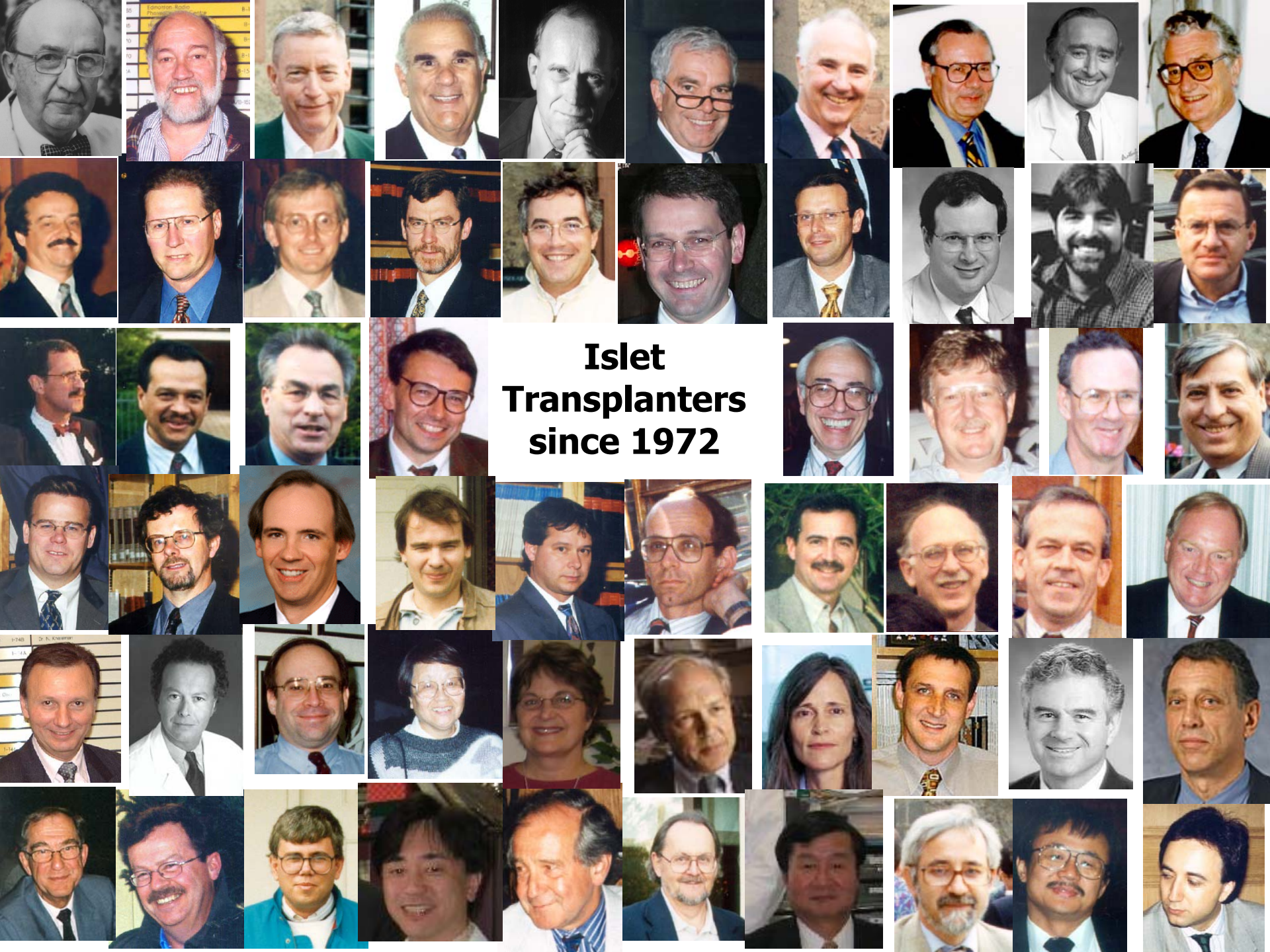
Islet Transplantation Past, Present, and Future

Bernhard J. Hering
Diabetes Institute for Immunology and Transplantation
University of Minnesota


Islet
Transplanters
since 1972

Islet Transplantation

- Past: Insulin independence
- Present: Implementation
- Future: Innovation

The Past

Viable Islet Mass Transplanted Inadequate

Low Engrafted Islet Mass

Insulin Action Impaired by Diabetes

High Metabolic Demand

Barriers to Insulin Independence

Engraftment Impaired by Hypoxia and Immunity

Insulin Action And Secretion Impaired by Diabetogenic Drugs

Immunologic Graft Loss

Innate Immune Response

Alloimmune Rejection

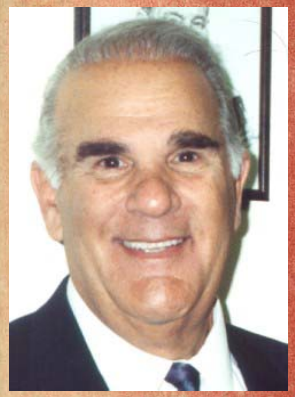
Autoimmune Recurrence

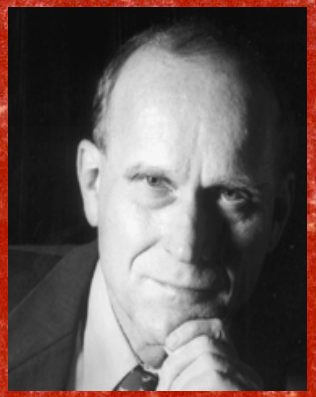
Hering & Ricordi; Graft 1999

VOL. IX, NO. 1 MARCH 1977

Sutherland

TRANSPLANTATION PROCEEDINGS





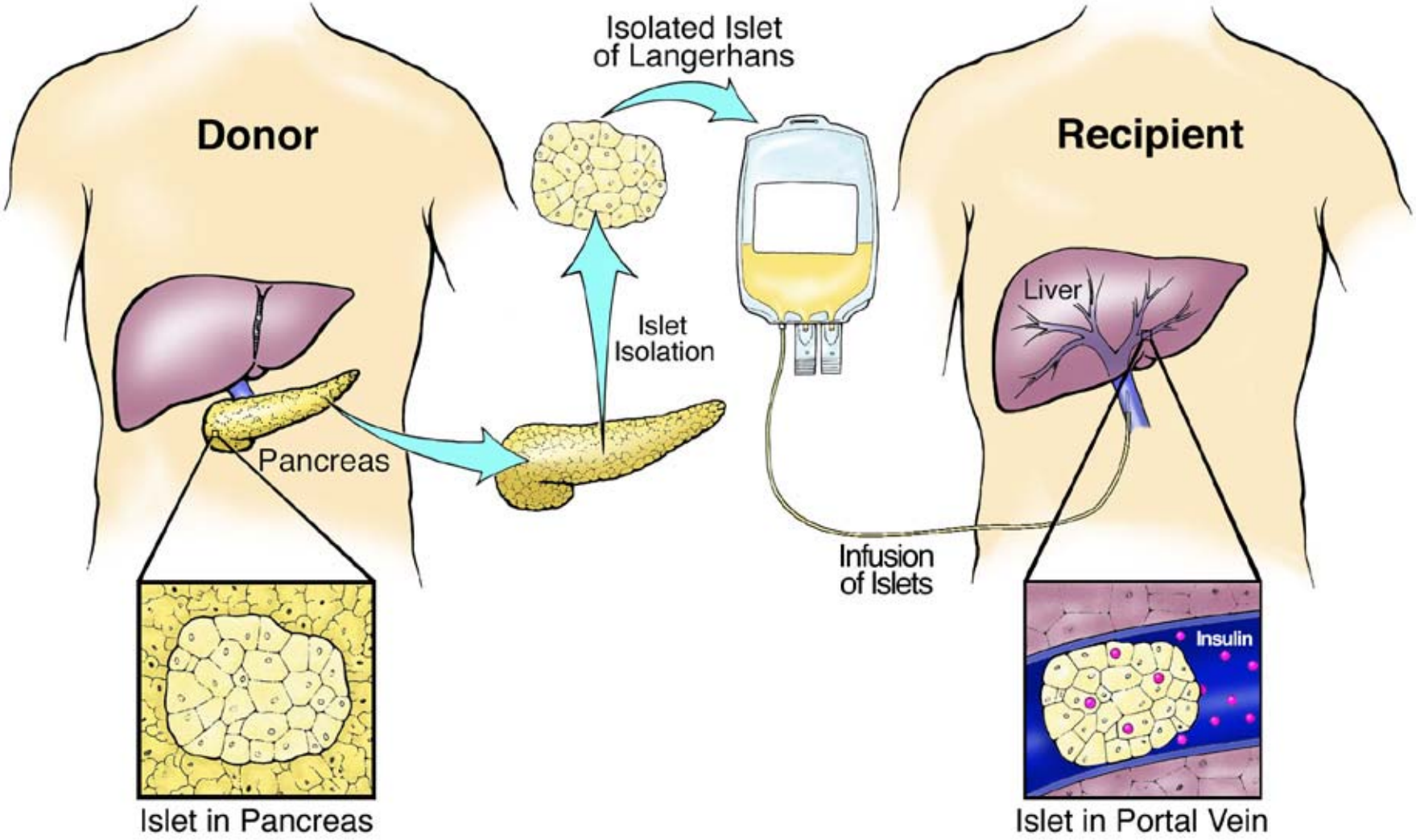
An Official Publication of
The Transplantation Society
The American Association for Clinical Histocompatibility Testing

Human Islet Transplantation: A Preliminary Report

J. S. Najarian, D. E. R. Sutherland, A. J. Matas, M. W. Steffes,
R. L. Simmons, and F. C. Goetz

Transplantation Proceedings, Vol. IX, No. 1 (March), 1977

The "1974" Islet Transplant Protocol

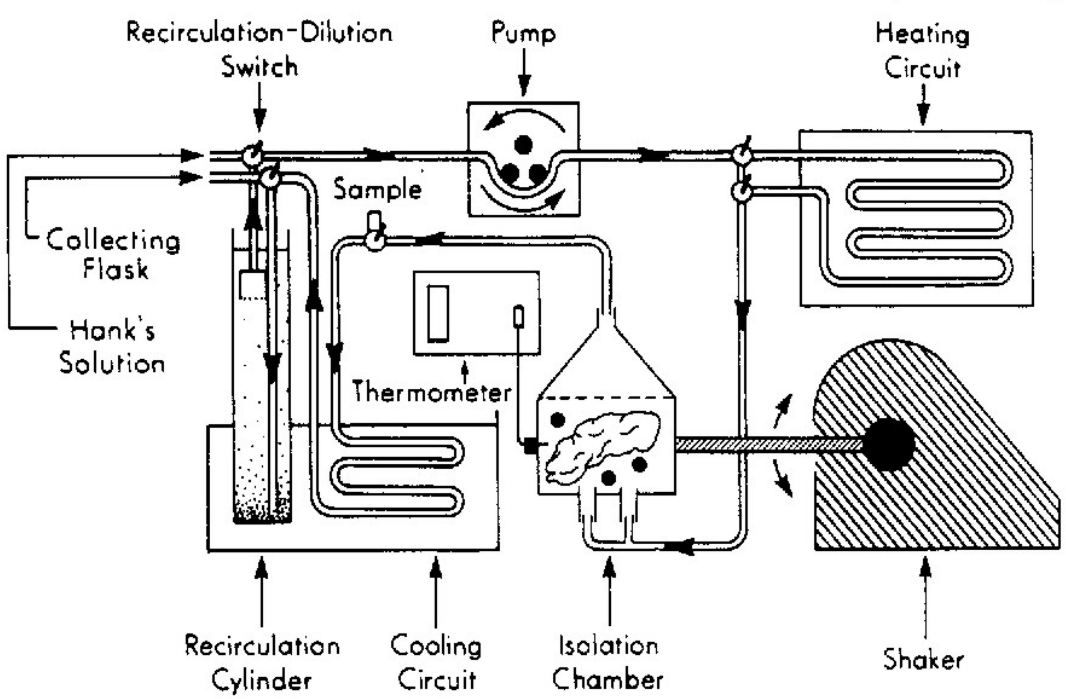


Key features: Deceased donor, collagenase, density gradients, portal vein, ALG

Automated Islet Isolation From Human Pancreas

CAMILLO RICORDI, PAUL E. LACY, AND DAVID W. SCHARP

DIABETES, VCL. 38, SUPPL. 1, JANUARY 1989



Ricordi C et al., Diabetes 1988

Insulin Independence After Islet Transplantation Into Type I Diabetic Patient

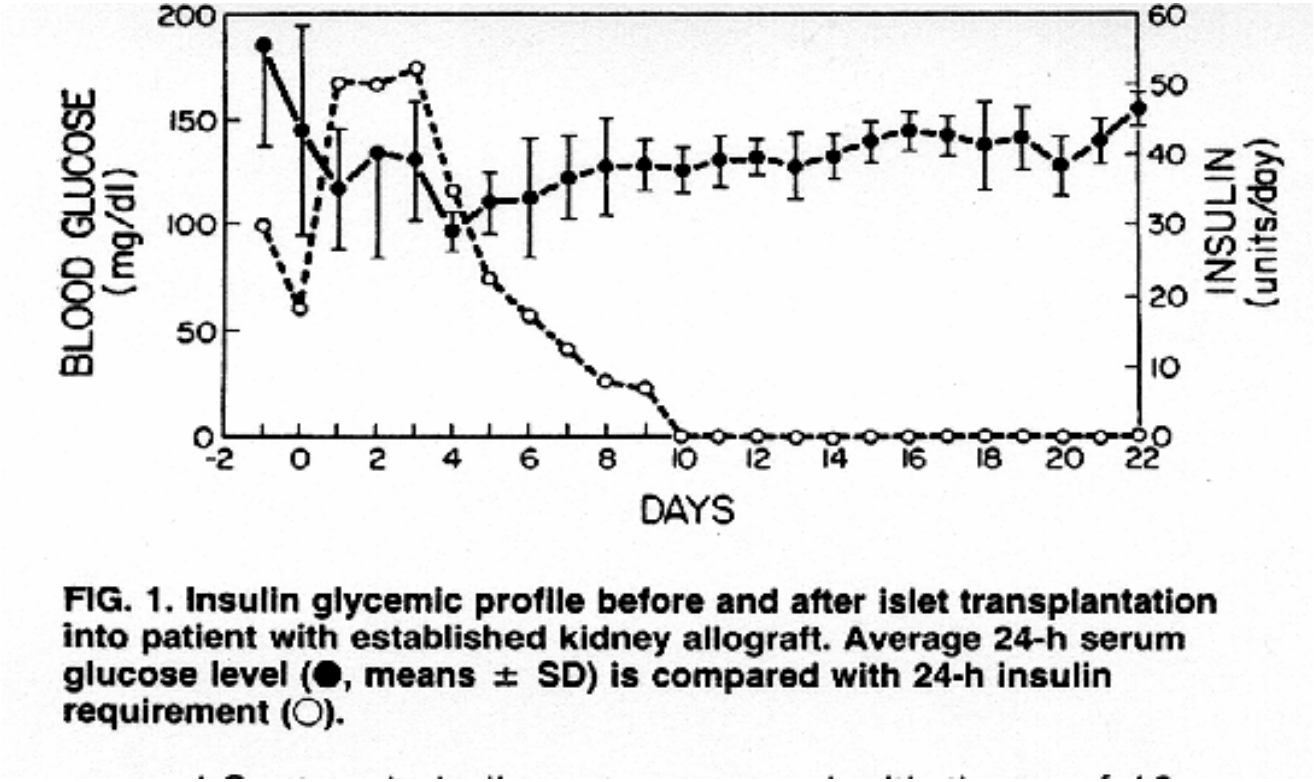
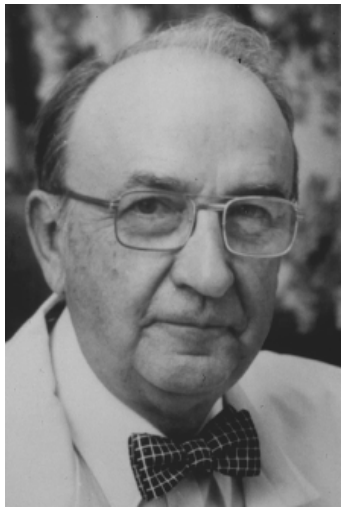


FIG. 1. Insulin glycemic profile before and after islet transplantation into patient with established kidney allograft. Average 24-h serum glucose level (●, means ± SD) is compared with 24-h insulin requirement (○).



Islets were prepared from 2 donor pancreases

Scharp DW, Lacy PE, Santiago JV et al., *Diabetes 1990*

THE LANCET

Pancreatic islet transplantation after upper abdominal exenteration and liver replacement

ANDREAS G. TZAKIS CAMILLO RICORDI RODOLFO ALEJANDRO
YIJUN ZENG JOHN J. FUNG SATORU TODO
ANTHONY J. DEMETRIS DANIEL H. MINTZ THOMAS E. STARZL

- Transplants:
  Simultaneous islet-liver transplants in 9 patients with hepatobiliary malignancies and surgical diabetes
- Immunosuppression:
  No steroids, tacrolimus monotherapy
- Results:
  7/9 pts became insulin-independent;
  5/9 insulin-independent at 1 yr

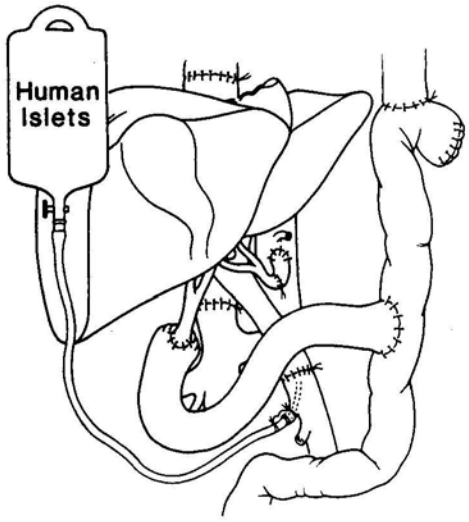
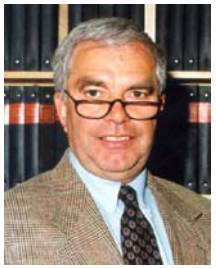


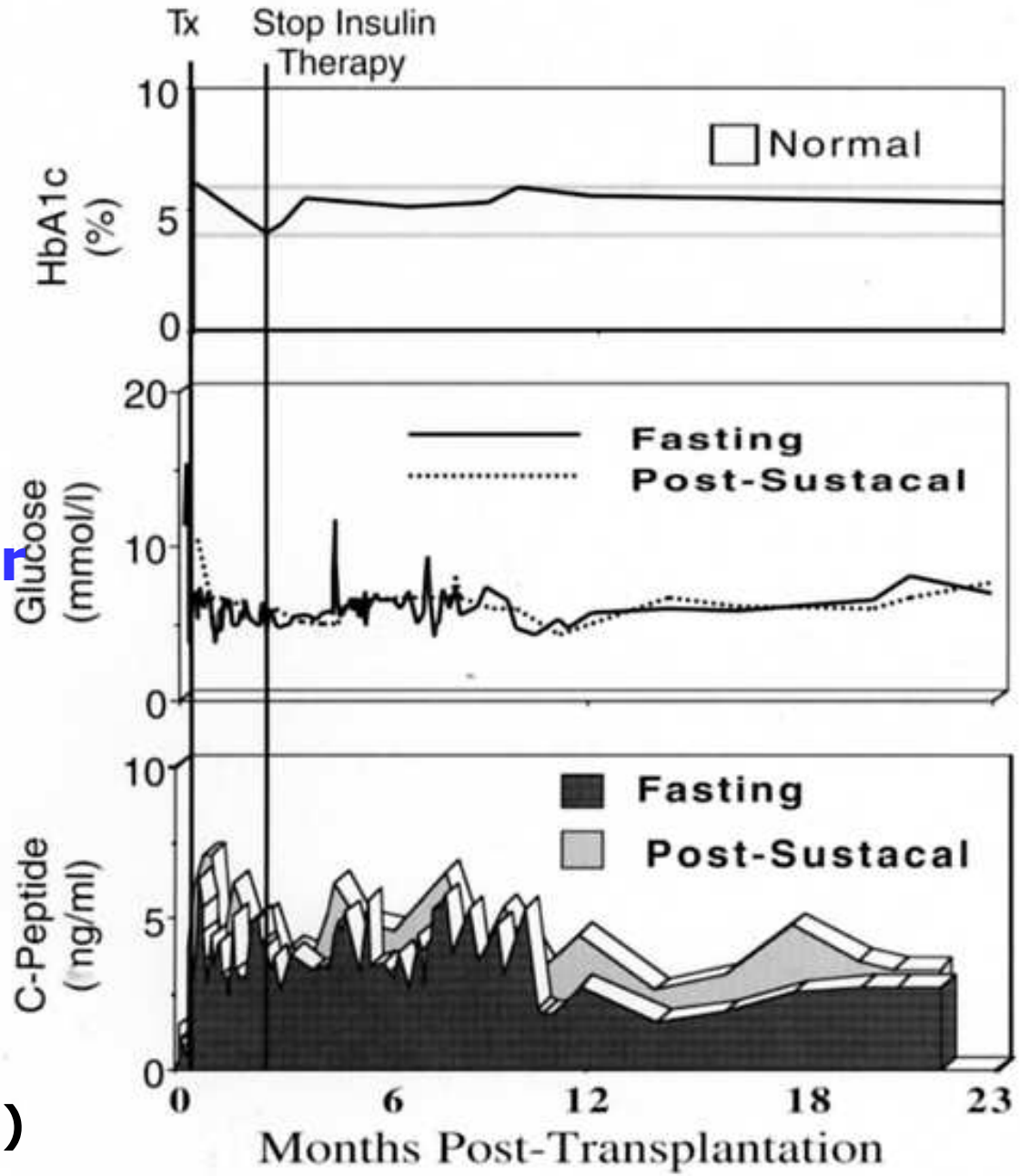
Fig 1—Liver and pancreatic islet transplantation after upper abdominal exenteration.

Lancet 1990; 336: 402-05



1st example of insulin independence and euglycemia for >1 year duration after islet transplantation

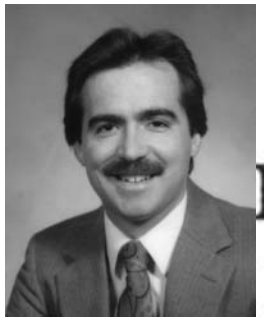
The graft contained 243,000 fresh IE from 1 donor (syngeneic with the kidney graft) and 368,000 cryopreserved IE from 4 donors (total 10,000 IE/kg)



Warnock GL et al., Diabetologia 1991/1992

THE LANCET

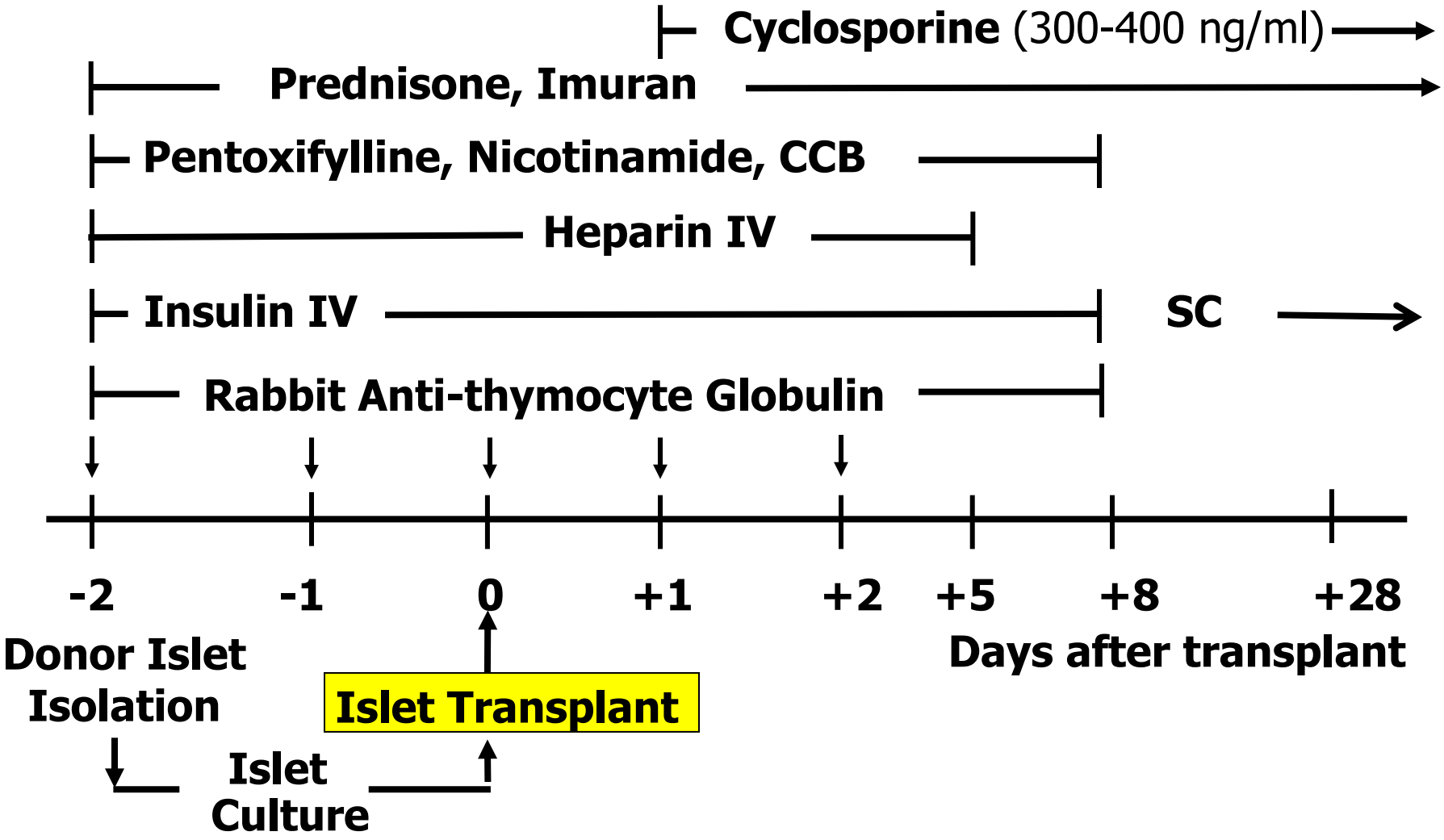
Insulin independence in type I diabetes after transplantation of unpurified islets from single donor with 15-deoxyspergualin



PAUL F. GORES JOHN S. NAJARIAN
EDIC STEPHANIAN J. J. LLOVERAS
SUSAN L. KELLEY DAVID E. R. SUTHERLAND

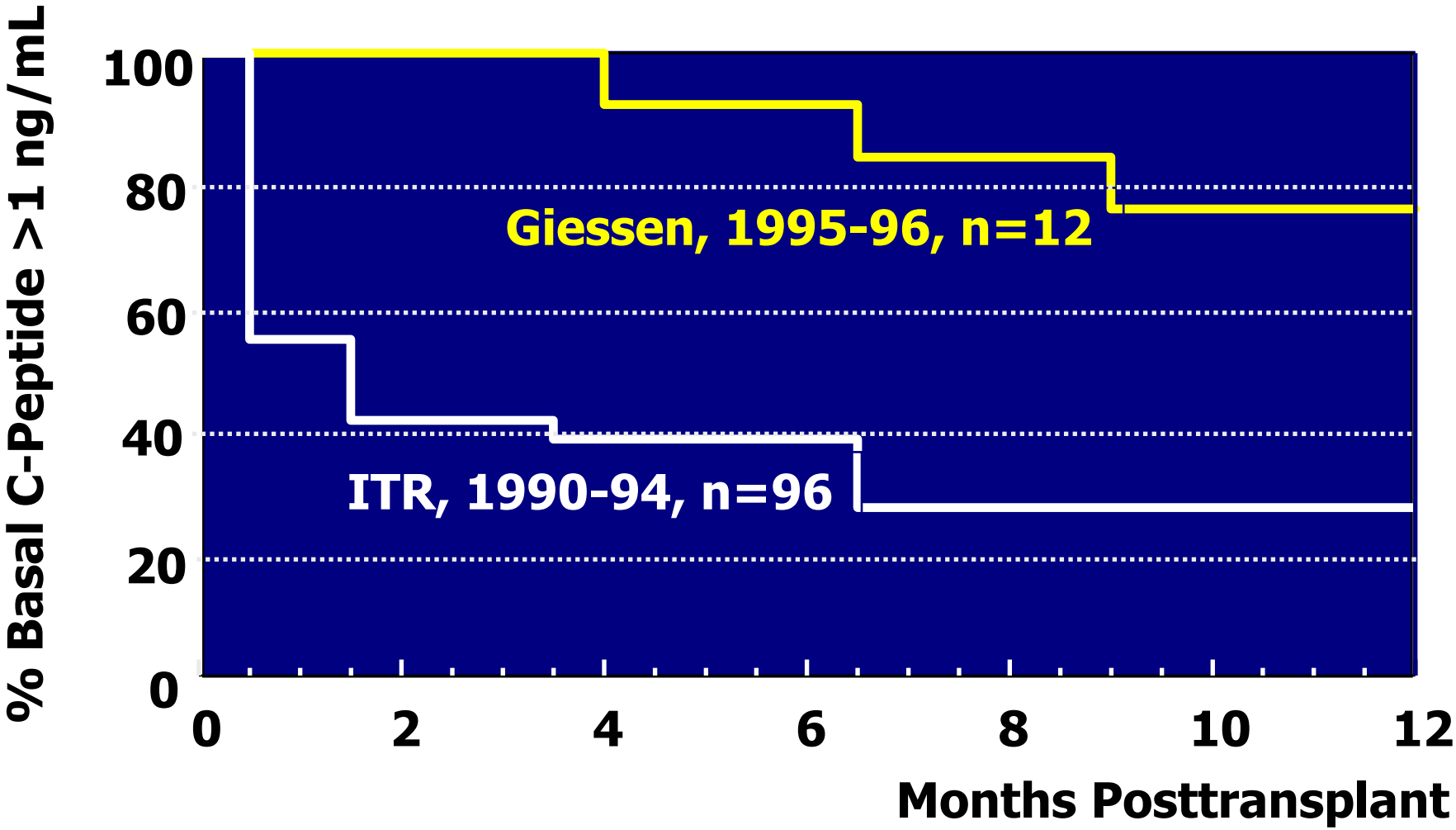
Lancet 1993; 341: 19-21

Giessen 1992 Protocol



Hering BJ et al., *Transplantation Proceedings* 1994

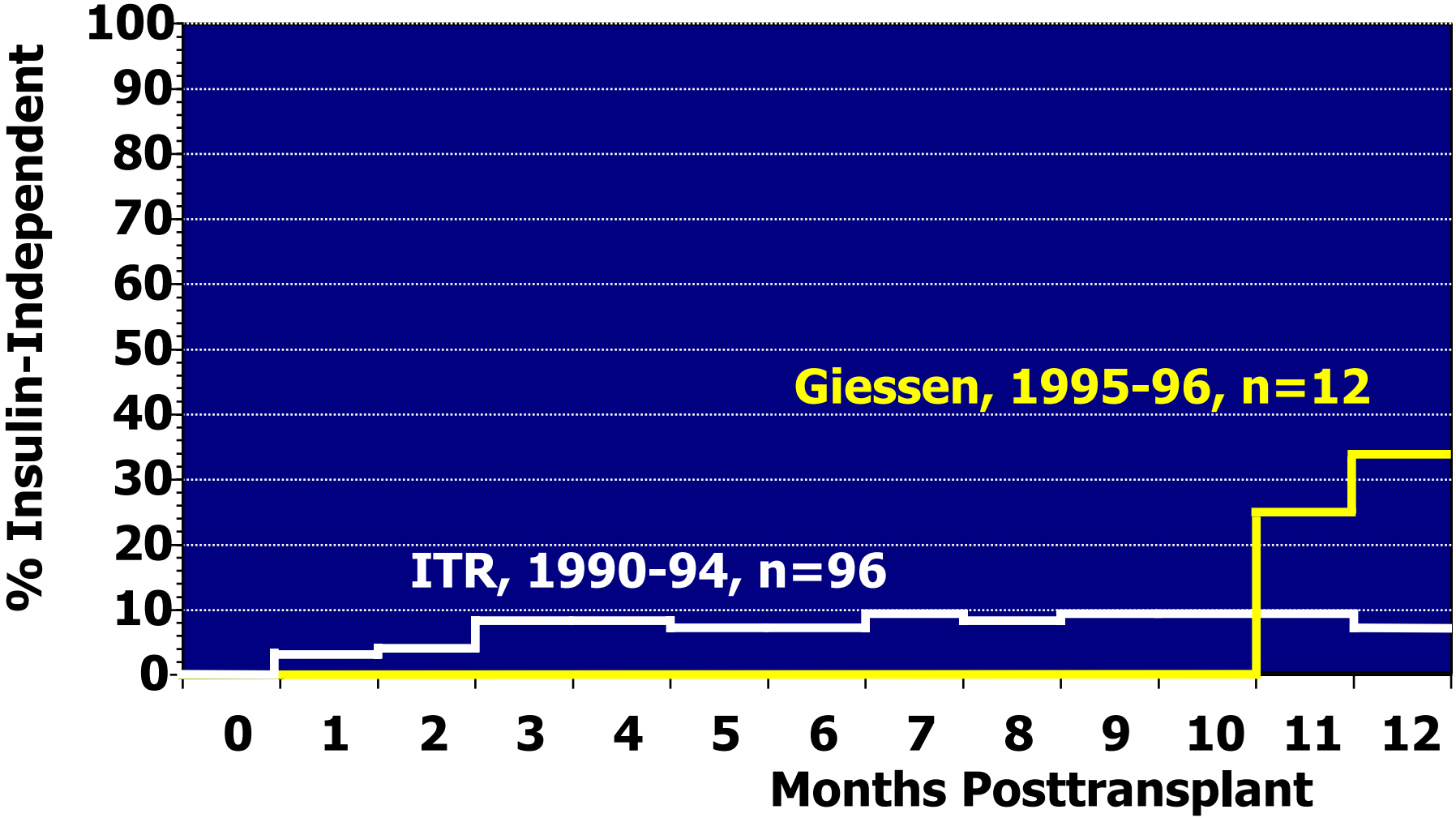
Islet Allograft Survival
in C-Peptide Neg. Type 1 Diabetic Recipients



Hering BJ et al., *Diabetes* 46 (Suppl. 1): 64A, 1997

Islet Allograft Survival

in C-Peptide Neg. Type 1 Diabetic Recipients



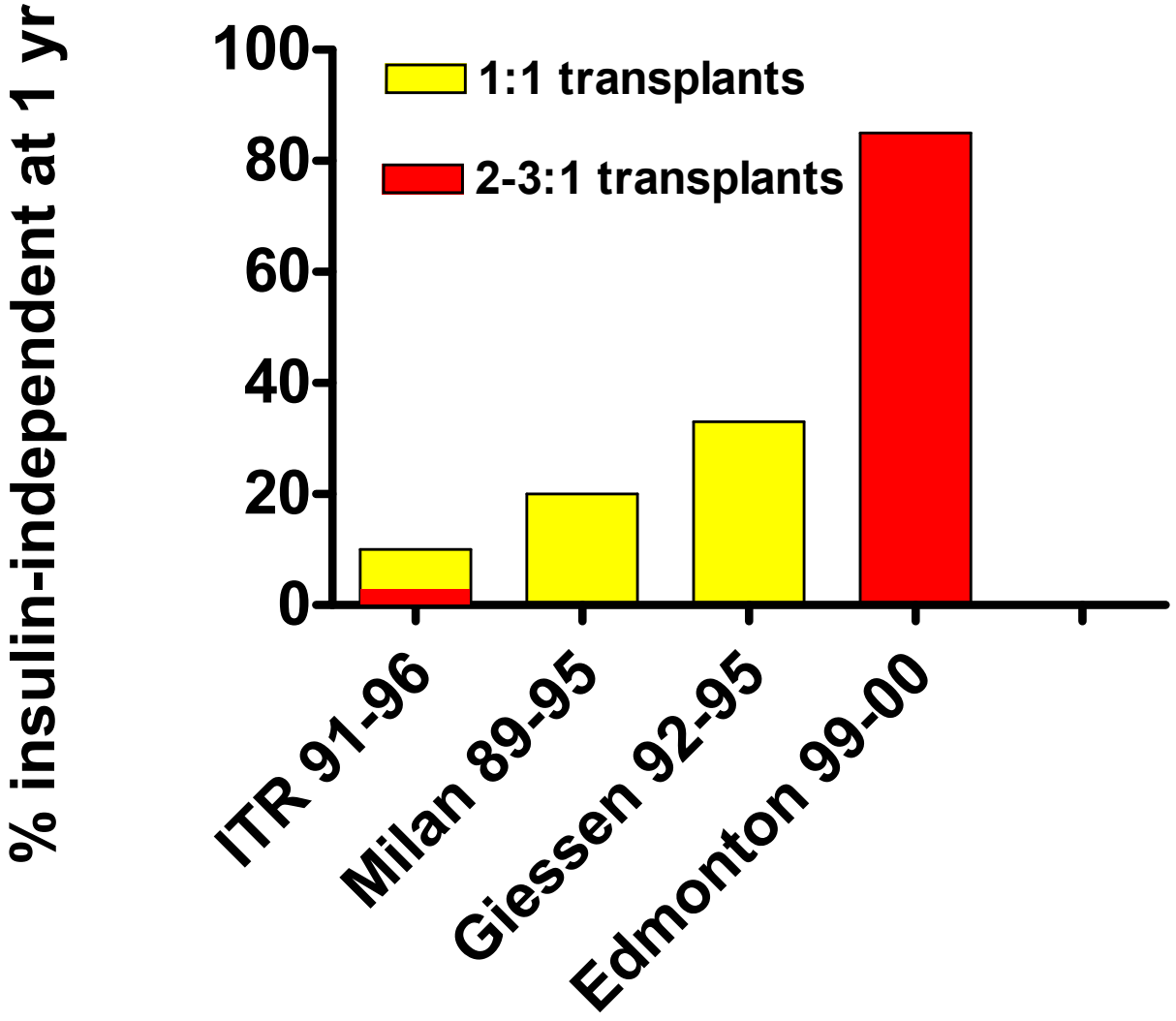
Hering BJ et al., *Diabetes* 46 (Suppl. 1): 64A, 1997

1998 First T1D Islet Recipient Insulin-Free for > 5 Years

- Type 1 diabetic recipient of an islet-after-kidney-allograft
- Washington University, St. Louis, MO)

Transplantation Proceedings 29, 2231-2133, 1997

Success rates of islet transplants for T1D



Human Islet Allotransplantation

The New England
Journal of Medicine

VOLUME 343 JULY 27, 2000 NUMBER 4

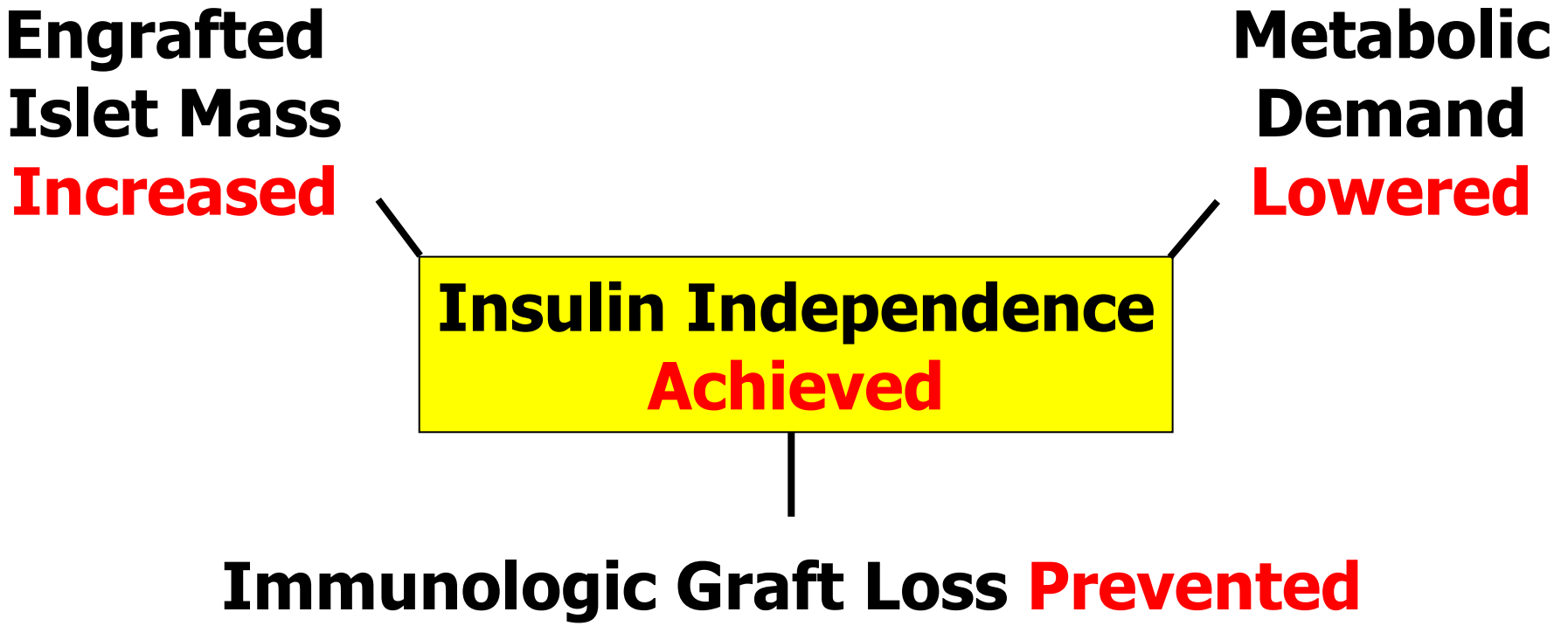
ISLET TRANSPLANTATION IN SEVEN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING A GLUCOCORTICOID-FREE IMMUNOSUPPRESSIVE REGIMEN

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.

- Immunosuppression:
  No steroids. Daclizumab + Rapamycin + Tacrolimus
- Donor tissue:
  Cadaver donor islets from 2-3 pancreata/recipient
- Current results:
  33 pts w/ T1D; insulin-free: 85% (1 yr), 71% (2 yrs)

Shapiro et al., NEJM 2000

The Past


Engrafted
Islet Mass
Increased
Metabolic
Demand
Lowered
Insulin Independence
Achieved
Immunologic Graft Loss Prevented

Islet transplant activity
(1999-2003)

Edmonton (58)
Miami (27)
Minneapolis (20)
NIH (6)
Northwestern (5)
U Penn (9)
Harvard (6)
Houston (7)
St Louis (8)
Cincinnati (6)
U. Maryland (1)
Seattle (6)
U Mass (2)
Memphis (3)
Emory (2)
Vancouver (6)

Nordic Network (11)
Geneva/GRAGIL (19)
Milan (35)
Zurich (10)
Giessen (27)
Kings (UK) (1)
Sydney (3)
Innsbruck (11)

Over 300 patients

Red = ITA
Blue= ITA and SIK/IAK
Black= SIK/IAK

The Present

Cost Utility and Longevity Unknown

Low Efficiency

Multiple Donor Pancreata Required

Poor Interaction with Diabetes Care Community

Uneven Integration

Procedural Risks Minimal But Present

Unproven Safety

Long-term Risks of New Drug Regimens Unknown

Barriers to Implementation

Limited Availability

Manufacturing Environment Can't Deliver Against Demand

Logistics of Pancreas Allocation Unresolved

3rd-Party Reimbursement Not Addressed

Present Priorities

- Single-donor Islet Transplants
- Steroid- and CNI-free Regimens
- FDA Biologics License Application
- **Randomized Clinical Trial (Islets vs Insulin)**

Single-donor islet transplants will …

- Reduce costs per patient by $75,000
- Allow ultimate validation of islet potency assays
- Facilitate evaluation of immunotherapeutic protocols

- Promote FDA approval and insurarance coverage
- Promote donor pancreas allocation to islet patients
- Promote overall availability of islet transplantation

Single-Donor Islet Transplantation

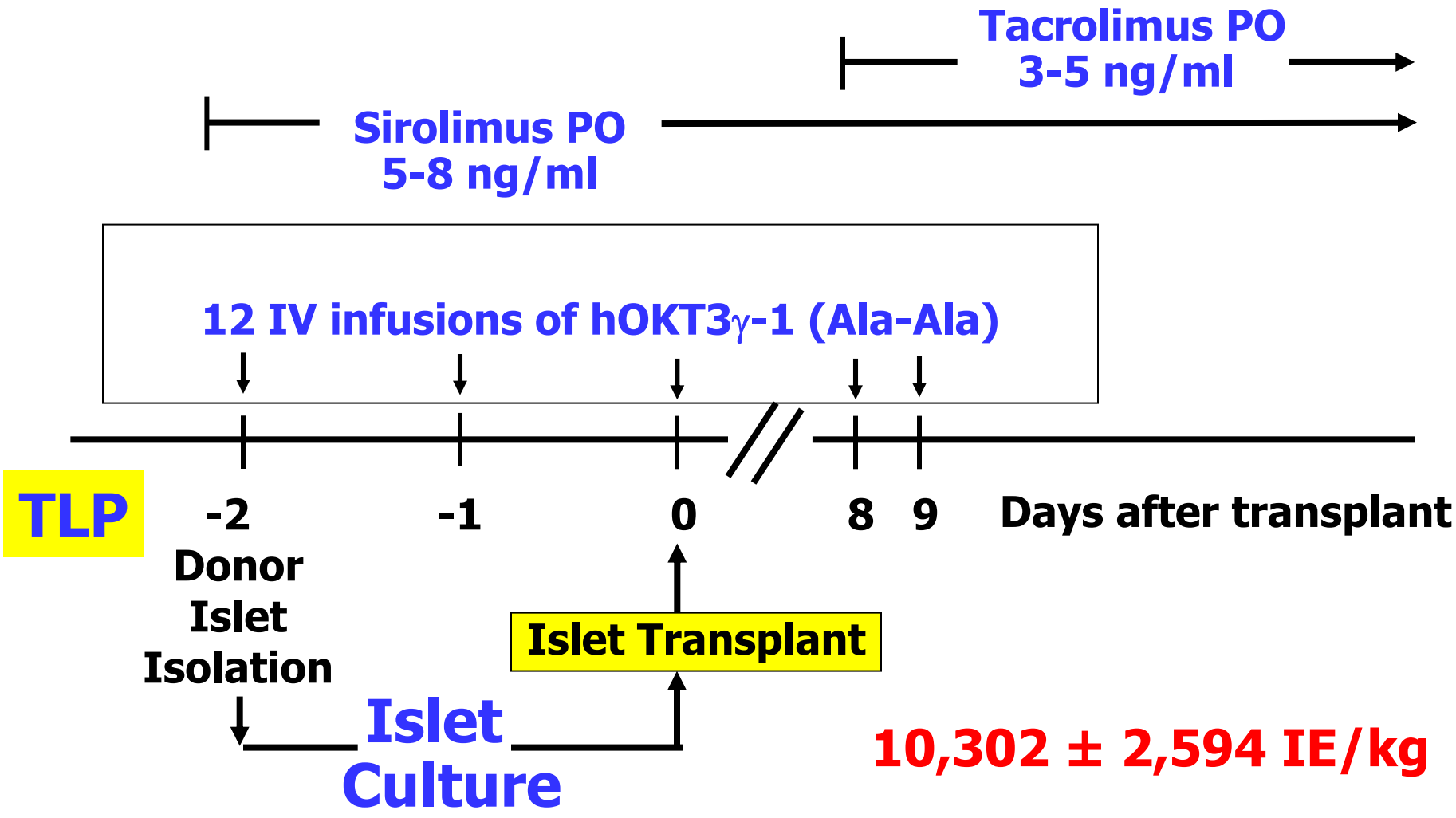
American Journal of Transplantation

Transplantation of Cultured Islets from Two-Layer Preserved Pancreases in Type 1 Diabetes with Anti-CD3 Antibody

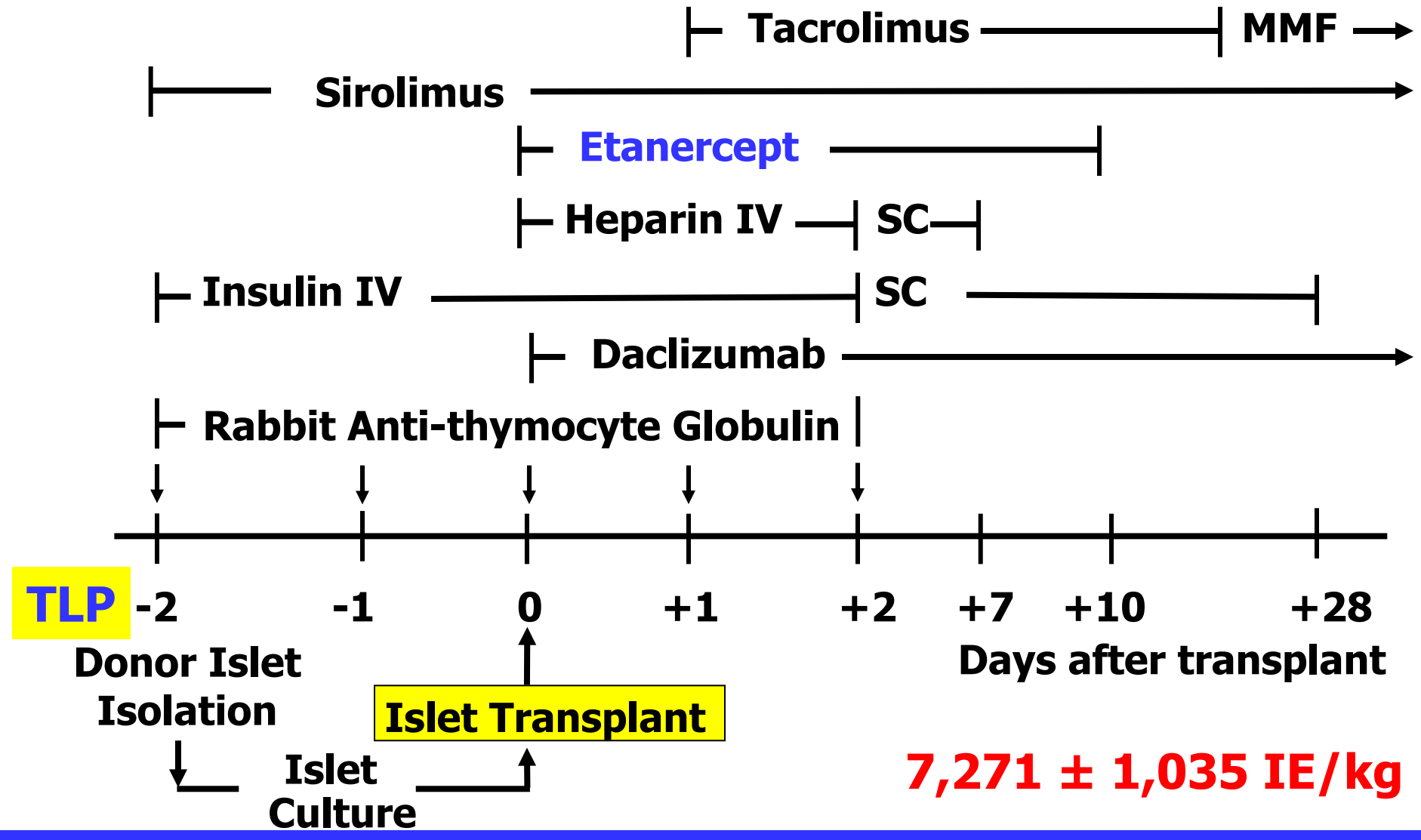
- **4 of 6 recipients achieved insulin independence after single-donor islet transplantation**
- **Induction immunotherapy with the anti-CD3 mAb hOKT3g1 (Ala-Ala) may facilitate minimization of maintenance immunosuppression**

Hering et al., Am J Transplantation 2004

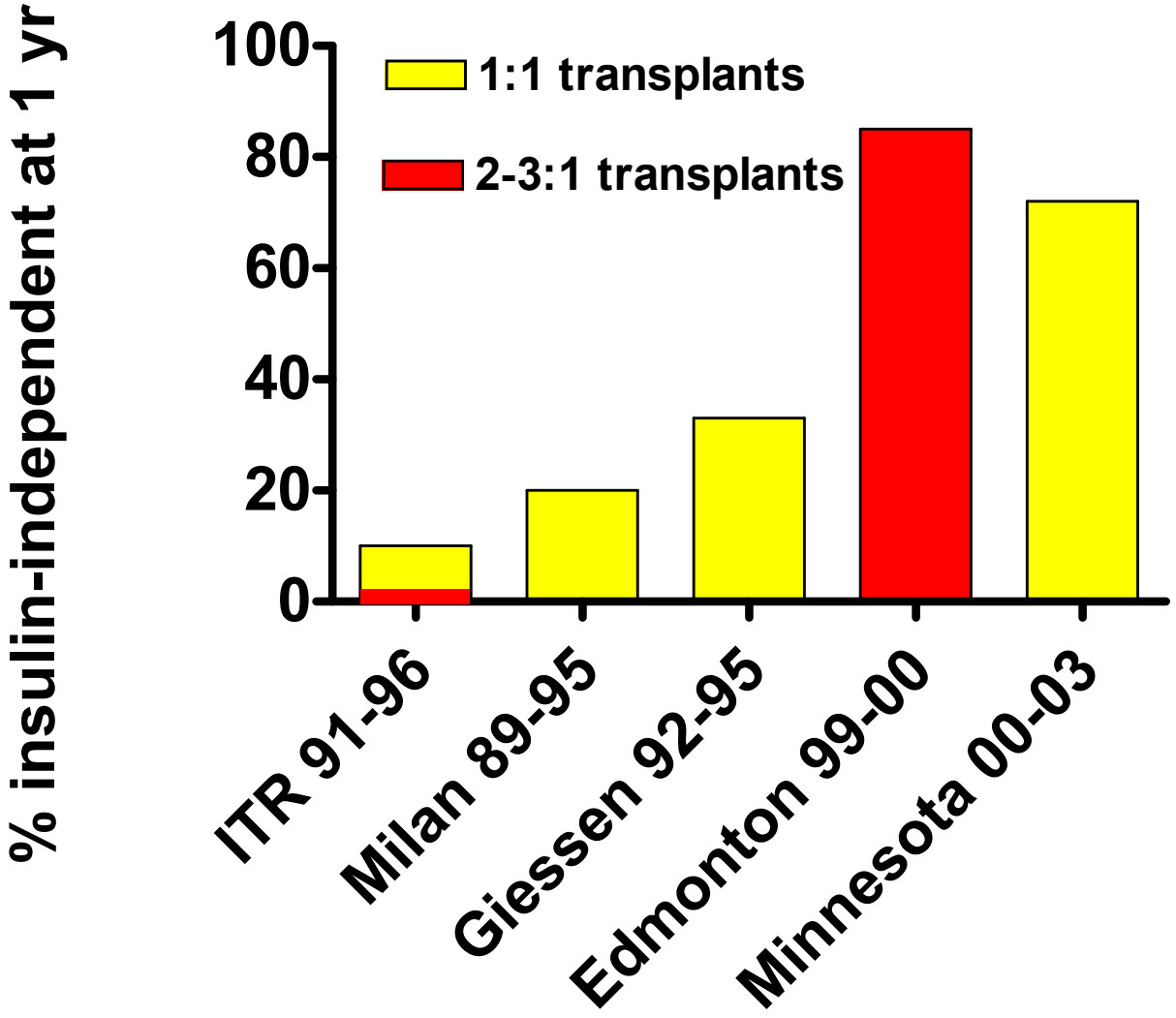
Transplant Protocol #1



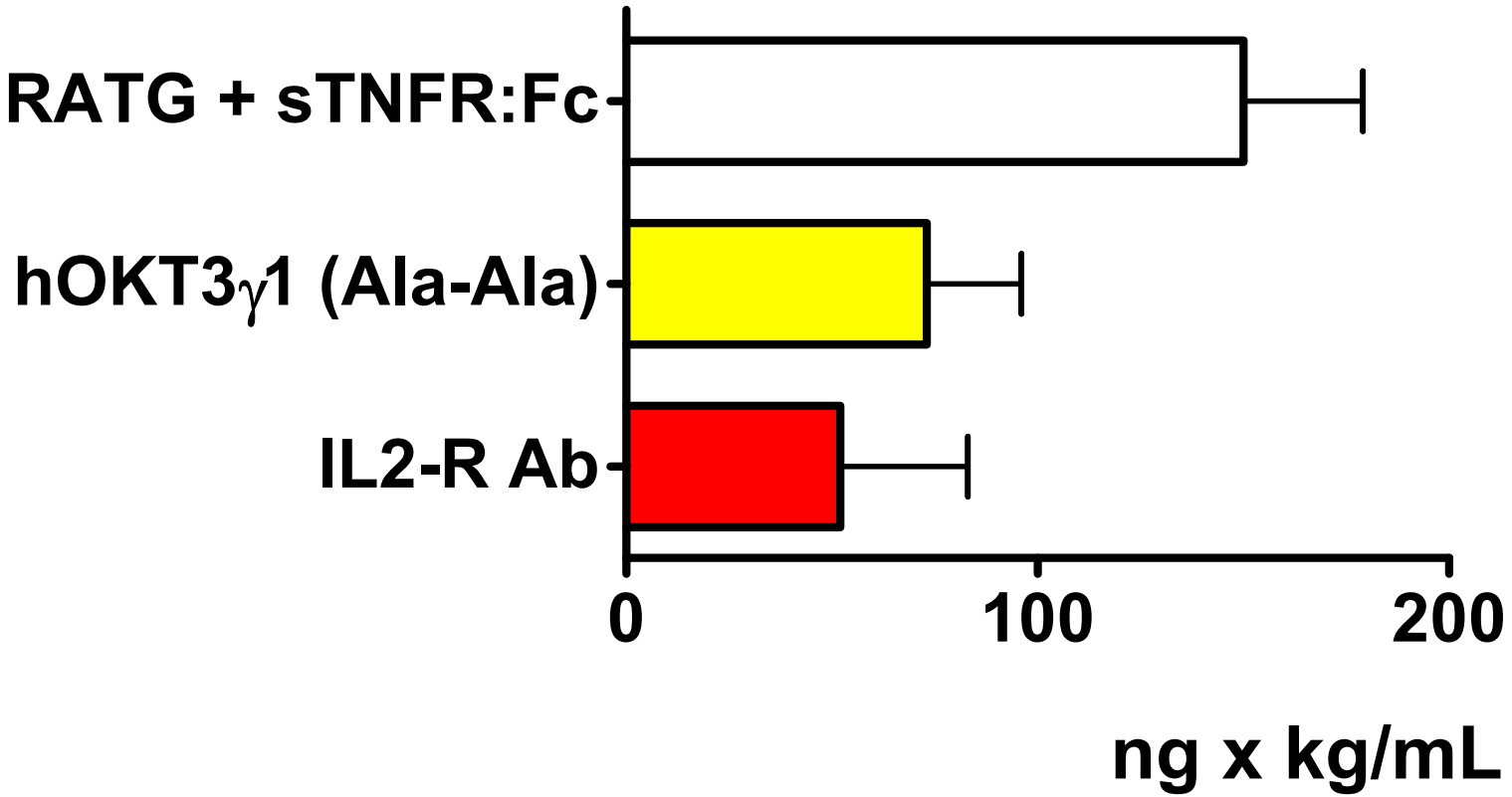
Islet Transplant Protocol #2



Success rates of islet transplants for T1D



Engraftment Index (ACP_{Arg}/IE/kg)



Metabolic monitoring

(first 10 recipients with sustained insulin independence after single-donor islet transplant)

- **Hypoglycemia:** **Avoided (10/10)**
- **HbA1c:** **<6.0% (10/10)**
- **OGTT 2-hr BG:** **<140 mg/dL (8/10)**
- **$ACR_{Arg/Glu}$:** **0.5 to 1.6 ng/mL (10/10)**
- **$AIR_{Arg/Glu}$:** **10 to 22 μU/mL (10/10)**

Adverse events

- Serious, unexpected, protocol-related: 0/20
- Severe
  - **Transient neutropenia 7/20**
  - **Transient anemia 1/20**
  - **Transient LFT elevations 3/20**
  - **Acute cholecystitis 1/20**

No procedural complications

No deaths, no cancers, no PTLD, no CMV

Single donor strategies (1): Increase islet mass and potency

- Donor pretreatment
- Pancreas preservation
- Recombinant enzymes
- Process engineering
- Gene transfer, protein transduction

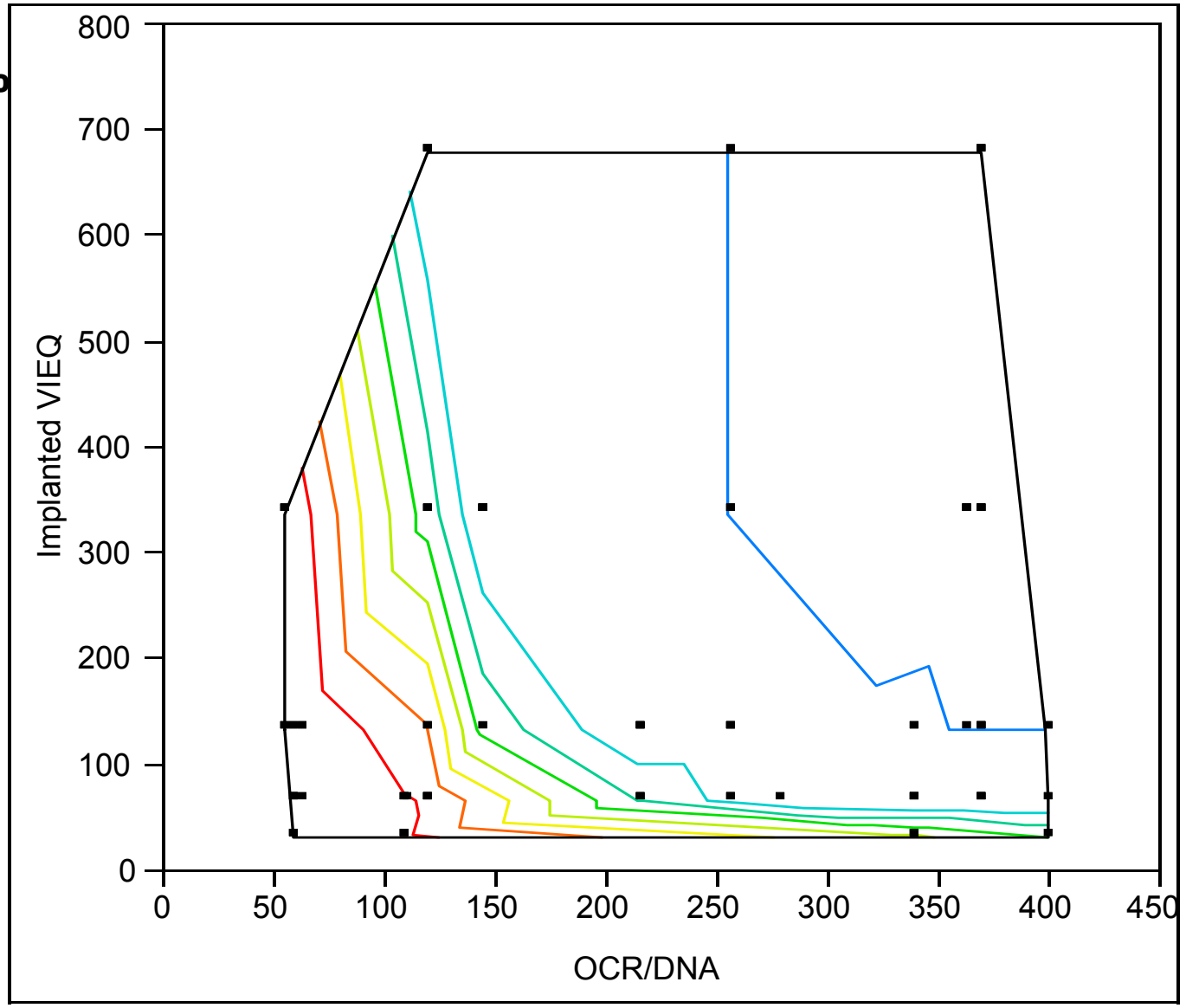
Islet Processing

Progress in pancreas procurement, preservation, and processing will depend on the development and validation of reliable, preferably real-time assays of islet beta cell mass and potency

- **Cellular composition (beta cells/kg)**
- **Oxygen consumption rate**
- **ATP**

Tx success probabilities based on OCR/DNA and VIEQ

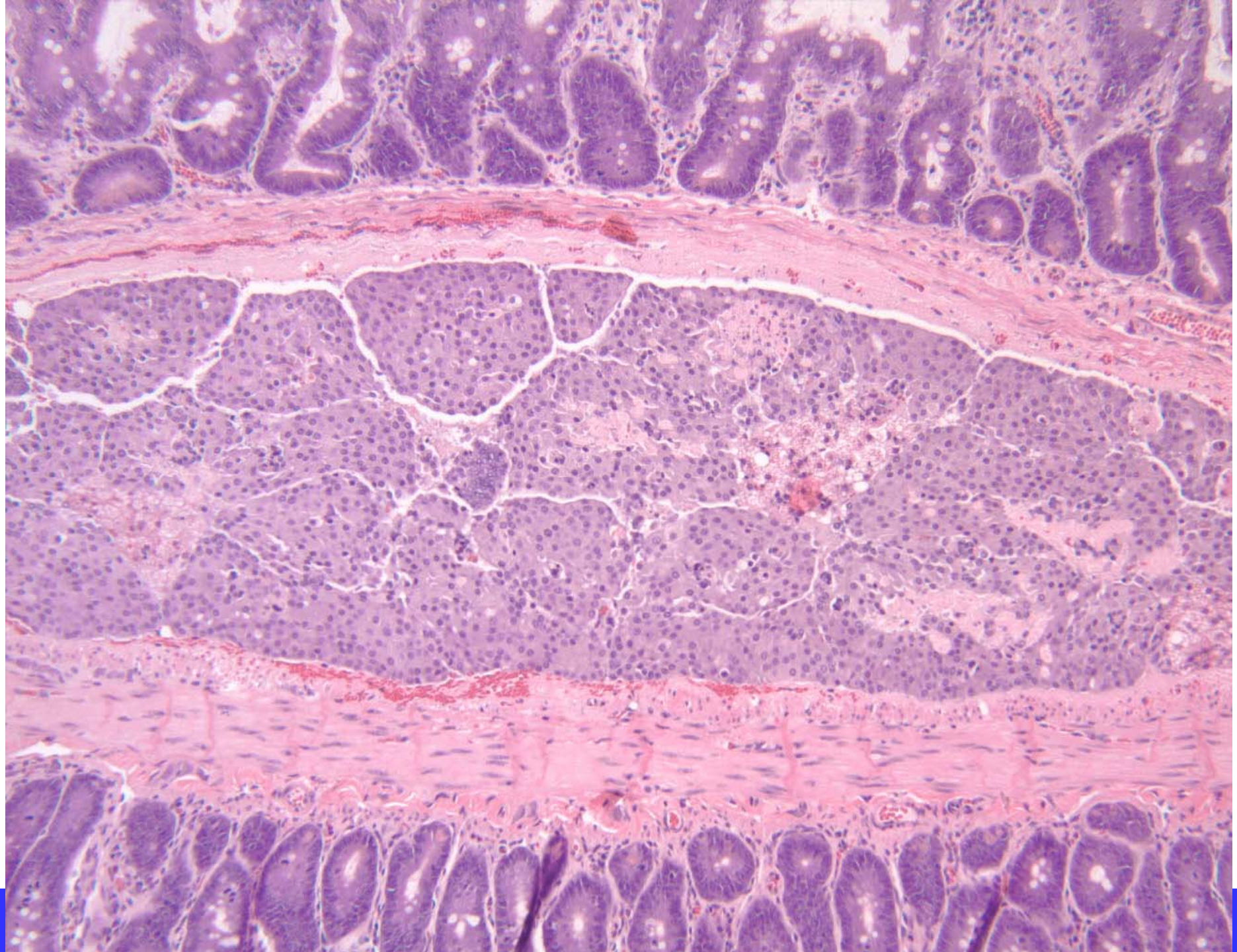
Rat-to-mouse model
Predictive value: 89 %
Sensitivity: 93%
Specificity: 94%



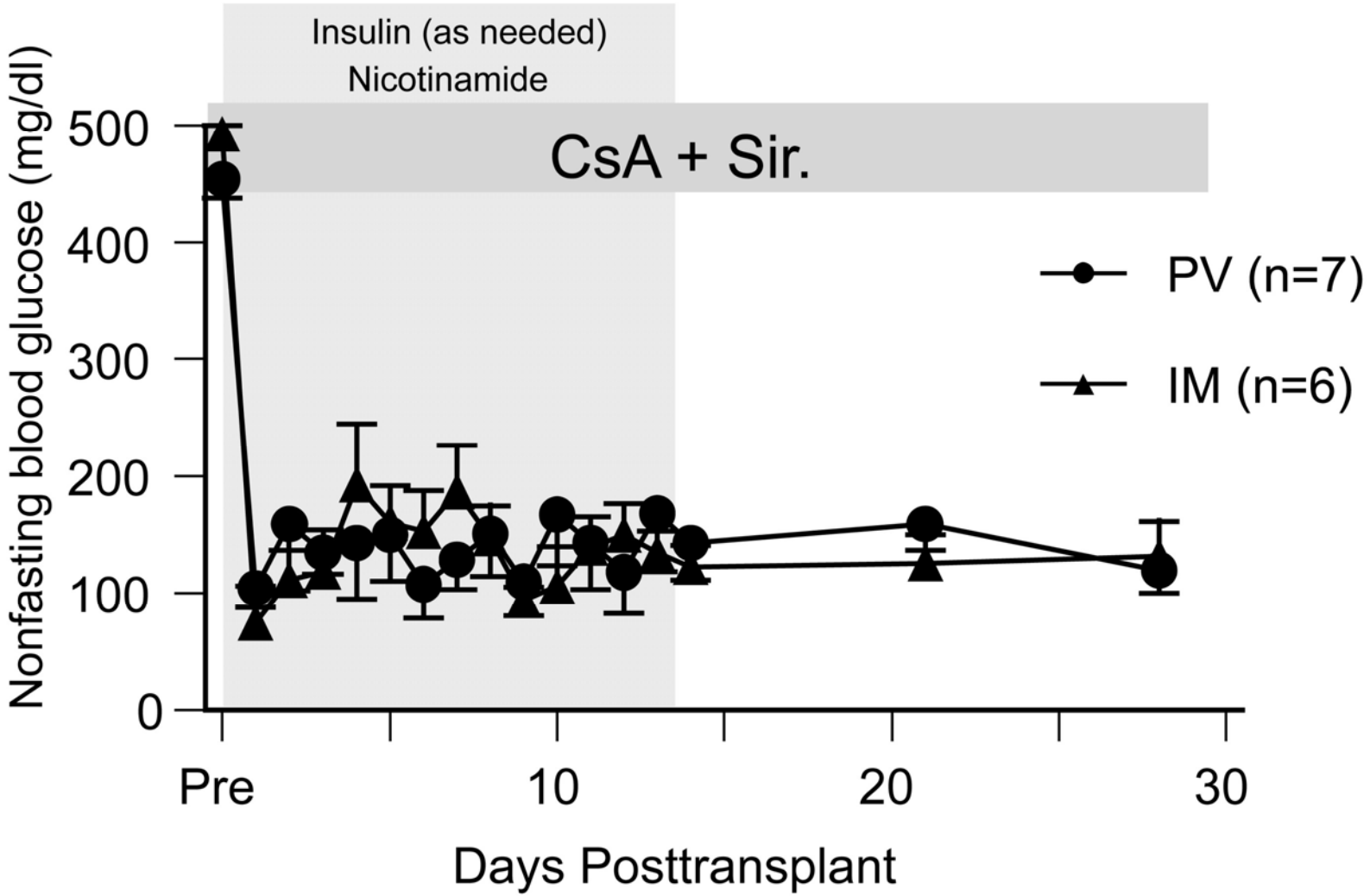
Courtesy Drs. Papas, Koulmanda, Weir, Colton, Ikle, and Nelson

Single donor strategies (2): Optimize islet engraftment

- Innate, auto-, and allo-immunity
- Growing list of antiinflammatory mediators
- Growing list of immunotherapeutic agents
- Prevascularized implant sites
- Biodegradable scaffolds releasing pro-angiogenic, anti-apoptotic, anti-inflammatory, immunoregulatory factors
- Small bowel subserosal space



Small intestine intramural space



Sageshima J et al, Transplant Proc 33: 171, 2001

Single donor strategies (3): Lower metabolic demand

- Reduce insulin resistance pretransplant
- Administer insulinotropic immunosuppressants
- Avoid both corticosteroids and calcineurin inhibitors

Steroid- and CNI-free immunosuppression

Calcineurin Inhibitor–Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates

Andrew B. Adams,[1] Nozomu Shirasugi,[1] Megan M. Durham,[1] Elizabeth Strobert,[2] Dan Anderson,[2] Phyllis Rees,[1] Shannon Cowan,[1] Huaying Xu,[1] Yelena Blinder,[1] Michael Cheung,[1] Dianne Hollenbaugh,[3] Norma S. Kenyon,[4] Thomas C. Pearson,[1,2] and Christian P. Larsen[1,2]

Diabetes 51:265-270, 2002

0041-1337/04/7706-827/0
TRANSPLANTATION

Vol. 77, 827–835, No. 6, March 27, 2004
Printed in U.S.A.

ISLET ALLOGRAFT SURVIVAL IN NONHUMAN PRIMATES IMMUNOSUPPRESSED WITH BASILIXIMAB, RAD, and FTY720[1]

MARTIN WIJKSTROM,[2,3] NORMA S. KENYON,[3,4,5] NICOLE KIRCHHOF,[2] NORMAN M. KENYON,[4] CLAUDY MULLON,[6] PHILIP LAKE,[6] SYLVAIN COTTENS,[6] CAMILLO RICORDI,[4,5,7] AND BERNHARD J. HERING[2,7,8]

Steroid- and CNI-free immunosuppression

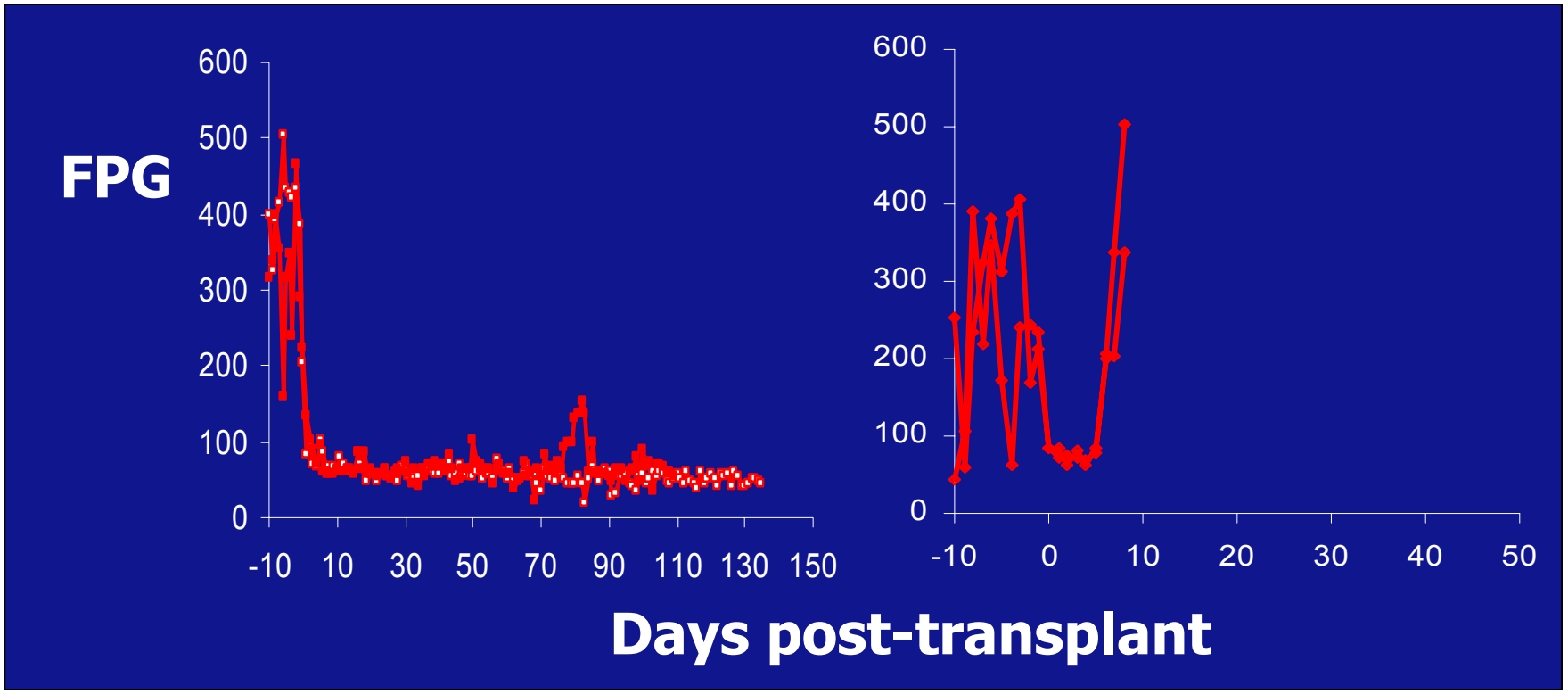
Edmonton **IL-2R Ab + FK506 + Rapamycin**

Emory **IL-2R Ab + LEA29Y + Rapamycin**

Minn/Miami **IL-2R Ab + FTY720 + Rapamycin**

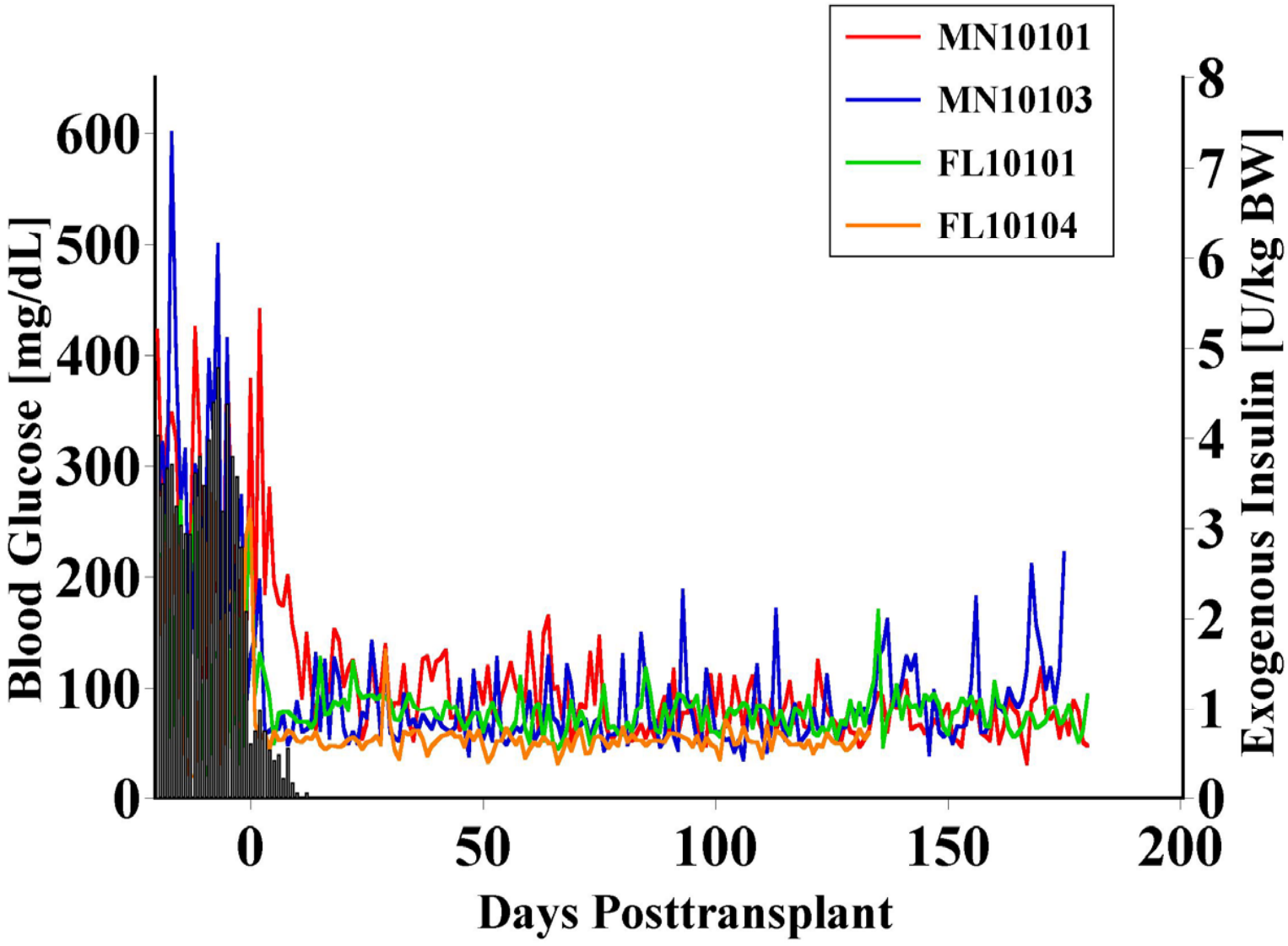
Lack of islet, kidney, and cardiovascular toxicity
Less impact on protective immunity?

LEA29Y/α-IL-2R/Sirolimus αIL-2R/Sirolimus



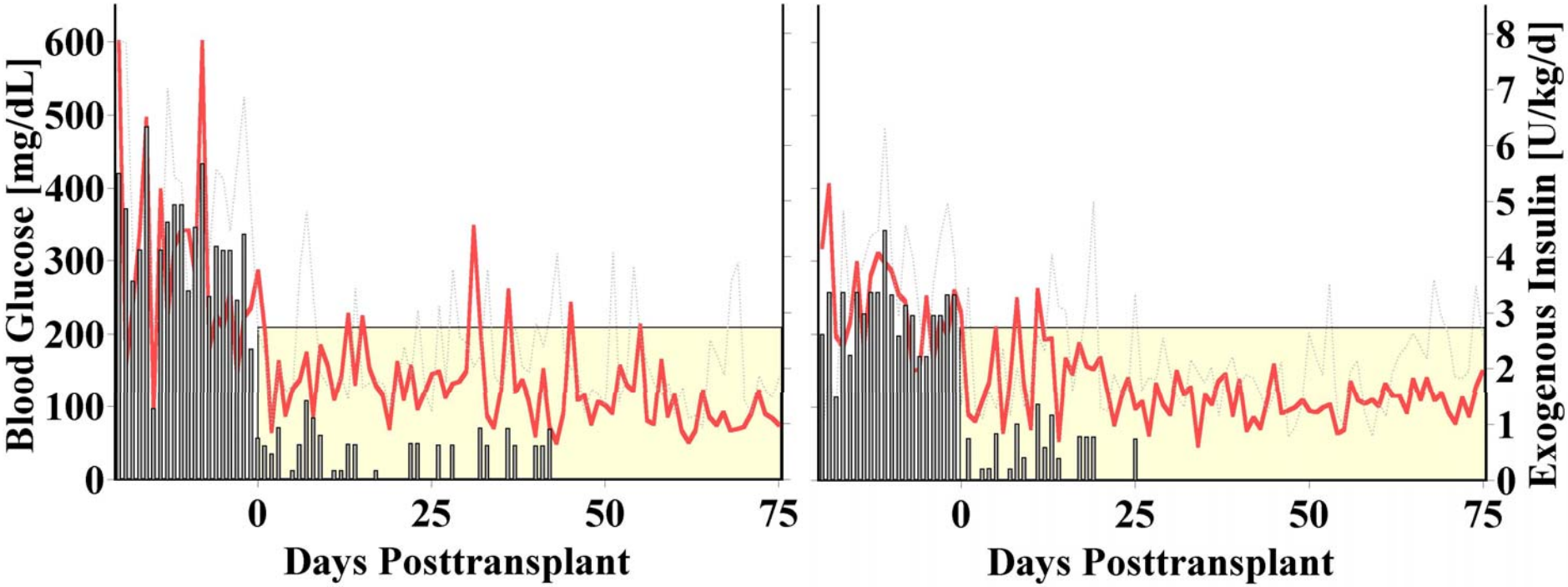
Diabetes 51:265-270, 2002

Basiliximab + FTY720 + RAD



Transplantation 77: 827-835, 2004

Marginal mass islet transplants (5 KIE/kg) with Basiliximab, FTY720, and RAD



Transplantation 77: 827-835, 2004

U.S. Food and Drug Administration

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Biological Response Modifiers Advisory Committee

Biologics License for Human Islets

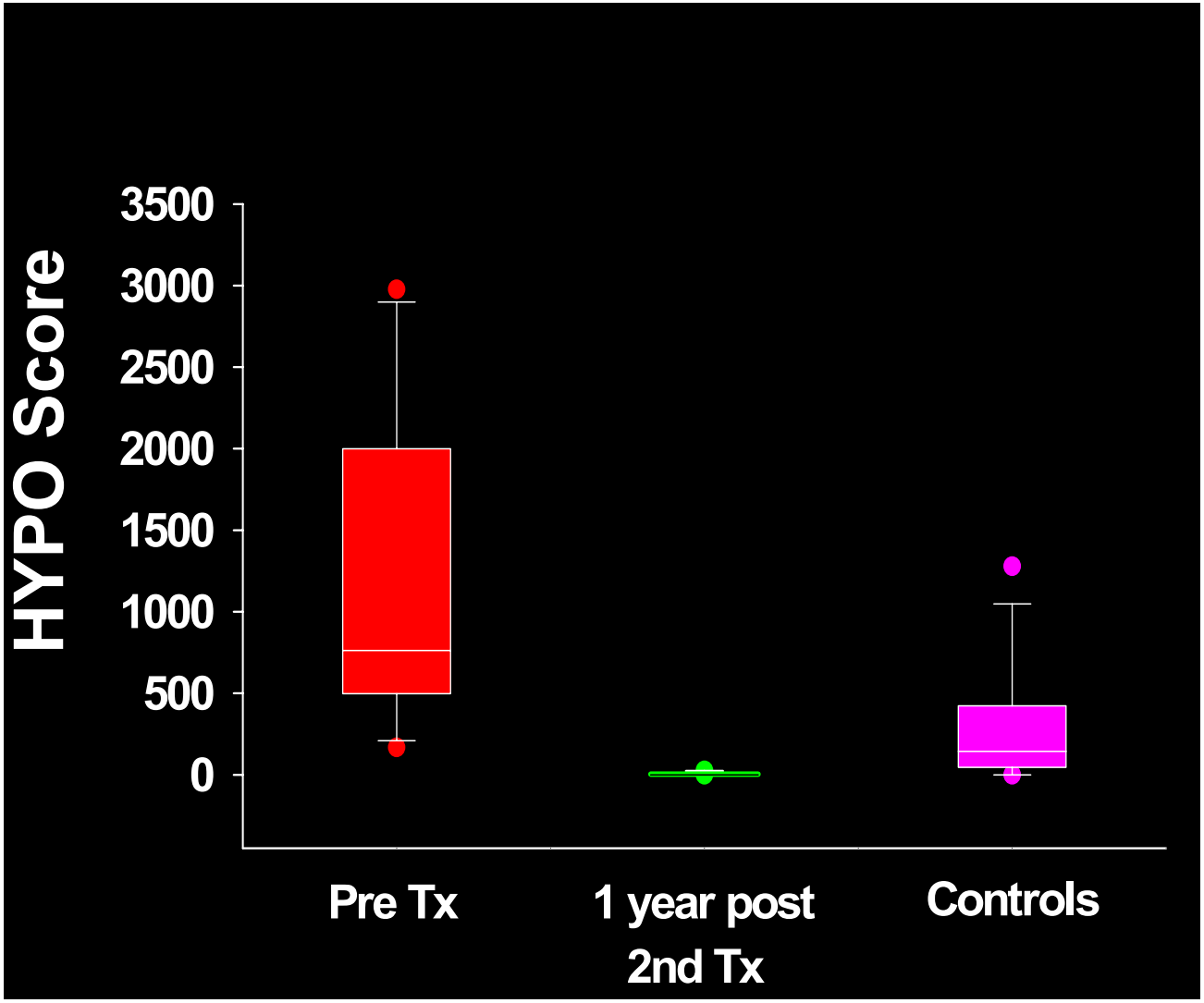
October 9 - 10, 2003 Meeting

- ✓ Control and consistency of islet manufacturing
- ★ Predictability of islet potency assays
- ? Substantial evidence of safety and effectiveness

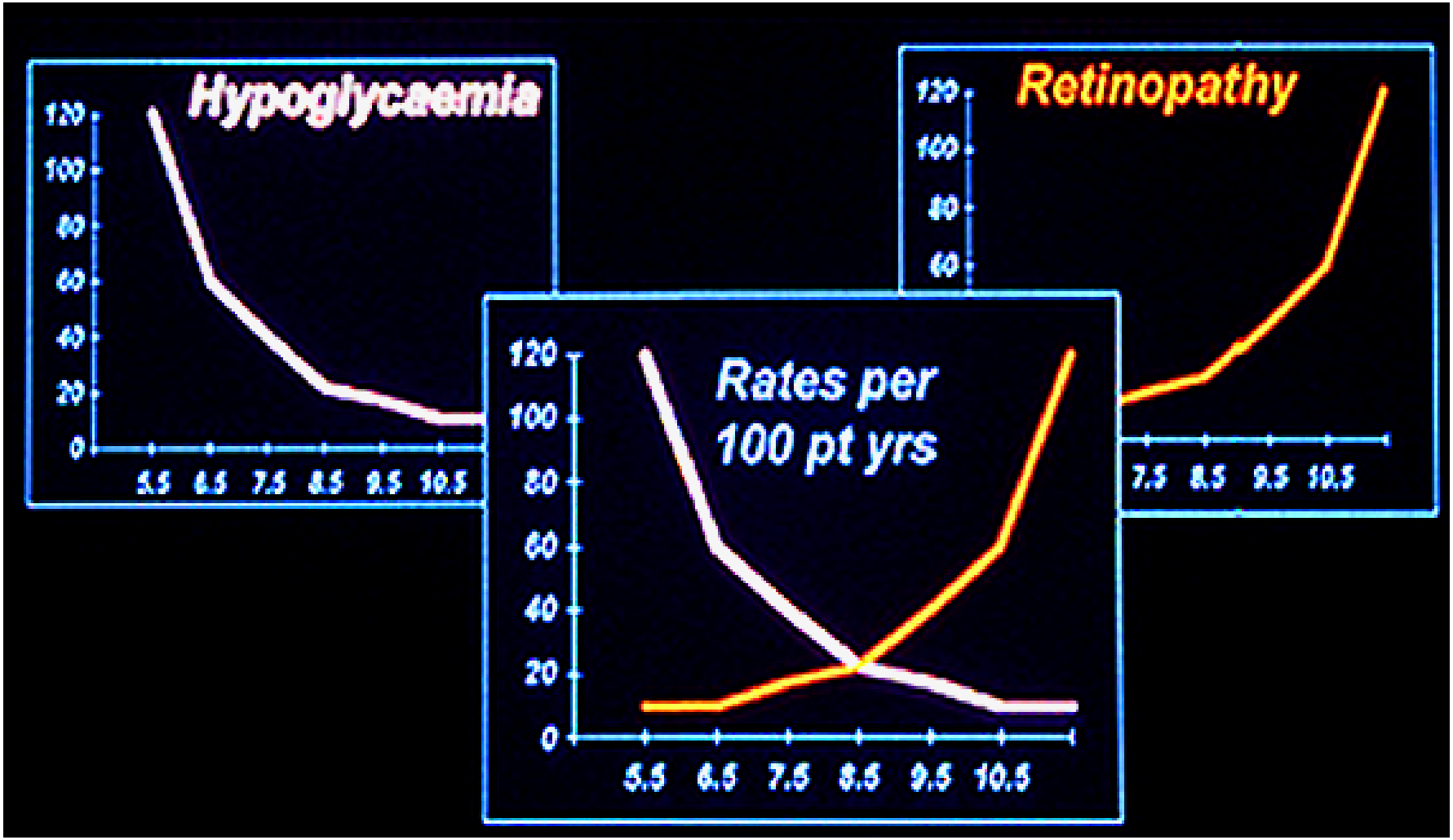
Proposed indication on label:

Restoring euglycemia in type 1 diabetes

Hypoglycemia Score



Ryan E et al., *Diabetes* 2004



Glycated Hb (%)

DCCT. NEJM; 1993

Randomized trial of islets vs ADA standard

- **Acute complications**
  - **Hypothesis:** Islet transplants lower costs per quality-adjusted life year in T1D patients with hypoglycemia-associated autonomic failure (HAAF)
  - **Study population:** T1D complicated by HAAF
  - **Endpoint:** Costs per quality-adjusted life year
- **Chronic complications**
  - **Hypothesis:** Microvascular lesions in T1D patients with microalbumiuria treated with RASB will continue to progress if normoglycemia is not restored
  - **Study population:** T1D complicated by **m**icroalbuminuria
  - **Endpoint:** Change in mesangial fractional volume after 5 yrs

NIH Research Networks

Islet Transplant Consortium

NCRR Islet Cell Resource Program

Immune Tolerance Network

citr
Collaborative Islet Transplant Registry

NHP Tx Tolerance Collaborative Study Group

Interaction critical

- FDA license
- Pancreas allocation
- Health insurance coverage

The Present

Cost Utility Assessment Planned

Increased Interaction with Diabetes Care Community

Procedural Risks Minimized

Integration

Efficiency Improved

Safety Improved

Implementation Underway

Single-Donor Transplants Successful

Steroid- and CNI-free Immunosuppression

Availability

Private Sector Shows Interest in Islet Manufacturing

Pancreas Allocation Being Discussed

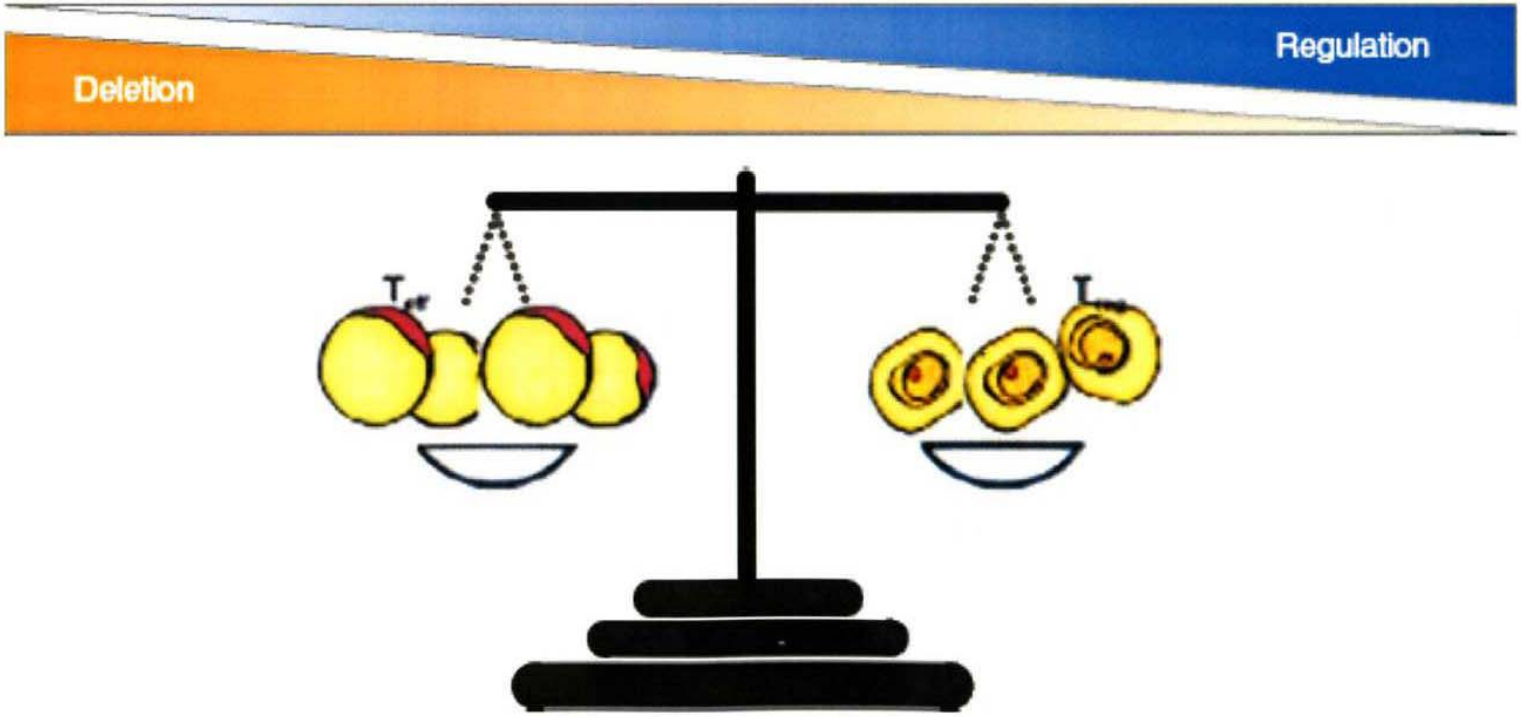
Islet Transplant Provision In Medicare Bill

The Future


Unlimited Beta Cell Source
Beta Cell Replication In Situ
Innovation
Immunologic Tolerance

The balance of deletion and regulation in allograft tolerance

BMT + lymphoablative Ab + irradiation MC tolerance Deletion 3+ Reg ± ?	BMT + Costimulation blockade + RPM MC tolerance Deletion 2+ Reg ±	Power-mix targeting activated T cells Tolerance Depletion 1+ Reg 1+
		DST + CD40L moAb; Non-depleting CD4 & CD8 moAbs Tolerance Depletion 1+ Reg 2+



Immunological Reviews 2003; 196:75-84

American Journal of Transplantation 2003; 3: 128–138
Blackwell Munksgaard

ISSN 1600-6135

Stable α- and β-Islet Cell Function After Tolerance Induction to Pancreatic Islet Allografts in Diabetic Primates

Juan L. Contreras[a], Stacie Jenkins[a], Devin E. Eckhoff[a], William J. Hubbard[a], Andrew Lobashevsky[a], Guadalupe Bilbao[b], Francis T. Thomas[a], David M. Neville Jr[a] and Judith M. Thomas[a,*]

Anti-CD3 IT + 15-DSG

- Peritransplant anti-CD3 immunotoxin to deplete T cells combined with a short course of 15-DSG to arrest proinflammatory cytokine production and dendritic cell maturation
- Effective both in kidney and islet transplant models in nonhuman primates

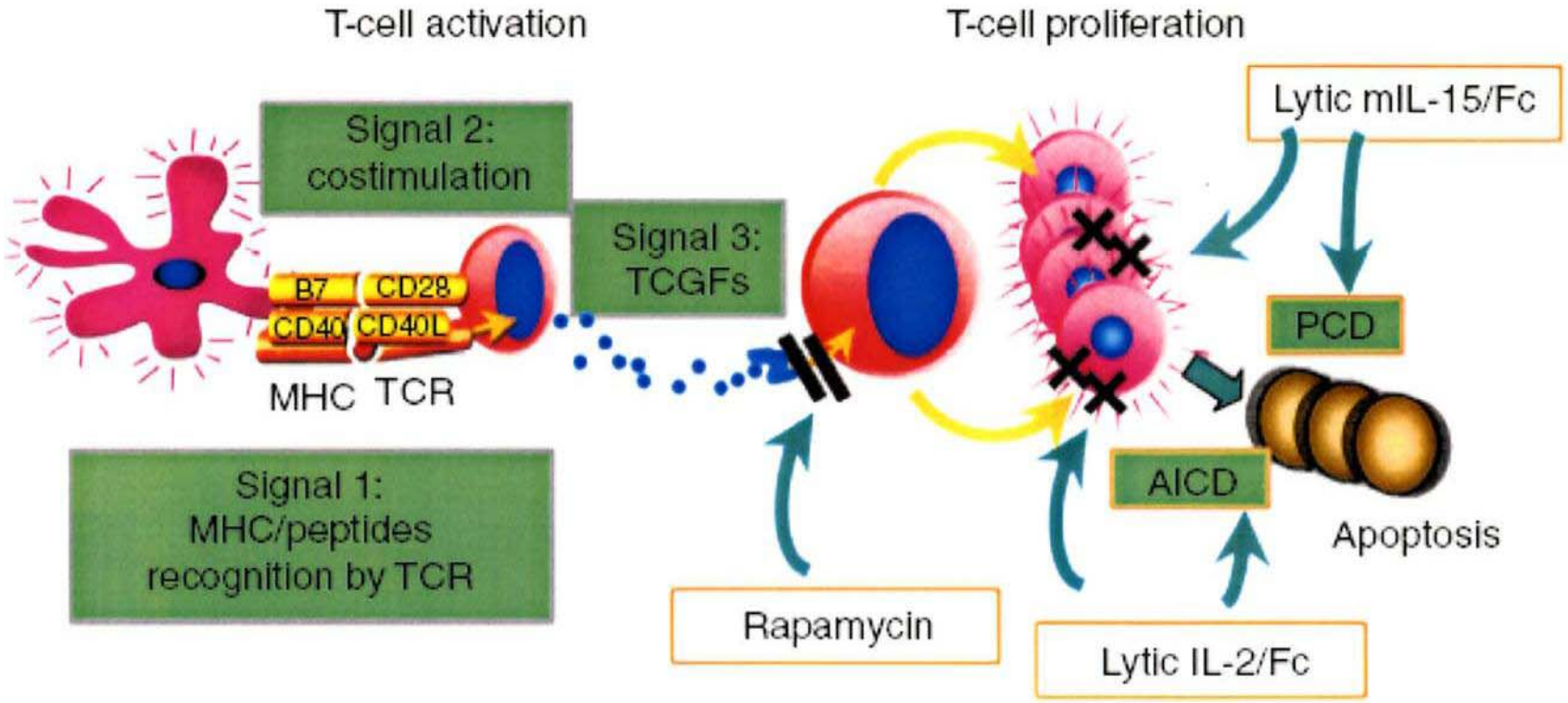
Operational tolerance in NHPs for >5 years

Courtesy to Judy and Frank Thomas

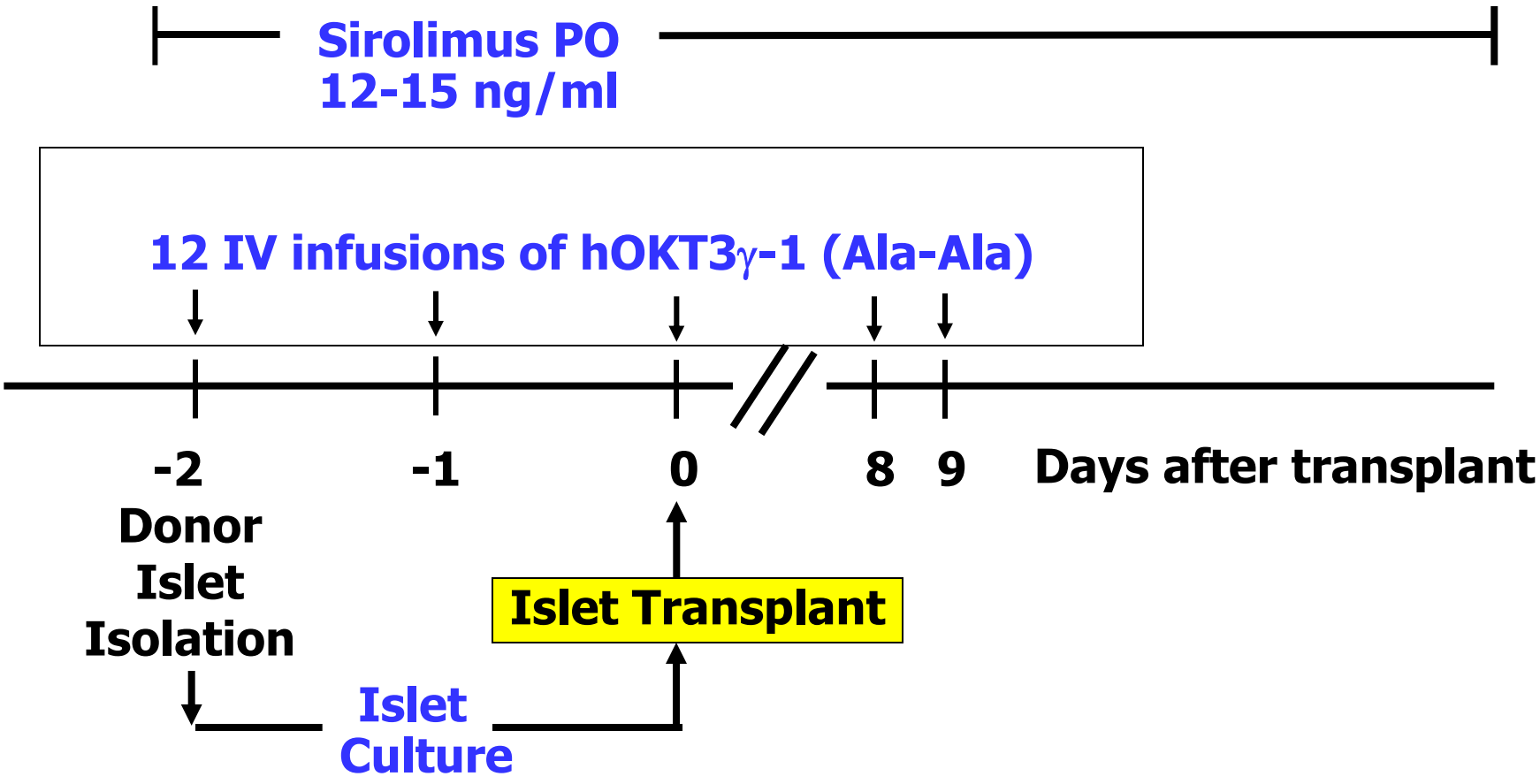
Immunity, Vol. 19, 503–514, October, 2003, Copyright ©2003 by Cell Press

Favorably Tipping the Balance between Cytopathic and Regulatory T Cells to Create Transplantation Tolerance

Xin Xiao Zheng,[1,3,*] Alberto Sánchez-Fueyo,[1,3]
Masayuki Sho,[2] Christoph Domenig,[1]
Mohamed H. Sayegh,[2] and Terry B. Strom[1,*]

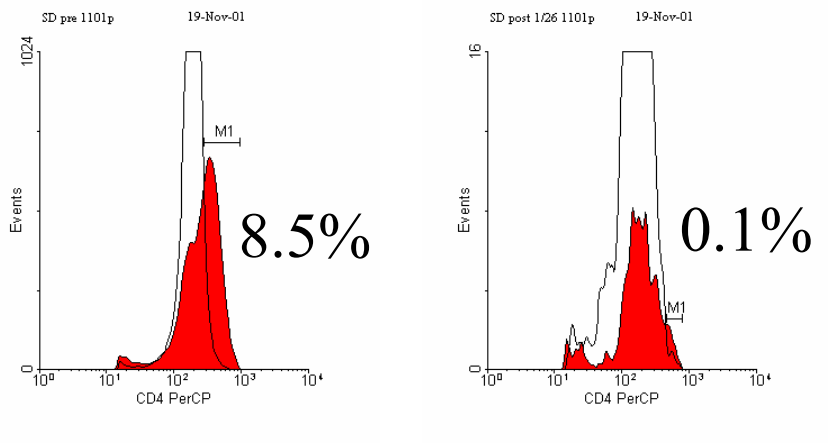


Peripheral Tolerance Protocol



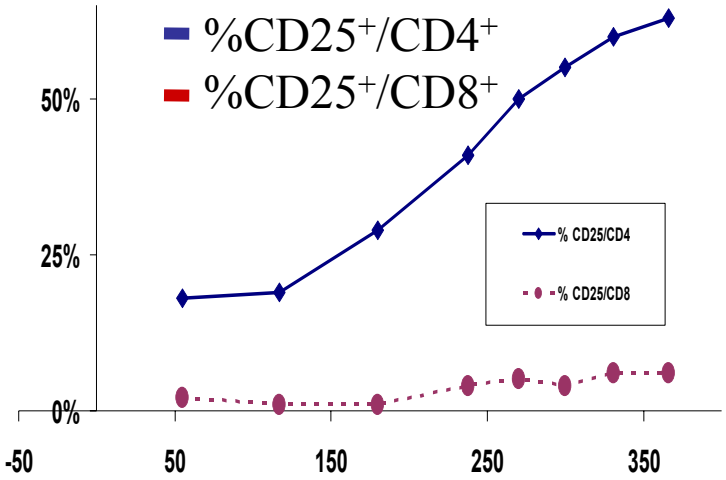
Peripheral tolerance

- Contraction of the anti-donor and anti-self T cell repertoire following anti-CD3 therapy



HLA-DR4-GAD65 tetramer activation profiles

- Induction of regulatory T cells controlling activated memory T cells following anti-CD3 therapy



Efficient expansion of regulatory T cells *in vitro* and *in vivo* with a CD28 superagonist

Chia-Huey Lin and Thomas Hünig

Eur. J. Immunol. 2003. *33:* 626–638

Direct expansion of functional $CD25^{+}CD4^{+}$ regulatory T Cells by antigen-processing dendritic cells

Sayuri Yamazaki1, Tomonori Iyoda2, Kristin Tarbell1, Kara Olson1, Klara Velinzon1, Kayo Inaba2 and Ralph M. Steinman

The Journal of Experimental Medicine 198, 235-247, 2003

Large scale in vitro expansion of polyclonal human $CD4^{+}CD25^{high}$ regulatory T cells

Petra Hoffmann, Ruediger Eder, Leoni A. Kunz-Schughart, Reingard Andreesen, and Matthias Edinger

Blood, prepublished online April 15, 2004

The infusion of ex vivo activated and expanded $CD4^{+}CD25^{+}$ immune regulatory cells inhibits graft-versus-host disease lethality

Patricia A. Taylor, Christopher J. Lees, and Bruce R. Blazar

BLOOD, 15 MAY 2002 _ VOLUME 99, NUMBER 10

Beta Cell Source

Maximization of deceased donor pancreas utilization

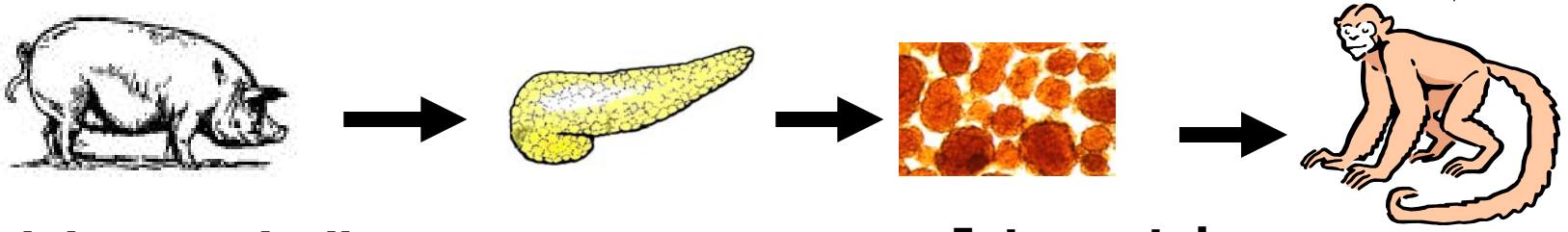
Living donor islet transplants

Xenogeneic islet transplants

Precursor cell-derived islet beta cell transplants

Beta cell replication in situ

Pig-to-primate islet xenografts



Streptozotocin

Adult, genetically unmodified donor pig

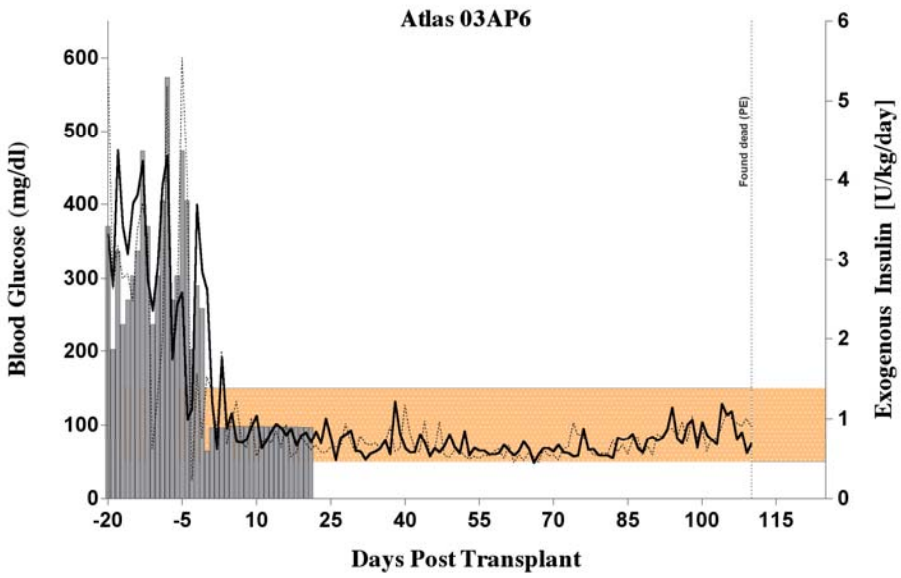
Intraportal infusion of 20,000 IE/kg; cultured for 48 hrs

Cynomolgus macaque

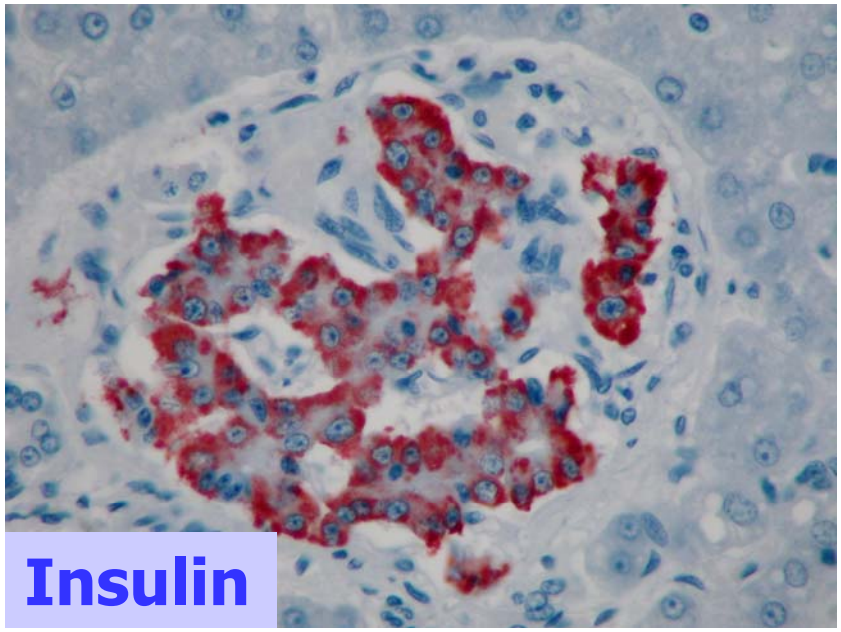
Immunosuppression

Multiple readouts for xenograft function and xenoimmunity

Glycemic Control

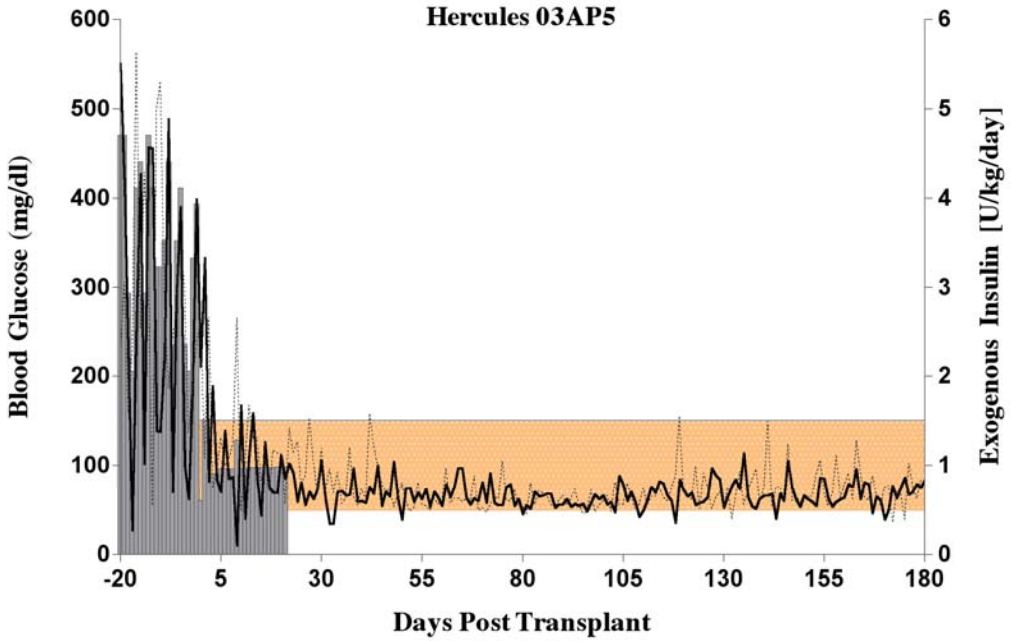


Histology day +111

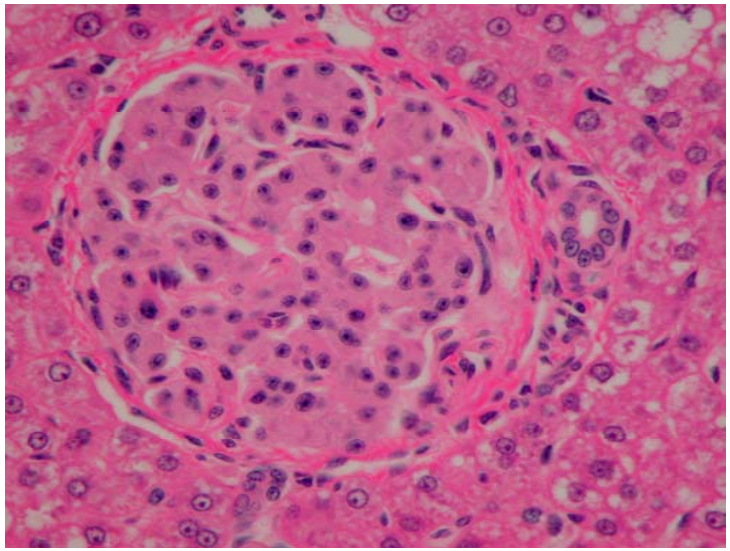


>90% of islets are without infiltration

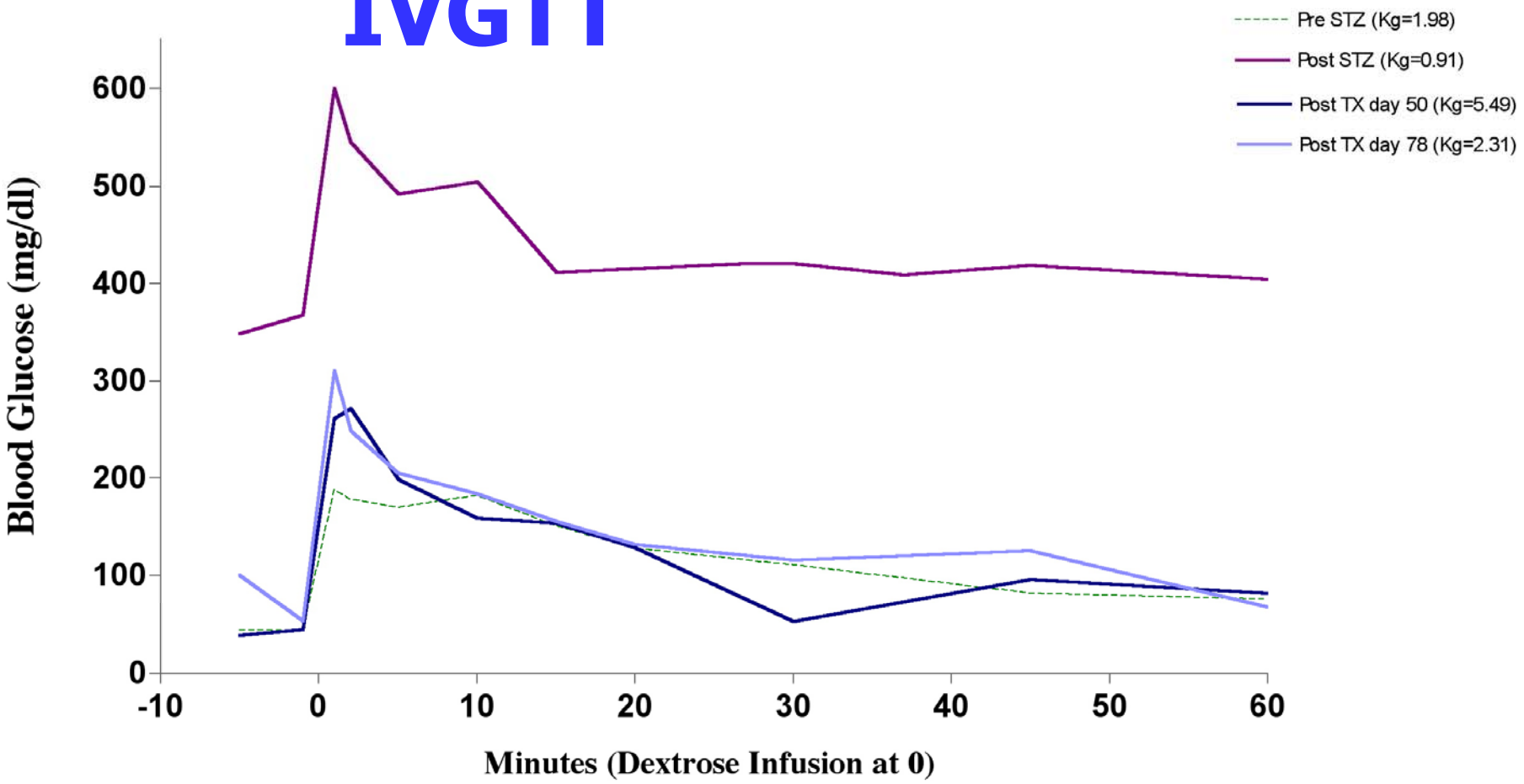
Glycemic Control



Histology day +180



IVGTT


Pre STZ (Kg=1.98)
Post STZ (Kg=0.91)
Post TX day 50 (Kg=5.49)
Post TX day 78 (Kg=2.31)
Blood Glucose (mg/dl)
600
500
400
300
200
100
0
-10
0
10
20
30
40
50
60
Minutes (Dextrose Infusion at 0)

Adult pancreatic β-cells are formed by self-duplication rather than stem-cell differentiation

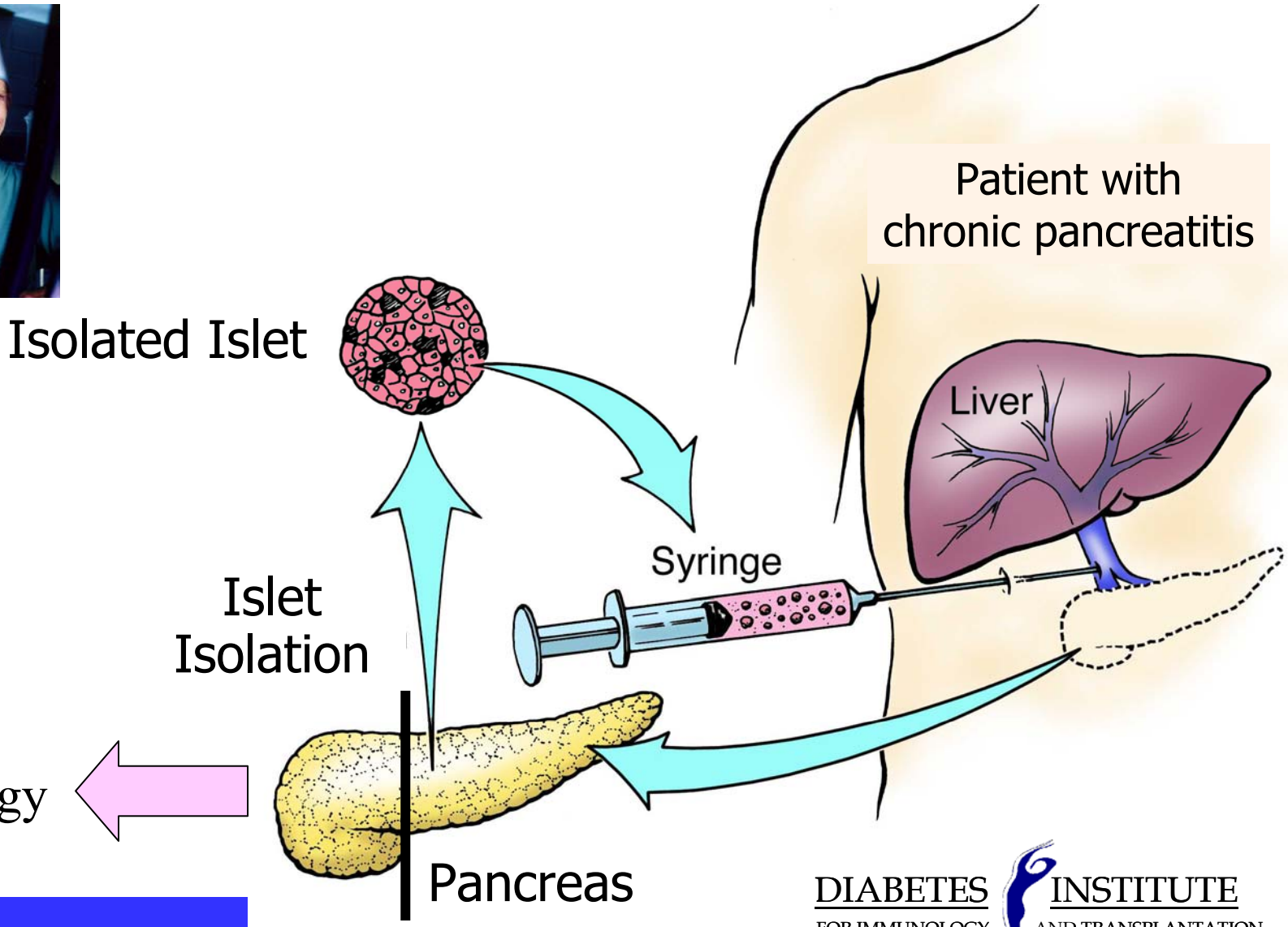
Yuval Dor, Juliana Brown, Olga I. Martinez & Douglas A. Melton

Department of Molecular and Cellular Biology and Howard Hughes Medical Institute, Harvard University, 7 Divinity Avenue, Cambridge, Massachusetts 02138, USA

- New beta cells are formed by self-duplication of preexisting beta cells and are not formed by stem or progenitor cells during adult life
- High proliferative capacity and turnover of terminally differentiated beta cells
- Can the proliferative capacity of adult beta cells be exploited for expansion to a clinically useful mass?
- Is the longevity of islet transplants determined by the proliferative potential of transplanted beta cells?

Yuval Dor … Douglas Melton; Nature 429; 41-46, 2004

Islet autotransplants

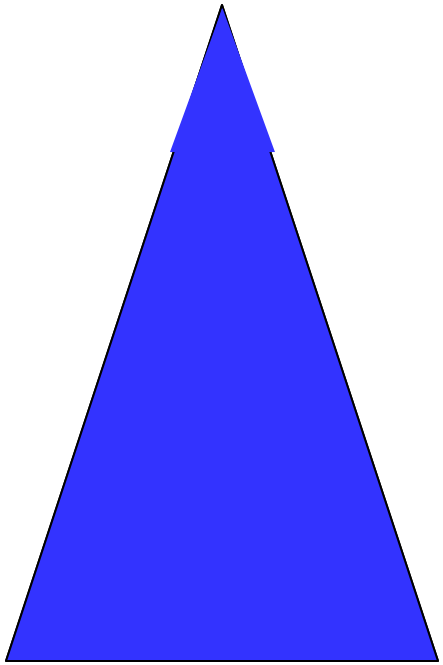


DIABETES INSTITUTE
FOR IMMUNOLOGY AND TRANSPLANTATION

Insulin-independent for 20 years

- Islet autotransplant after total pancreatectomy
- 2,500 IE/kg maintain insulin independence long-term
- No cold storage, preexisting diabetes, adaptive immunity, or immunosuppression
- **Evidence of intrahepatic islet replication and/or neogenesis?**

***Diabetes* 50; 47-50, 2001**



Supply

Human islets

Xenogeneic islets

Replicated beta cells

Immuno-suppression

Conclusion

- Cell-based therapeutics (CBTs) will soon play an increasingly significant role in diabetes care
- Documentation of benefits of islet transplants using clinically relevant endpoints will be critical
- Considerable efforts and new concepts will be needed to overcome translational obstacles in the implementation and integration of CBTs into the health care system

Juvenile Diabetes Research Foundation International

dedicated to finding a cure

Winston & Maxine Wallin Fund
Eunice L. Dwan Endowment
Golf Classic 'fore' Endowment
Iacocca Foundation
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David Sutherland
Camillo Ricordi
James Shapiro
Bruce Blazar
Catherine Verfaillie

Jeff Bluestone
Judy Thomas
Frank Thomas
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Diabetes Institute for Immunology & Transplantation Staff