2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Debate: Cell Replacement Therapies as the Goal for Treating Type 1 Diabetes

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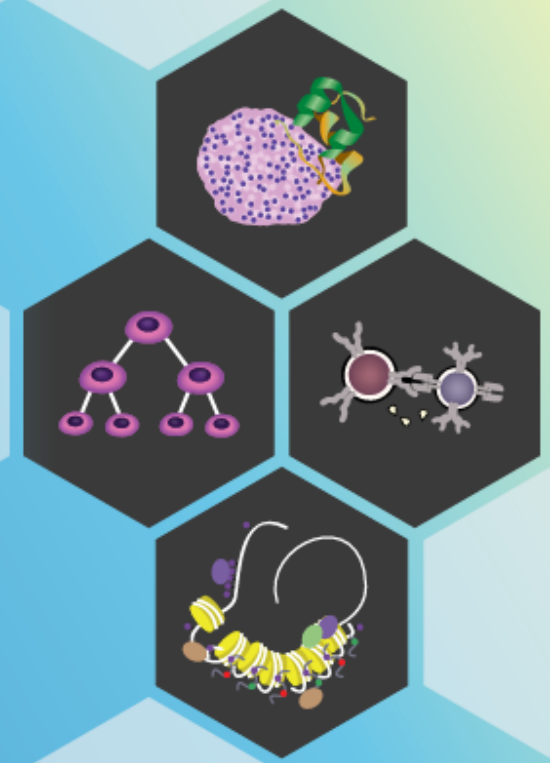


Disclosures

- Grant/Research Support from Dompé farmaceutici SpA.
- Consultant for Sernova Corp., and Vertex Pharmaceuticals.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Stem Cell-Derived Islets will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

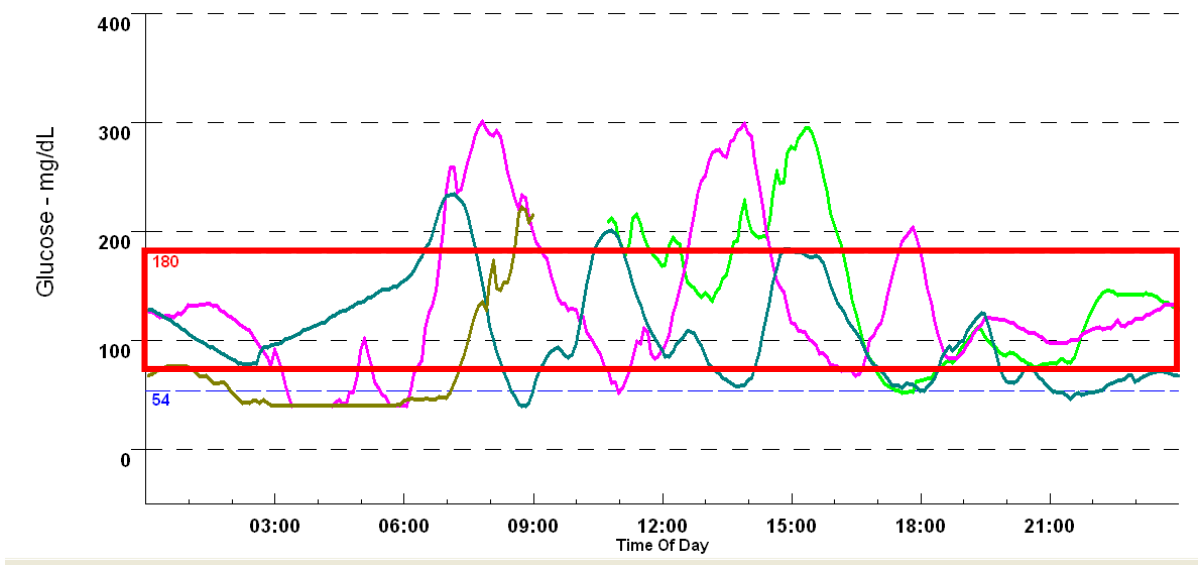
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Impact of social determinants of health on diabetes self care and impaired awareness of hypoglycemia.*
- *Challenges with glycemic control would be solved if patients and their providers tried harder.*

Case

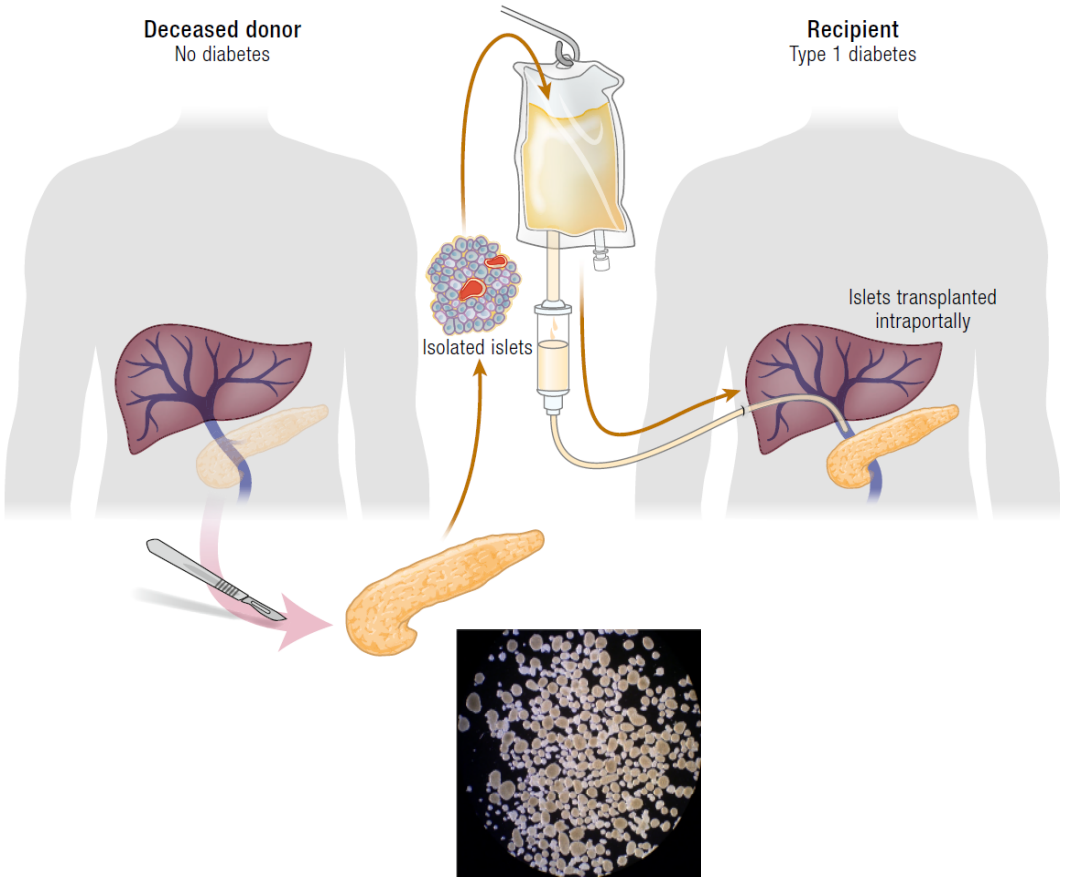
- 35-year-old woman with type 1 diabetes for 16 years
- No microvascular complications
- Hypoglycemia unawareness
- 6 severe hypoglycemia episodes in the past year requiring glucagon or EMS
- Employs intensive insulin therapy with flexible insulin dosing by infusion pump



Marked glucose variability
Significant hypoglycemia exposure

Current Standard of Cellular Therapy for Diabetes

Procedure for Islet Transplantation



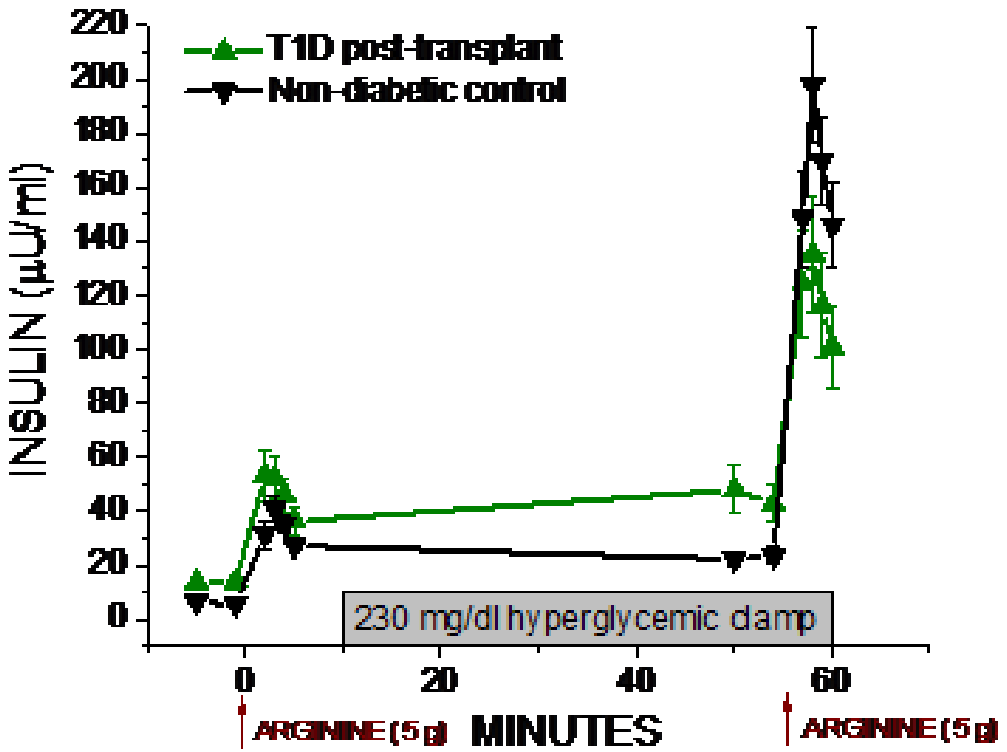
Rickels & Robertson *Endocrine Rev* 40: 631, 2019

Current Limitations

- Regional cGMP Facility for Islet Isolation
  - FDA requirements for biologic licensure has resulted in only one approved commercial facility (CellTrans; Chicogo, IL) in the US
- Immunosuppression
  - Excludes those with modest impairment of kidney function (unless already requiring immunosuppression for a kidney transplant)

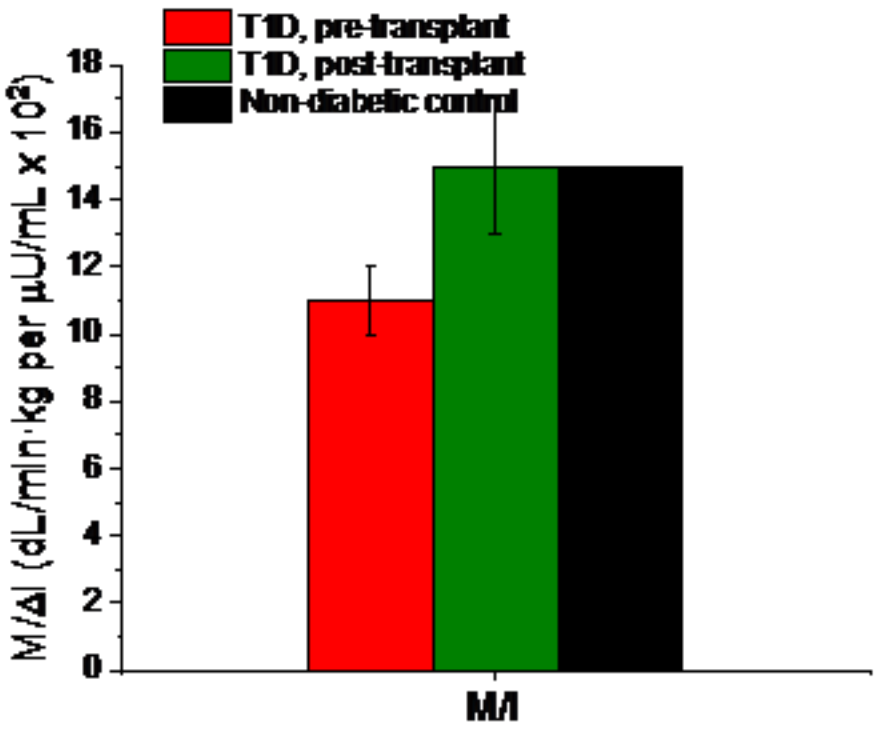
Advantages of Physiologic Insulin Delivery with Islet Transplants

Normal insulin secretory dynamics



Rickels et al. *Diabetes* 62: 2890, 2013

Normal insulin sensitivity / action



Rickels et al. *J Clin Endocrinol Metab* 98: E1780, 2013

First License-Enabling Trials of Islets and Artificial Pancreas in the US

	Purified Human Pancreatic Islets (PHPI; N = 48)			Hybrid Closed Loop Insulin Delivery (Medtronic 670G; N = 94)	
Baseline	Median (IQR)			Mean ± SD	
Female (%)	60			56	
Age (years)	48 (26 – 66)			45 ± 13	
Diabetes duration (years)	29 (11 – 57)			26 ± 12	
BMI (kg/m^2)	25 (19 – 30)			27 ± 5	
Insulin requirement ($U \cdot kg^{-1} \cdot d^{-1}$)	0.5 (0.2 – 0.8)			0.6 ± 0.2	
Follow-up	Baseline	1 year	2 years	Baseline	3 months
Severe hypoglycemia (%)	100	4	6.25*	N.R.	0
HbA1c (%)	7.2	5.6	5.6	7.2	6.7
< 7.0% (%)	40	87.5	81.25	38	59

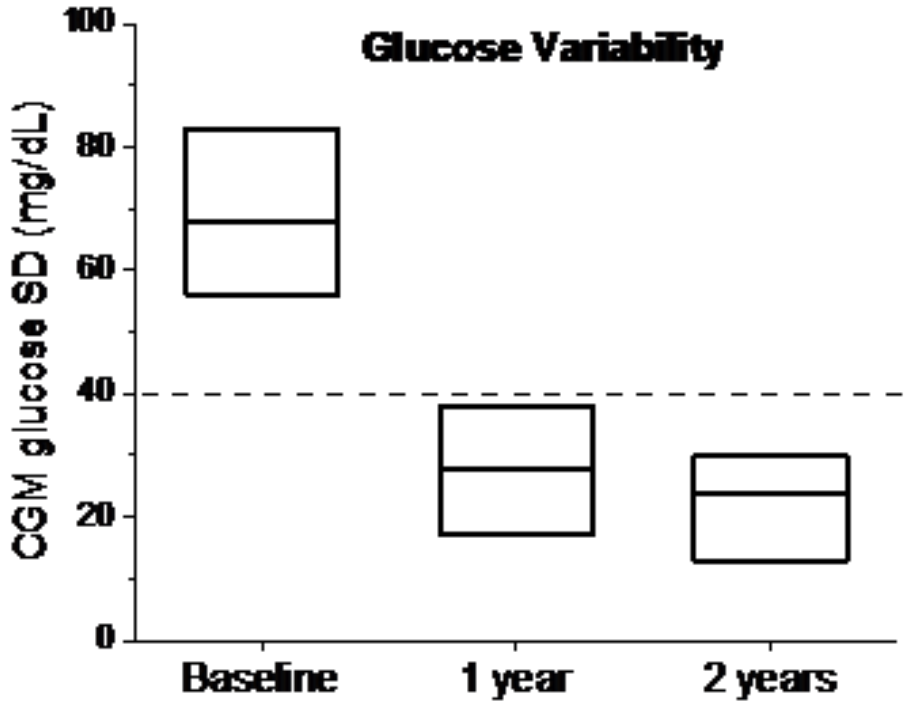
Hering et al. *Diabetes Care* 39: 1230, 2016

Bergenstal et al. *JAMA* 316: 1407, 2016

Garg et al. *Diabetes Technol Ther* 19: 155, 2017

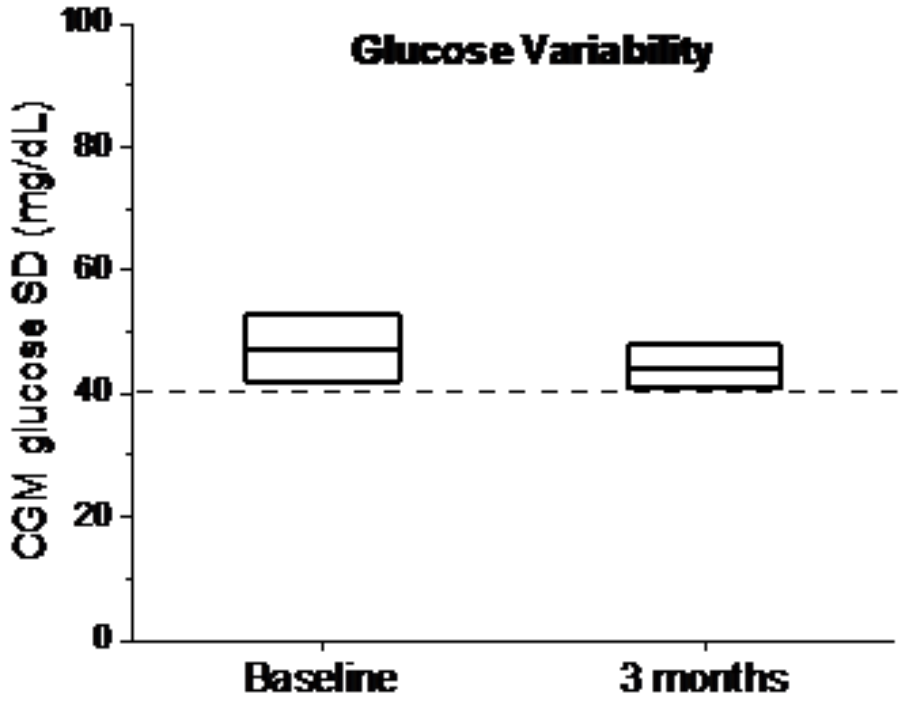
Effect of Islets vs. Artificial Pancreas on Glucose Variability

Islet Transplantation (PHPI)



Hering et al. *Diabetes Care* 39: 1230, 2016

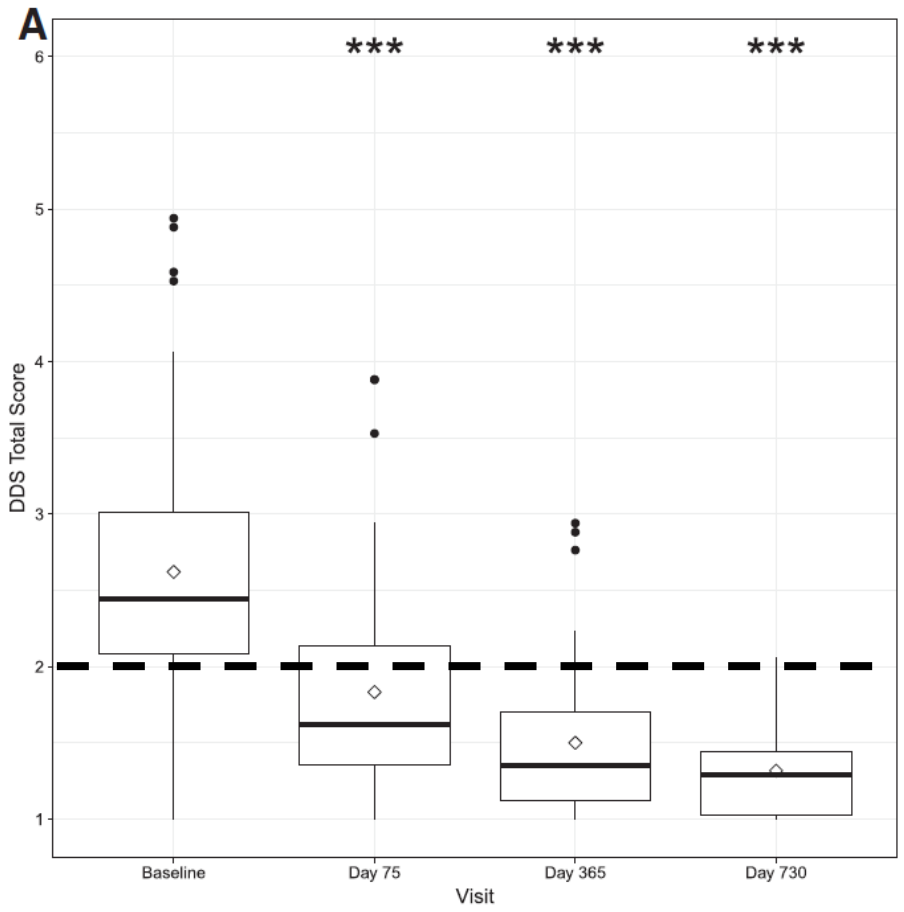
Hybrid Closed Loop (Medtronic 670G)



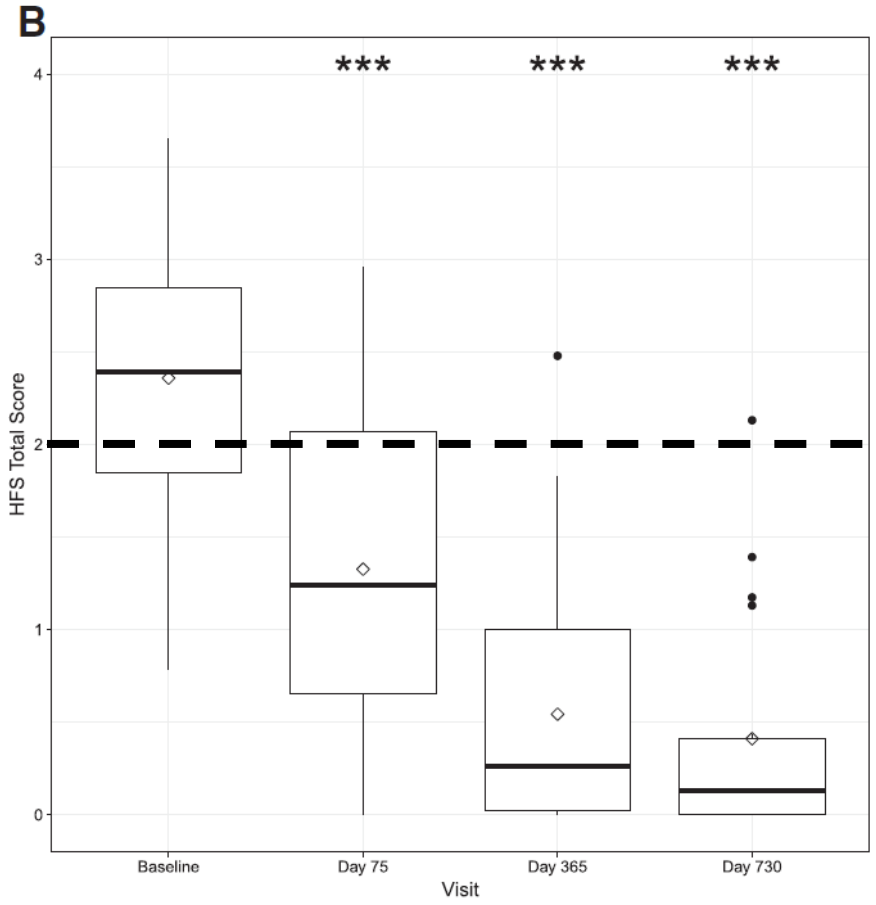
Bergenstal et al. *JAMA* 316: 1407, 2016
Garg et al. *Diabetes Technol Ther* 19: 155, 2017

Effect of Islet Transplantation (PHPI) on QoL in the Phase 3 Trial

Diabetes Distress Scale



Hypoglycemia Fear Survey

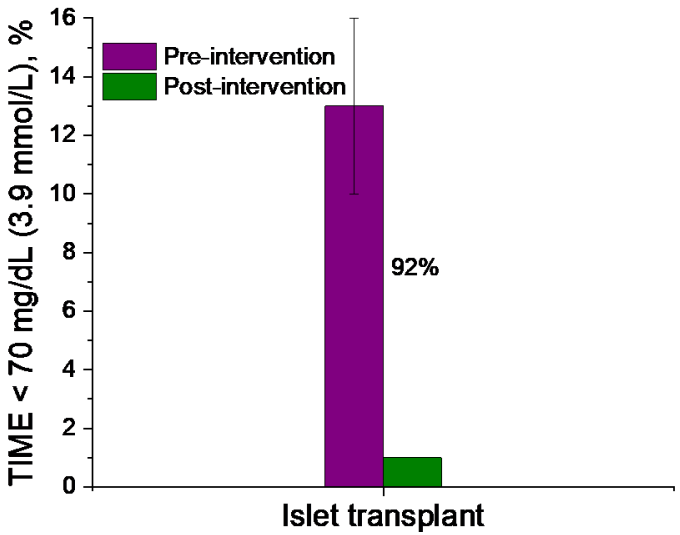


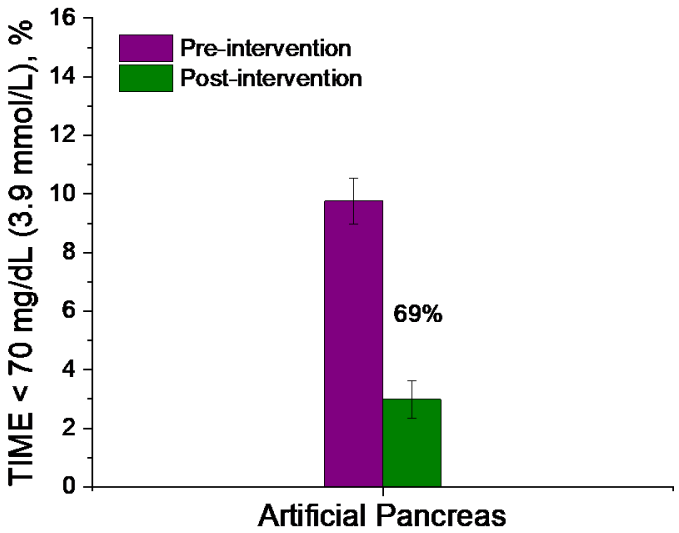
Foster et al. *Diabetes Care* 41: 1001, 2018

Physiologic vs. Pharmacologic Insulin Replacement

Baseline Characteristics	Islet Transplantation (N = 10)	Automated Insulin Delivery (N = 10)
Female (%)	70	70
Age (years)	43 ± 9	49 ± 16
Diabetes duration (years)	27 ± 13	34 ± 16
BMI (kg/m^2)	25 ± 3	24 ± 1
Insulin requirement (U·kg^{-1}·d^{-1})	0.5 ± 0.2	0.5 ± 0.1
HbA1c (%)	7.3 ± 0.9	6.8 ± 1.1
Severe hypoglycemia (%)	100	100

Effect of intervention on hypoglycemia avoidance ->

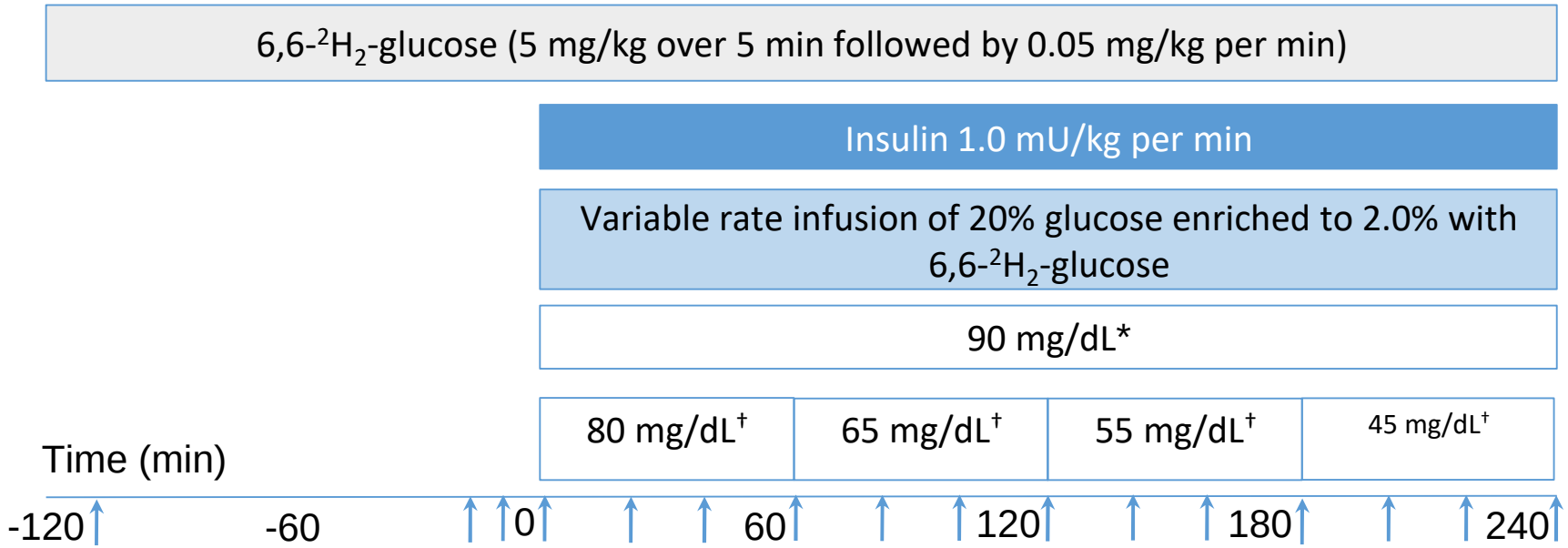




Rickels et al. *J Clin Endocrinol Metab* 101: 4421, 2016

Flatt et al. *Diabetes Technol Ther* 25: 302, 2023

Assessment of Glucose Counterregulation: Hyperinsulinemic Paired Eu- and Hypoglycemic Clamps

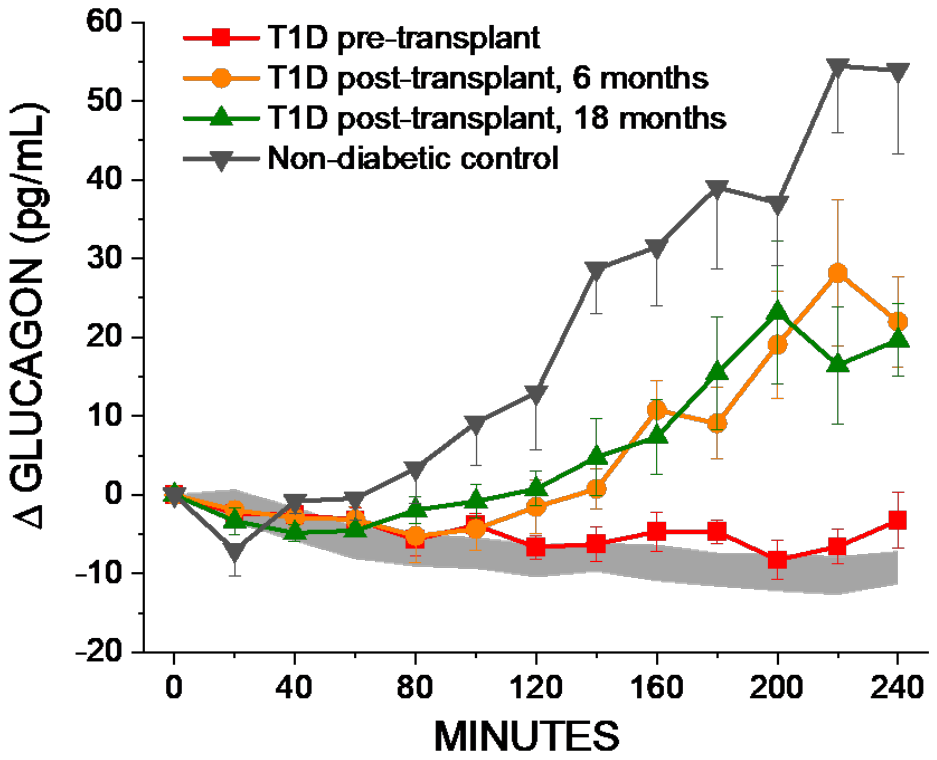


***Target glucose value euglycemic clamp; †Target glucose value hypoglycemic clamp; Arrow: plasma sampled**

Rickels et al. *J Clin Endocrinol Metab* 101: 4421, 2016
Flatt et al. *Diabetes Technol Ther* 25: 302, 2023

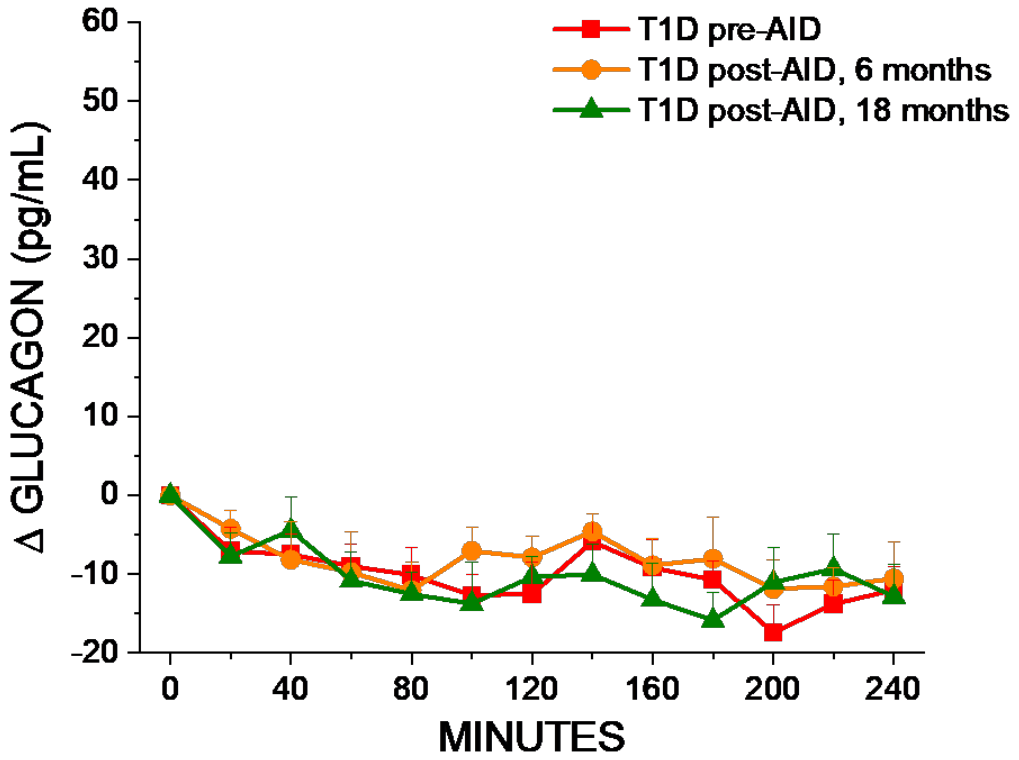
Effect on Islet α-Cell Function to Defend against Hypoglycemia

Islet Transplantation



Rickels et al. *J Clin Endocrinol Metab* 101: 4421, 2016

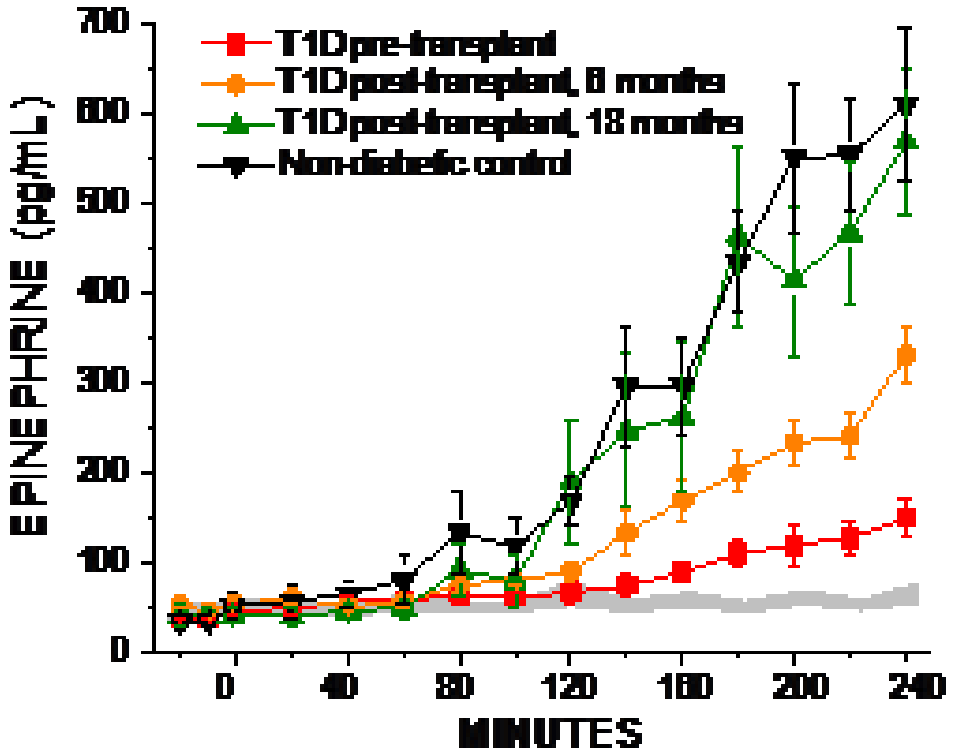
Automated Insulin Delivery



Flatt et al. *Diabetes Technol Ther* 25: 302, 2023

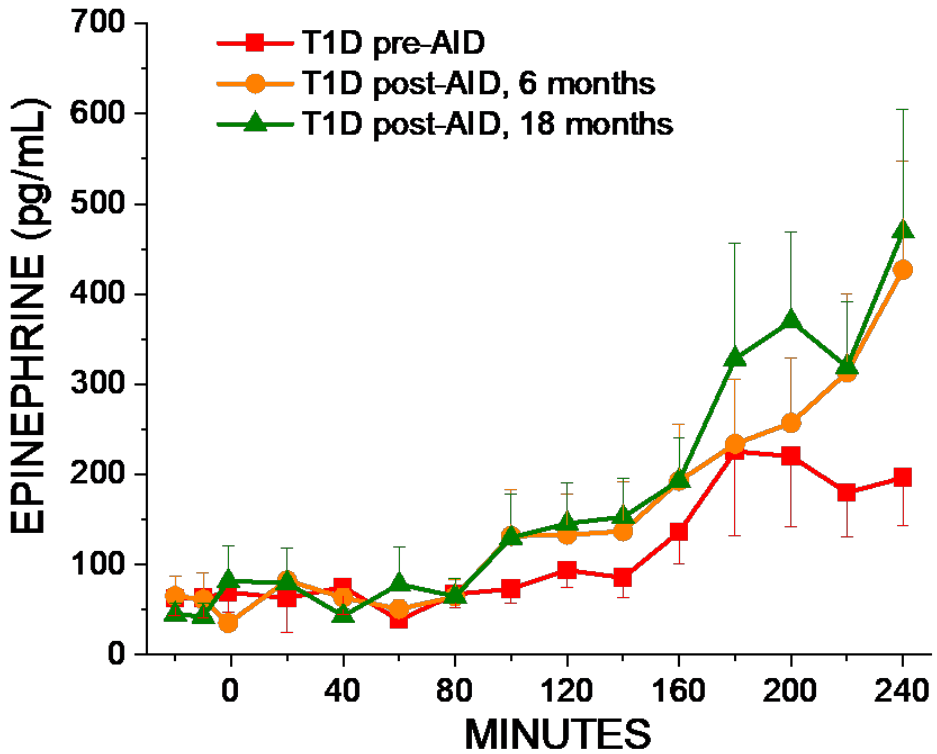
Effect on Epinephrine Secretion to Defend against Hypoglycemia

Islet Transplantation



Rickels et al. *J Clin Endocrinol Metab* 101: 4421, 2016

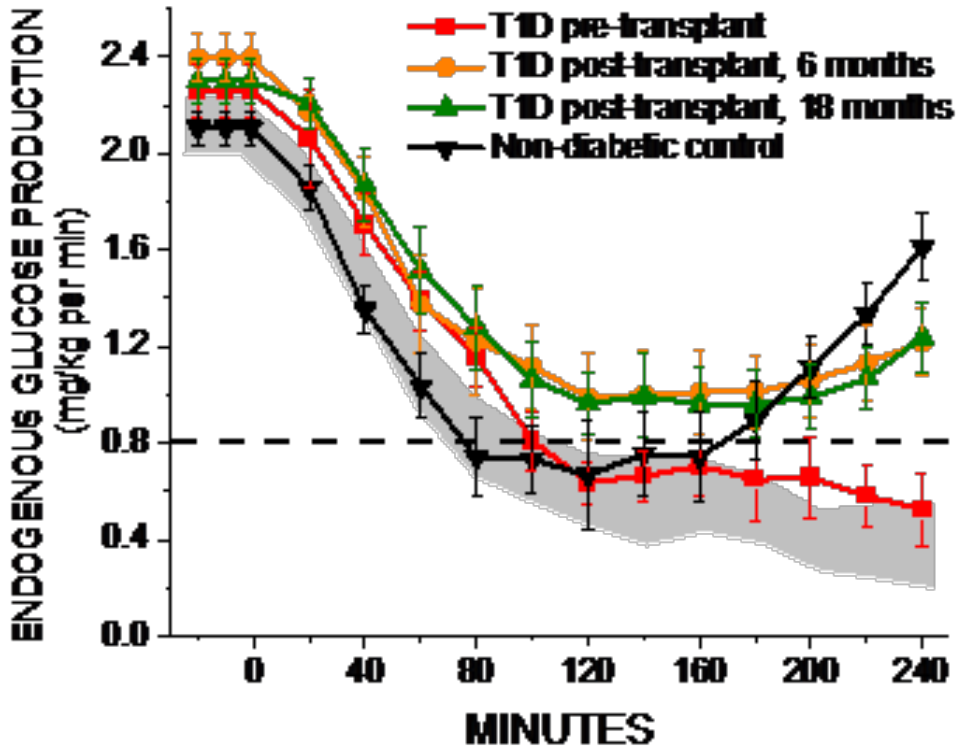
Automated Insulin Delivery



Flatt et al. *Diabetes Technol Ther* 25: 302, 2023

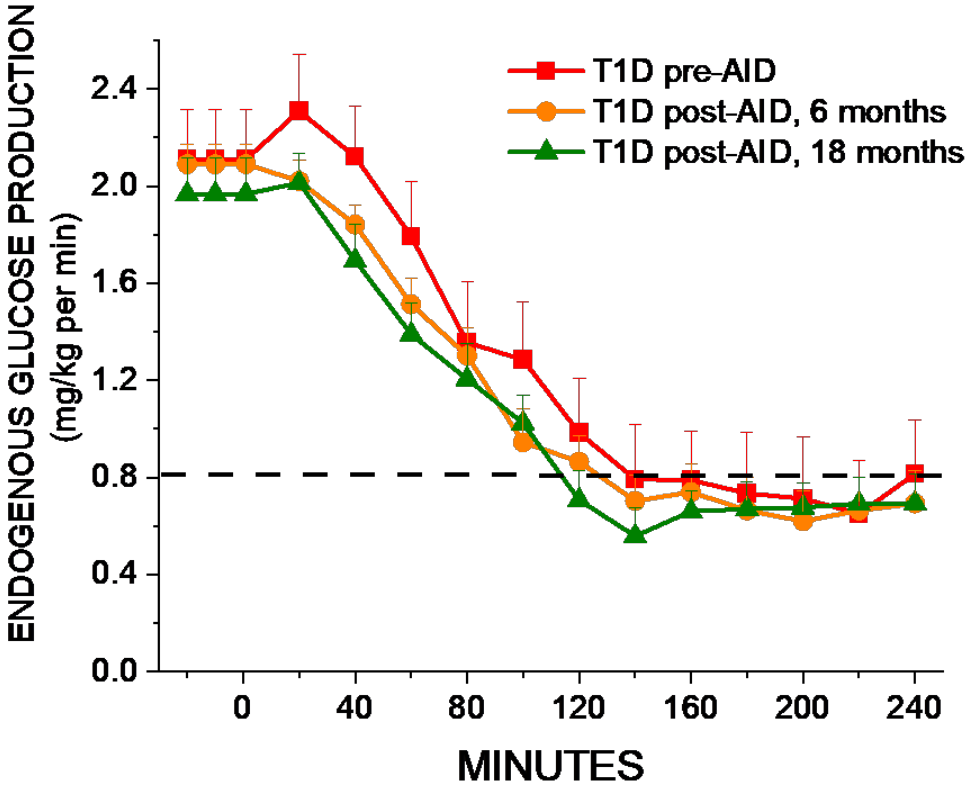
Effect on Hepatic Glucose Production to Defend against Hypoglycemia

Islet Transplantation



Rickels et al. *J Clin Endocrinol Metab* 101: 4421, 2016

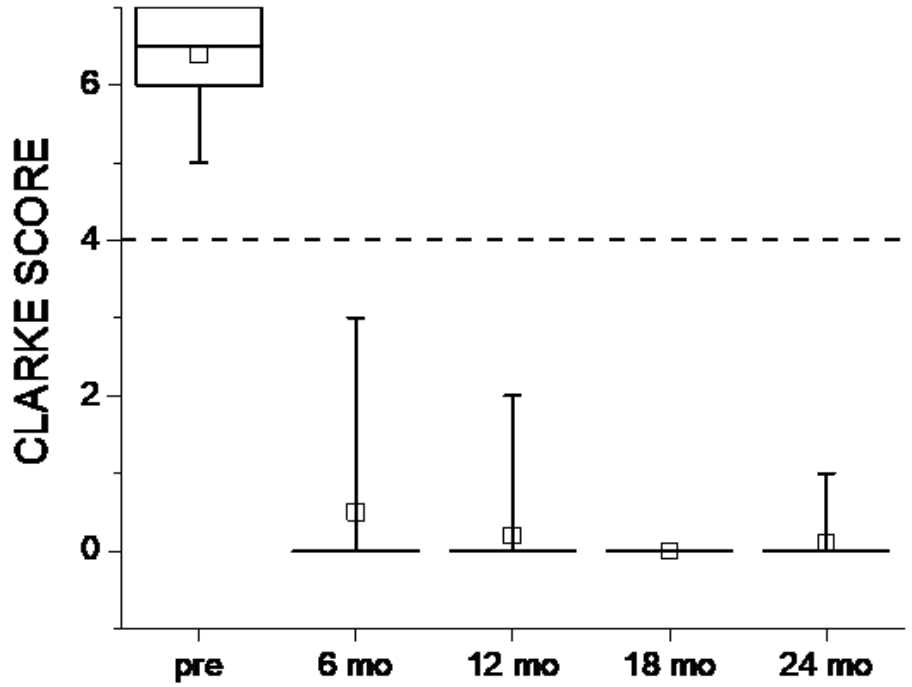
Automated Insulin Delivery



Flatt et al. *Diabetes Technol Ther* 25: 302, 2023

Effect on Impaired Awareness of Hypoglycemia and SHEs

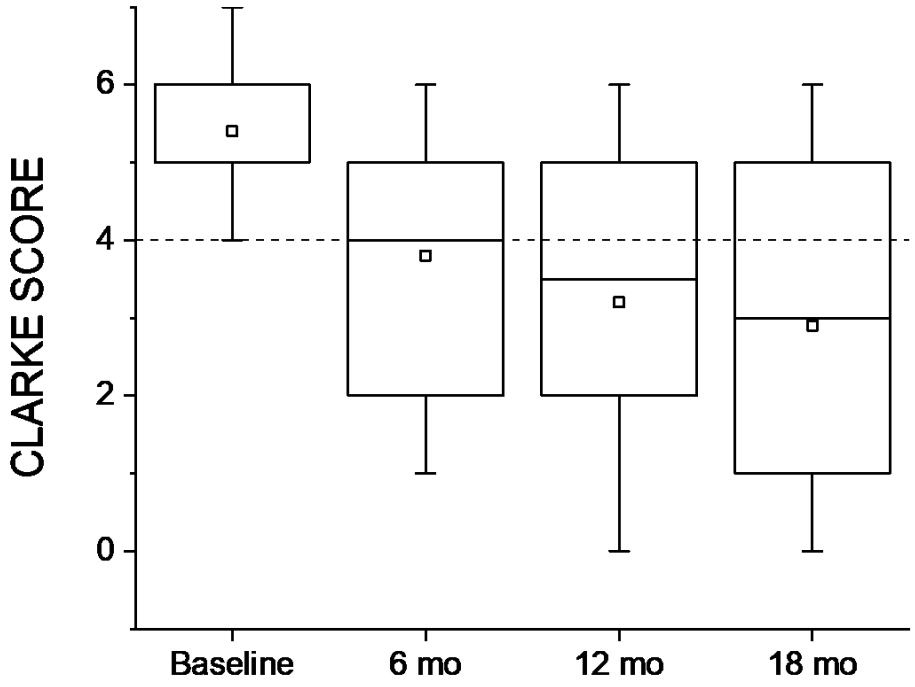
Islet Transplantation



None with recurrence of severe hypoglycemia events (SHEs)

Rickels et al. *J Clin Endocrinol Metab* 101: 4421, 2016

Automated Insulin Delivery

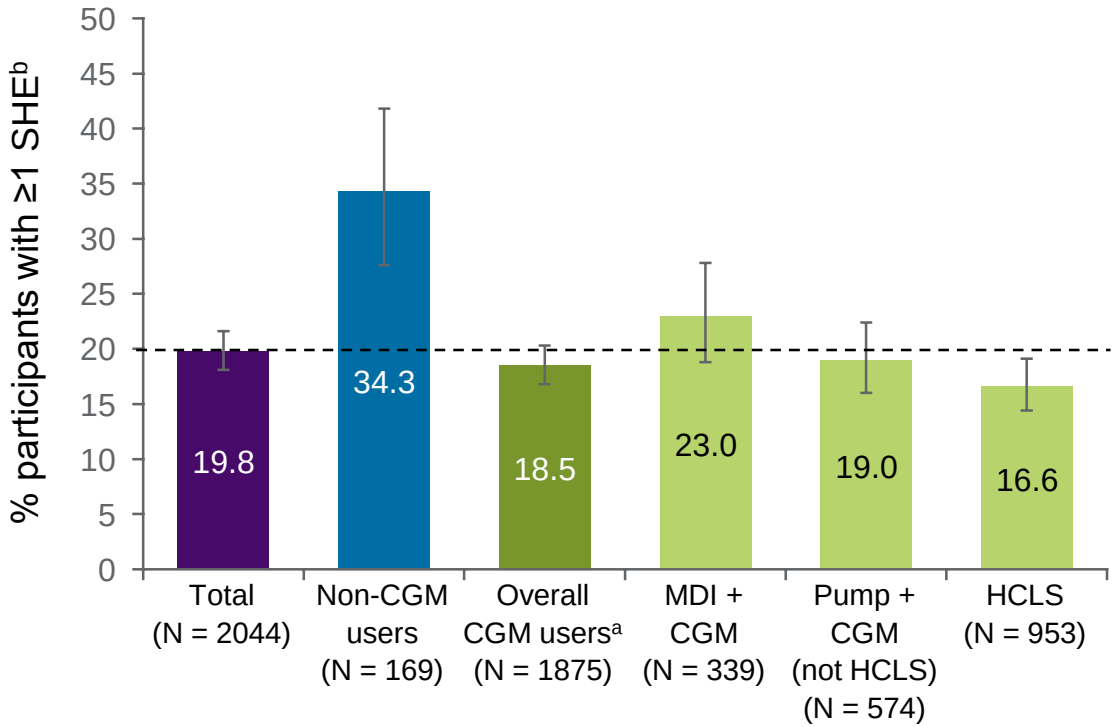


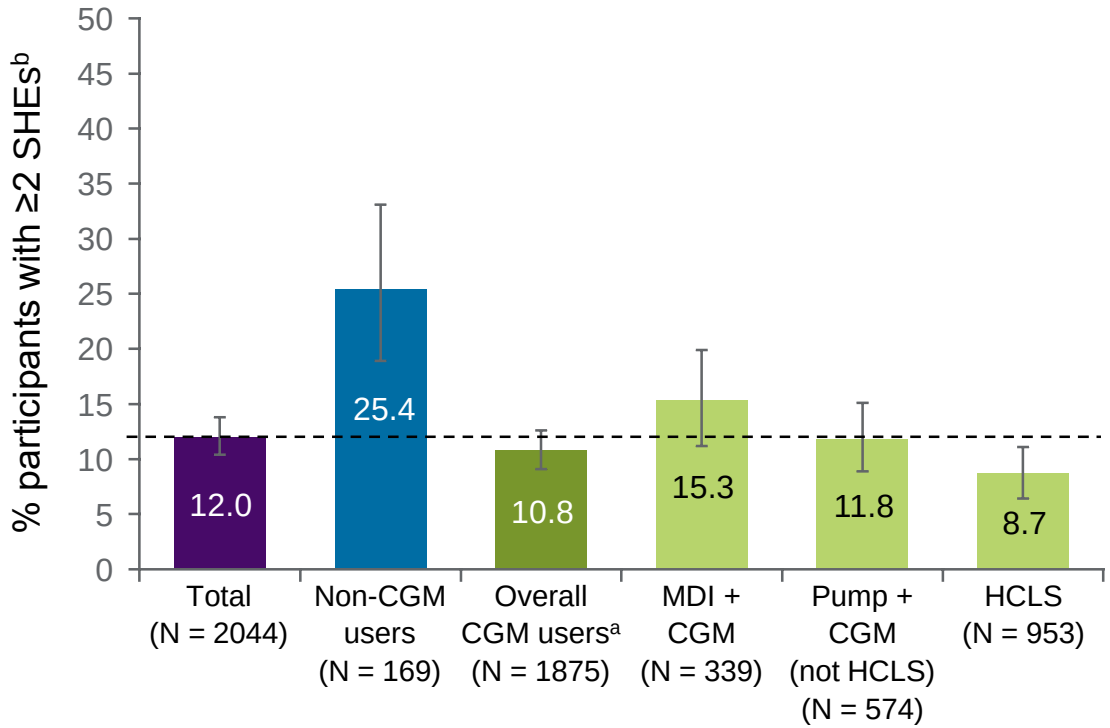
4/10 experienced 5 episodes of severe hypoglycemia

Flatt et al. *Diabetes Technol Ther* 25: 302, 2023

Substantial Proportion on Closed-Loop Continue to Experience SHEs

- Real-world data from the T1D Exchange registry and on-line community (N = 2044 survey respondants)
- Majority of these events occurred in those with IAH that affected 30% of cohort regardless of tech use



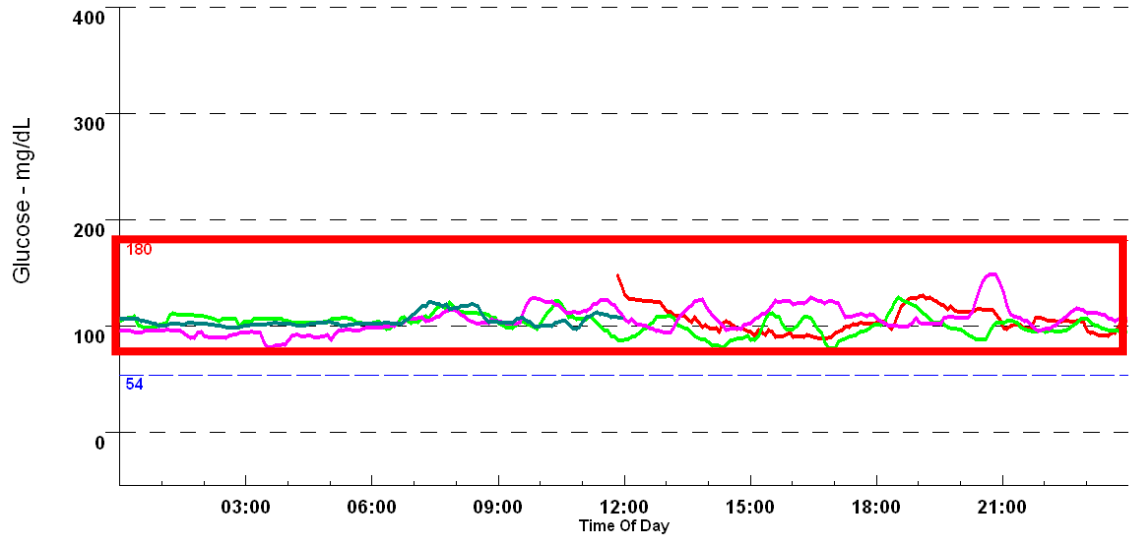


CGM, continuous glucose monitor; HCLS, hybrid closed-loop system; MDI, multiple daily injections; SHE, severe hypoglycemic event

Sherr et al. *Diabetes Care* 47: 941, 2024

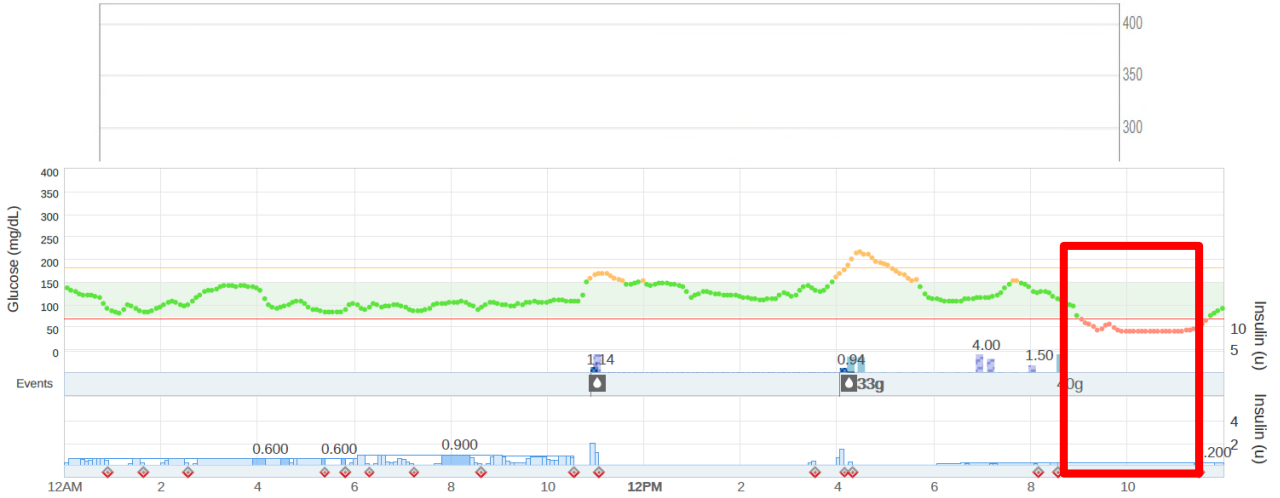
Case

Islet Transplantation - PHPI



No hypoglycemia exposure
Normal glucose variability

Automated Insulin Delivery - CIQ

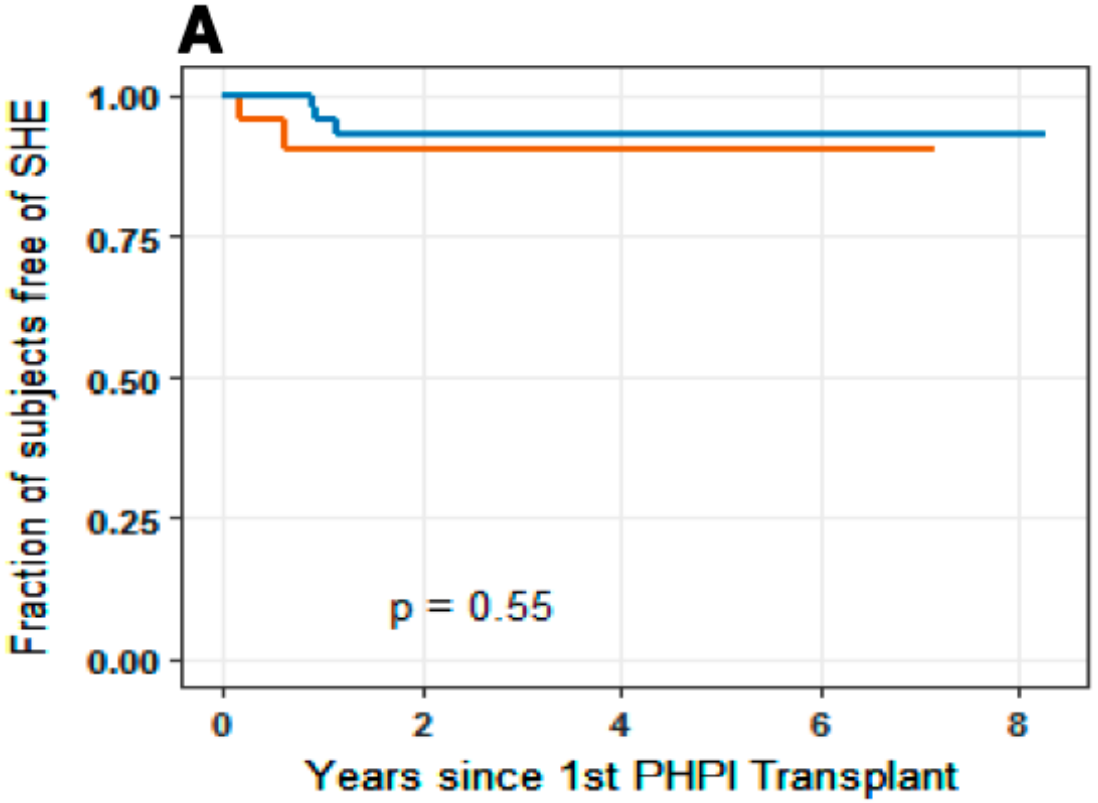


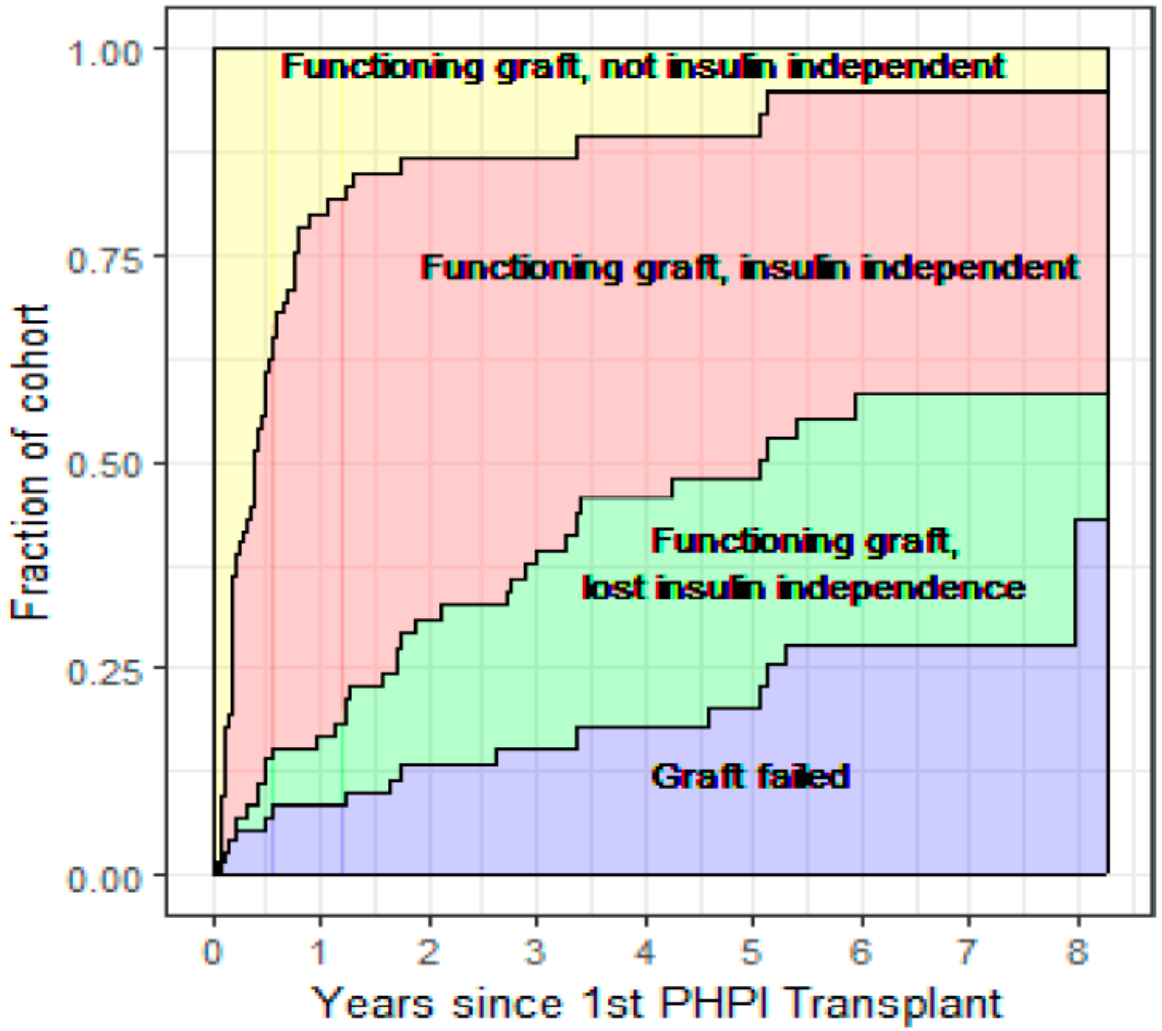
On-going hypoglycemia exposure
Excessive glucose variability

Rickels et al. *J Clin Endocrinol Metab* 101: 4421, 2016

Flatt et al. *Diabetes Technol Ther* 25: 302, 2023

Long-Term Outcomes with Islet Alone and After Kidney Transplantation

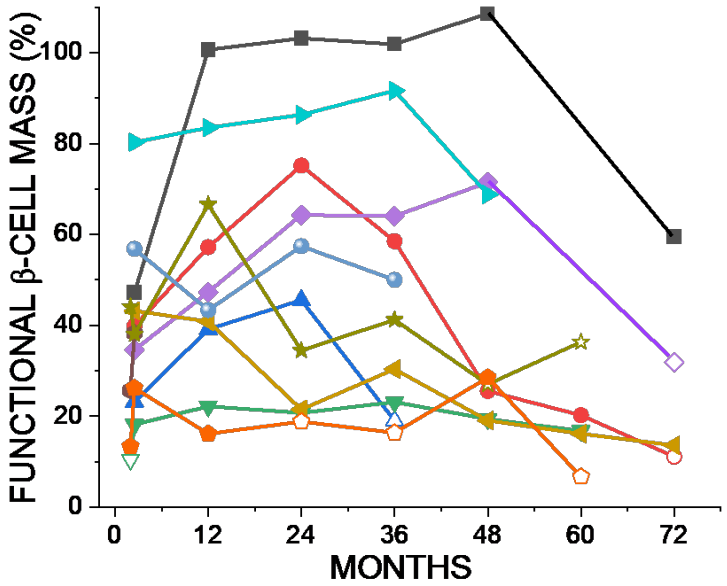


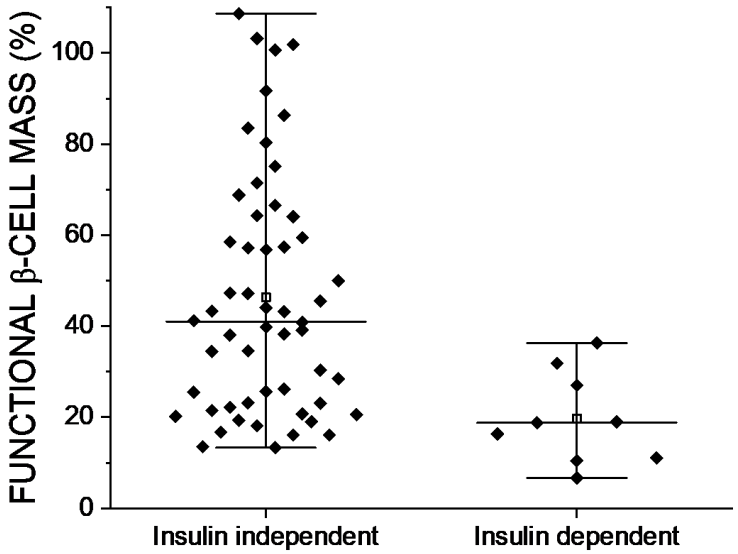


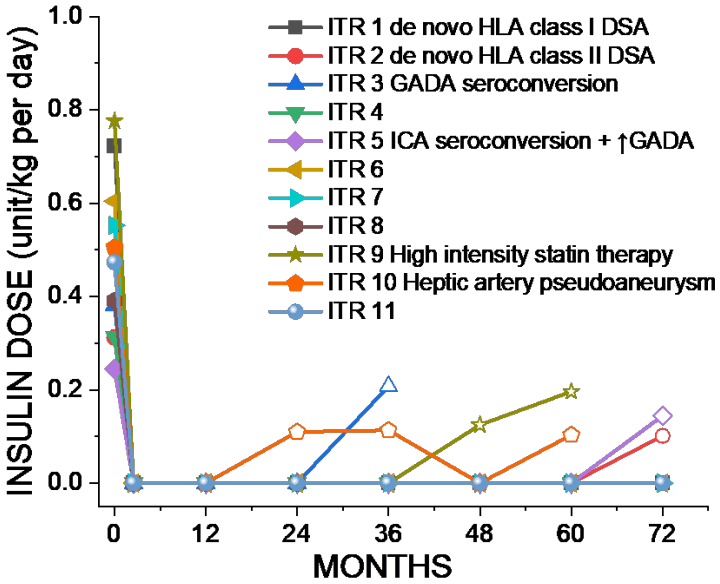
"Islet transplantation results in durable islet graft survival permitting achievement of glycemic targets in the absence of severe hypoglycemia for most appropriately indicated recipients having impaired awareness of hypoglycemia, with acceptable safety of added immunosuppression."

Rickels et al. *Diabetes Care* 45: 2967, 2022

Heterogeneity of Islet Engraftment and Long-Term Survival

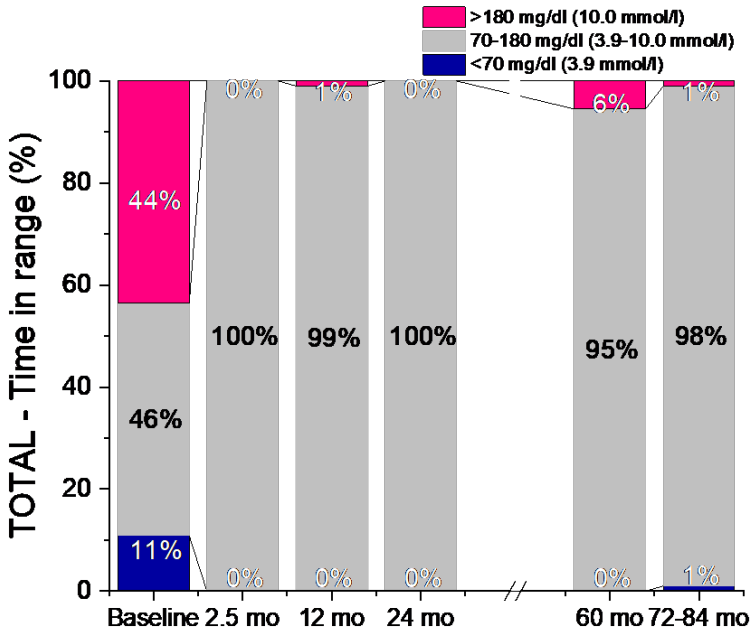


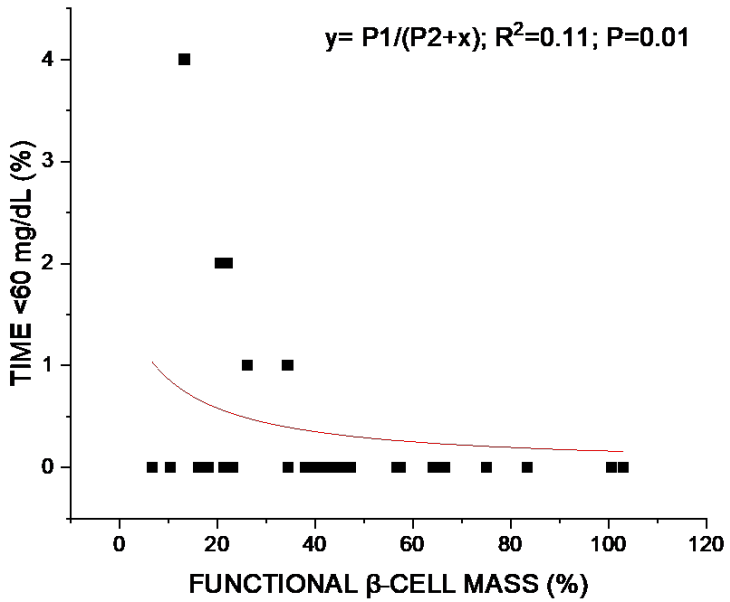


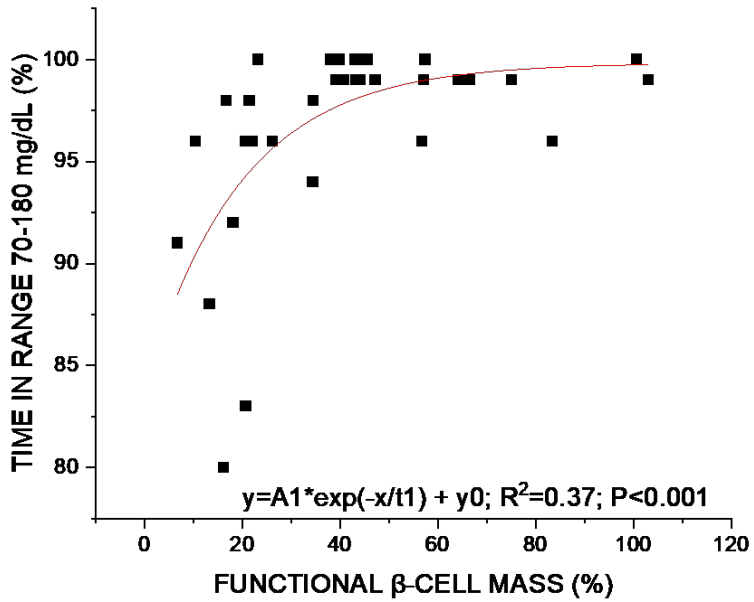


Flatt et al. *American Diabetes Association 84th Scientific Sessions* 1507-P (Saturday), 2024

Relationship of Functional β-Cell Mass to Glycemic Control

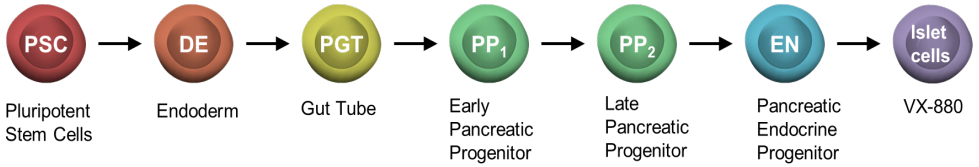




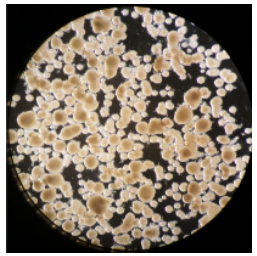


Flatt et al. *American Diabetes Association 84th Scientific Sessions* 1507-P (Saturday), 2024

Novel Cell Source for Islet Cell Therapy in Clinical Development for Type 1 Diabetes Complicated by Severe Hypoglycemia



VX-880 is an investigational allogeneic stem cell-derived, fully differentiated, insulin-producing **islet cell therapy**



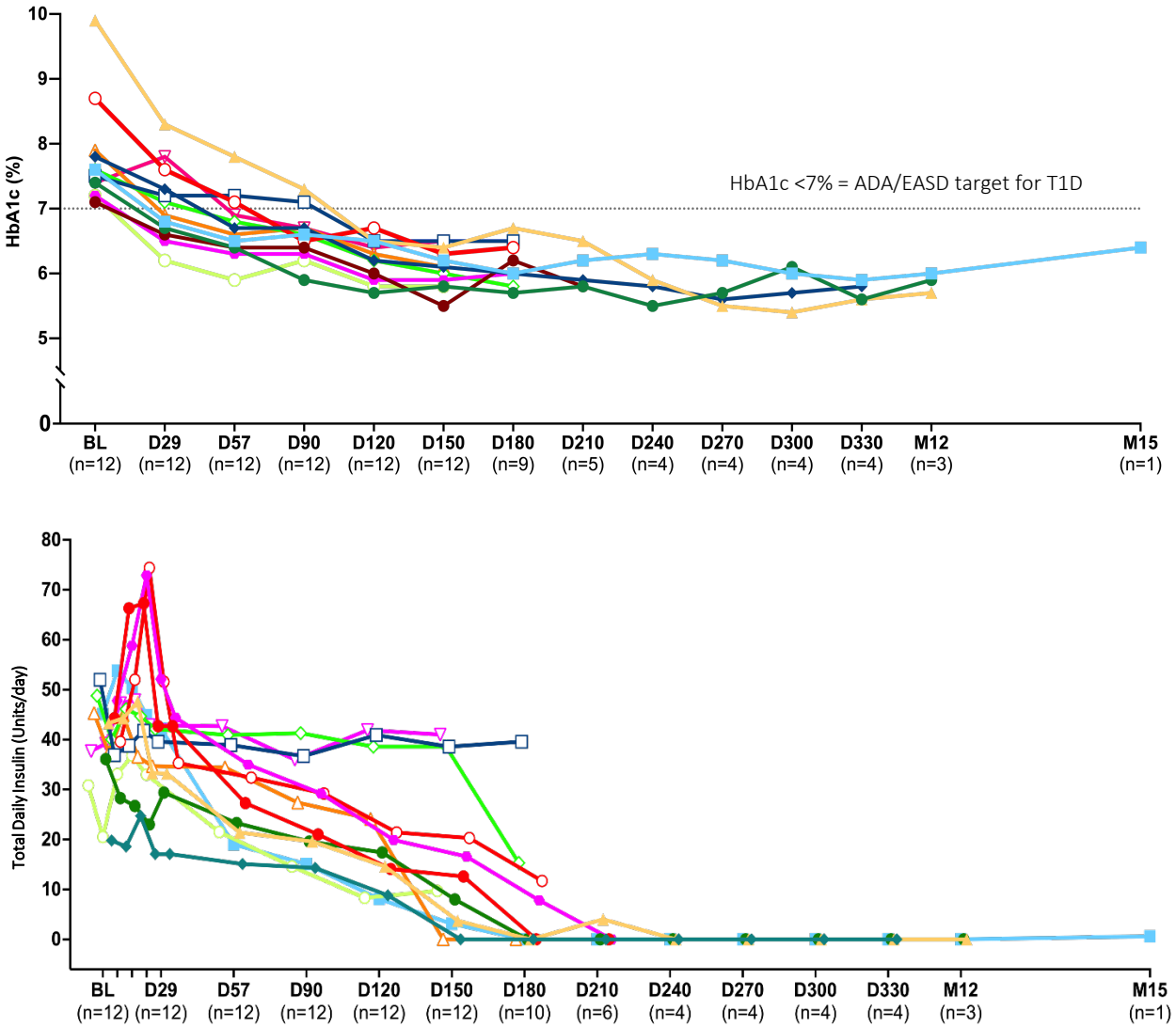
VX-880 is delivered by an **infusion into the hepatic portal vein**

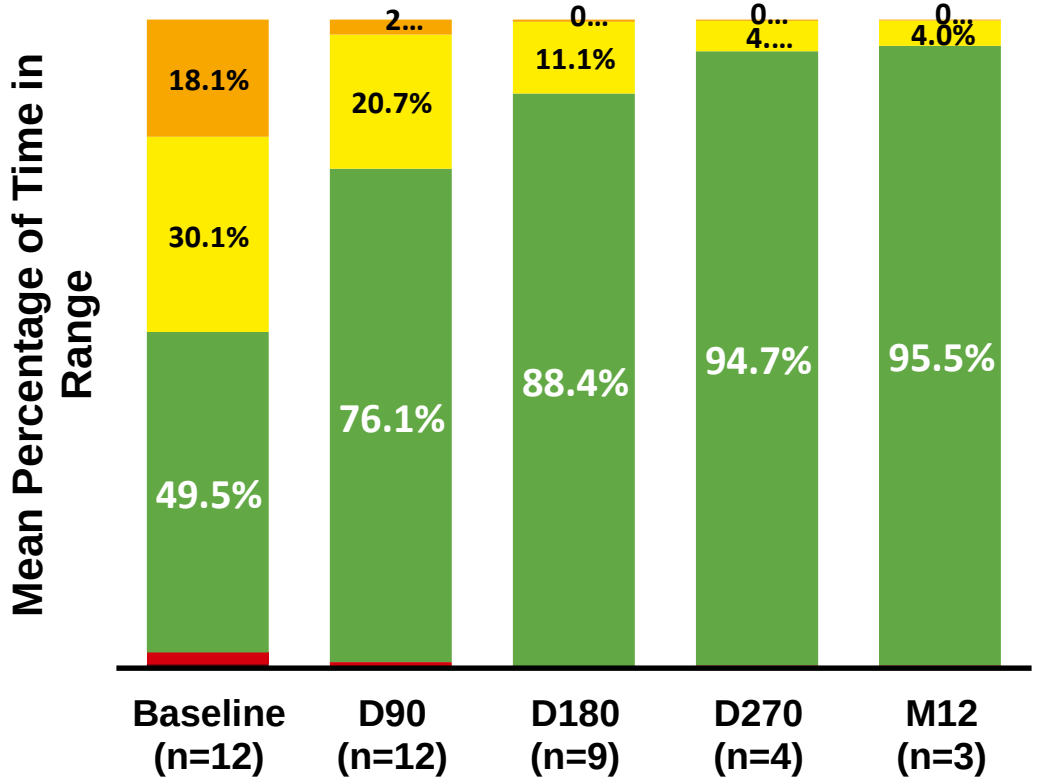
An induction (anti thymocyte globulin) and maintenance (tacrolimus and sirolimus) **immunosuppression regimen** is used to protect the cells from the immune system

The cellular delivery protocol and immunosuppression regimen have been established for deceased donor islet cell therapy (PHPI)

Figure adapted from Pagliuca et al. *Development* 140: 2472, 2013

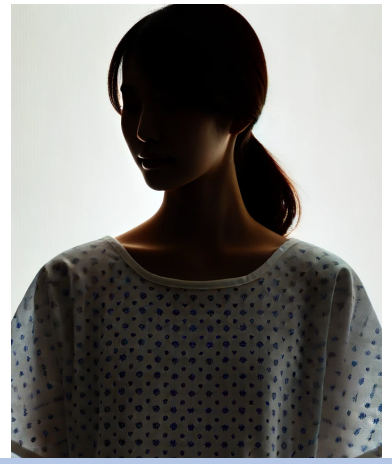
Consistent Transplant Results with Stem Cell-Derived Islet Product



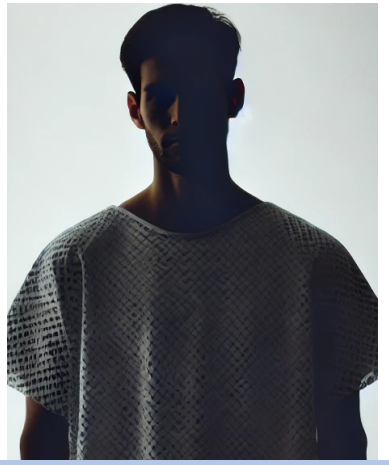


Witkowski et al. *American Diabetes Association 84th Scientific Sessions* IBC-SY05 (Friday), 2024

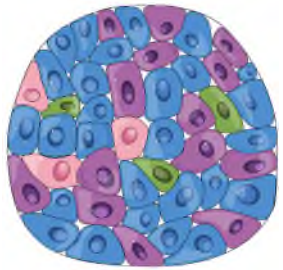
Type 1 Diabetes Patient Heterogeneity for Islet Cell Therapy



Very few T1D patients



Many T1D patients



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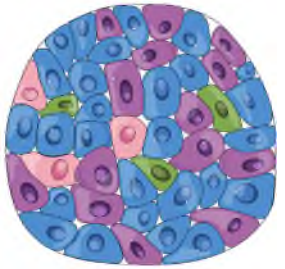
Islets + Immunosuppression



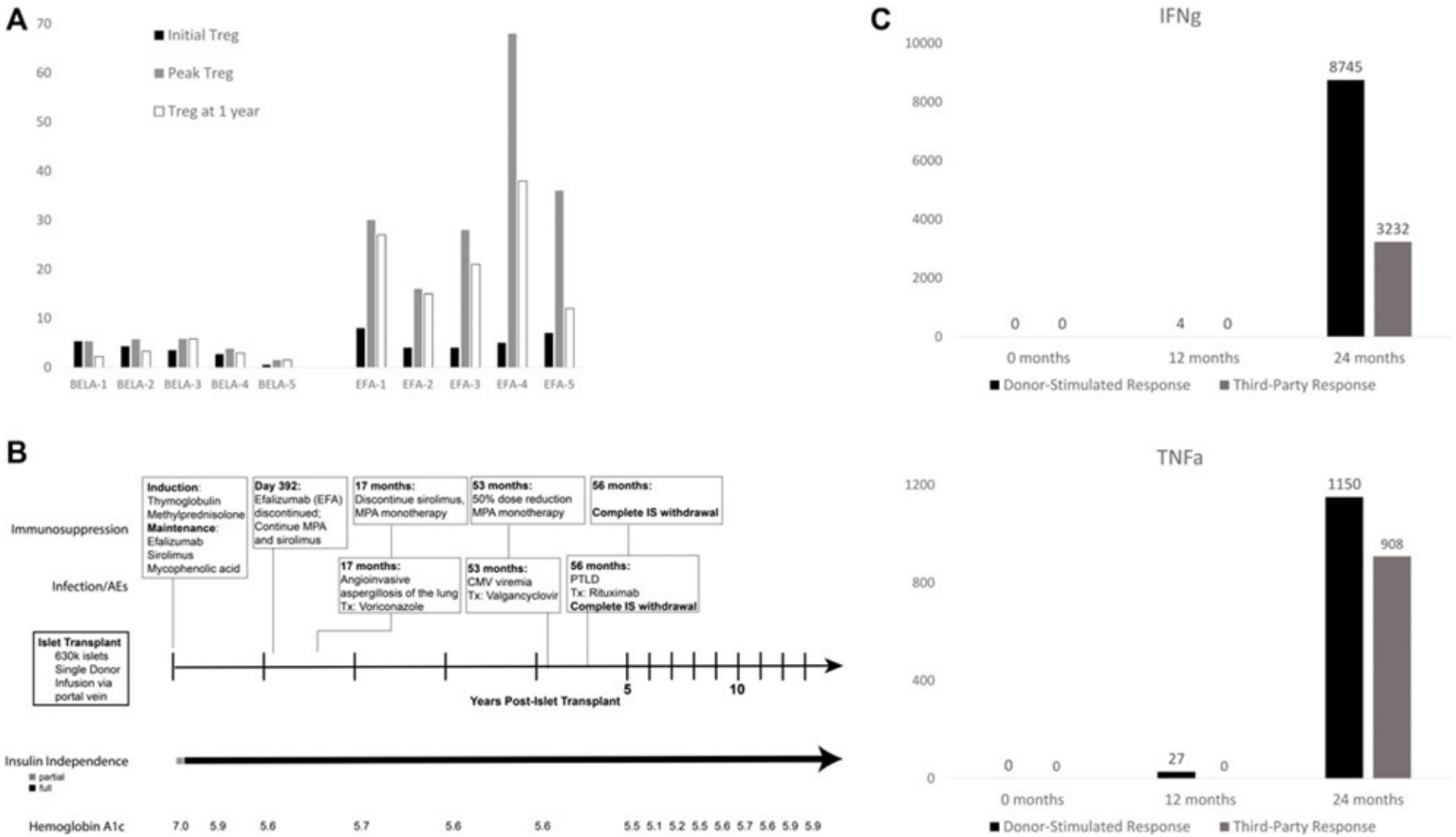
- Operational Tolerance
- Hypoimmune Islets

Immunoprotected Islets

Slide curtesy of Jeff Millman

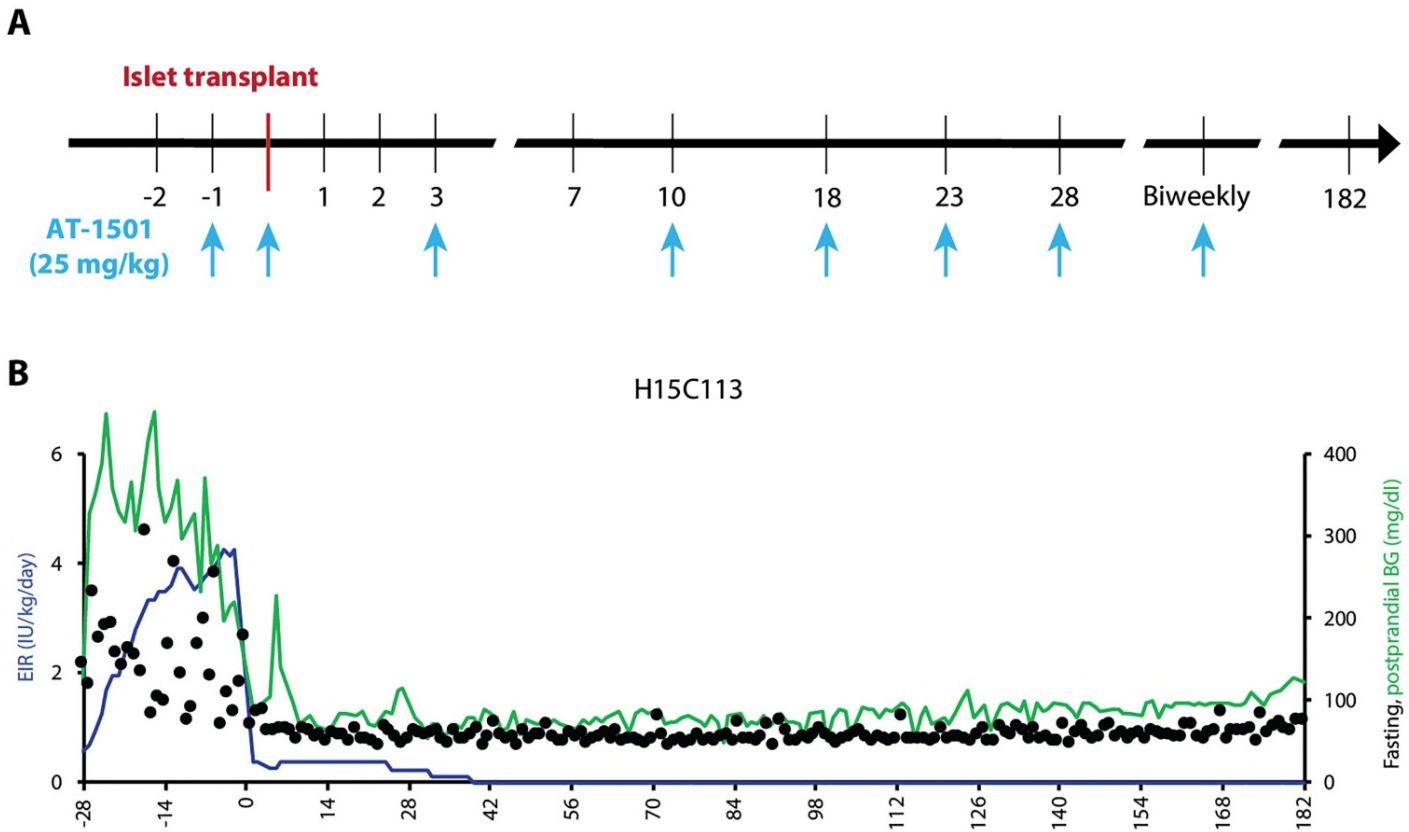
diabetes | Diabetes Care | Diabetologia

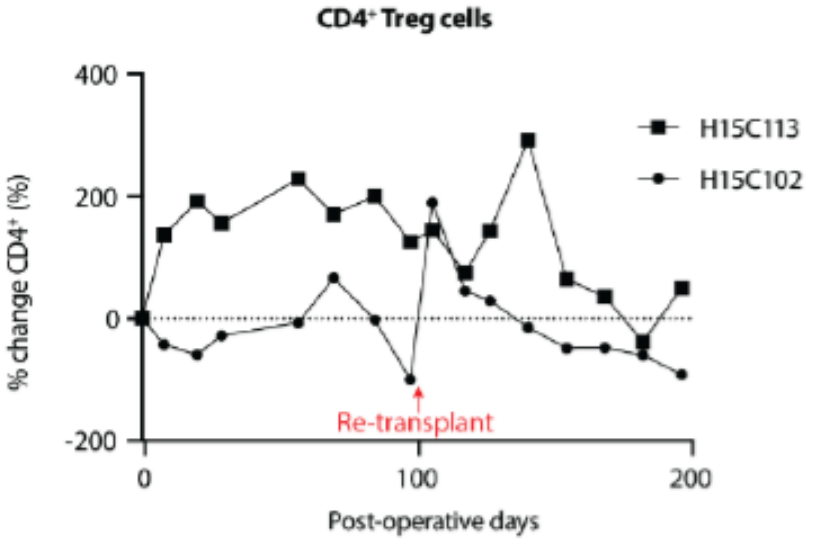
Operational Tolerance in an Islet Transplant Recipient



Wisel et al. *Science Transplant Int* 36: 11367, 2023

Anti-CD40L Promotes CNI-free Immunosuppression in Macaques



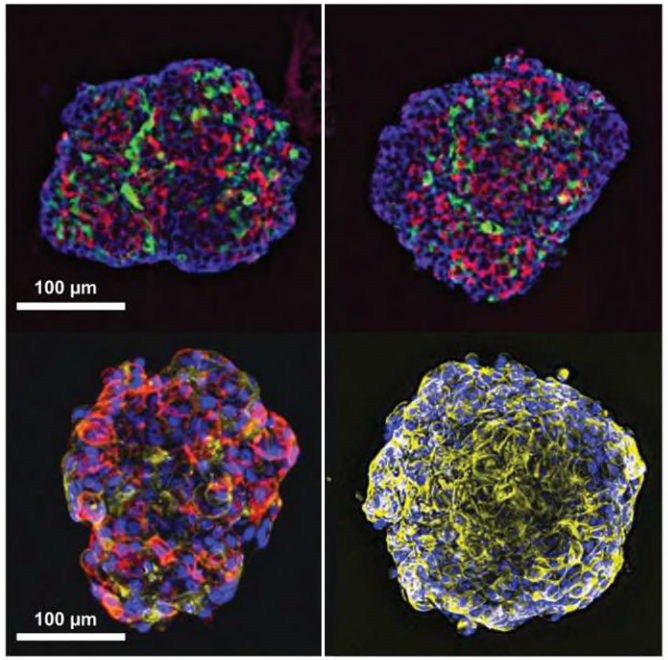


Anwar et al. *Sci Transl Med* 15: eadg6376, 2023

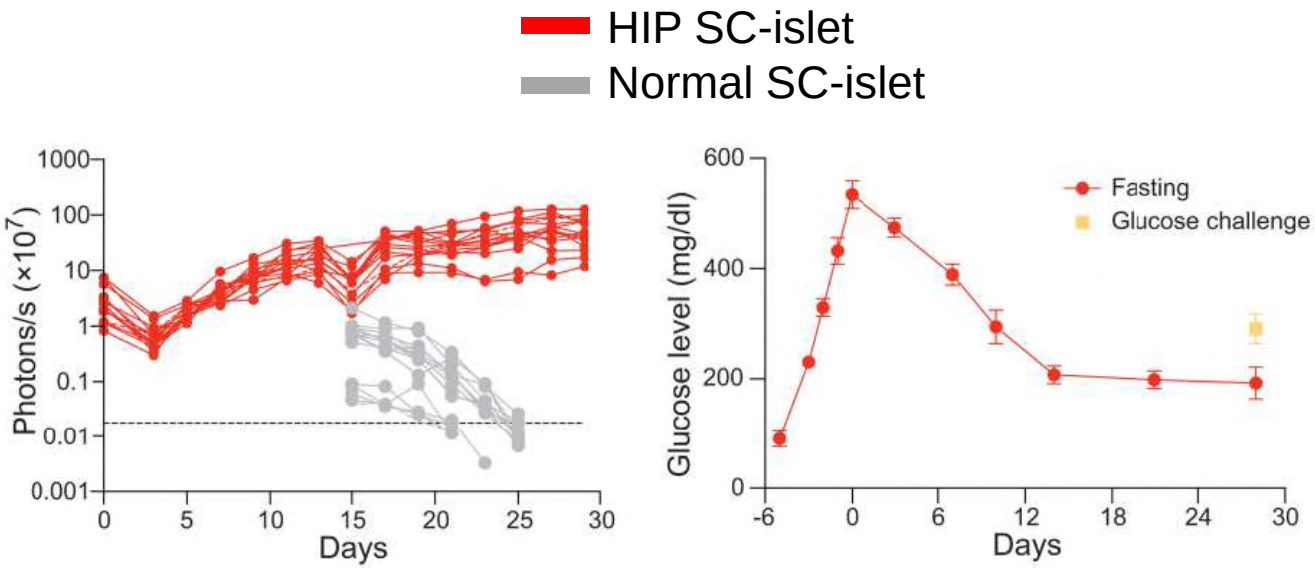
ClinicalTrials.gov ID: NCT06305286

Genome Editing for Hypoimmunity of Islets

Normal SC-islet HIP SC-islet



HIP SC-islet Transplantation

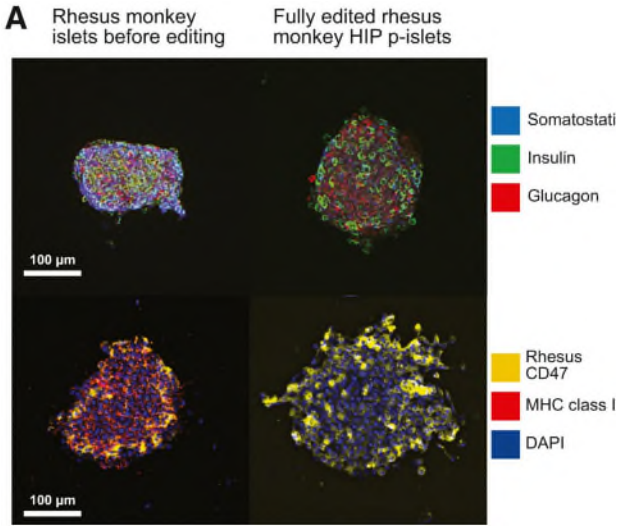


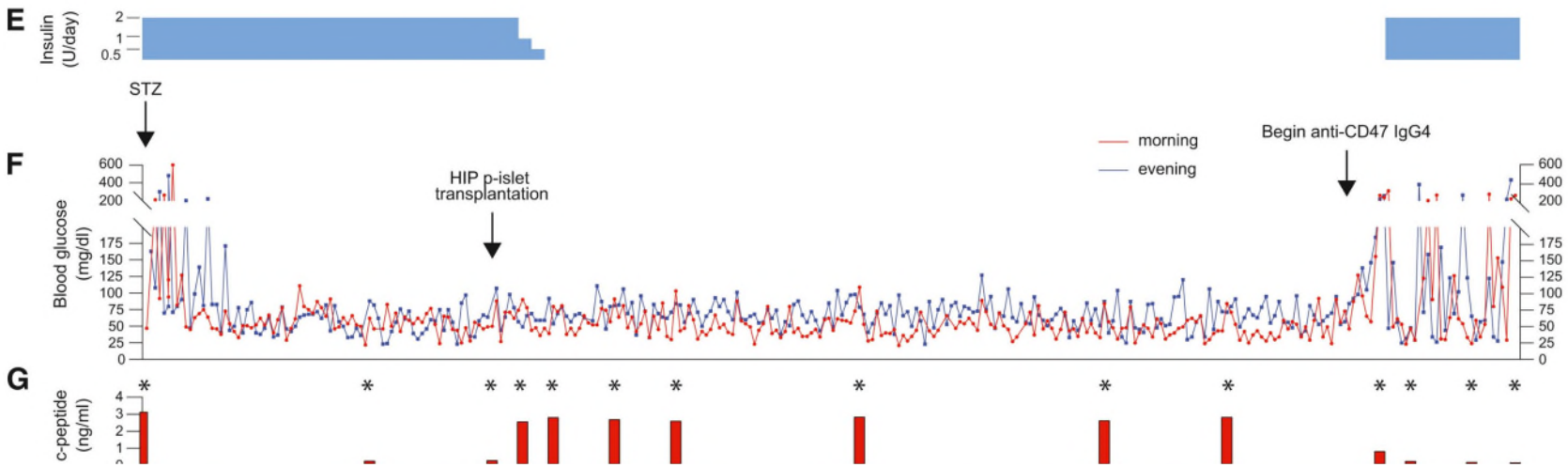
Hypoimmune (HIP) SC-islets with HLA knockout and CD47 overexpression

Hu et al. *Sci Transl Med* 15: eadg5794, 2023

Slide curtesy of Jeff Millman diabetes | Diabetes Care | Diabetologia

Hypoimmune Islets without Immunosuppression in Macaques





Hu et al. *Cell Stem Cell* 31: 334, 2024

ClinicalTrials.gov ID: NCT06239636

Current and Future Approaches to Islet Cell Replacement

KEY: Current | Proof-of-Concept | Future

β-cell source	Transplant site	Protection from the immune system
Allogeneic islets isolated from a deceased donor	Intrahepatic, via portal vein infusion	Induction and maintenance immunosuppression
Allogeneic islets derived from a human pluripotent stem cell line[1]	Intra-omental, via thrombin bio-scaffold[2]	Induction immunomodulation with operational tolerance[3]
Xenogeneic islets isolated from a pathogen-free porcine herd	Intramuscular	Immune evasion via genetic engineering[4] or local immunosuppression
Autologous islets derived from an inducible pluripotent stem (iPS) cell line	Subcutaneous, via a device-less space or cell-permeable or -impermeable device	Immune protection via macroencapsulation device

1. Witkowski et al. *ADA* IBC-SY05, 2024
2. Baidal et al. *N Eng J Med* 376: 1887, 2017
3. Wisel et al. *Transplant Int* 36: 1, 2023
4. Hu et al. *Sci Transl Med* 15: eadg5794, 2023

Acknowledgments

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Anneliese Flatt, MBBCh, MRCP
Austin Matus, BSN, PhD
Jorge Jo Kamimoto, MD
Amy Peleckis, MSN, CRNP
Ginger Bakes, MS, CCRC
Eileen Markmann, BSN, RN
Huong-Lan Nguyen, BS
Stephanie Kong, MS, MD
Nina Ran, MD
Elizabeth Chen, MD
Joseph Naji, MD
Sarah Ilany

Funding

NIH (NIDDK, NCATS)
Juvenile Diabetes Research Foundation
W.W. Smith Charitable Trust

Collaborators at Penn

Karen Teff, PhD
Ali Naji, MD, PhD
Chengyang Liu, MD
James Markmann, MD, PhD
Mark Schutta, MD
Heather Collins, PhD
John Millar, PhD
Robert Gallop, PhD
Darko Stefanovski, PhD
Insup Lee, PhD
James Weimer, PhD
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Updated Data from the Phase 1/2 FORWARD Study of VX-880 Stem Cell-Derived, Fully Differentiated Islets in Participants with Type 1 Diabetes, Impaired Awareness of Hypoglycemia and Severe Hypoglycemia

Piotr Witkowski, MD on behalf of the VX-880 authors

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Witkowski et al. *American Diabetes Association 84th Scientific Sessions* IBC-SY05 (Friday), 2024