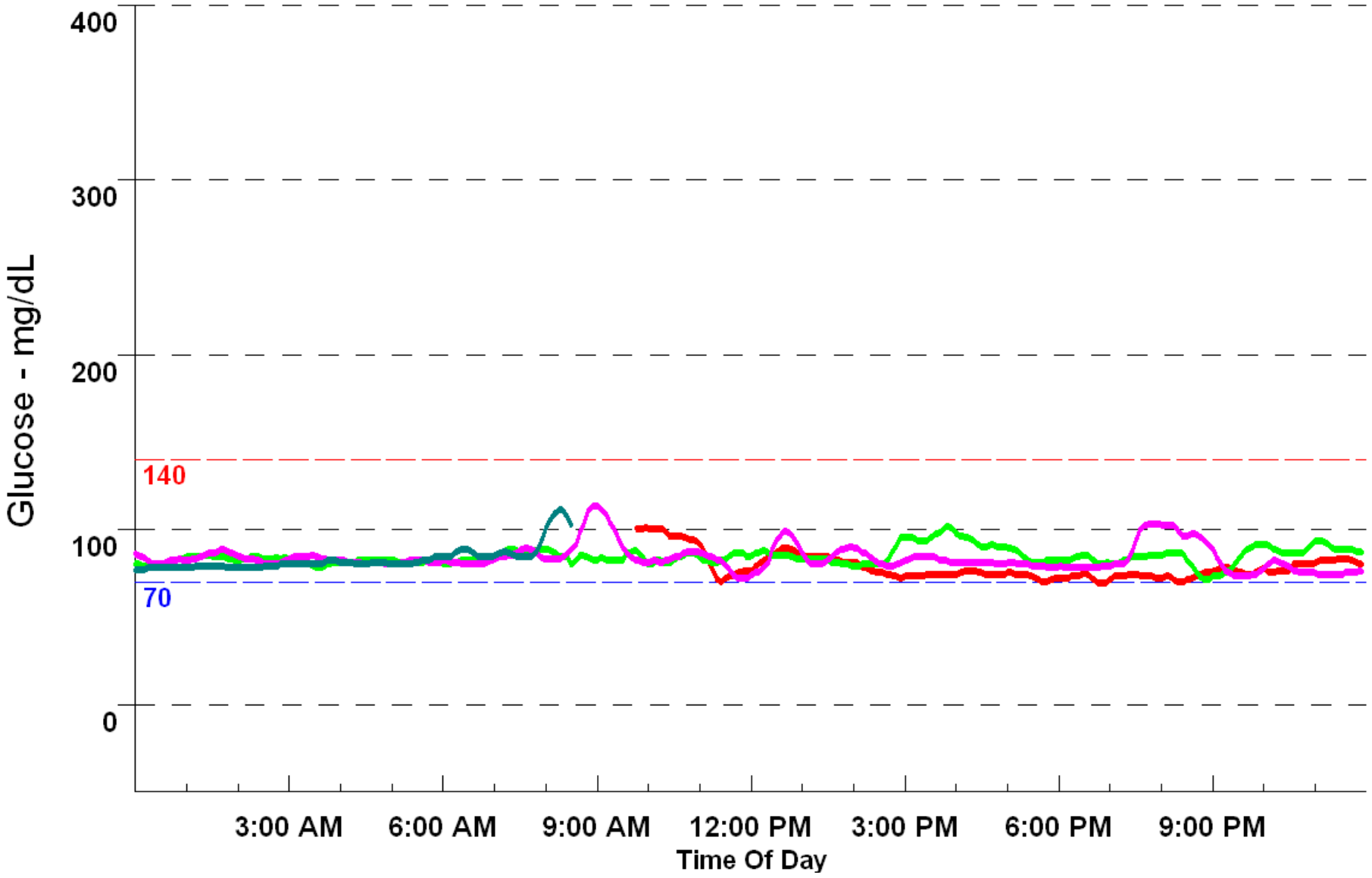


Clinical islet transplantation at UIC - Phase 1/2 trial

Glucose Variability Before (Insulin Pump) and After Islet Transplantation



Glucose Variability (CGMS)
Two Years After Islet Transplantation



American Journal of Transplantation
OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

Islet Transplantation for Brittle Type 1 Diabetes: The UIC Protocol

A. Gangemi , P. Salehi , B. Hatipoglu , J. Martellotto , B. Barbaro , J. B. Kuechle , M. Qi , Y. Wang , P. Pallan , C. Owens , J. Bui , D. West , B. Kaplan , E. Benedetti and **J. Oberholzer** ,
, University of Illinois at Chicago, Chicago, IL
** Corresponding author: José Oberholzer,*

29 Apr 2008 - Volume 8 - Issue 6 - pp 1250-1261

Clinical Islet Transplantation Consortium

- **Phase II Pilot Clinical Trials (5 trials IA)**
- **Phase III Licensure (2 trials; IA, IAK)**
- **Extended Follow Up after Islet Transplantation in Type 1 DM**

2004 – 2018

NIAID

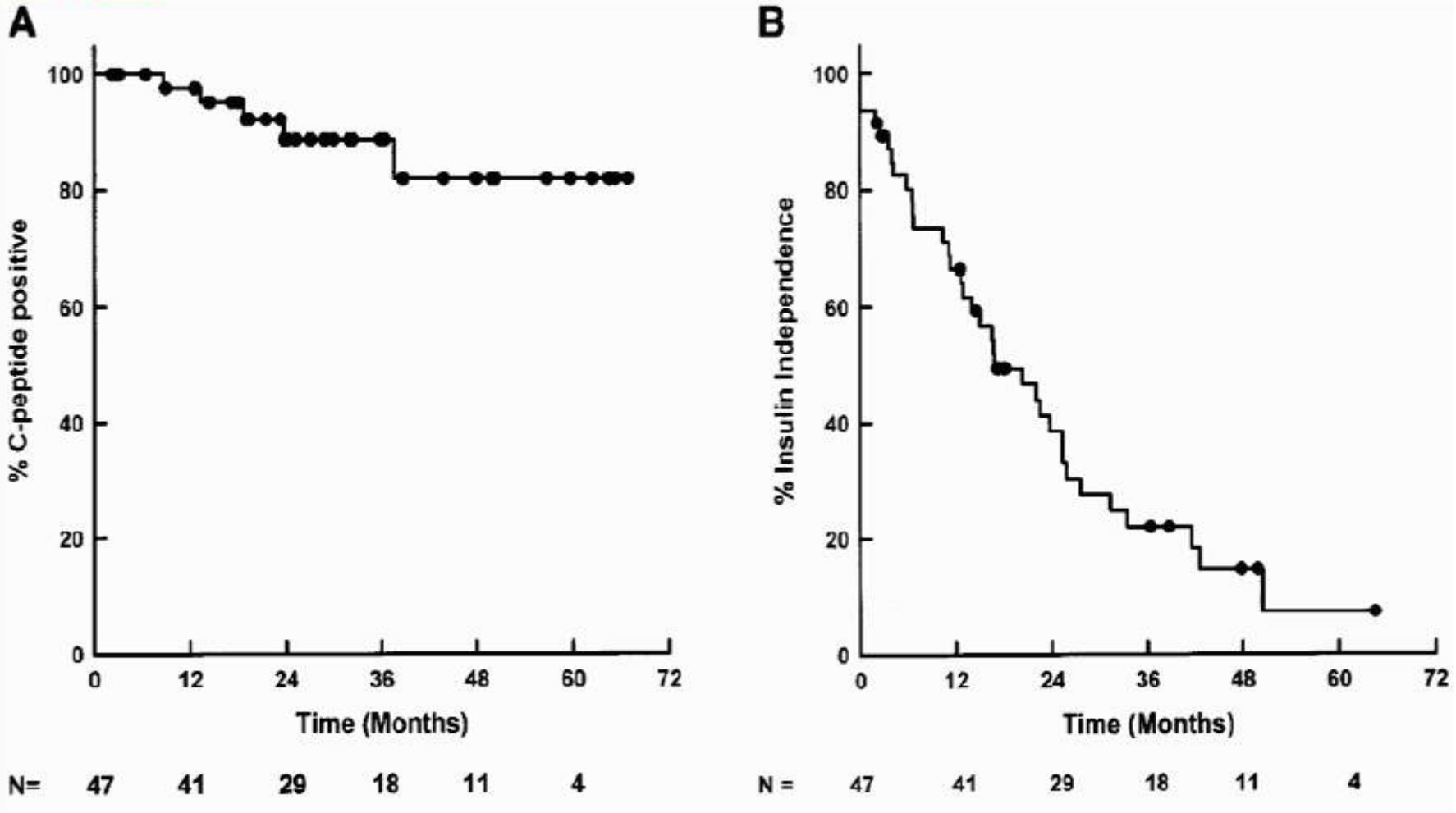
DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NATIONAL INSTITUTES OF HEALTH

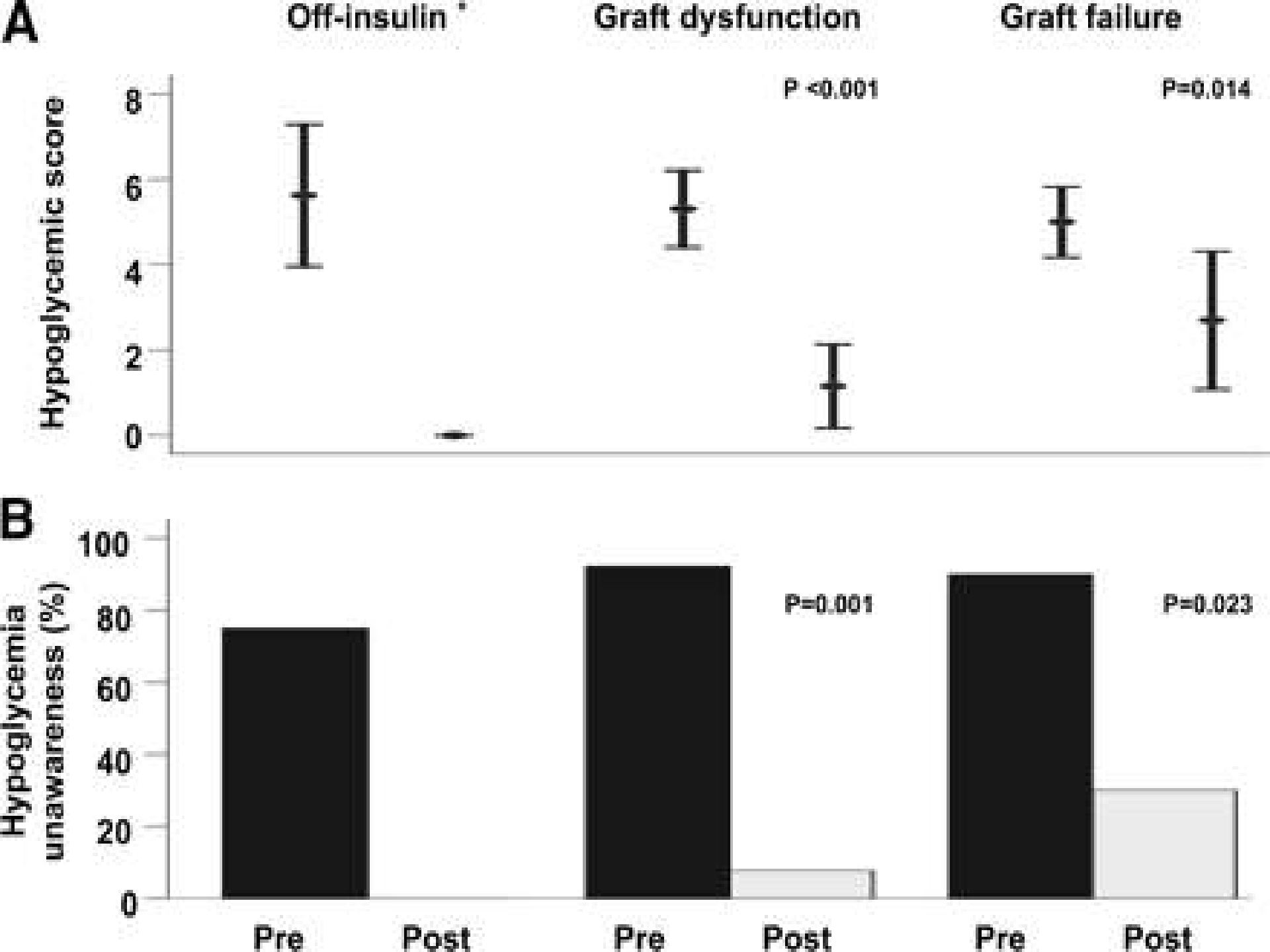
NIDDK

www.citisletstudy.org

5 year follow up - Edmonton



Diabetes 54:2060–2069, 2005


A
Off-insulin *
Graft dysfunction
Graft failure
Hypoglycemic score
8
6
4
2
0
P <0.001
P=0.014
B
Hypoglycemia unawareness (%)
100
80
60
40
20
0
P=0.001
P=0.023
Pre
Post
Pre
Post
Pre
Post

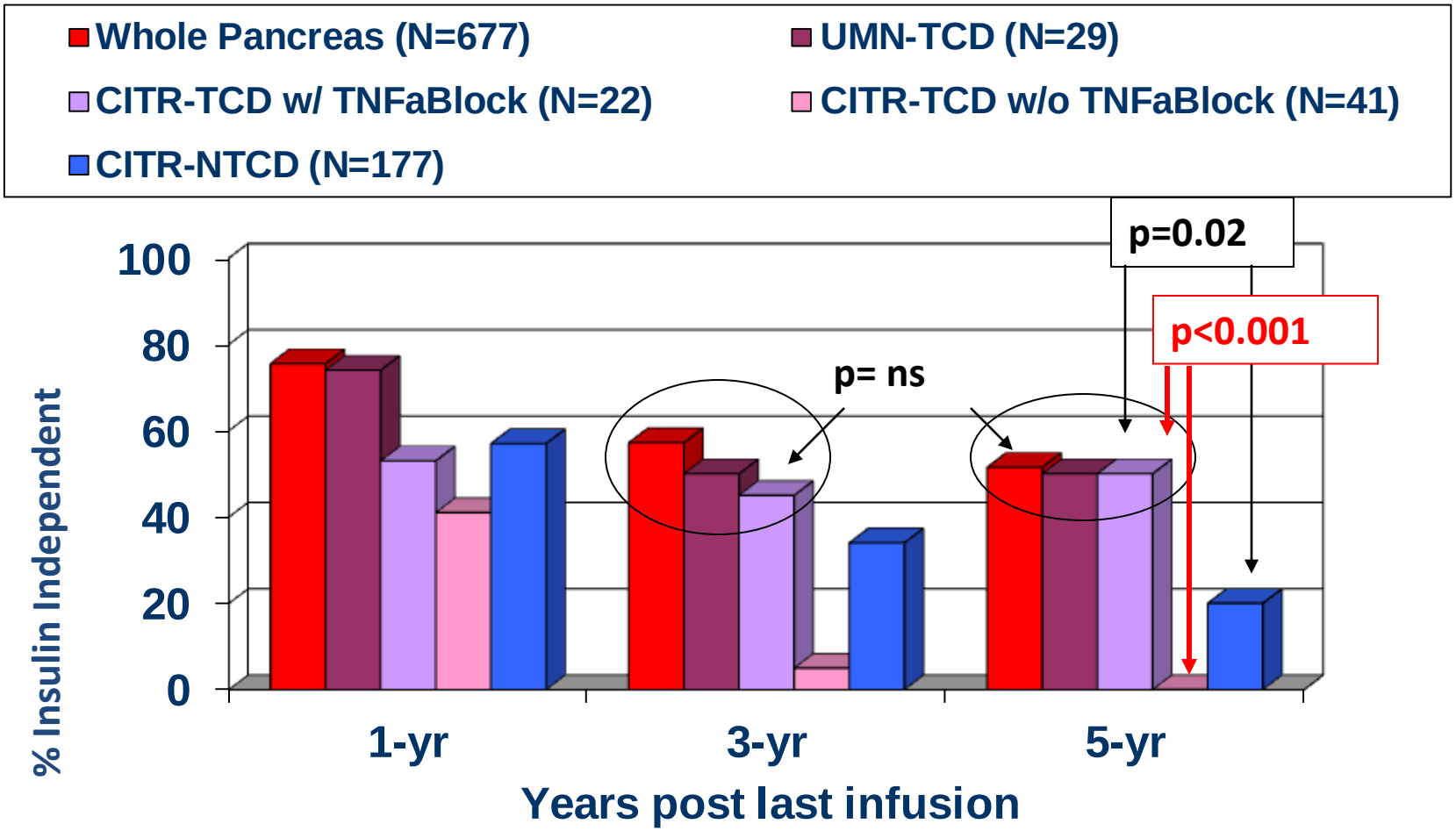
Islet Transplantation in Type 1 Diabetic Patients Using Calcineurin Inhibitor-Free Immunosuppressive Protocols Based on

T-Cell Adhesion or Costimulation Blockade

Achieves 50% 5-year insulin independence

Bellin MD, Barton FB, Heitman A, Harmon J, Balamurugan AN, Kanaswamy R, Sutherland DE, Alejandro R and Hering BJ. American Journal of Transplantation, 2012.

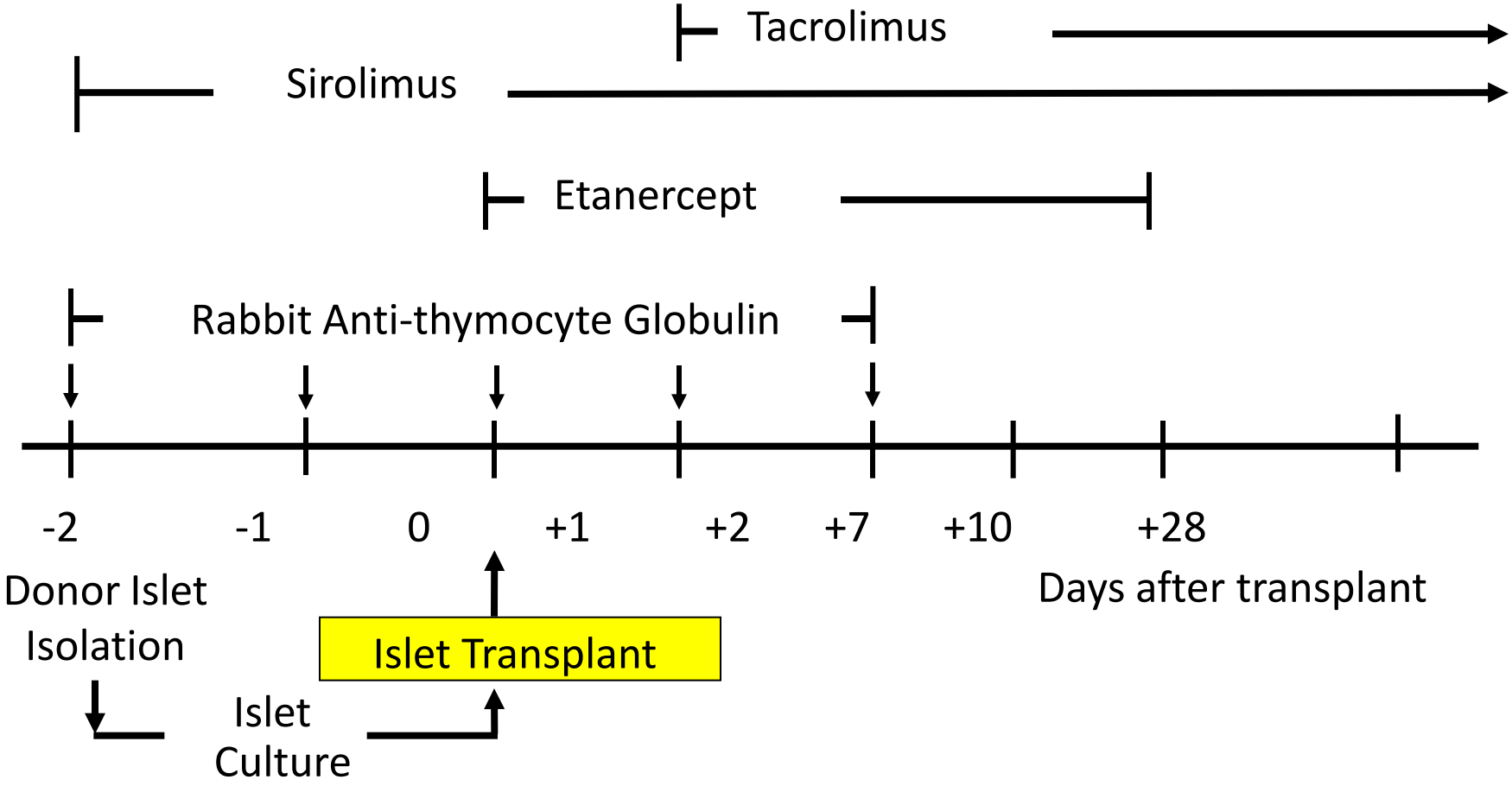
Peri-Transplant Anti Inflammatory Immunomodulation and Long Term Insulin Independence



Potent Induction Immunotherapy Promotes Long-Term Insulin Independence After Islet Transplantation in Type 1 Diabetes MD Bellin , FB Barton , A Heitman…R Alejandro, B J Hering AJT 2012;12(6):1576-83

CIT-07 Treatment Protocol

Adapted from
JAMA 293; 830-5, 2005



Subjects will receive up to 3 separate infusions of islets
Basiliximab instead of ATG for 2nd and 3rd transplants

Transplantation, 2014

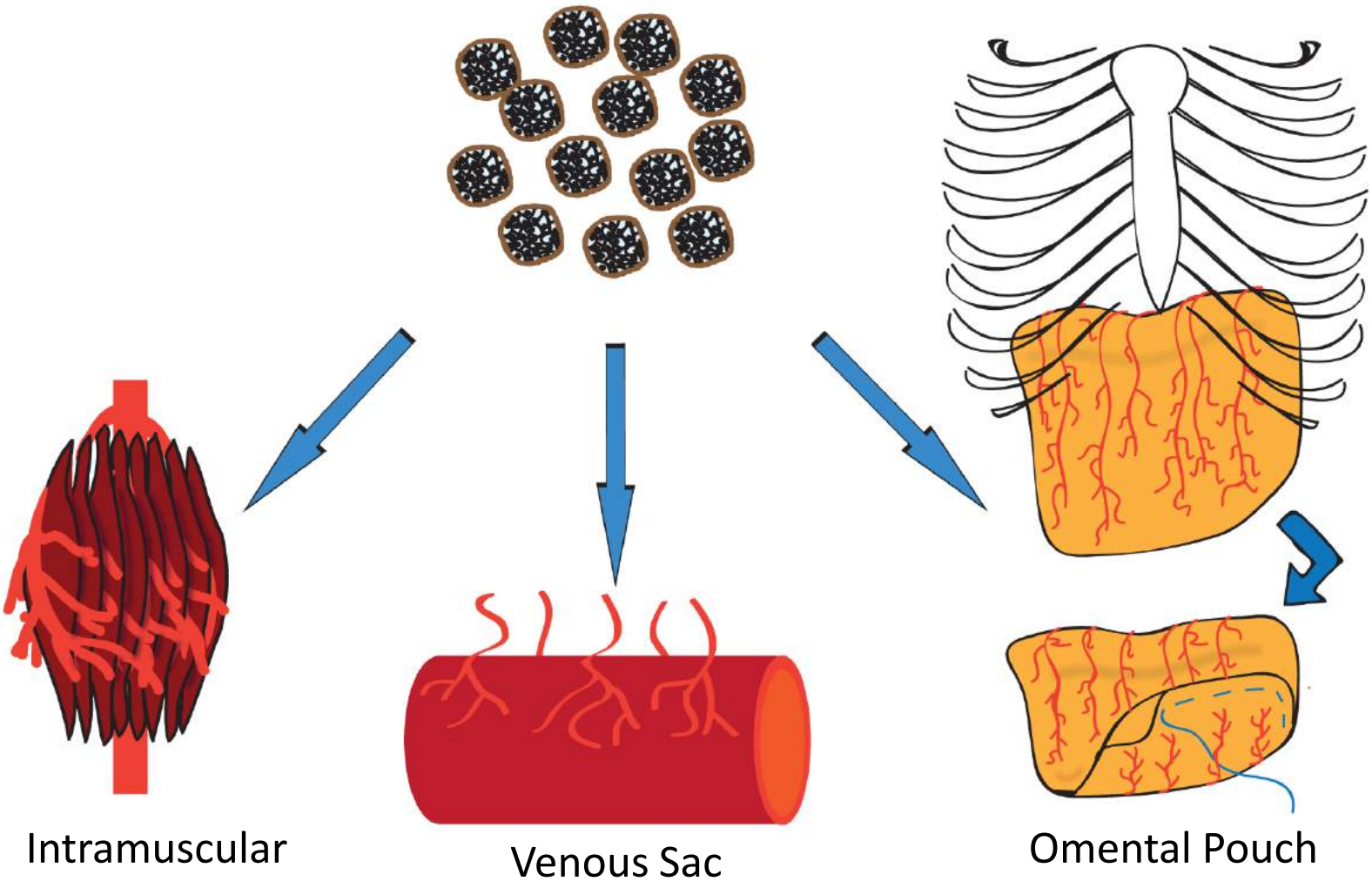
The Path for Tolerance Permissive Immunomodulation in Islet Transplantation

Camillo Ricordi

treatment could include the selected peritransplant anti-inflammatory strategy and recipient treatment with granulocyte colony stimulating factor (GCSF), whose administration has been associated with tolerance-permissive, regulatory cell-promoting effects. Interestingly, the association of low-dose ATG (2.5 mg/kg, intravenous) followed by pegylated GCSF (Neulasta; 6 mg SQ q2 weeks × 6 doses) was recently reported to have a significant effect on the preservation of AUC C-peptide in the subject with T1DM compared to placebo-treated subjects (Haller et al. ADA 2014, 173-OR), and this effect was associated with preservation of regulatory T cells

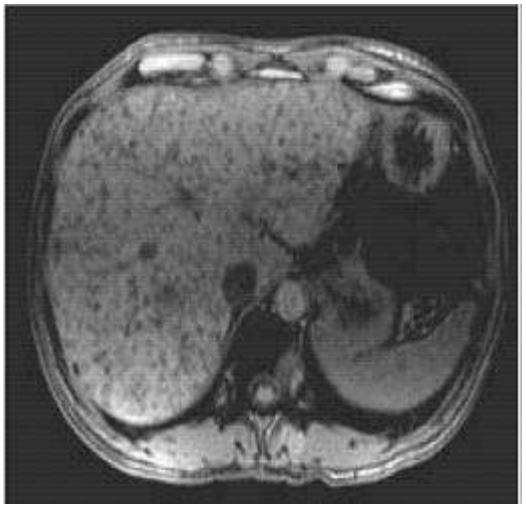
Engineering the “Optimal” Site

Engineering an ideal site:

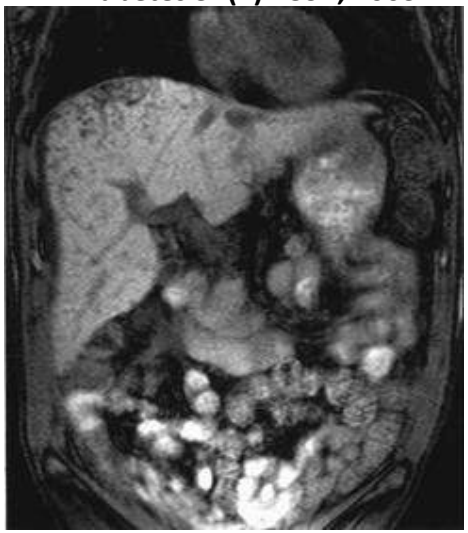


Steatosis after islet transplantation

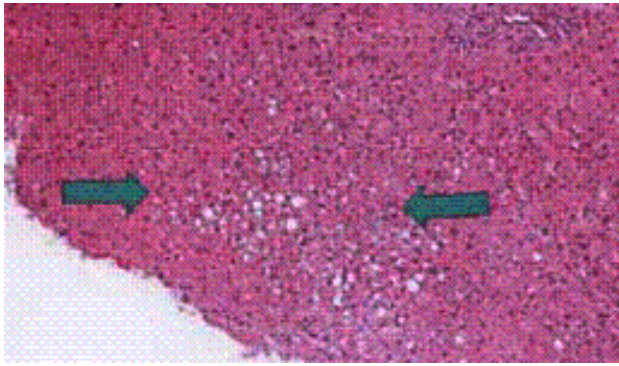
Pennsylvania (2/4)
Diabetes 52(7):1591, 2003



Miami (2/26)
AJT 5:2037, 2005



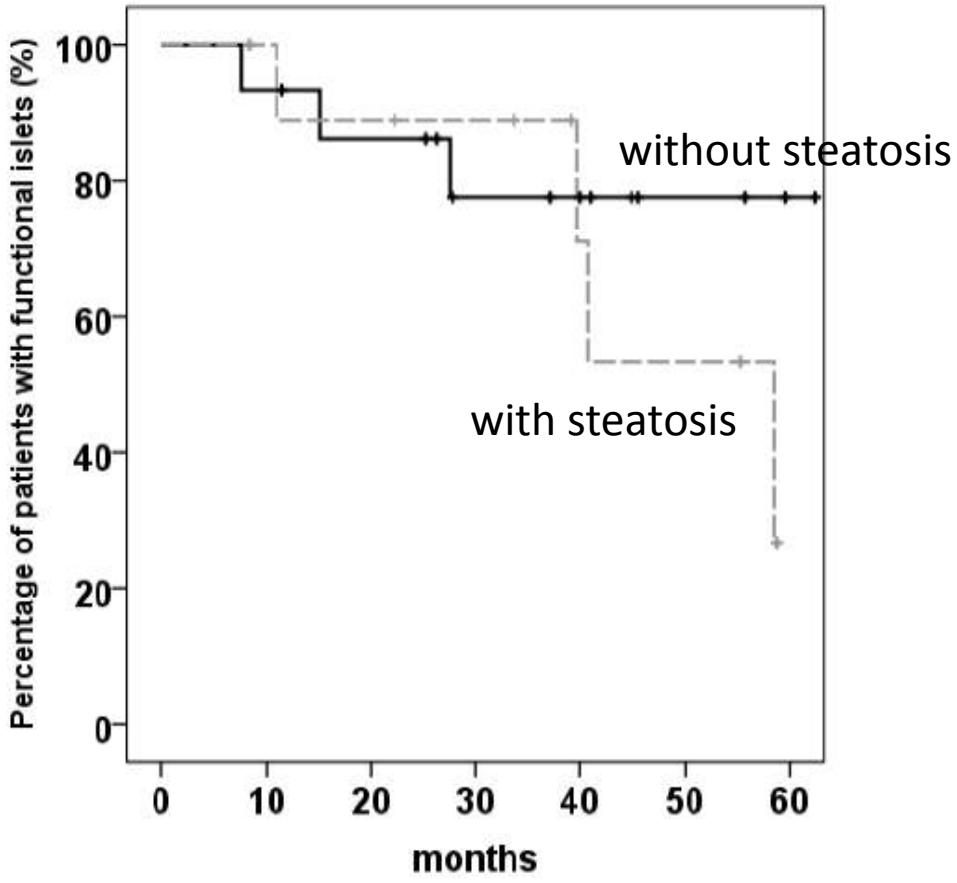
Edmonton (6/30)
Diabetes 52(7):1591, 2003



Italy - IAK (9/31)
Cell Transpl 14:727, 2005

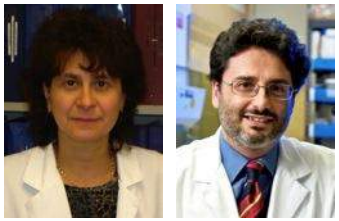
Islet Graft Survival and Grade 1 Steatosis(MRI signal change ≥ 3% at graft dysfunction)

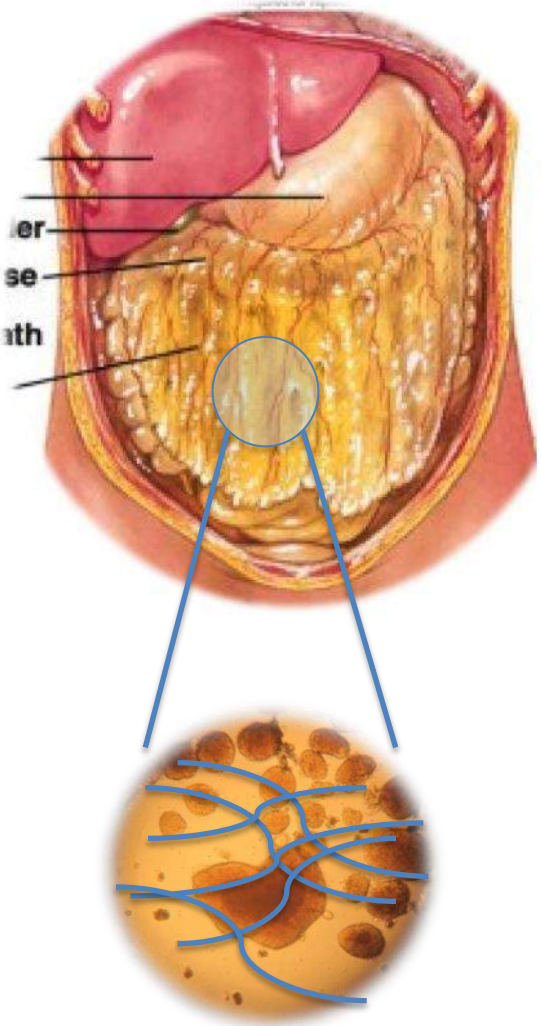
Leitão C.B.,Westphalen A ,Peixoto EML, Mireles-Zavala L., Lauriola V, Bernetti K, RicordiC, **Alejandro R.** Liver Fat Accumulation and Islet Graft Survival Cell Transplant. 2014;23(10):1221-7

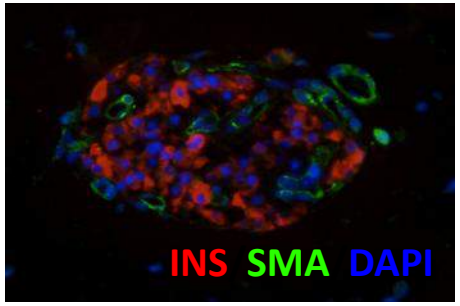


DIABETES RESEARCH INSTITUTE
UNIVERSITY OF MIAMI

Intra-Omental Islet Transplantation into Biologic Scaffolds







PILOT CLINICAL TRIAL TIMELINE

IND Submission: 01/30/2014
IND Approval: 02/27/2014

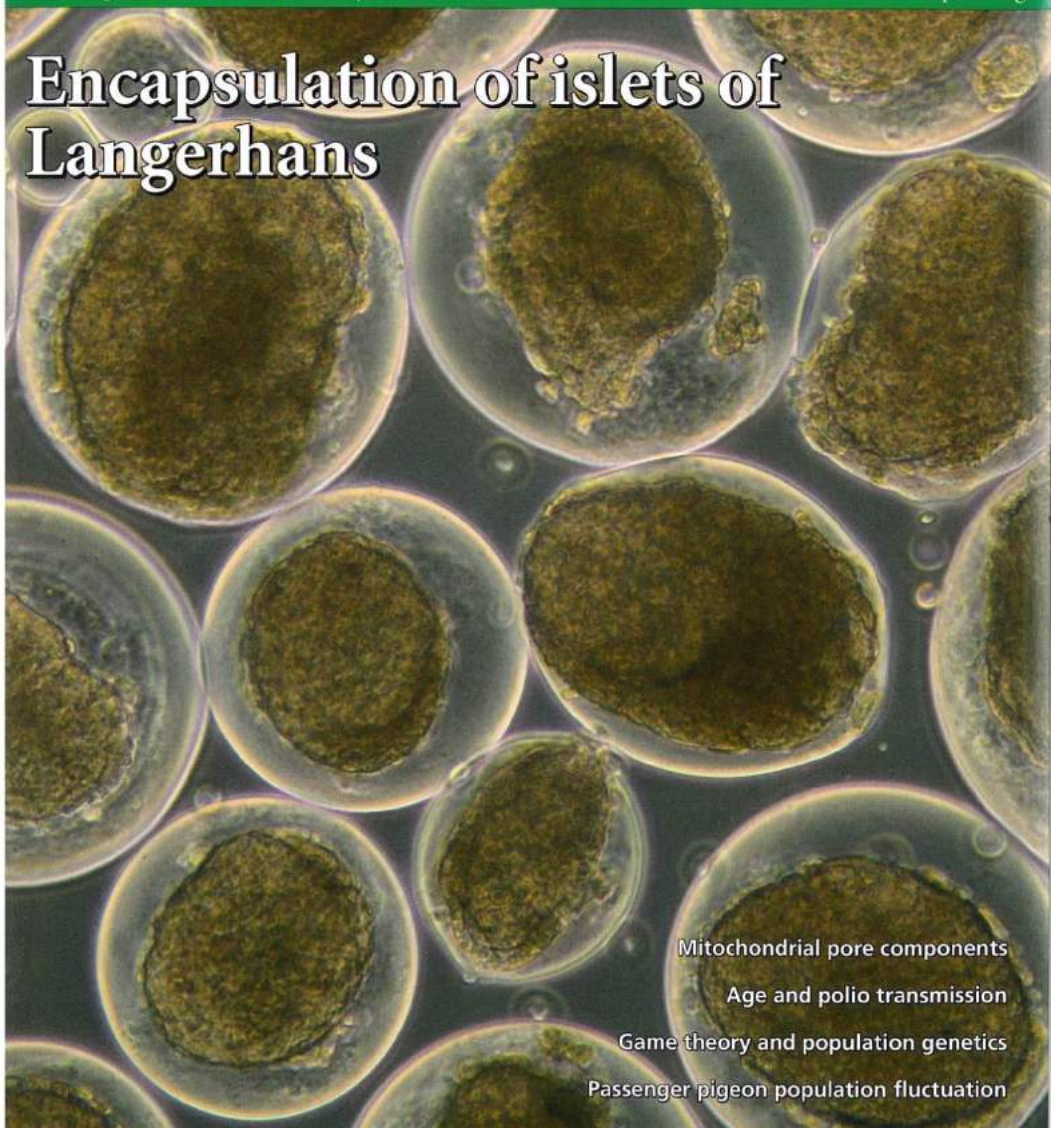
IRB Submission: 04/15/2014
IRB approval: July 2014

1st Patient: Aug 2014
2nd Patient: Nov 2014
3rd Patient: Feb 2015
(3 months apart as per IND)

July 22, 2014 | vol. 111 | no. 29 | pp. 10391–10780

PNAS

Proceedings of the National Academy of Sciences of the United States of America www.pnas.org



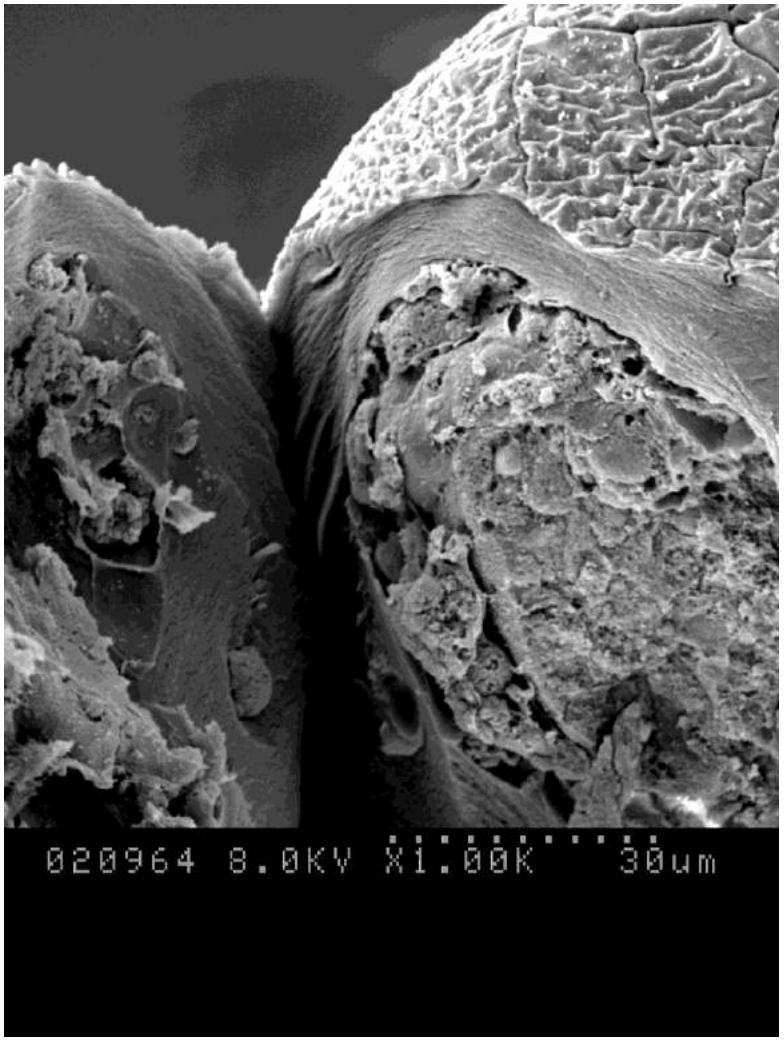
Mitochondrial pore components

Age and polio transmission

Game theory and population genetics

Passenger pigeon population fluctuation

SEM of encapsulated HI



Islet-derived progenitors as a source of in vitro islet regeneration

Hanley S, Rosenberg L.

Department of Surgery, and Centre for Pancreatic Diseases, McGill University Health Centre, Montreal, Quebec, Canada.

Methods Mol Biol. 2009;482:371-85.

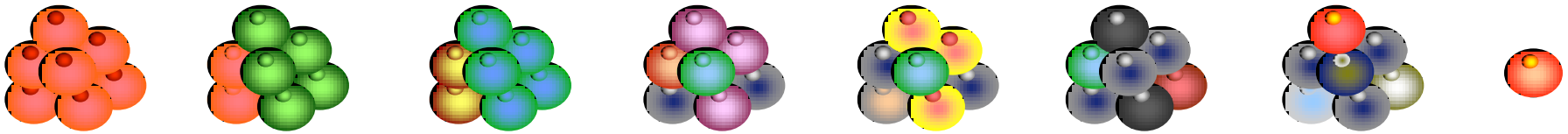
***In vivo* characterization of transplanted human embryonic stem cell-derived pancreatic endocrine islet cells**

A. Eshpeter, J. Jiang, M. Au, R. V. Rajotte, K. Lu, J. S. Lebkowski, A. S. Majumdar and G. S. Korbutt

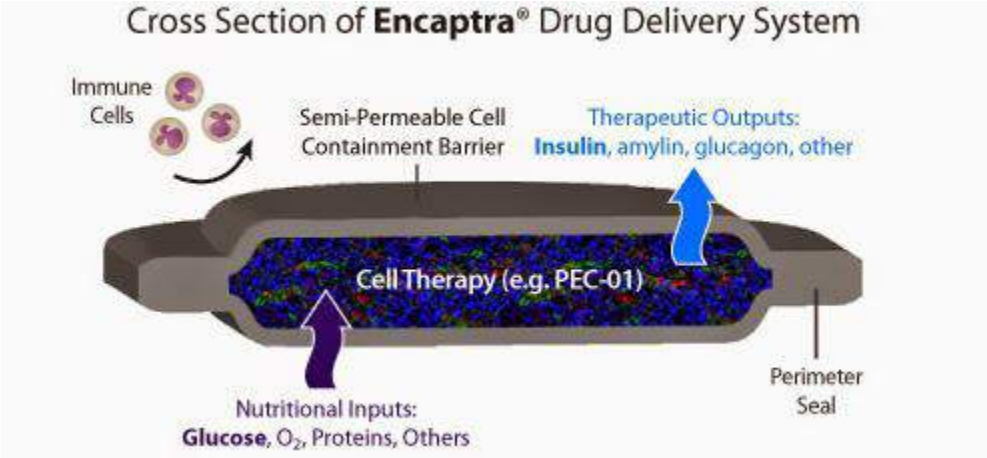
Alberta Diabetes Institute and Department of Surgery, University of Alberta, Edmonton, Canada, and Geron Corporation, Menlo Park, CA, USA

Cell Proliferation 2008;Volume 41,Issue 6**,** Pages 843 - 858

The Sequence of Development for Deriving Islets from Stem Cells Is Known

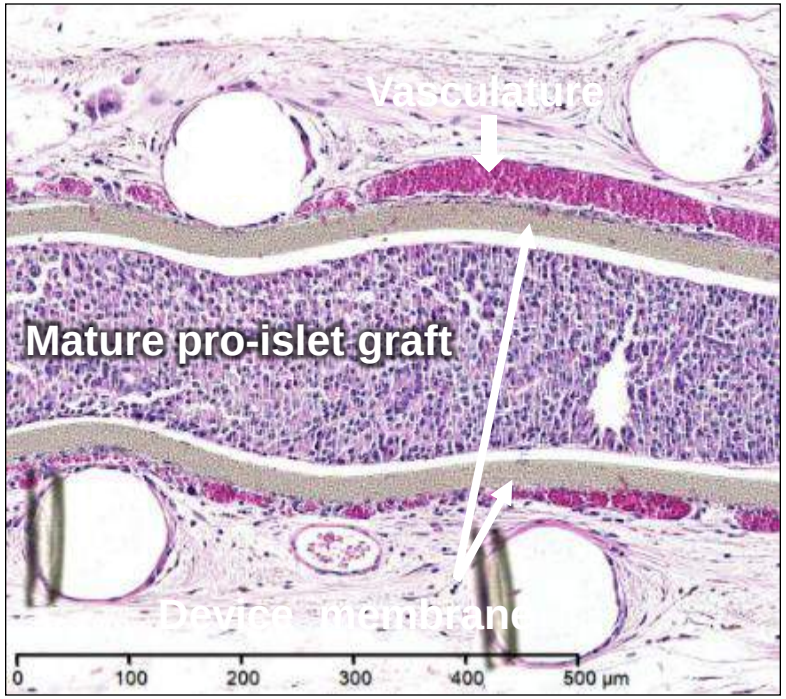


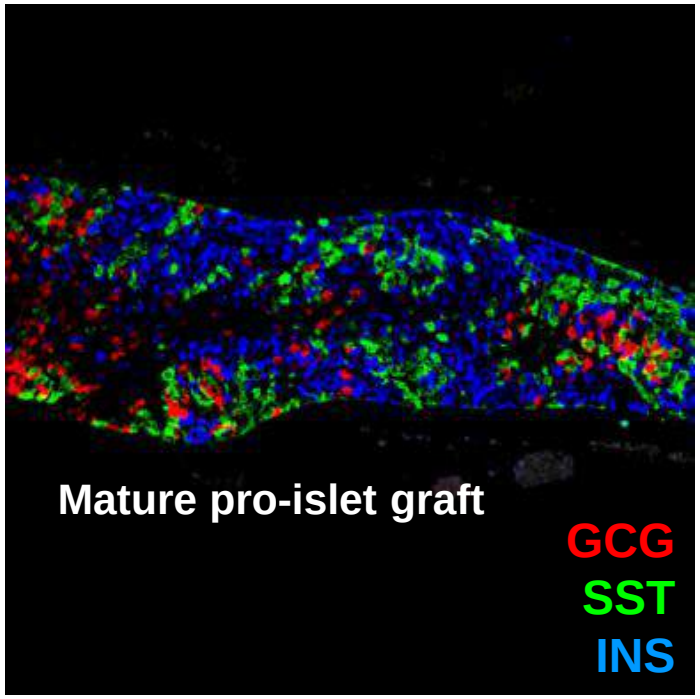
Transplantation of HESC-derived Pancreatic Cells Makes Functional Islets *In Vivo*



Glucagon
Somatostatin
Insulin

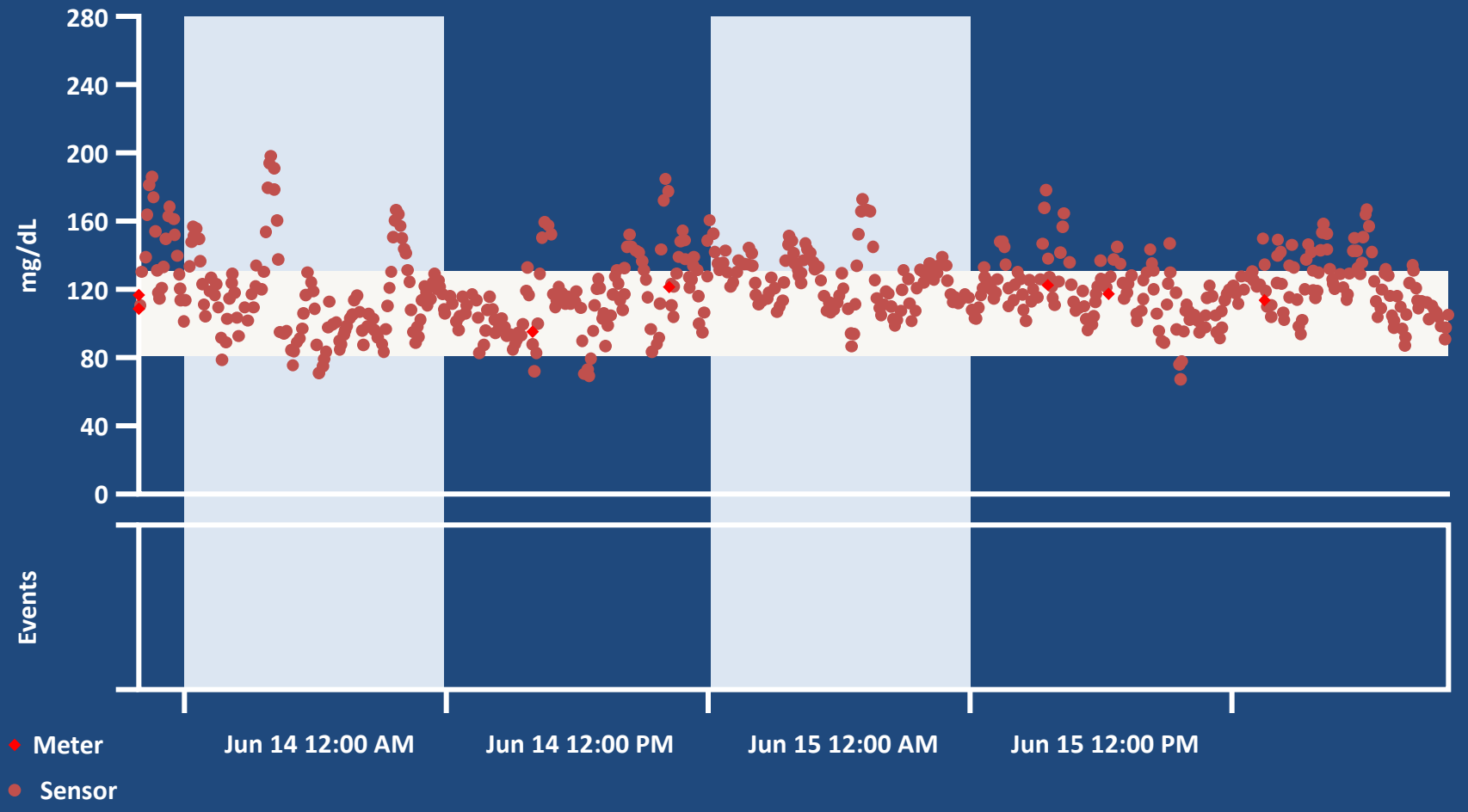
Encapsulated Pro-islet Grafts Mature in vivo to Functioning Islets



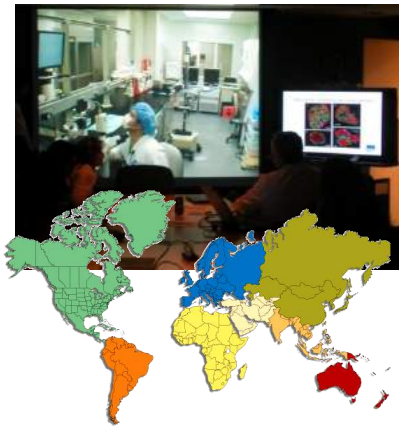


Fasting	0.79
60 min	2.34

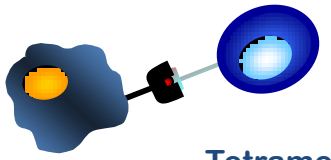
Continuous Glucose Monitoring Using DexCom Seven CGM in Rats with Viacyte Device



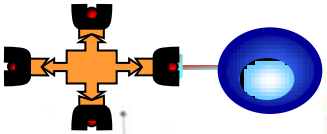
A Robins, Cell Transplant Society, Oct 24, 2011



Telescience DRI Federation

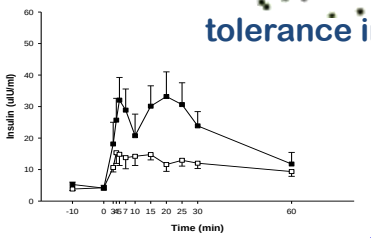


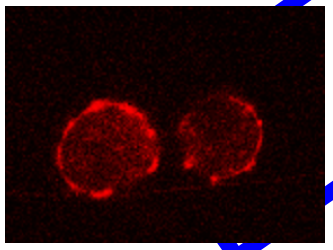
Tetramers



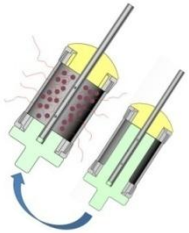
Gene therapy

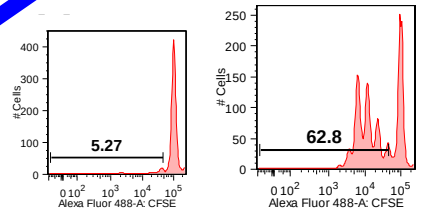
tolerance induction



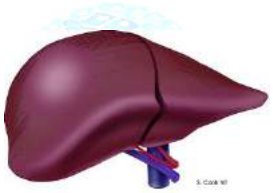


Tolerogenic DCs

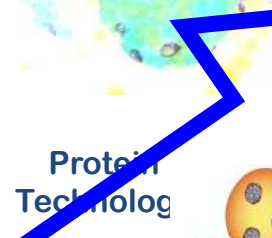




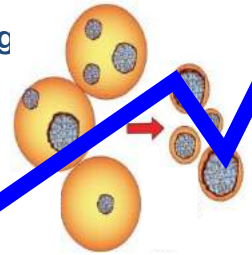
Xenotransplantation



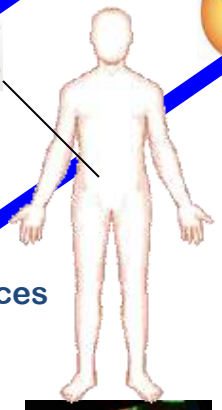
liver transdifferentiation



Protein Technology

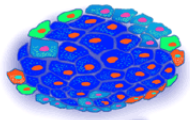


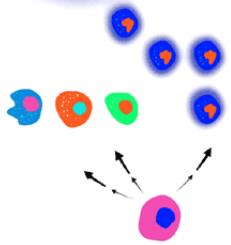
Improved Preservation and New Implantation Sites



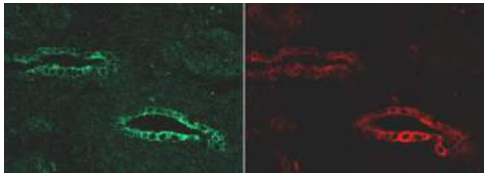
Hybrid Devices

Multi-Photon In-Vivo Imaging





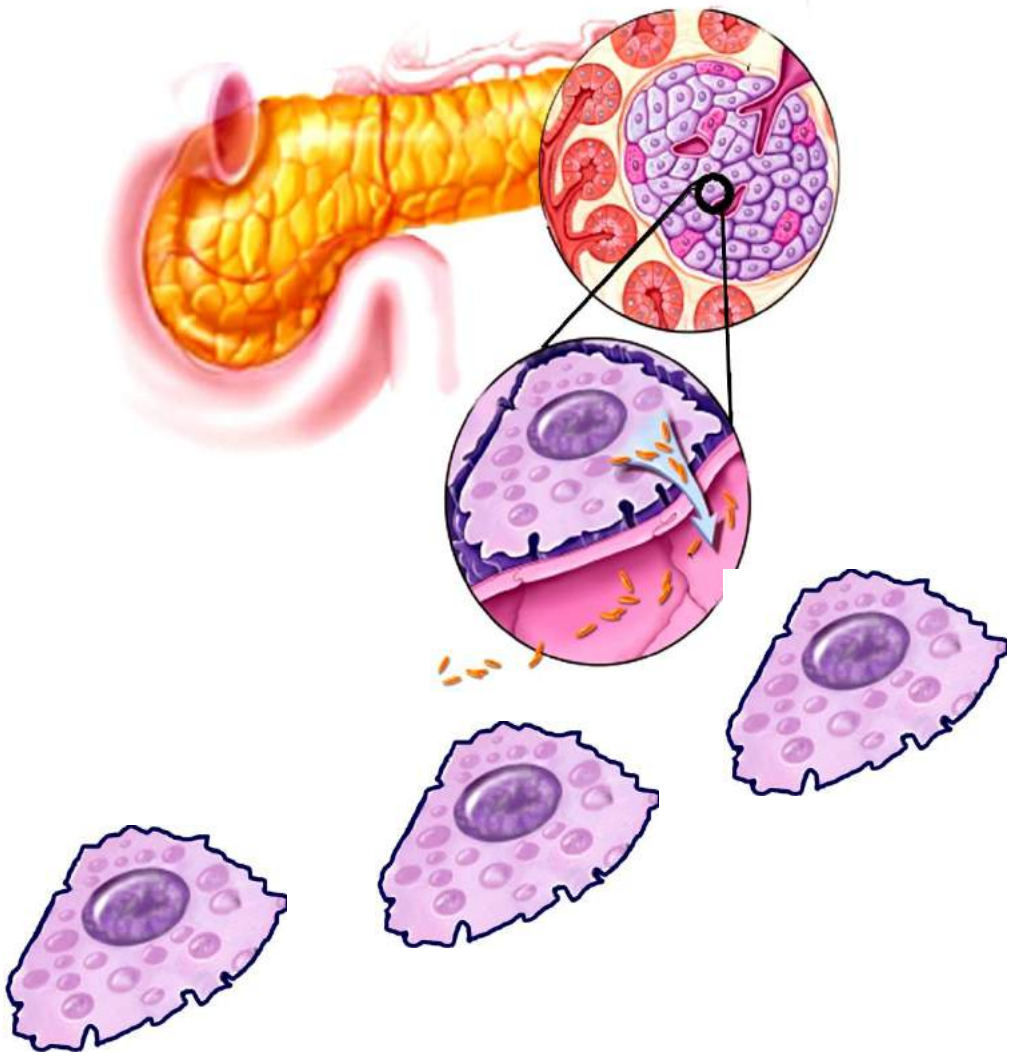
Stem Cells

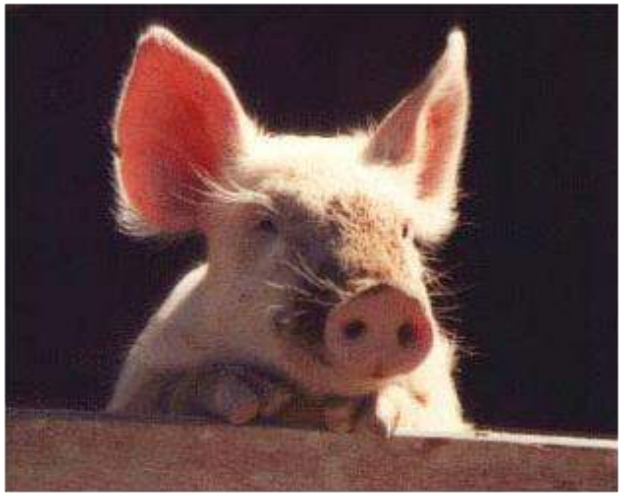


Regeneration

FAST-TRACK

The Cell Source





Wolters Kluwer Health | Lippincott Williams & Wilkins

Transplantation

THE OFFICIAL JOURNAL OF THE TRANSPLANTATION SOCIETY

Reduced Progression of Diabetic Retinopathy After Islet Cell Transplantation Compared With Intensive Medical Therapy

Thompson, David M.1,5; Begg, Iain S.2; Harris, Claire1; Ao, Zilaing3; Fung, Michelle A.1; Meloche, R Mark3; Keown, Paul1; Meneilly, Graydon S.1; Shapiro, R Jean1; Ho, Stephen4; Dawson, Keith G.1; Ghofaili, Khalid Al1; Riyami, Loay Al1; Mehthel, Mohammed Al1; Kozak, Sharon E.1; Tong, Suet On1; Warnock, Garth L.3

Volume 85(10), 27 May 2008, pp 1400-1405

Curr Diab Rep.

- **Impact of Islet Transplantation on Diabetes Complications and Quality of Life**
  - Roberto Bassi & Paolo Fiorina
  - 2011 Oct;11(5):355-63

Diabetes Care

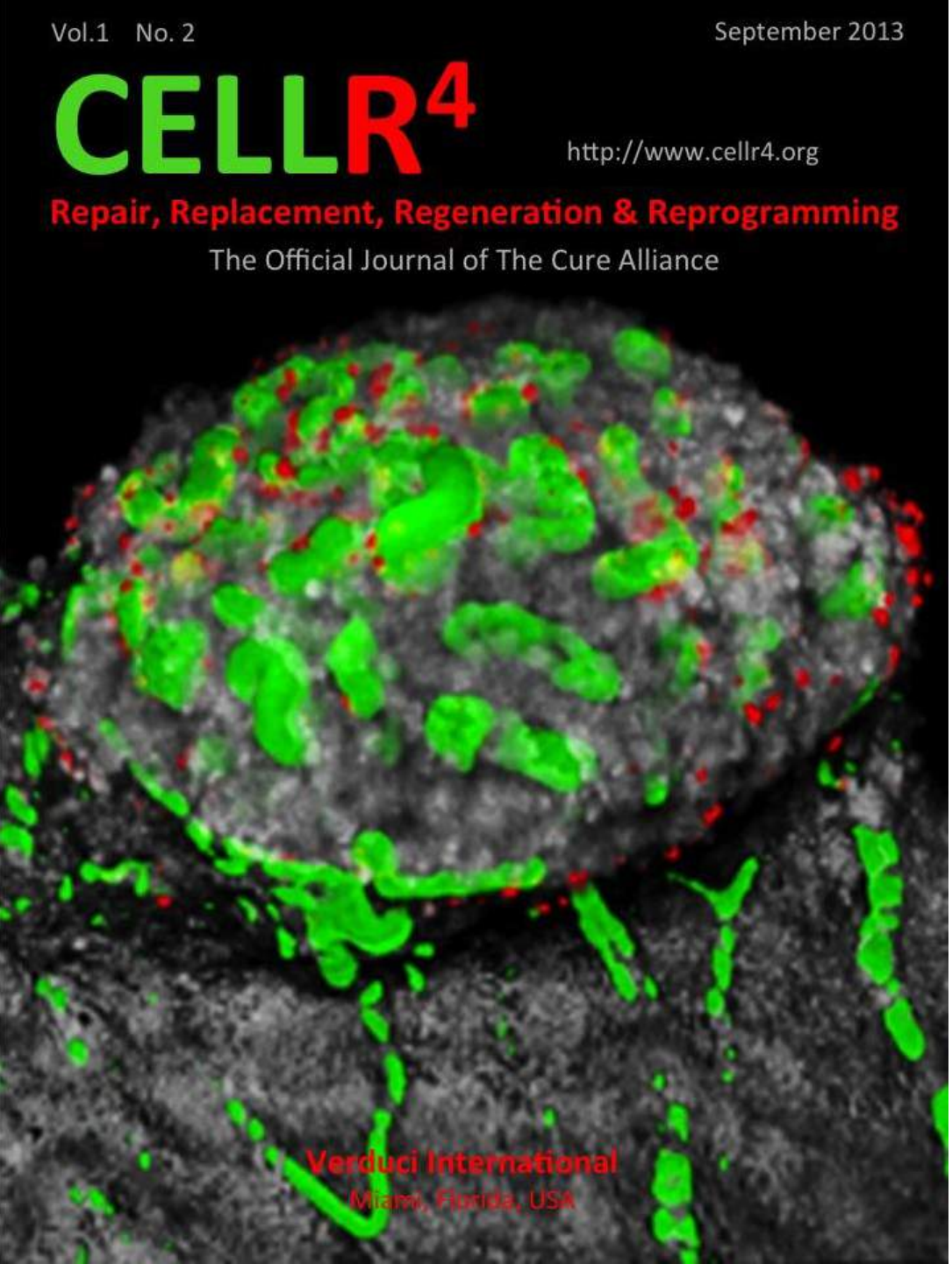
Reduction in carotid intima-media thickness after pancreatic islet transplantation in patients with type 1 diabetes.

Danielson KK**, Hatipoglu B**, Kinzer K, Kaplan B, Martelloto J, Qi M, Mele A, Benedetti E, Oberholzer J.

Diabetes Care 2013 Feb;36(2):450-6.

Cleveland Clinic

Every life deserves world class care.



www.CellR4.org

The Cure Alliance

An **international not-for-profit** association of scientists, physicians and committed individuals who share the **vision to promote international collaborations** while **overcoming the impediments and barriers to** the development of **cures** for disease conditions now afflicting humankind

Facebook: The Cure Alliance
Twitter: @CureAlliance

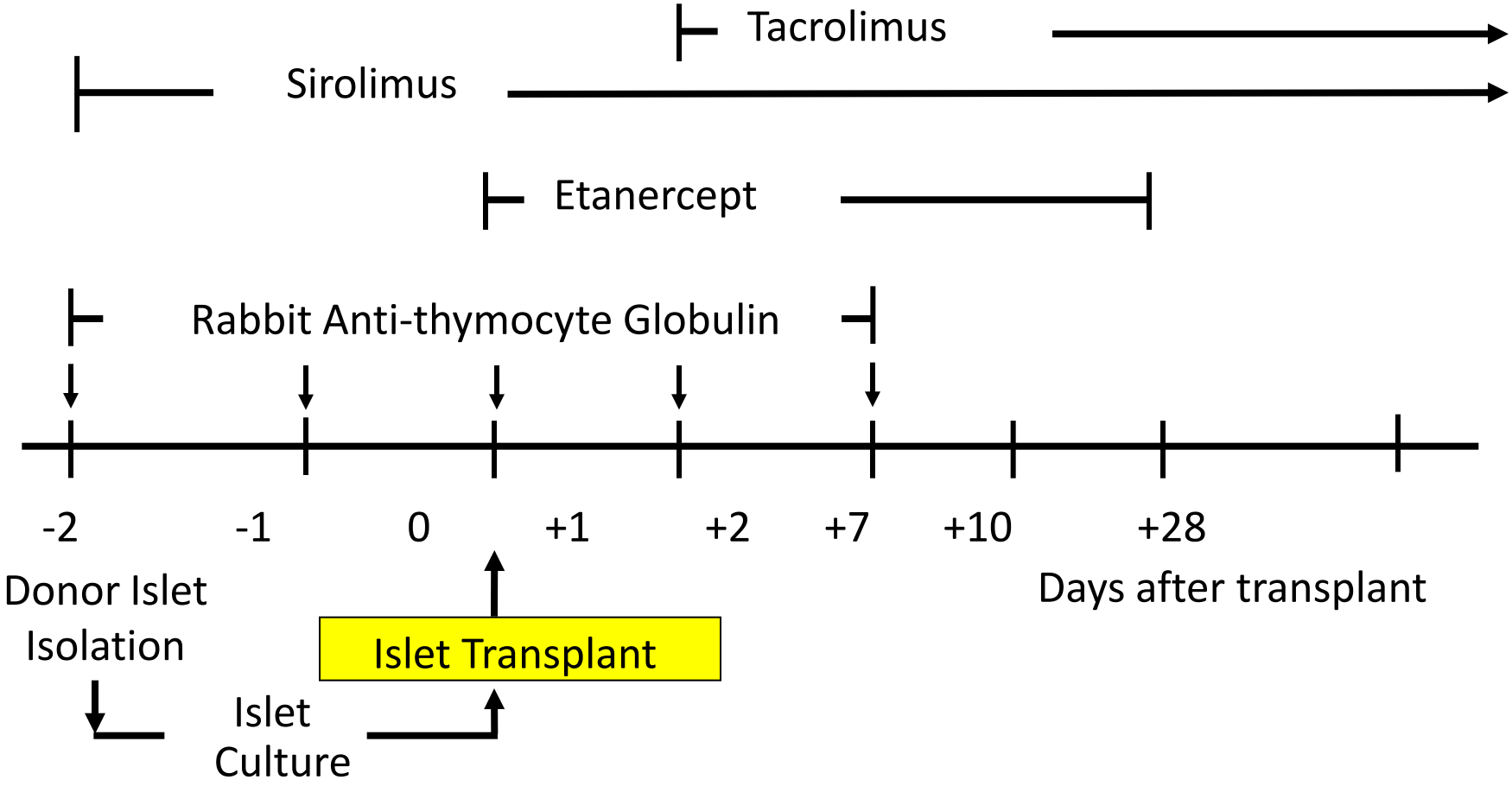
WWW.THECUREALLIANCE.ORG
THE CURE ALLIANCE

CIT-07

- A prospective, single-arm, multi-center **Phase III** study testing human islets in T1D
- Subjects will receive up to 3 separate infusions of islets within 8 months
- Accrual objective: **48 transplanted subjects** followed for at least 24 months (2year F/up 9/14)
- **Primary endpoint: The proportion of subjects with HbA1c < 7.0% at day 365 and free of severe hypoglycemic events from Day 28 to Day 365 following the first islet transplant**

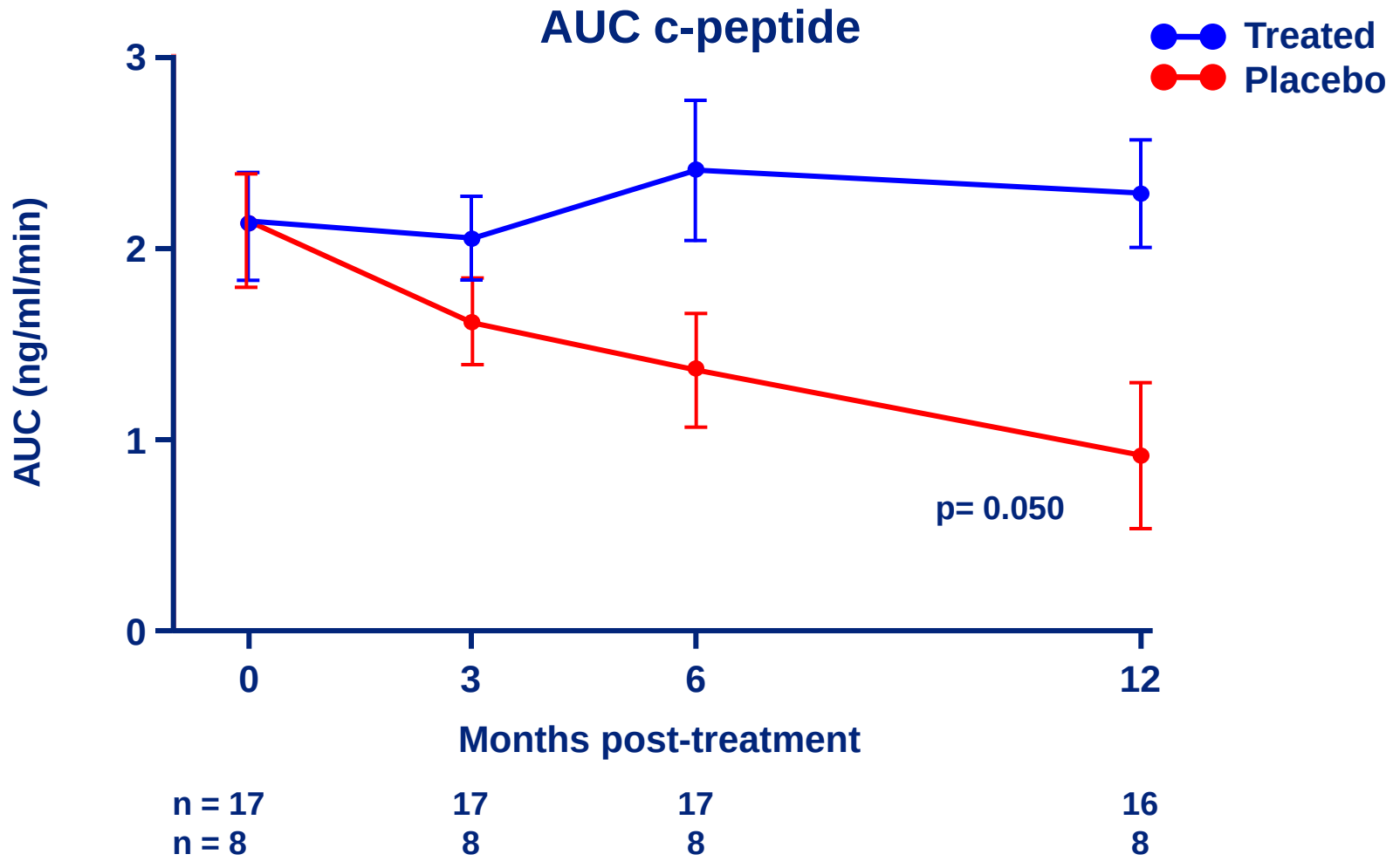
CIT-07 Treatment Protocol

Adapted from
JAMA 293; 830-5, 2005

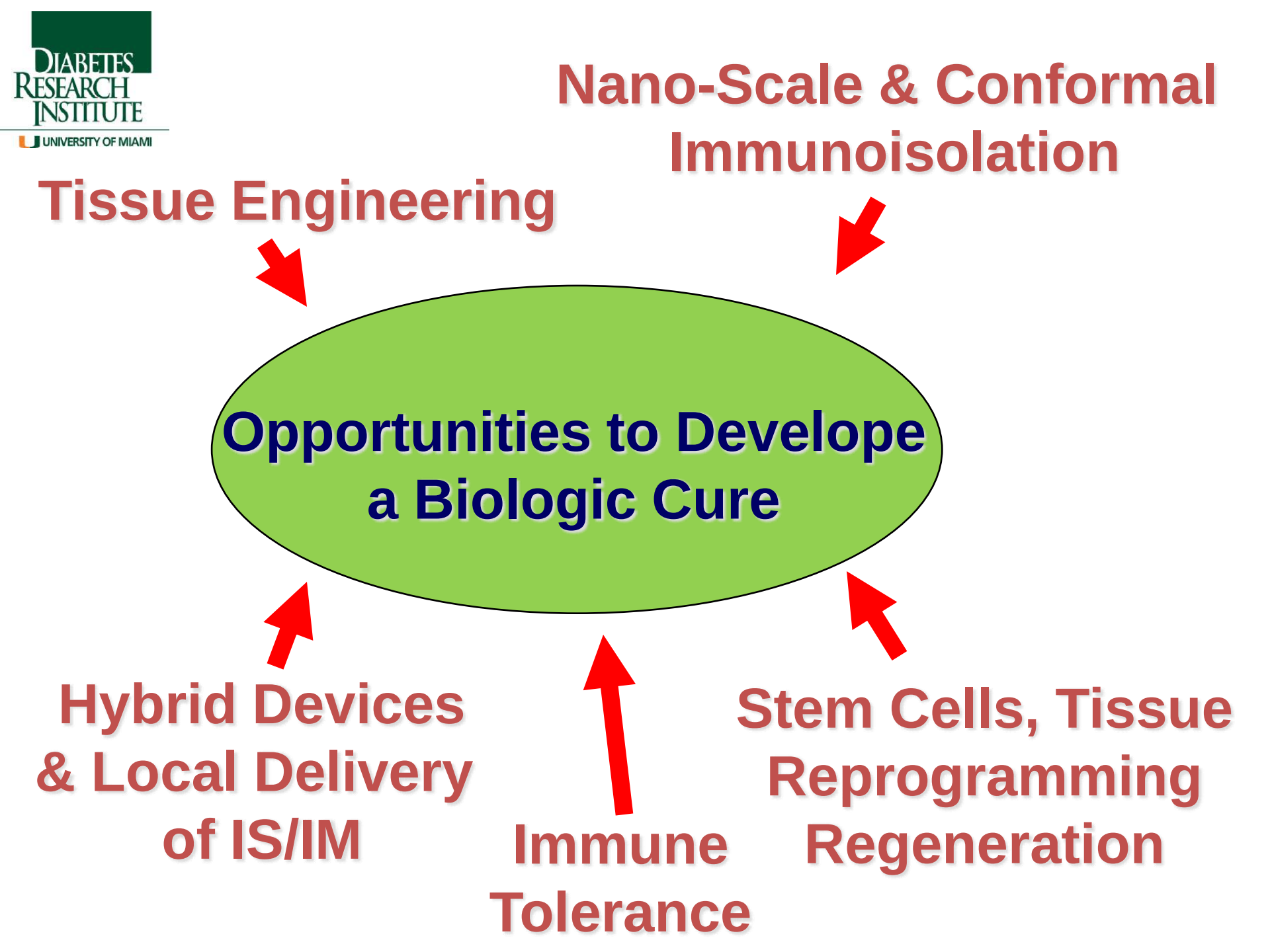


Subjects will receive up to 3 separate infusions of islets
Basiliximab instead of ATG for 2nd and 3rd transplants

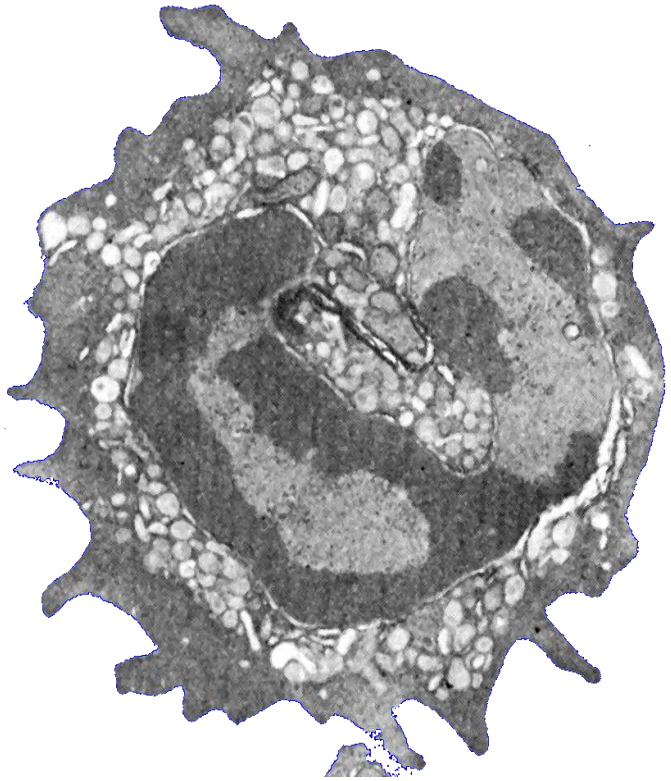
ATG/GCSF Combo Pilot Study Data Summary



Haller et al. ***Journal of Clinical Investigation*** 2015; In Press


Diabetes Research Institute
University of Miami
Nano-Scale & Conformal Immunoisolation
Tissue Engineering
Opportunities to Develope a Biologic Cure
Hybrid Devices & Local Delivery of IS/IM
Immune Tolerance
Stem Cells, Tissue Reprogramming Regeneration

Definition of the Facilitating Cell



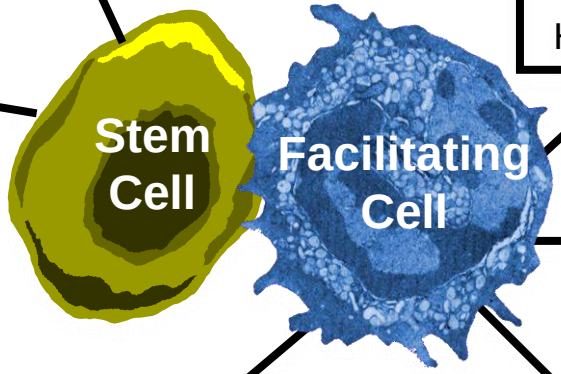
- $CD8^+$
- $\alpha\beta/\gamma\delta$ TCR^-
- Distinct from Stem Cell
- 65% resemble tolerogenic plasmacytoid dendritic cells ($B220^+/CD11c^+/CD116^-$)
- Induces antigen-specific T_{reg}
- Induces B_{reg}

Kaufman et al, *Blood* 1994, 84(8):2436-2446
Fugier-Vivier et al, *J Exp Med* 2005, 201(3):373-383
Huang et al, *Blood* 2010, 117(8):2494-2905

Regenerex
Facilitating cell therapy

Institute for Cellular Therapeutics

Facilitating Cell Mechanism of Action



Induces IL-10^{-} B_{reg} *in vitro*

Induces antigen-specific T_{reg} *in vivo*

Taylor KN, *J Immunol 2007,* 15;179(4):2153-62
Huang Y, *Blood* 2011, 117(8):2494-2505

Enhances homing and migration DOCK2

Wen, *Stem Cells*, 2014 32(10):2732-43

Prevents apoptosis of HSC

Rezzoug F, *J Immunol* 2008, 180(1):49-57

↑Clonogenicity of HSC

Fugier-Vivier I, *J Exp Med* 2005, 201(3):373-383
Rezzoug F, *J Immunol* 2008, 180(1):49-57

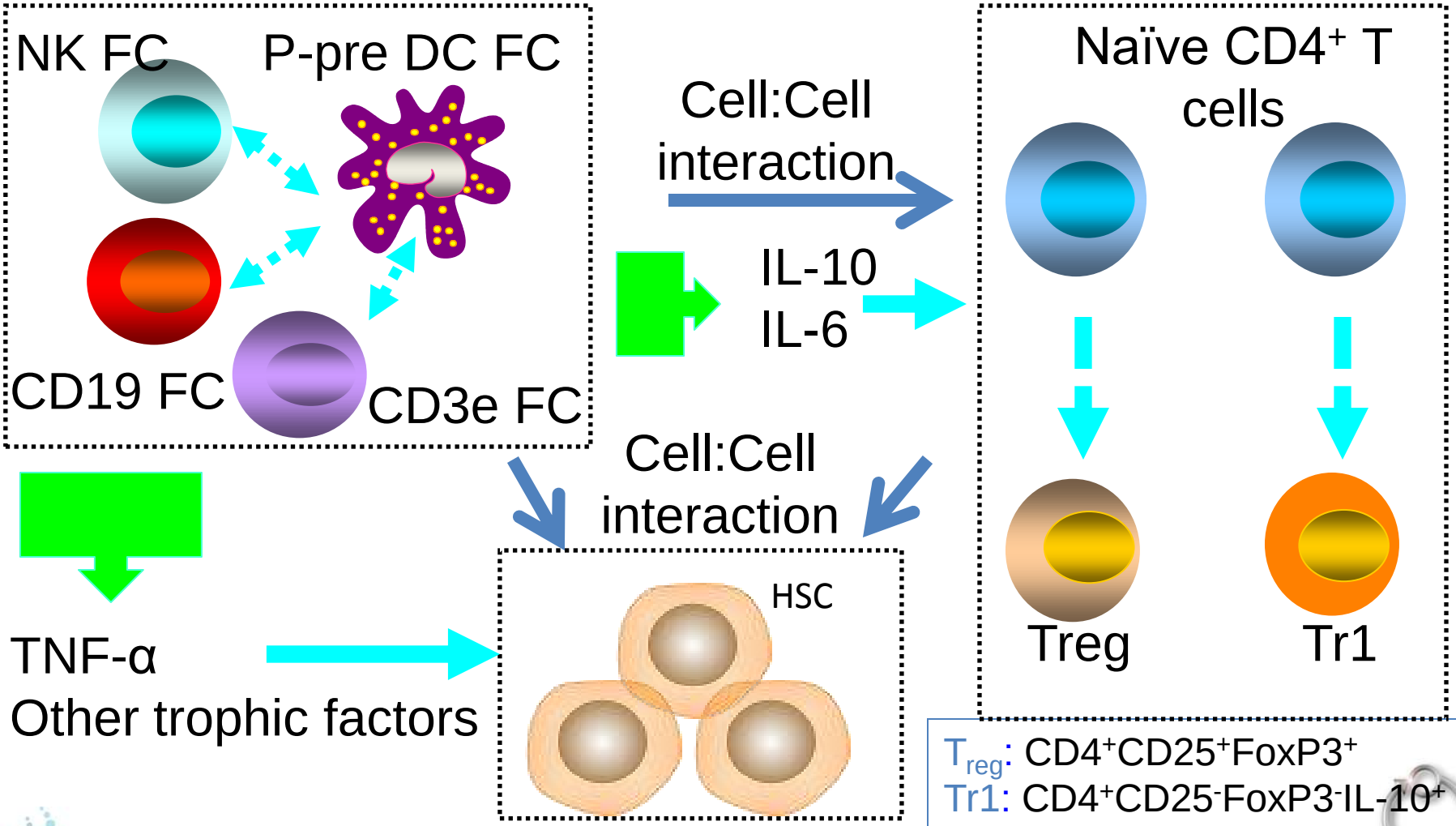
Prevents GVHD in mice

Taylor KN, *J Immunol 2007,* 15;179(4):2153-62

Regenerex
Facilitating cell therapy

Institute for Cellular Therapeutics

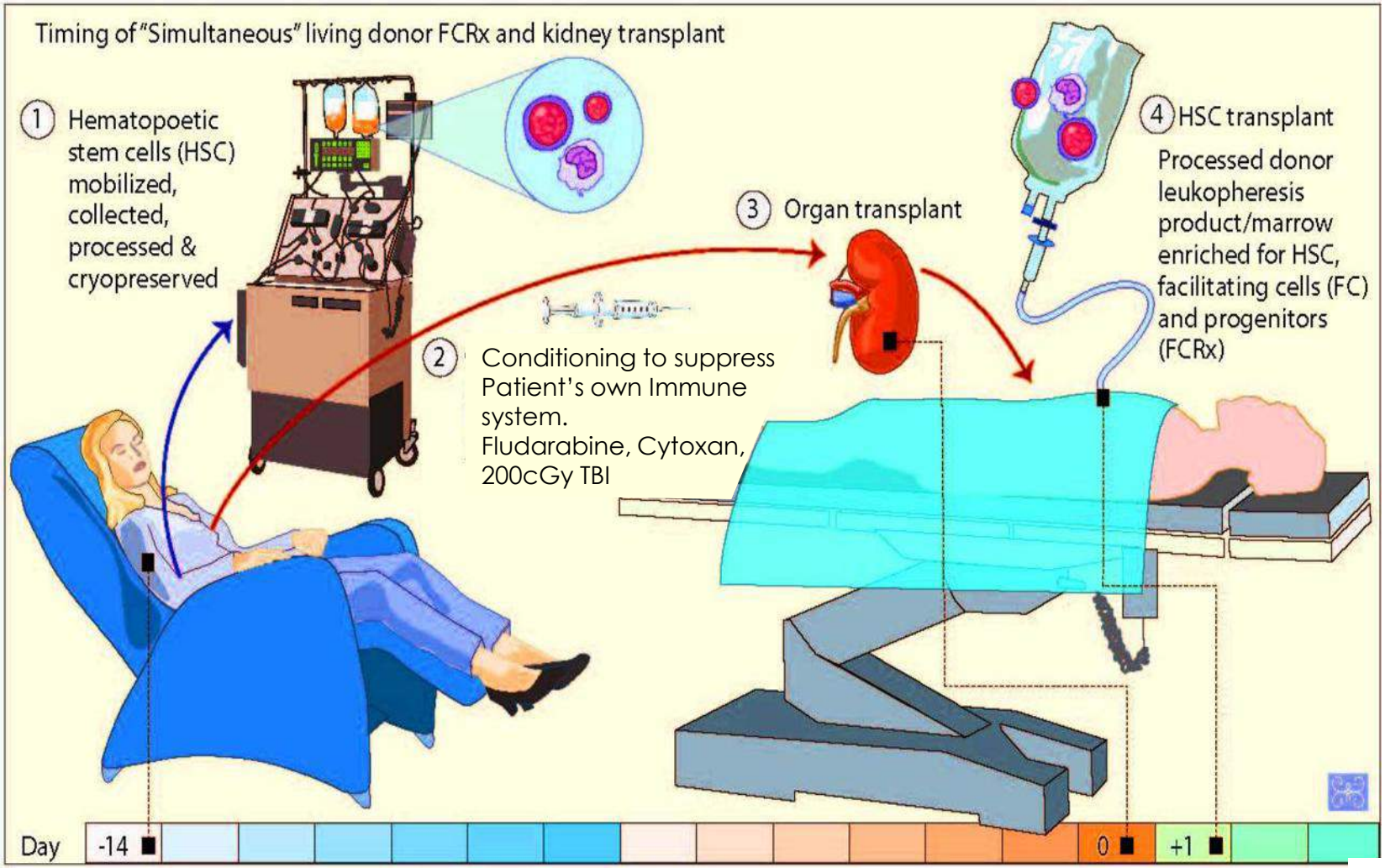
Mechanism by which FC Enhance HSC Engraftment without GVHD



Regenerex
Facilitating cell therapy

Institute for Cellular Therapeutics

Simultaneous FCRx + Kidney Transplant



Leventhal J et al, *J Clin Pharmacol Thera*, September 2012

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UNIVERSITY OF MIAMI

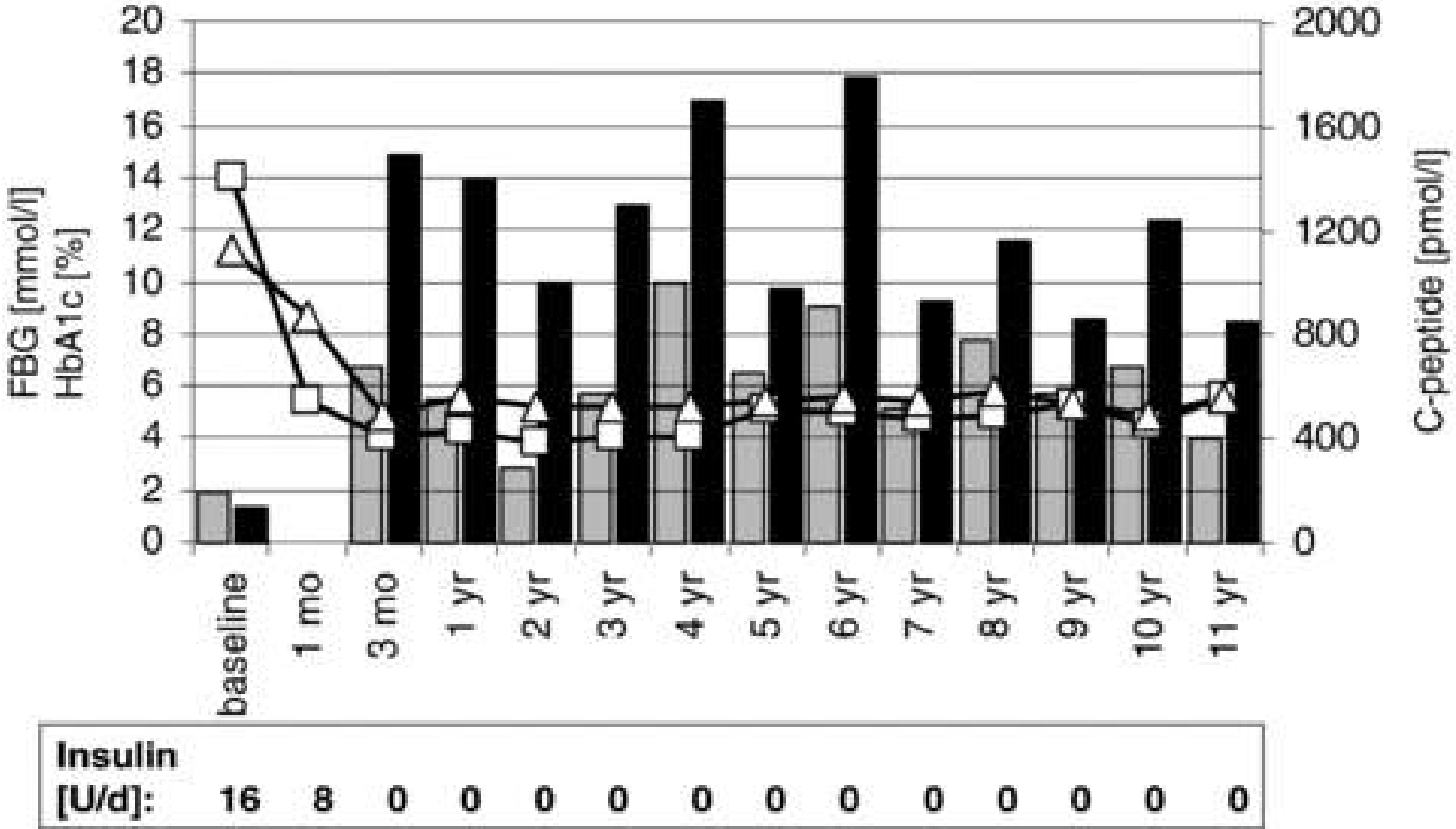
DRI FEDERATION

American Journal of Transplantation
AST ASTS
OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF TRANSPLANTATION AND THE AMERICAN SOCIETY OF TRANSPLANT SURGEONS

Long-Term Insulin-Independence After Allogeneic Islet Transplantation for Type 1 Diabetes: Over the 10-Year Mark

T. Berneya, S. Ferrari-Lacrazb, L. Buhlera,J. Oberholzera, N. Marangond, J. Philippee, J. Villardb and P. Morela

American Journal of Transplantation 2009; 9: 419–423



Wolters Kluwer Health | Lippincott Williams & Wilkins

Transplantation

THE OFFICIAL JOURNAL OF THE TRANSPLANTATION SOCIETY

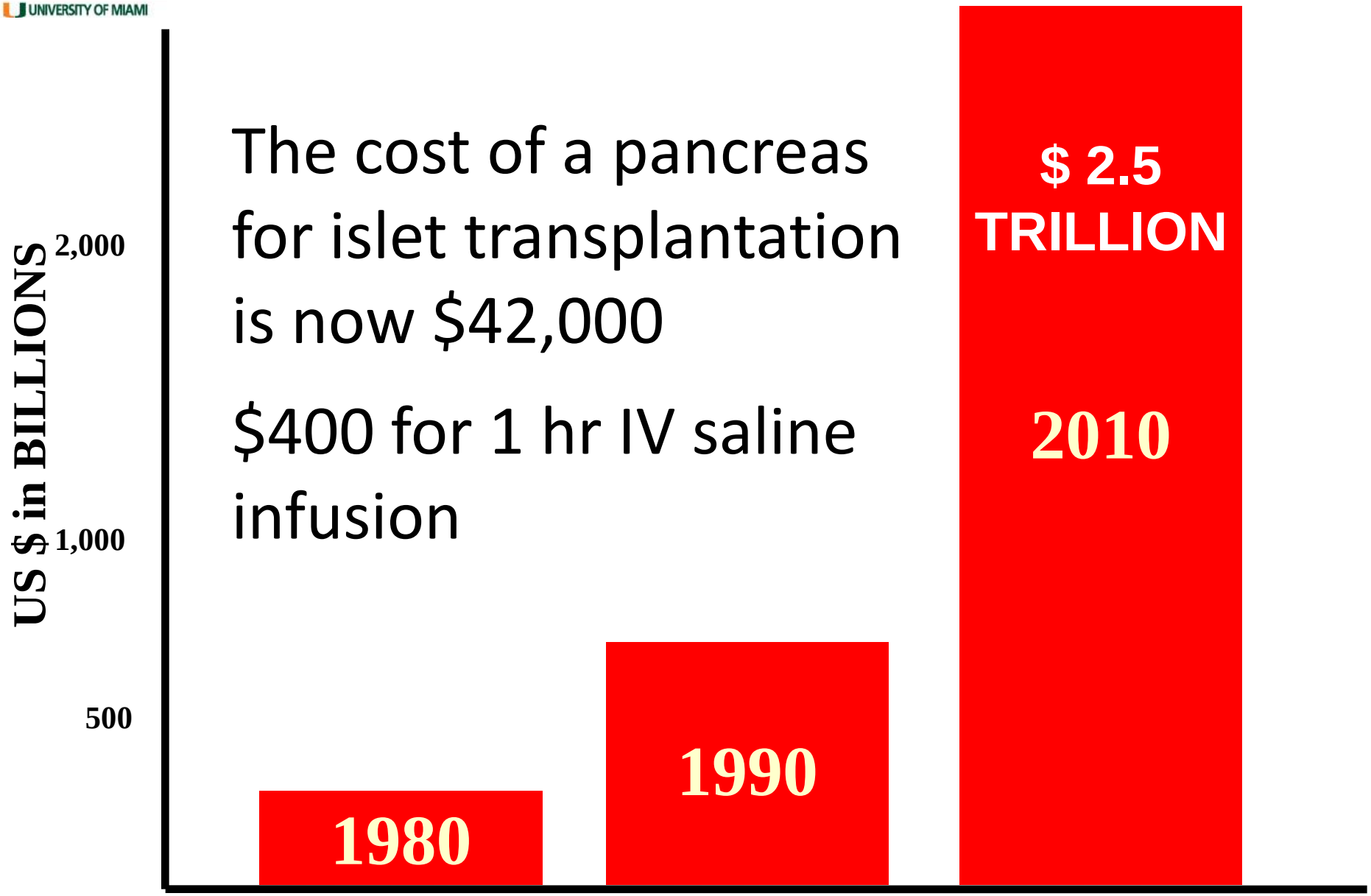
Pathology of an Islet Transplant 2 Years After Transplantation: Evidence for a Nonimmunological Loss

Smith, R Neal; Kent, Sally C.; Nagle, Julie; Selig, Martin; Iafrate, A John; Najafian, Nader; Hafler, David A.; Auchincloss, Hugh; Orban, Tihamer; Cagliero, Enrico

Volume 86(1), 15 July 2008, pp 54-62

DIABETES RESEARCH INSTITUTE
UNIVERSITY OF MIAMI

USA Health Care Spending

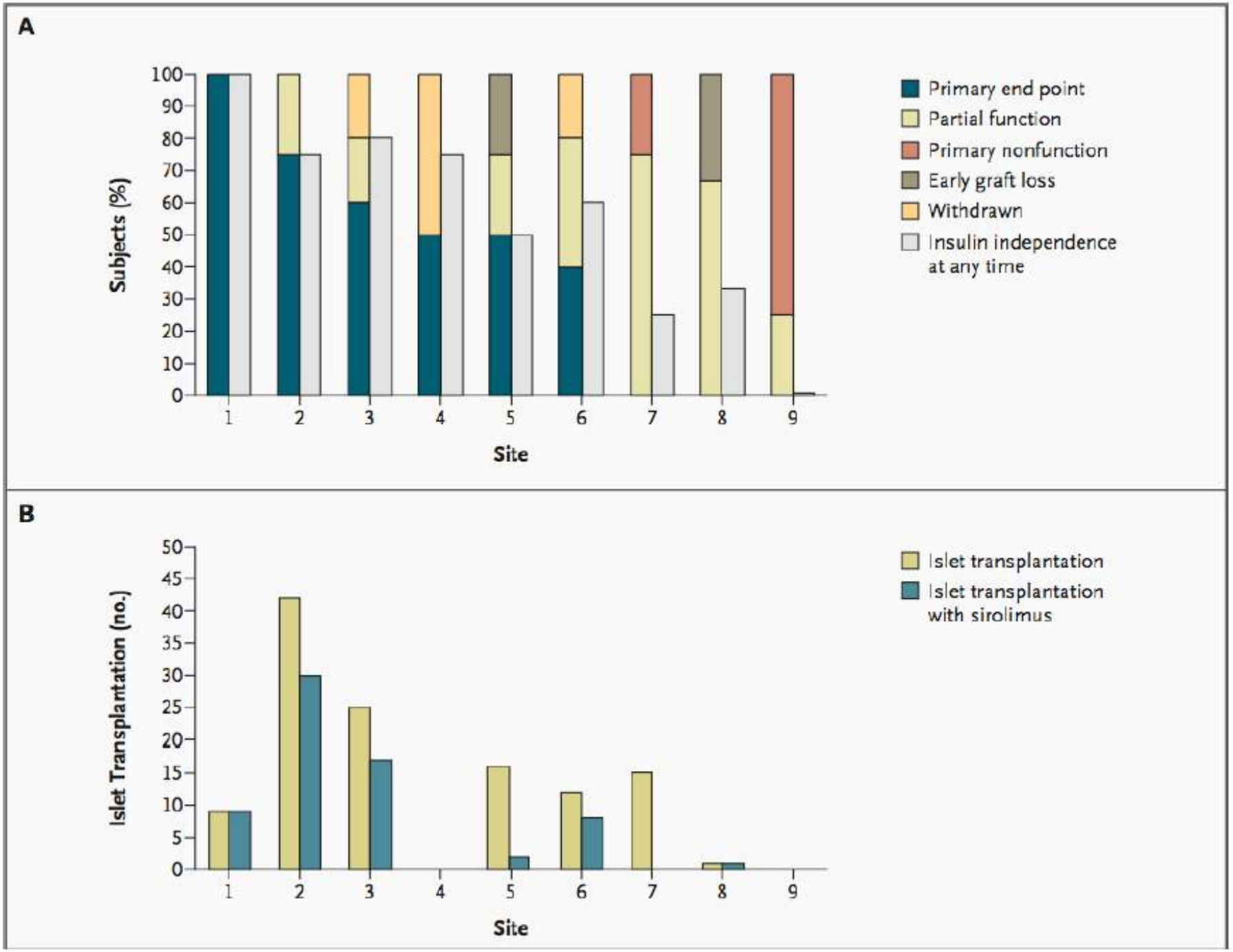


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

International Trial of the Edmonton Protocol for Islet Transplantation

A.M. James Shapiro, M.D., Ph.D., Camillo Ricordi, M.D., Bernhard J. Hering, M.D., Hugh Auchincloss, M.D., Robert Lindblad, M.D., R. Paul Robertson, M.D., Antonio Secchi, M.D., Mathias D. Brendel, M.D., Thierry Berney, M.D., Daniel C. Brennan, M.D., Enrico Cagliero, M.D., Rodolfo Alejandro, M.D., Edmond A. Ryan, M.D., Barbara DiMercurio, R.N., Philippe Morel, M.D., Kenneth S. Polonsky, M.D., Jo-Anna Reems, Ph.D., Reinhard G. Bretzel, M.D., Federico Bertuzzi, M.D., Tatiana Froud, M.D., Raja Kandaswamy, M.D., David E.R. Sutherland, M.D., Ph.D., George Eisenbarth, M.D., Ph.D., Miriam Segal, Ph.D., Jutta Preiksaitis, M.D., Gregory S. Korbutt, Ph.D., Franca B. Barton, M.S., Lisa Viviano, R.N., Vicki Seyfert-Margolis, Ph.D., Jeffrey Bluestone, Ph.D., and Jonathan R.T. Lakey, Ph.D.


A
Subjects (%)
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
9
Site
Primary end point
Partial function
Primary nonfunction
Early graft loss
Withdrawn
Insulin independence at any time
B
Islet Transplantation (no.)
50
45
40
35
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
9
Site
Islet transplantation
Islet transplantation with sirolimus