Islet Isolation Program for The Leona M. & Harry B. Helmsley Charitable Trust Alpha Cell Initiative

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Why are we Having this Webinar?

- To announce that nPOD is undertaking an effort to supply the HCT alpha cell initiative with islets from intermediate to long-term T1D donors.
- We believe this initiative, with focus on human alpha cells, is quite unique in the T1D research space.
- Our purpose today is to share our vision for this program and answer questions.
- We seek active engagement from all parties and are open to suggestions on how to best support this line of research.
- Why is this a “closed” webinar?

Invitation-Only Funding Opportunity

Call for Expressions of Interest

- Define the molecular mechanisms of alpha and delta cell dysfunction in human T1D;
- Identify and develop early-stage therapies to restore glucagon secretion in T1D; or
- Clinically validate therapeutic approaches to restore normal glucagon secretion.

Alpha Cell News Release

nPOD Alpha Cell Website

How Did We Get Here?
Challenge a Dogma

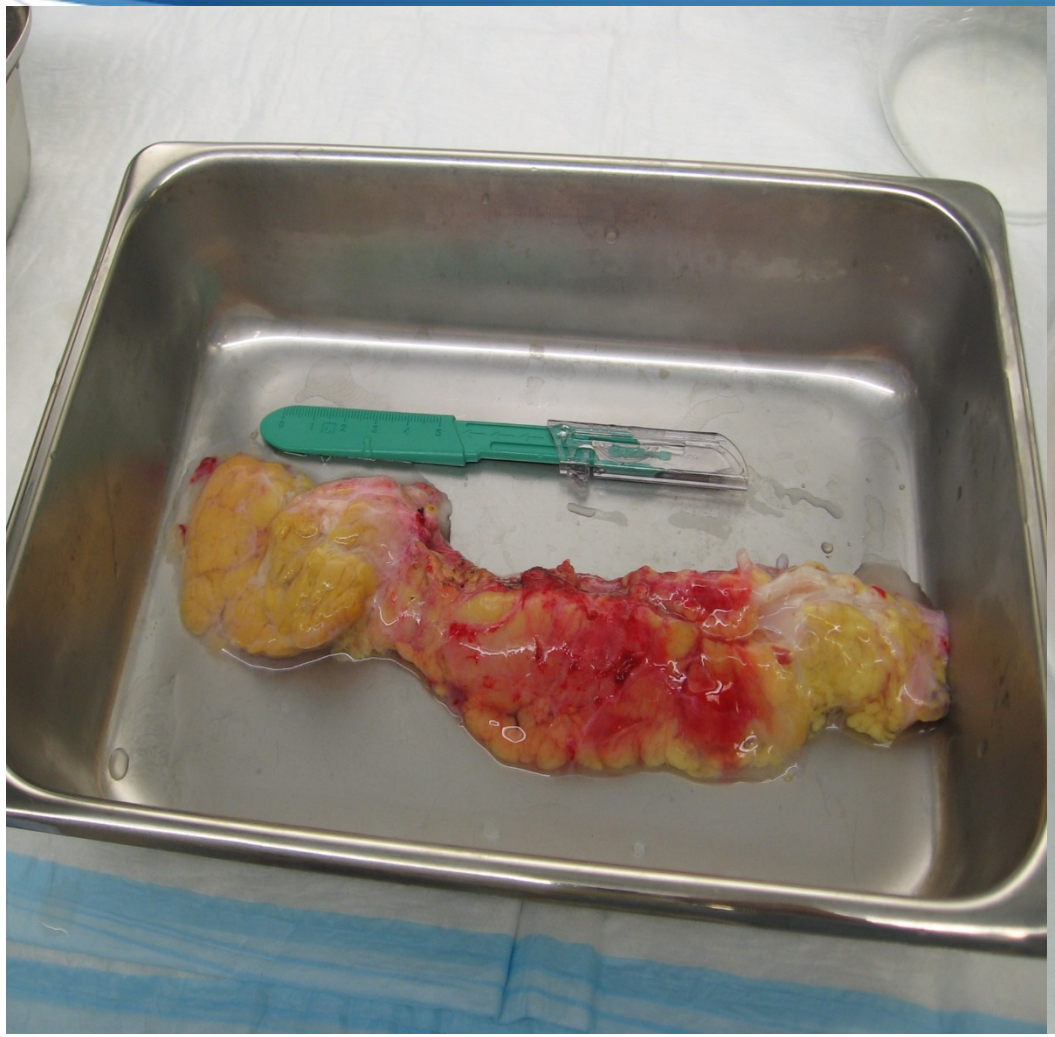
- You cannot isolate islets from a donor with type 1 diabetes

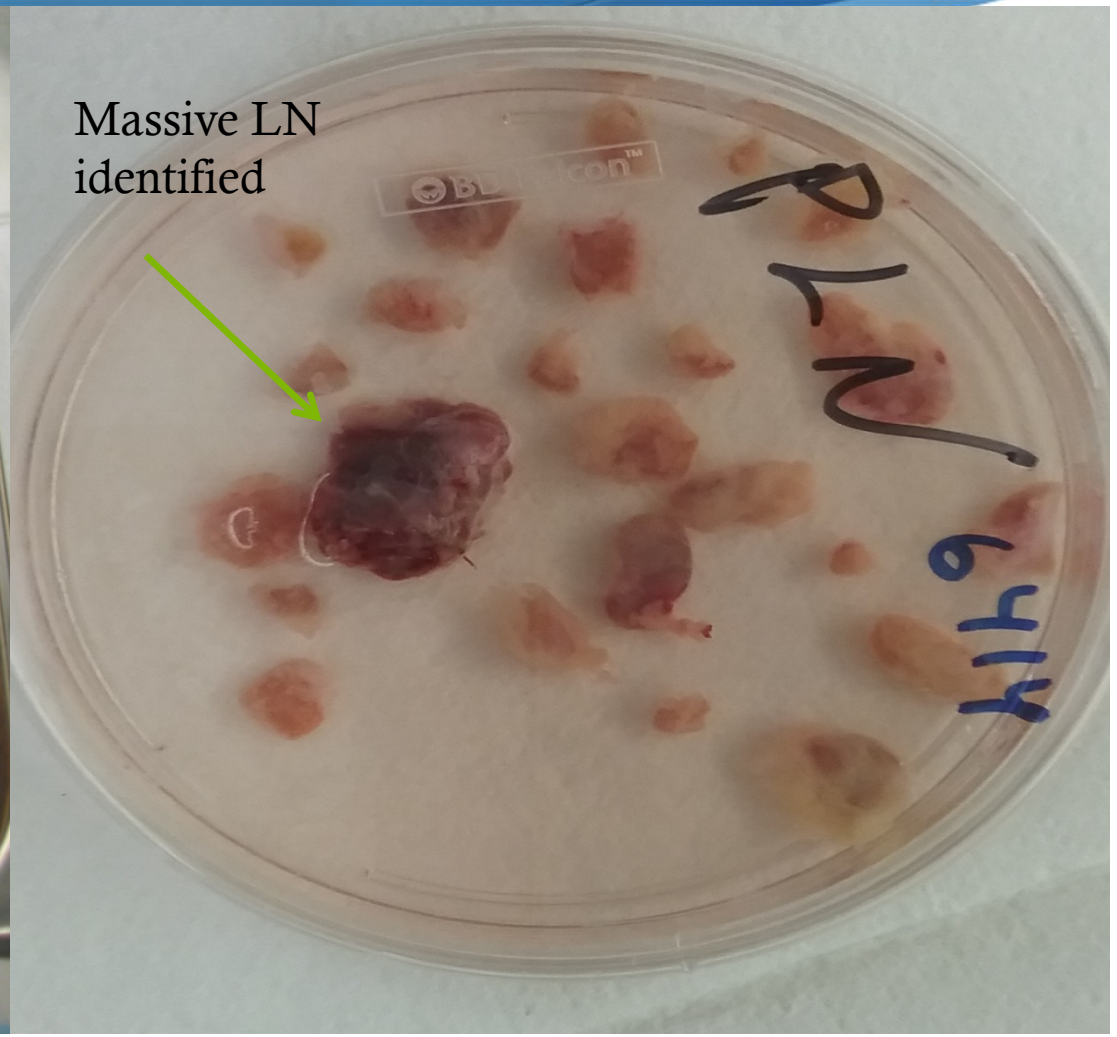
Islet Isolation in T1D - Example

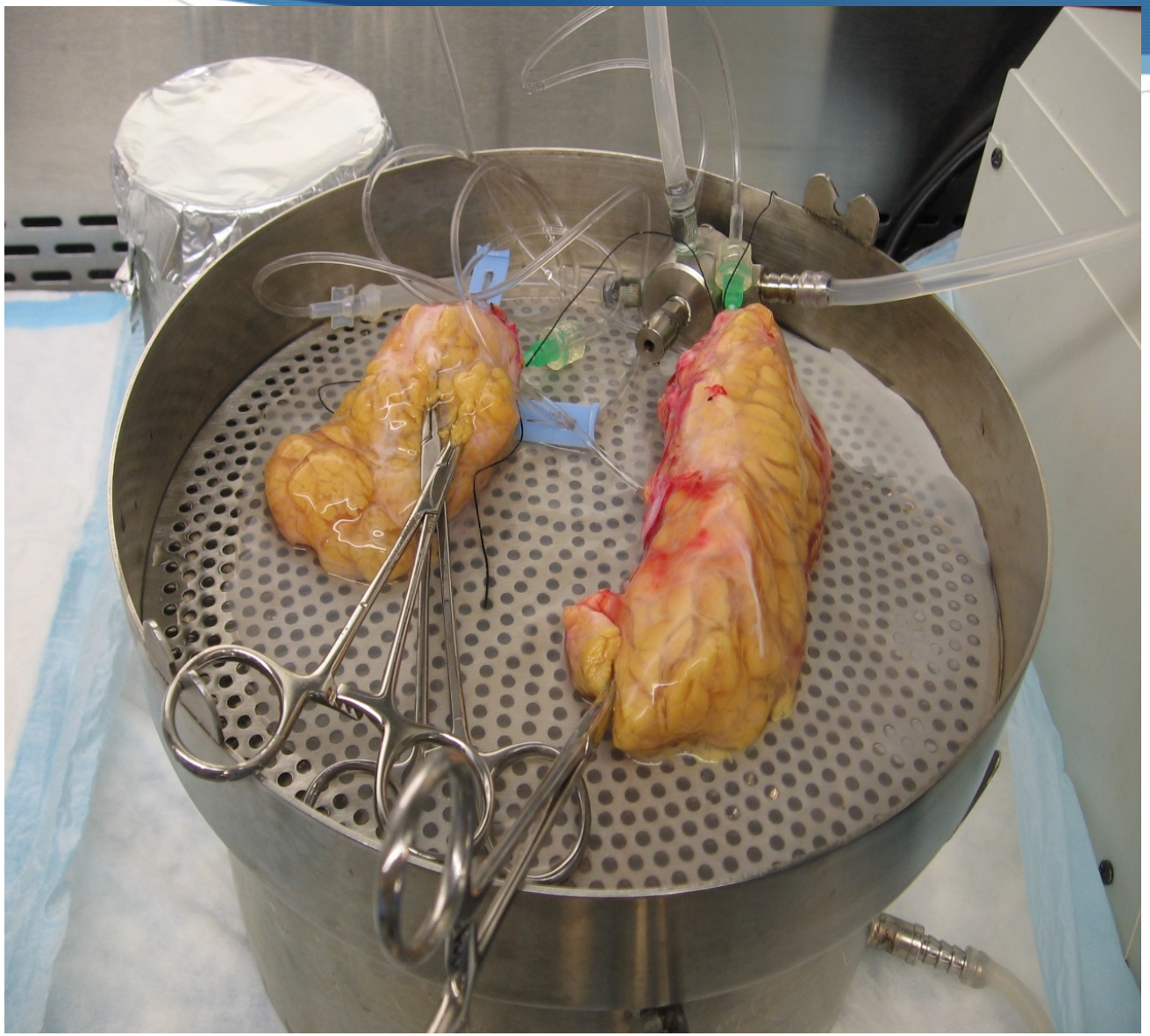
nPOD CASE ID: 6414

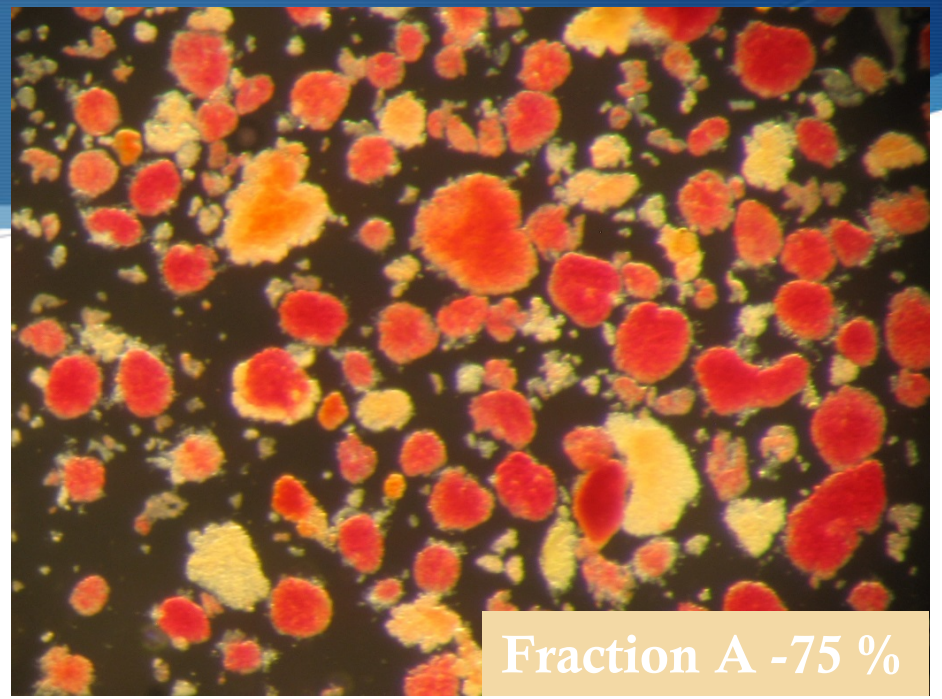
Age:	23.1
Gender:	Male
Race:	African American
Accepted as:	T1D (disease duration 5 months)
AutoAb:	GADA+, ZnT8+, mIAA+
C-peptide	0.16ng/ml
HbA1c:	14
BMI (chart):	28.4
HLA:	A*01/23 B*07/08 DR*17/09 DQ*02/-
COD:	Anoxia (suicide)
Clinical History:	The donor has a history of diabetes, treated with insulin. He had a family history of diabetes (brother and sister, unknown type)

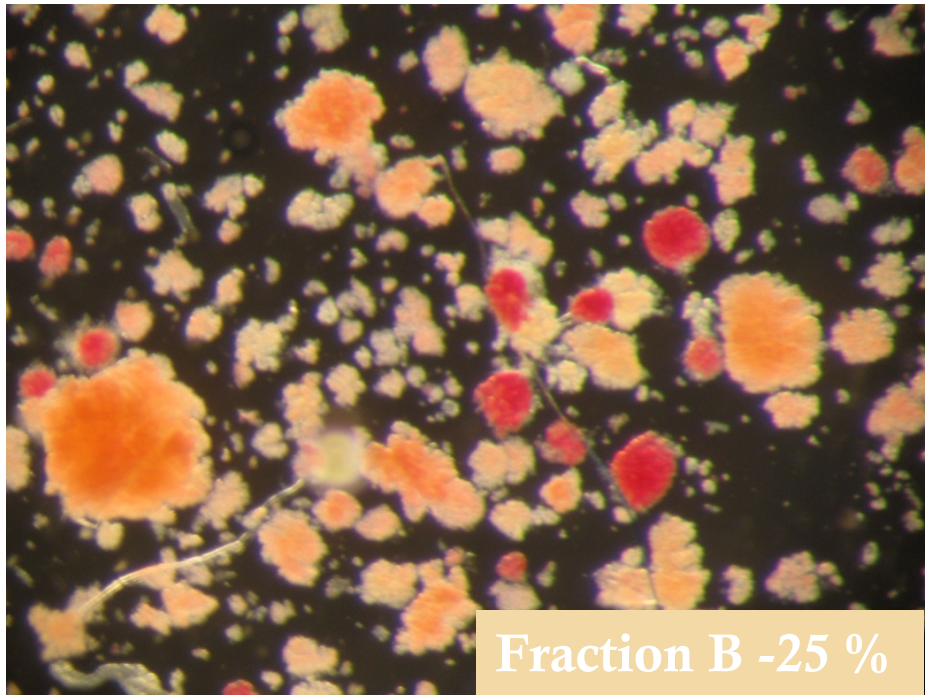
nPOD Islet Isolation Pilot





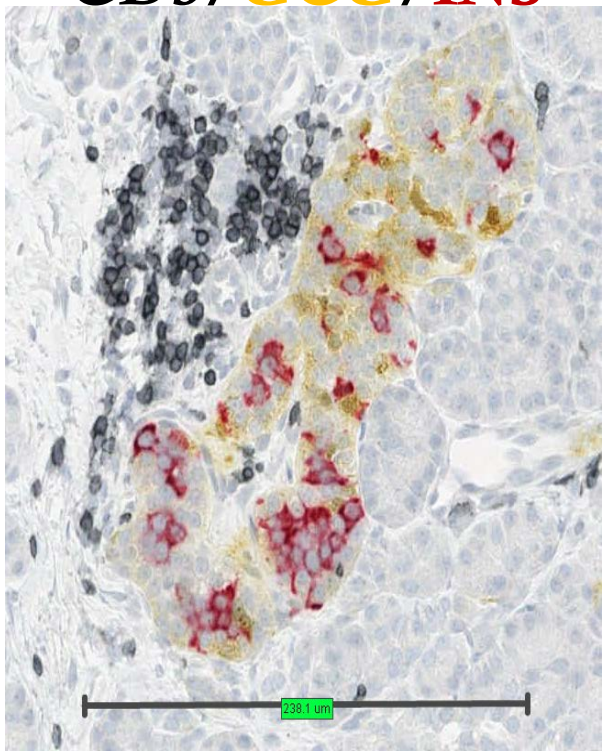



Fraction A -75 %

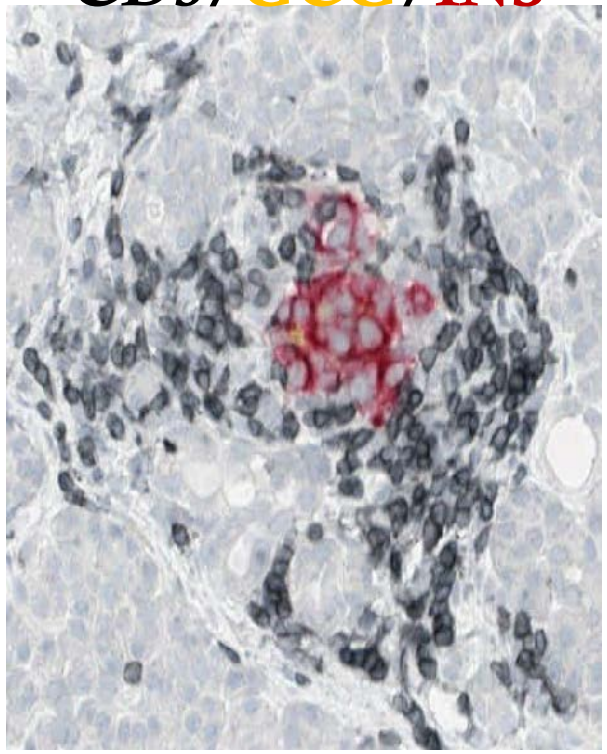

Fraction B -25 %

6414 Histopathology – Multiple Forms of Islets

CD3/GCG/INS



CD3/GCG/INS



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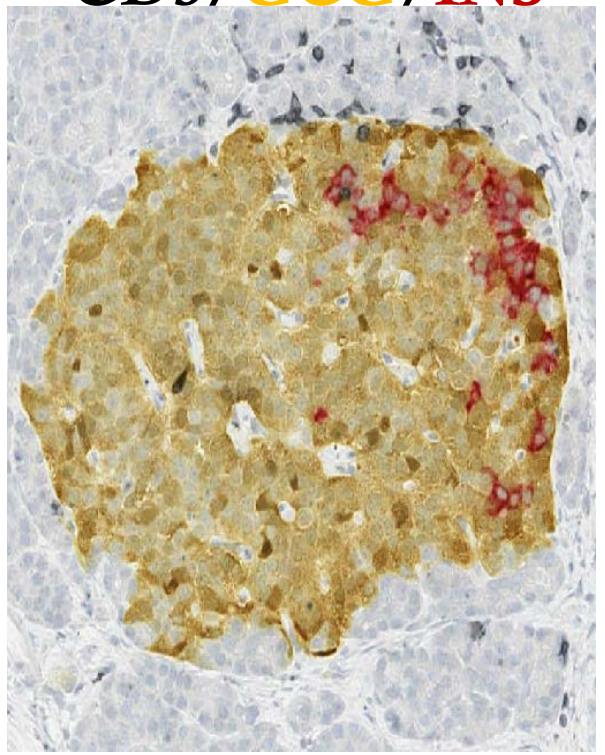
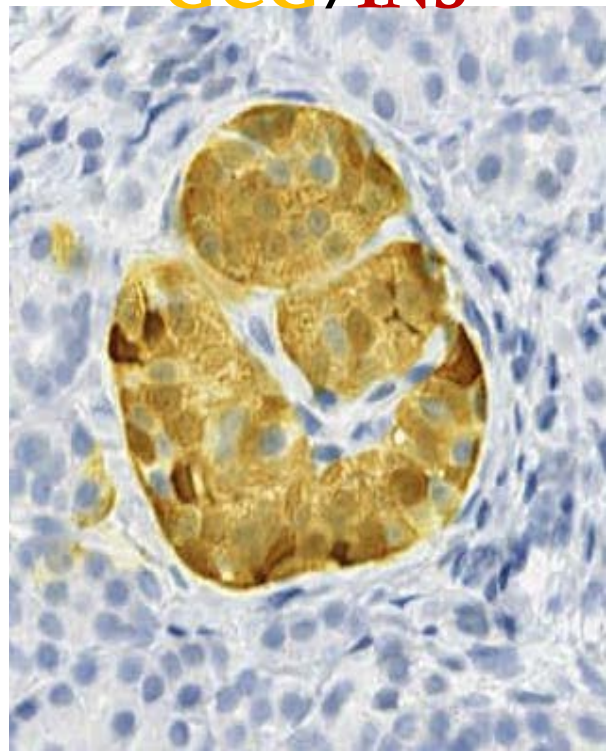


GCG/INS



Preliminary Report:

Ins+/Gluc+ islets (majority). Ins- islets and Insulitis present, both aggregate and diffuse type.
Exocrine atrophy and perilobular fibrosis.

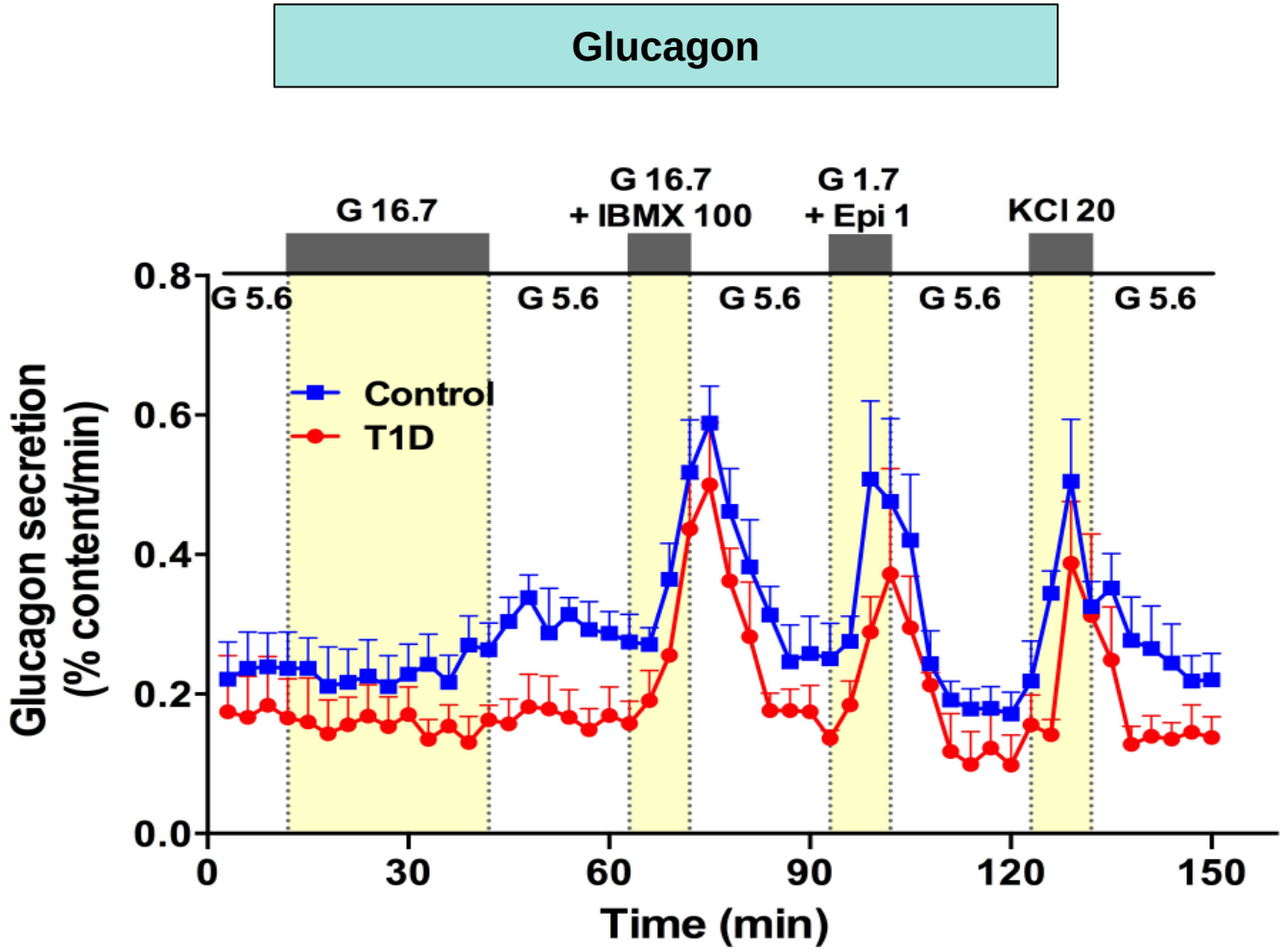
Dogma Busted

Case ID	Age	T1D Duration	Gender	Race	BMI	HbA1c	C-peptide	COD	ICU days	Transit Time(h)	N Islets Isolated	Isolation Site
6306	19.00	5	Male	C	24.50	10.10	0.001	Head Trauma	2.64		**No Islets-** Technical reason	Pittsburgh
6323	22.00	6	Female	C	24.70	6.60	0.001	Anoxia	2.14		**Total N= 108,500** IEq 33,500 IEq 75% 75,000 IEq 40%	Pittsburgh
6342	14.00	2	Female	C	24.30	9.20	0.260	Anoxia	3.13	14.18	**Total N=27,000** IEq	Miami
6367	24.00	2	Male	C	25.70	8.80	0.390	Anoxia	4.62	13.32	**Total N= 95,000** IEq	Pittsburgh
6414	23.10	0.43	Male	AfrAm	28.40	14.00	0.160	Anoxia	4.63	12.12	**Total N=83,000** IEq 67,000 IEq 75% 16,000 IEq 25%	Pittsburgh

OPEN ACCESS
CellPress

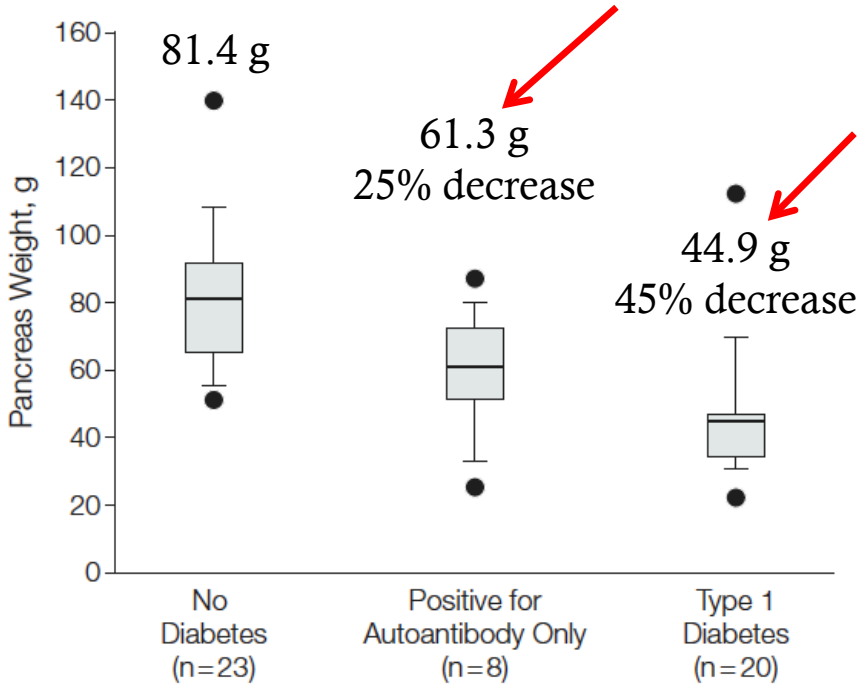
α Cell Function and Gene Expression Are Compromised in Type 1 Diabetes

Cell Reports 22:2676, 2018



Challenges Exist - Pancreas Weight is Reduced in Type 1 Diabetes

Figure. Pancreas Weight of Organ Donors by Disease Status Using an Analysis of Covariance Model



	No Diabetes (n=23)	Positive for Autoantibody Only (n=8)	Type 1 Diabetes (n=20)
Upper and lower box values	91.4 and 65.8 g	72.0 and 51.8 g	46.5 and 34.8 g
Mean value	81.4 g	61.3 g	44.9 g
95th and 5th percentiles	108.5 and 55.6 g	79.8 and 33.2 g	69.8 and 31.0 g
Upper and lower outlier values	139.0 and 52.7 g	83.8 and 25.0 g	117.4 and 23.4 g

Campbell-Thompson, et al. JAMA 2012

The boxes represent the mid 50% of the data, the line within box represents the group mean value adjusted for age and body mass index. The high and low whiskers represent the 95th and 5th percentiles, respectively. The filled black circles represent outliers. Using the *t* test, the comparison between donors without diabetes and those positive for a single autoantibody only yielded a *P* value of .02; and for the comparison between donors without diabetes and those with type 1 diabetes yielded a *P* value of less than .001. A comparison between the donors positive for a single autoantibody only and those with type 1 diabetes was not performed. Statistical significance was indicated at a Bonferroni-corrected nominal α level of .025. Of note, although age and body mass index were poorly correlated with pancreas weight and failed to meet one of the assumptions of analysis of covariance, both were included into the final model because linear models that included age or body mass index by disease status group interaction terms showed that the interaction was not statistically significant.

The New Program
nPOD Islet Isolation Long-Term T1D
(nPOD IIPLT)

- Organ donors with T1D Dx 4-10 years duration (note: nPOD is starting a new program for 0-3 years duration)
- Attempt to isolate islets from 6-8 T1D organ donors in the next two years
- **Potential technical difficulties are likely (as discussed earlier)**
- No control islets (note: look to existing NIH IIDP program)
- Distribute islets after isolation (no extended culture)
- No charge on islets. Investigators pay for shipping

IMPORTANT DISCLAIMERS

- This is a pioneering effort. While we have reasonable confidence in the program, these are organ donors and numbers cannot be assumed.
- Islet isolation from type 1 diabetes cases is extremely challenging.
- We will do our best to provide interested investigators with islets but, understand, unforeseeable challenges may make this difficult.
- In addition to the above indicated challenges (largely technical), NIH HPAP collects T1D donors to 7 years hence, some potential tissues will be lost to this new program (i.e., overlap in interest).
- There may not be many islets even if the islet isolation is successful.
- Likely < 10,000 IEQ/investigator, so miniaturizing your assay is crucial.

Process Moving Forward

- Submit a brief proposal (deadline September, 21 2018)
  - Goal, rationale, specific needs (number of islets, etc.) – 1 page maximum
  - Note: since projects already approved by HCT, these will not be approved for science BUT, for matters of feasibility
  - MTA must be submitted (Download)
  - IRB/Ethics approval must be provided (Email to Mingder Yang)
- Proposals will be reviewed by October 1 and if feasible, approved. A letter of approval will be sent to investigators for.
- Importantly, islets evaluated by NIH Human Islet Phenotyping Program (HIPP); data can be downloaded for evaluation.
- Matters of data sharing will be handled by the HCT.
- We are working out details (with HCT) on distributions (???) to investigators whose HCT projects are not approved for continued funding.

Key Dates for New Helmsley Program (Ben)

Event/Activity	Scheduled Date
Applicants invited to submit EOIs	**July, 2018**
EOIs and pilot project updates due by mail	**October 15, 2018**
Selected applicants invited to submit full grant proposal	**November 15, 2018**
Link to online application will be emailed	**December 1, 2018**
Full grant proposal due	**December 21, 2018**
Notification of awards	**February 15, 2019**
Earliest grant start date	**April 1, 2019**
Working group in-person meeting	**Summer, 2019**

THANK YOU!
Questions?

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Funding

- Duration of up to 36 months.
- Lab-based project: Total budget (direct and indirect costs) up to $250,000 per year
- Clinical studies: Total budget up to $400,000 per year.
- 10% indirect costs

Proposed Activities

- Developing research tools to study the human disease, such as reagents or clinical tests;
- Modeling human glucagon secretion in the context of T1D (e.g. ex vivo or humanized mice);
- Collecting, analyzing, and testing hypotheses using human samples;
- Studying human alpha, delta, or other relevant human cells, including their signaling pathways, physiology, microanatomy in the context of T1D;
- Screening and validating new drug targets;
- Testing preclinical proof-of-principle therapies;
- Examining human pathophysiology or conducting mechanistic clinical studies; and
- Use existing agents to clinically demonstrate whether the pancreas retains the ability to release physiologically-relevant levels of glucagon in response to real-life hypoglycemic situations such as skipped meals, high prandial insulin doses, or exercise.

Exclusions

- Type 2 diabetes;
- Biological questions without a clear relation to T1D;
- Converting alpha cells into beta cells;
- Hypoglycemia unawareness;
- Long-term complications of diabetes; and
- Rodent studies without human validation.