A New Perspective in T1D: Targeting the β Cell

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JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

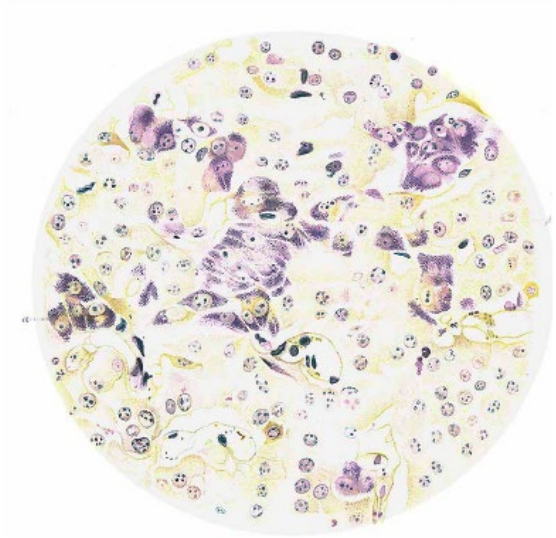
THE UNIVERSITY OF CHICAGO

NIH National Institute of Diabetes and Digestive and Kidney Diseases

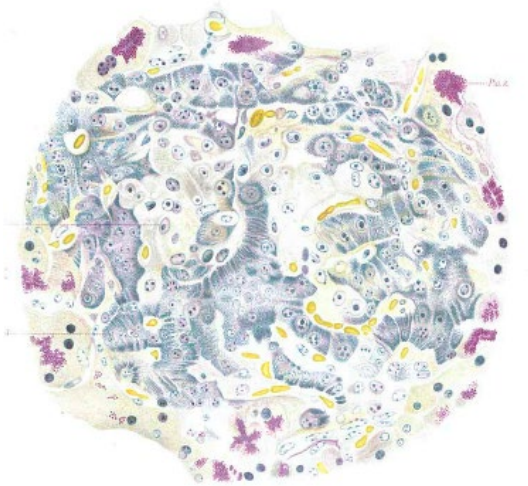
Discovery of Insulin, 1921

Banting and Best

α



Alcohol-precipitable granules



Chrome-sublimate precipitable granules

β

THE CYTOLOGICAL CHARACTERS OF THE AREAS OF LANGERHANS.

BY

M. A. LANE.

From Hull Laboratory of Anatomy, University of Chicago.

WITH 1 PLATE.

Sugar Theory:

"…..the adherents of [this theory] have consistently held that the islets produce a substance which, in one or another way, controls carbohydrate metabolism."

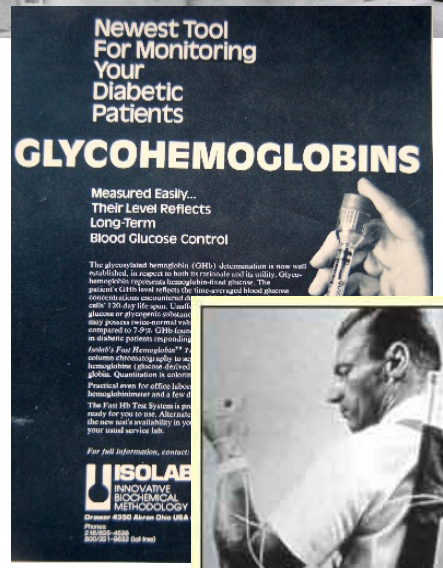
From: Amer J Anatomy 7:22,1907
Courtesy: Al Powers, Vanderbilt Univ.

James Havens, 1922

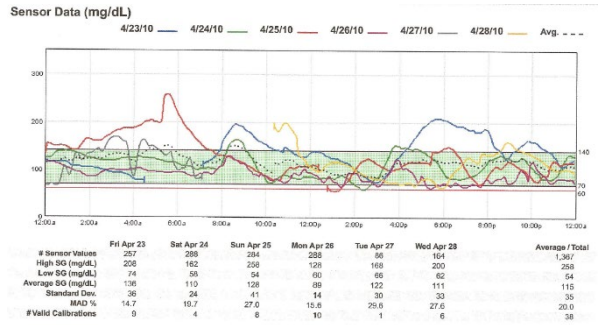
Whether it is possible that nature will restore the diseased pancreas when the strain is taken off [it] by administering this extract and while the other functions of the body and bodily strength is restored, is merely a hope. It may be possible."

Advances in T1D Treatments

1922



1970's



Today

Kinds of Research

Basic Research

- Cell-free systems
- Cell Culture
- Animal Models

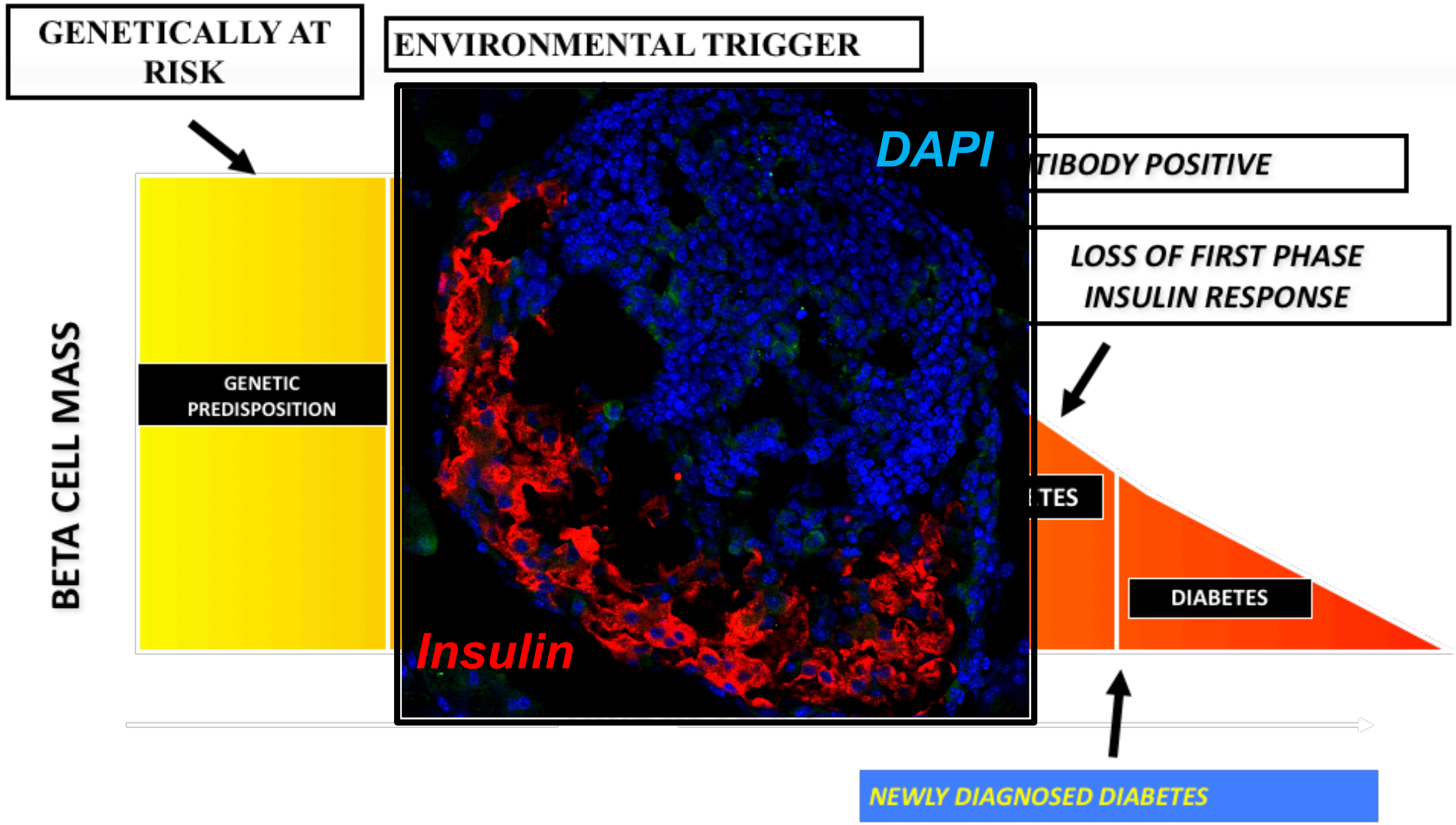
Translational Research

- Patient samples
- Pre-clinical drug testing
- Biomarker identification

Clinical Research

- Testing new treatments
- Comparing Treatments
- Defining disease biology

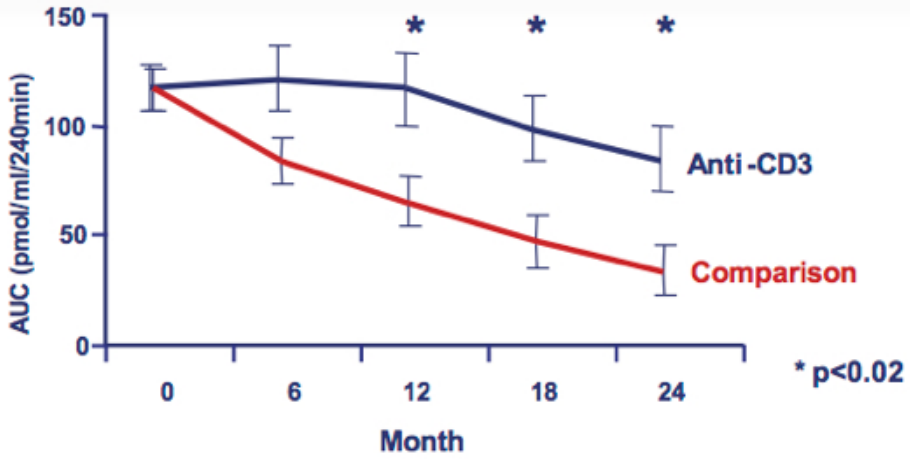
Loss of β Cell Mass in T1D



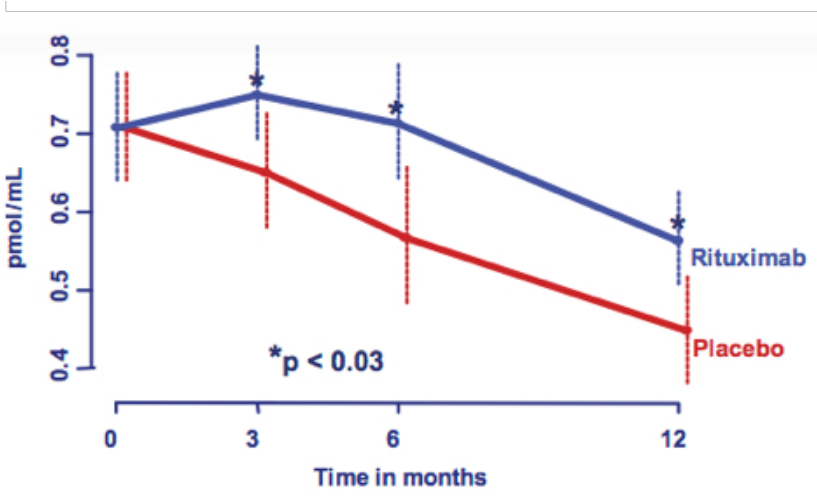
G. Eisenbarth, J. Skyler

Limited Effects of Immune-based Therapies

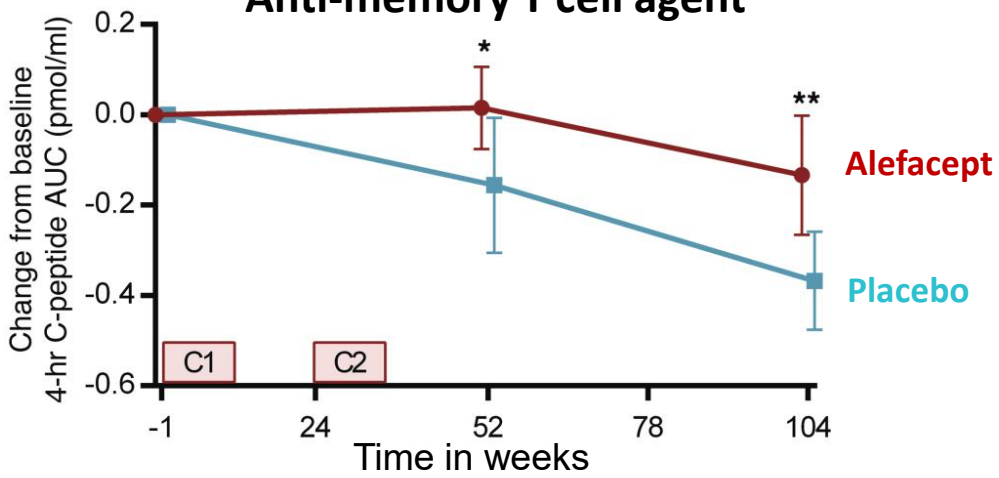
Anti-T Cell agent



Anti-B Cell agent

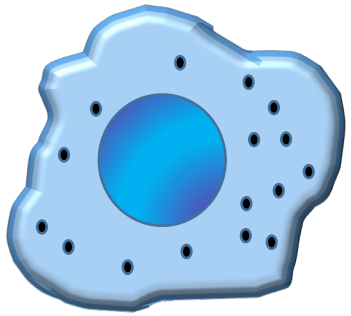


Anti-memory T cell agent



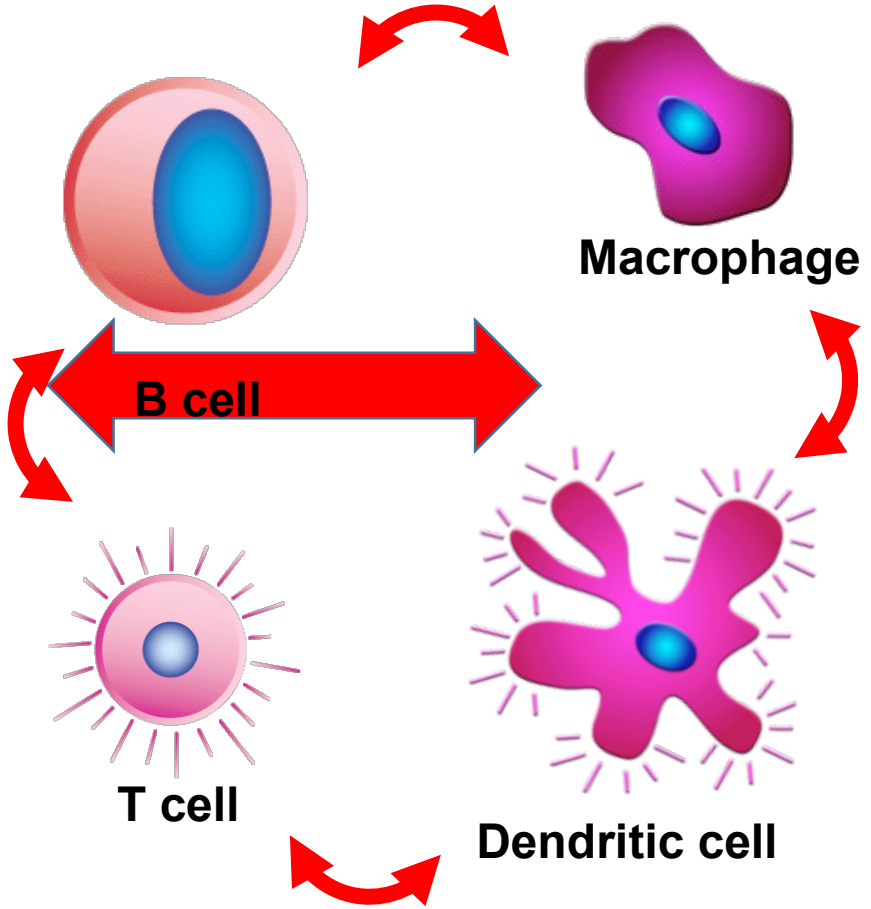
Herold, et al. 2005 Pescovitz, et al. 2009 Rigby, et al 2015

T1D Pathogenesis: A Dialog Between Different Cell Types



β cell

Ability to succumb to stress
Mass
Function



Autoimmunity vs. Something More: Why does it matter?

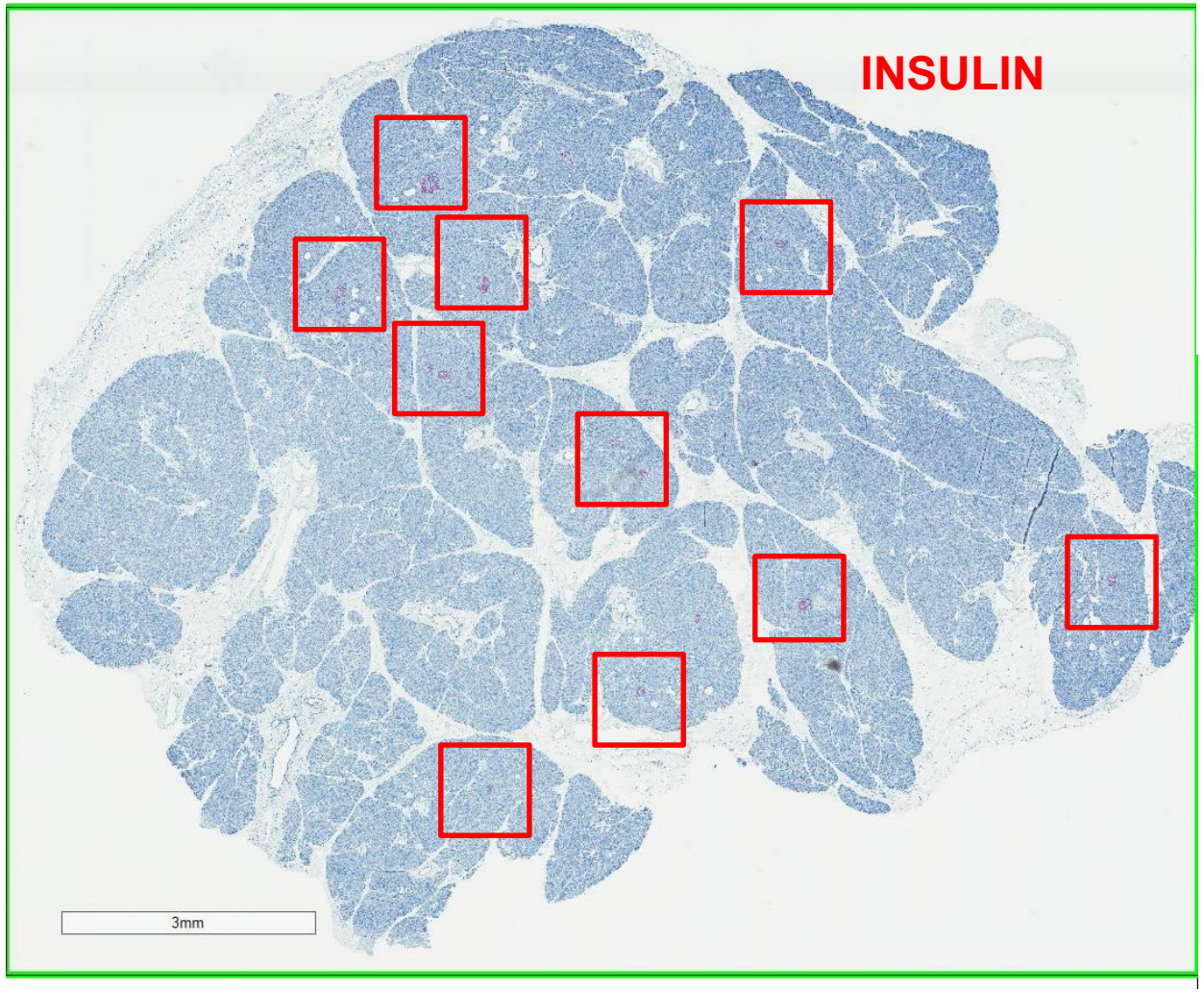
1. **Diagnosis of the disease:** Does it change our criteria for diagnosis?

2. **Treatment of the disease:** Are there targets that we should be considering in addition to the immune system? Personalized medicine

3. **Prevention of the disease:** When do you begin prevention, and what are you targeting? Personalized medicine

4. **Prevalence/Incidence of the disease:** how are healthcare resources placed?

Insulin positive islets after 8 years of T1D



6046
18 years old
8 year duration
Caucasian
Female

AutoAb: IA2A+ZnT8+

C peptide: <0.05 ng/ml
BMI: 25.2

Courtesy: nPOD (Case 6046)

Can we do more than we are currently doing?

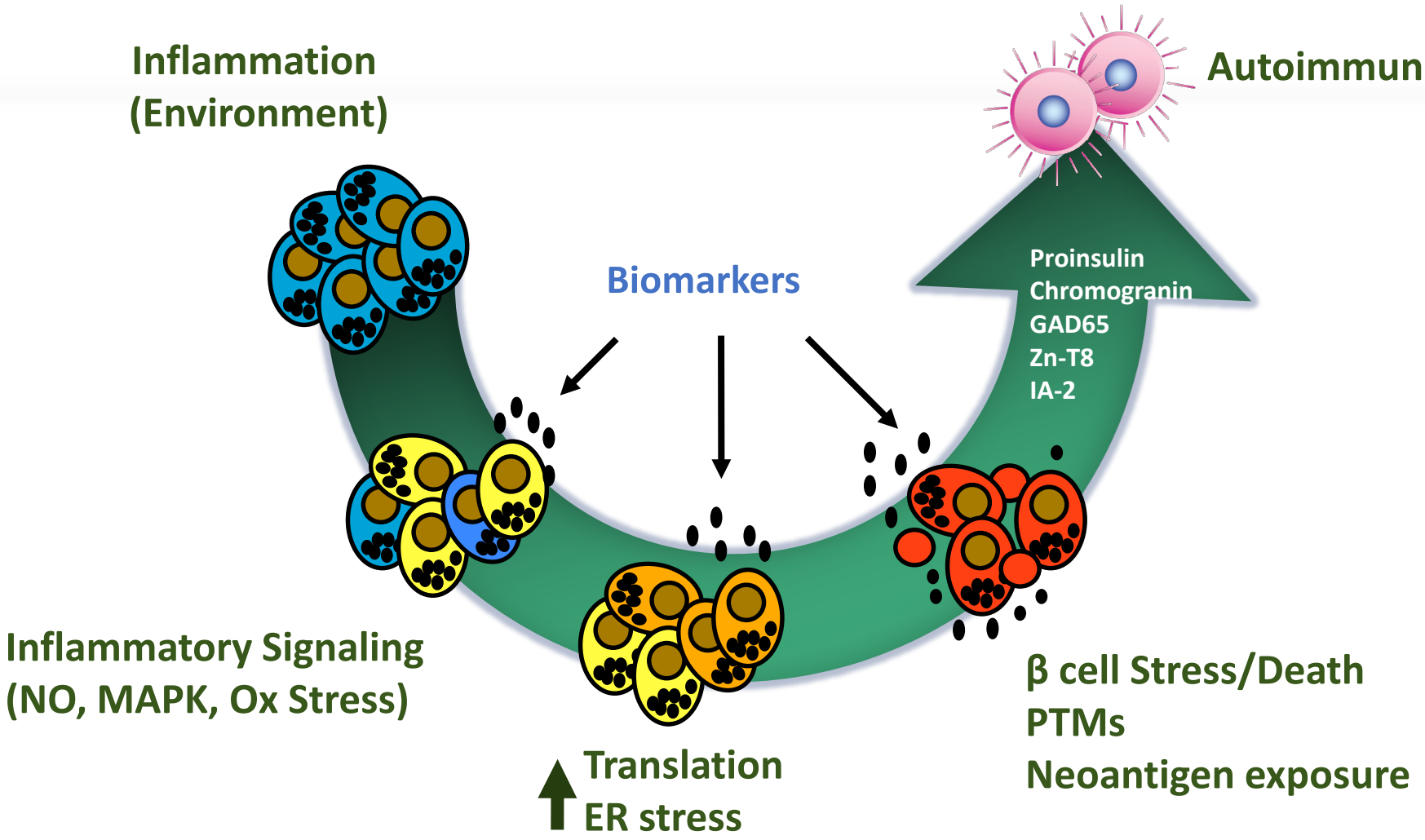
Data suggest that preserving the β cells that are still present at diagnosis can help persons with T1D:

Decrease average blood sugars
Decrease blood sugar variability
Decrease rates of severe hypoglycemia
Decrease long-term complications of the disease

Unmet Clinical Needs

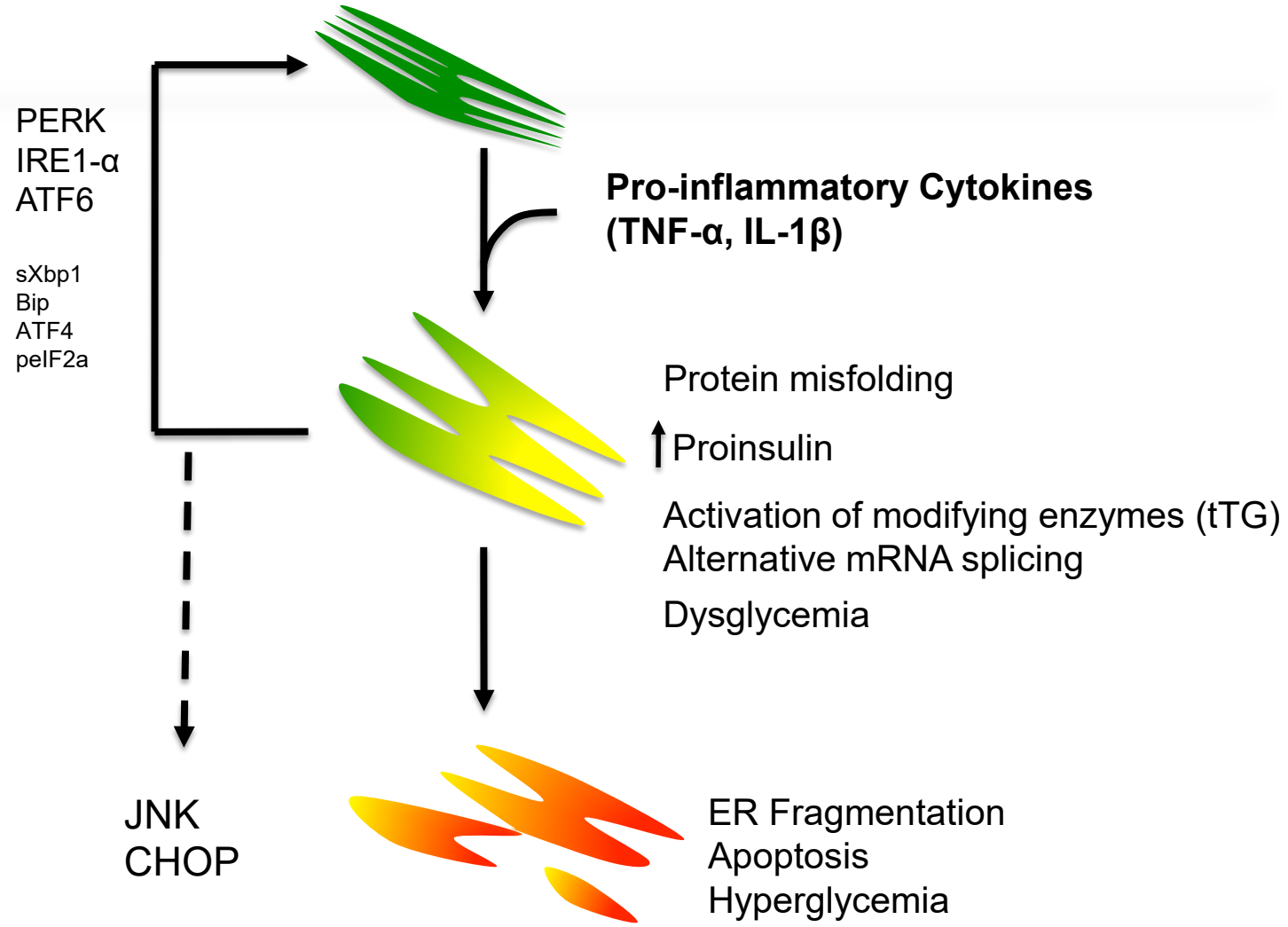
- Safe, tolerable drug therapies that will preserve remaining residual β cell insulin production
- Drugs may need to be used in combinations, targeting different parts of the process that results in T1D

β Cell Dysfunction and Neoantigen Production Precede Development of Autoimmunity

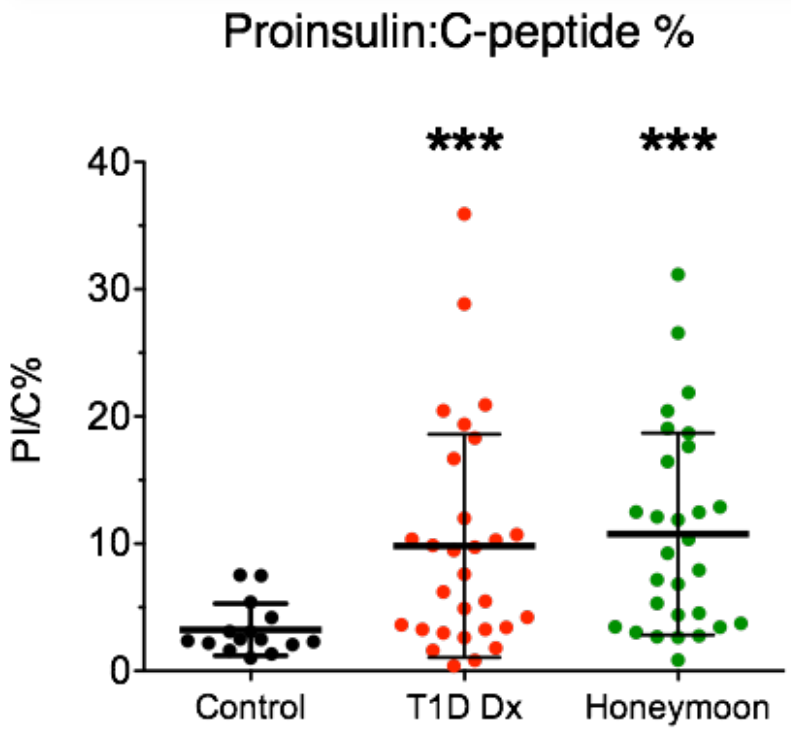


Maganti, et al, Islets 2014

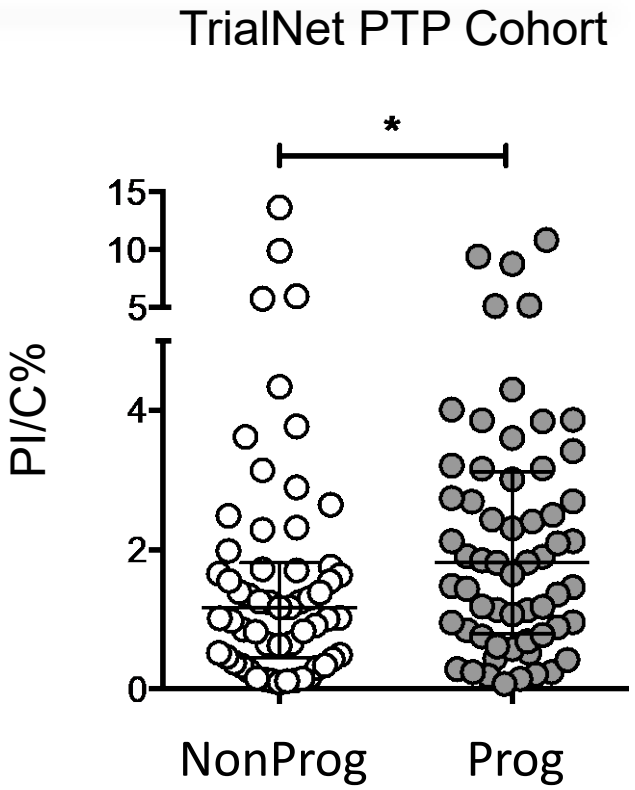
β Cell ER stress in the Development of T1D



Elevated proinsulin:C-peptide ratio in humans with new onset T1D

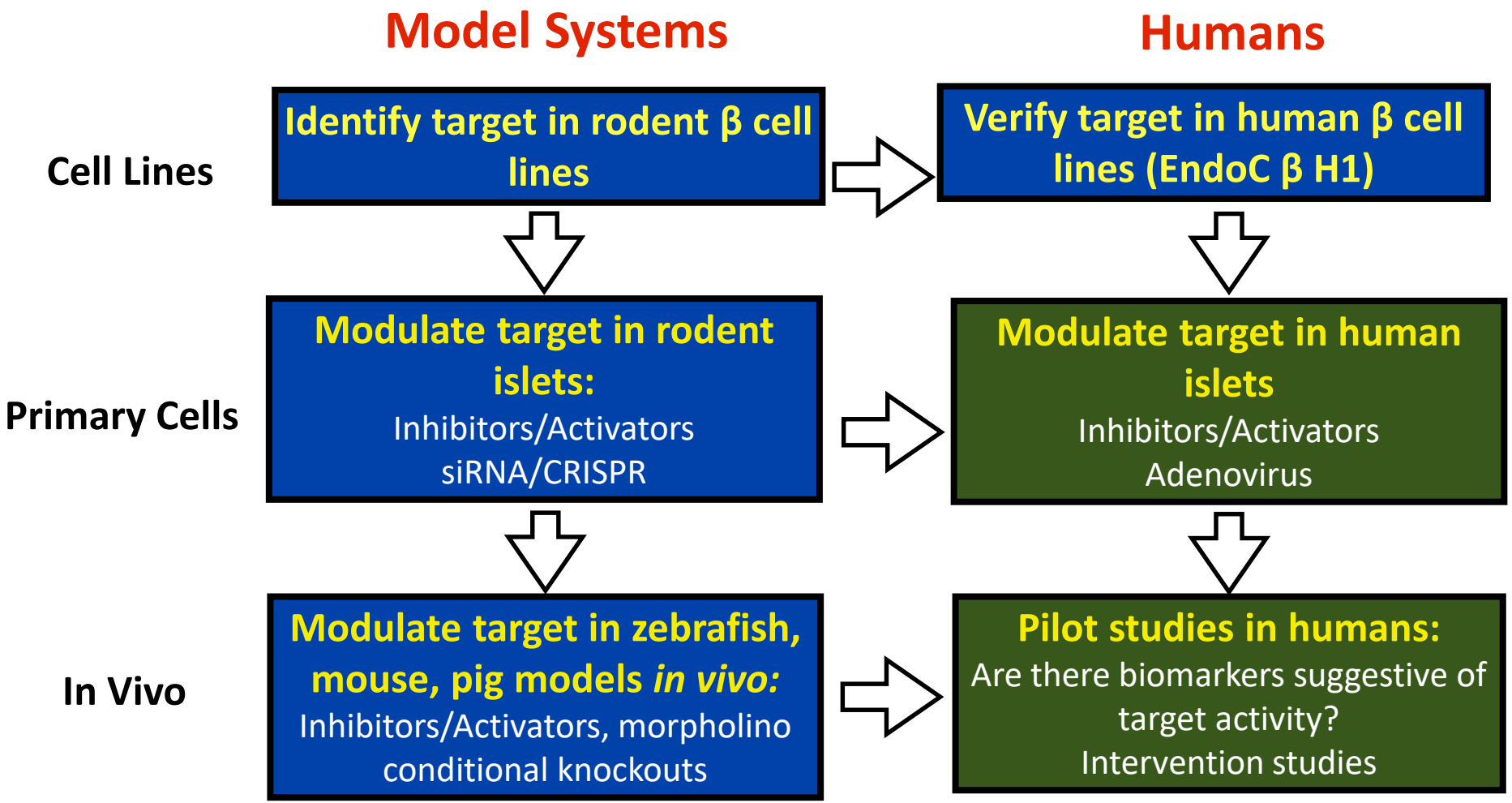


Williams, et al. Transl. Res. 2015

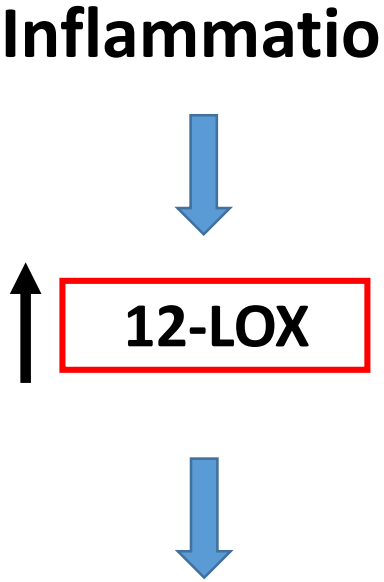


Sims, et al. Diabetes Care 2016

The Mirmira Lab Strategy for Identifying and Engaging Targets for Diabetes

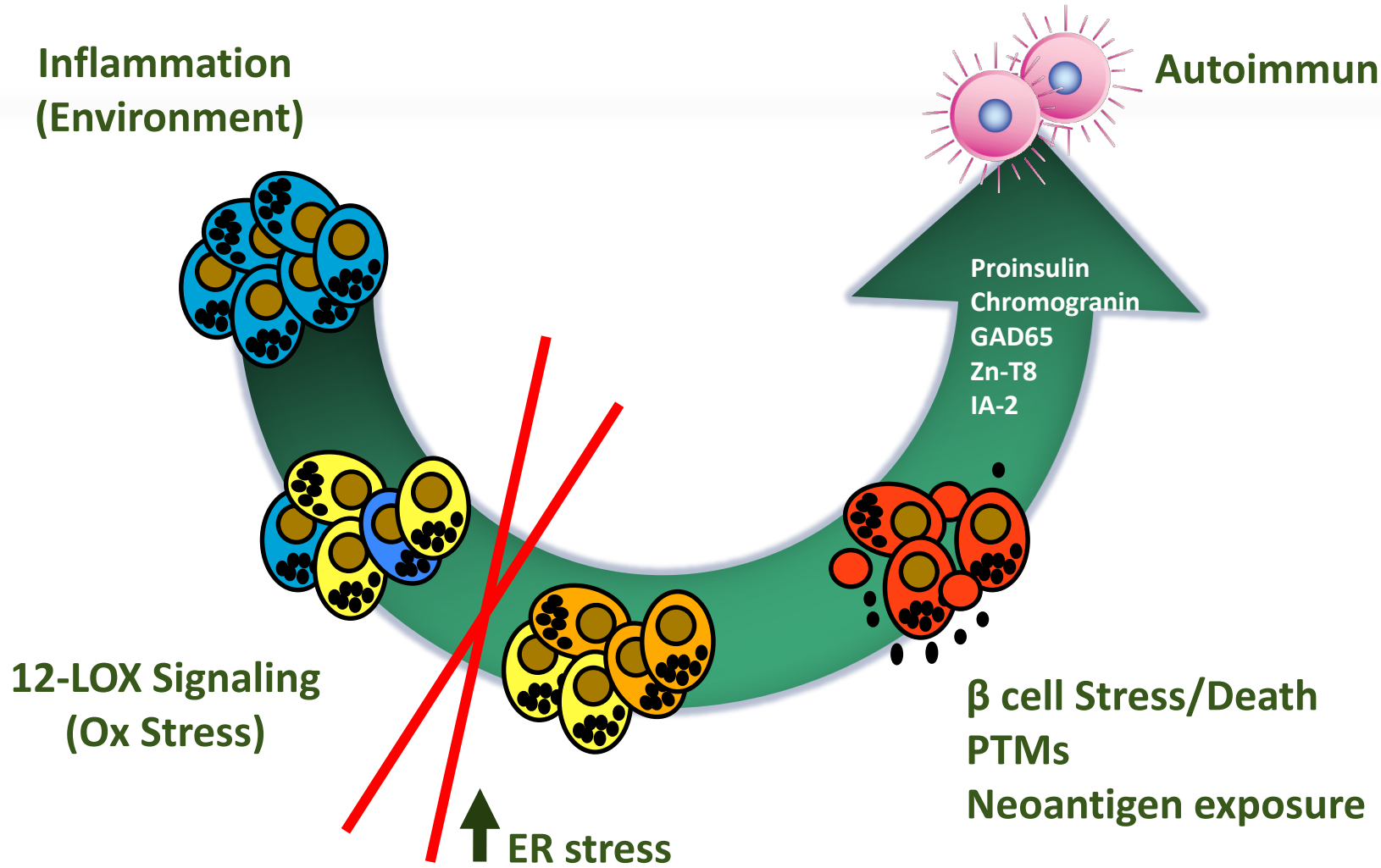


Can reduction of β-cell "stress" modify the course of T1D?



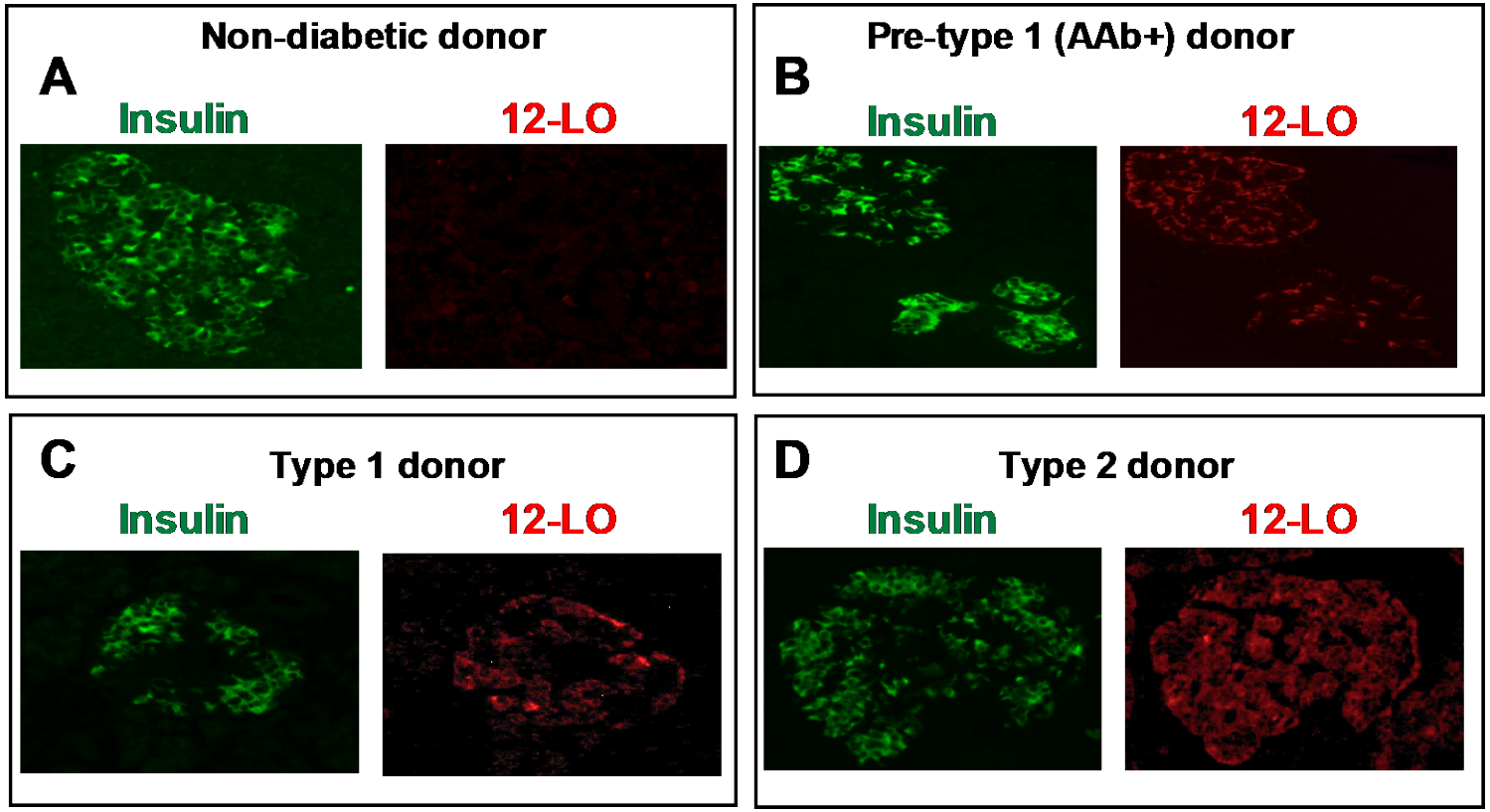
Tersey, et al. Mol Cell Biol 2014; Tersey et al. Mol. Endocrinol. 2015

Blockade of 12-LOX early in T1D pathogenesis may halt autoimmunity



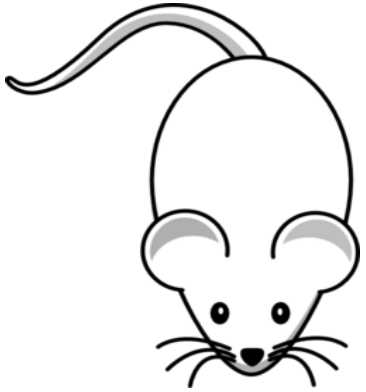
From: Maganti, et al, Islets 2014

12-LOX staining increased in T1D islets



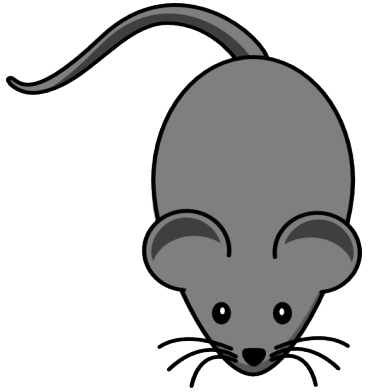
Grzesik et al., *JCEM* 2015

Generation of Islet-specific 12-LOX Knockout Mice on a T1D prone strain of mice

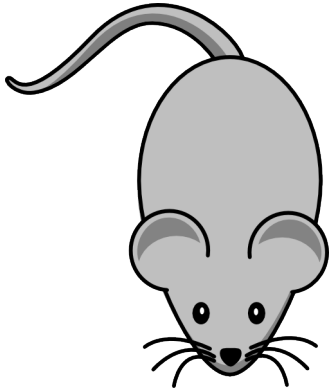


NOD-Alox15-fl/fl

X



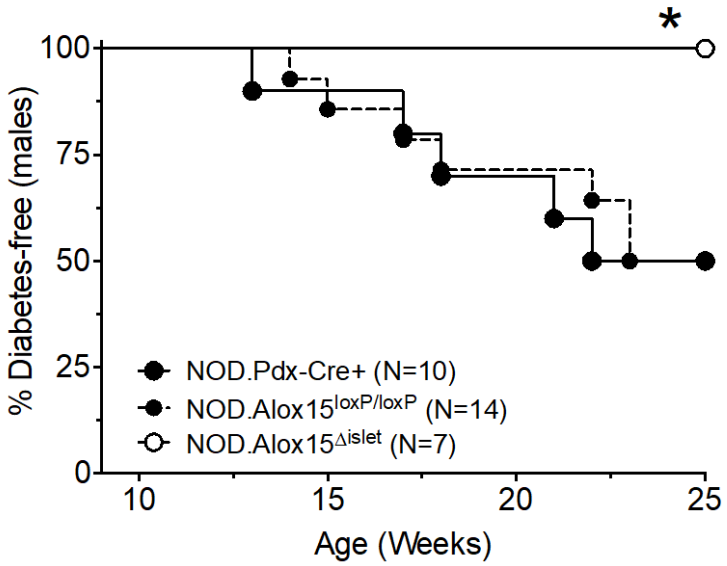
NOD-PdxPB-Cre



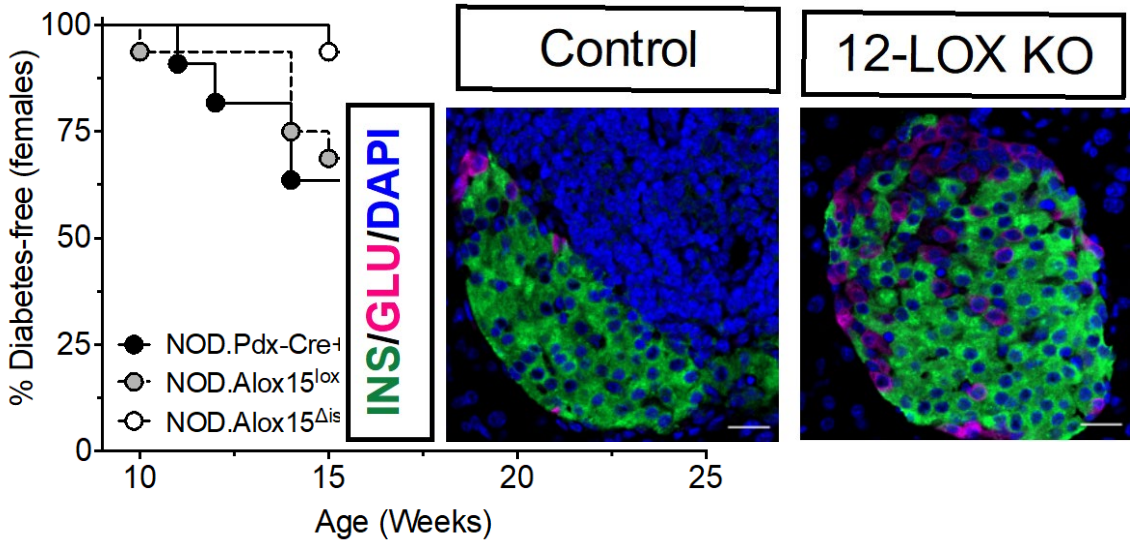
NOD Islet-specific Knockout Mice

Islet 12-LOX knockout protects animals from type 1 diabetes with reduced insulitis

Males

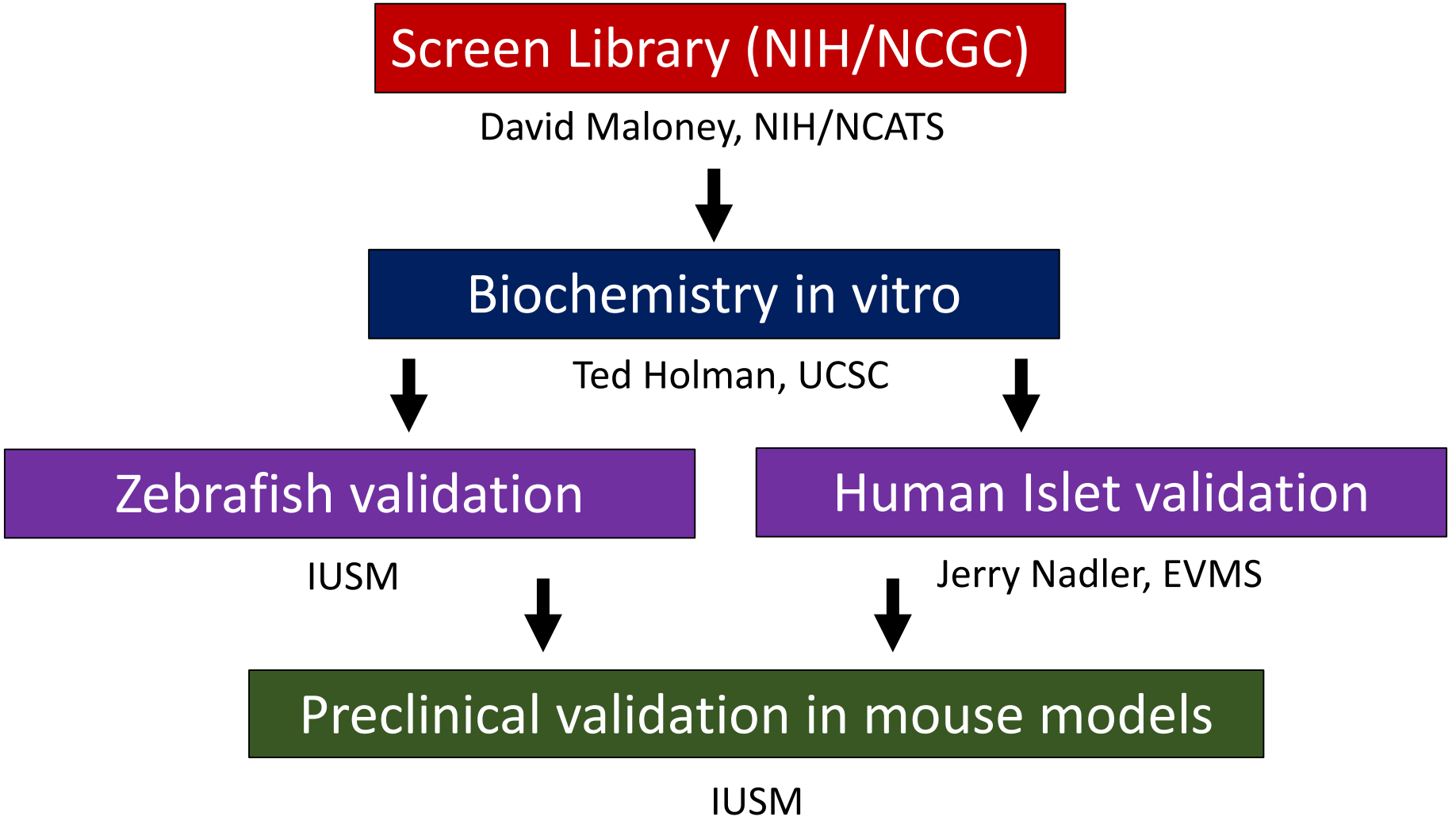


Females

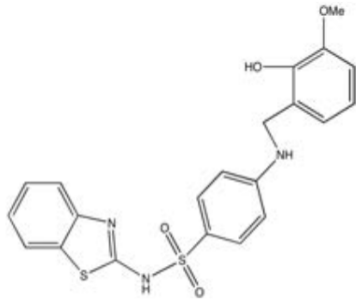


Piñeros,, et al. Unpublished

12-LOX Inhibitors—Team Science

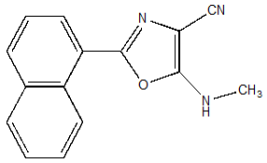


12-LOX Inhibitors exhibit species specificity



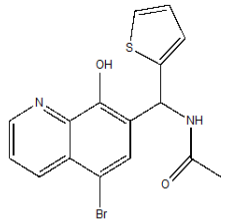
ML355

Human specificity



ML351

Mouse specificity



ML127

Human and Mouse

Zebrafish alox orthologs are inhibitable with ML compounds

Zebrafish 12LOX IC_{50} data

	IC50 (uM)	Max Inhibition
ML355	**5.5+/-2**	**65%**
ML127	**0.34+/-0.3**	**33%**
ML351	**>100**	

Human 12LOX IC_{50} data

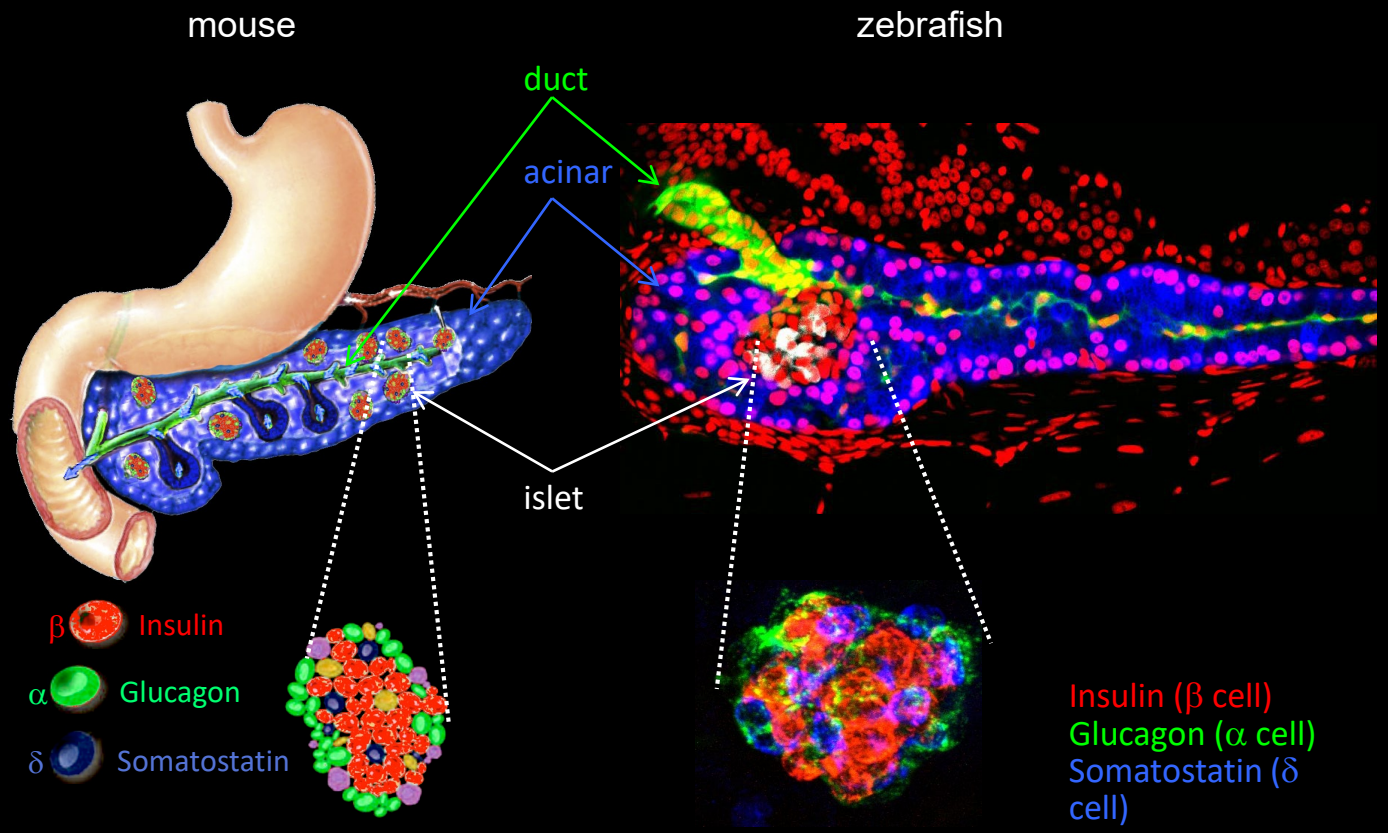
	IC50 (uM)	Max Inhibition
ML355	**0.34+/-0.1**	**95%**
ML127	**1.0+/-0.2**	**95%**
ML351	**>50**	

Hernandez-Perez, et al. Unpublished

Mammals and fish have similar pancreata

Abhi Kulkarni

Ryan Anderson, PhD

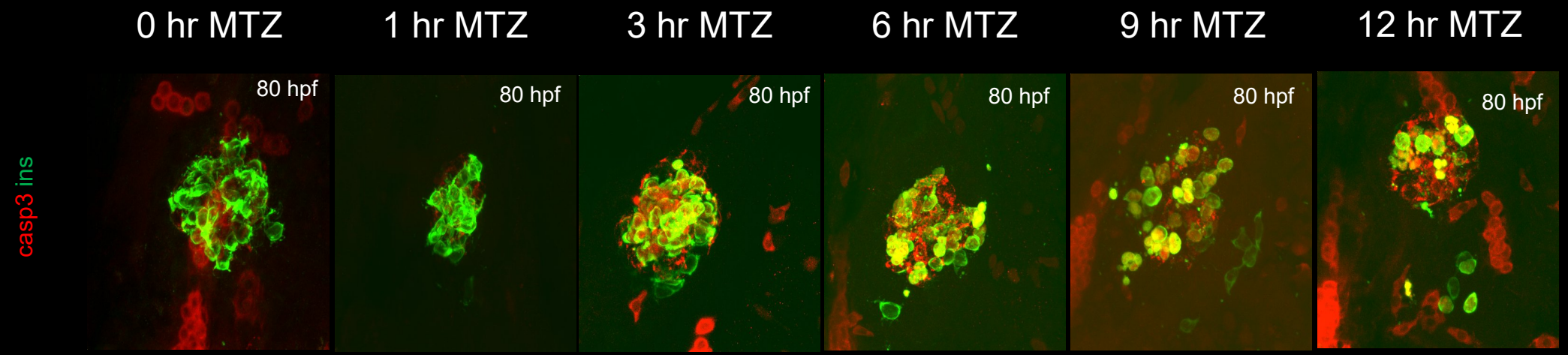


A T1D Model in Zebrafish—no, really!

Tg(insulin:NTR)^{s950} fish

→ Metronidazole (MTZ) →

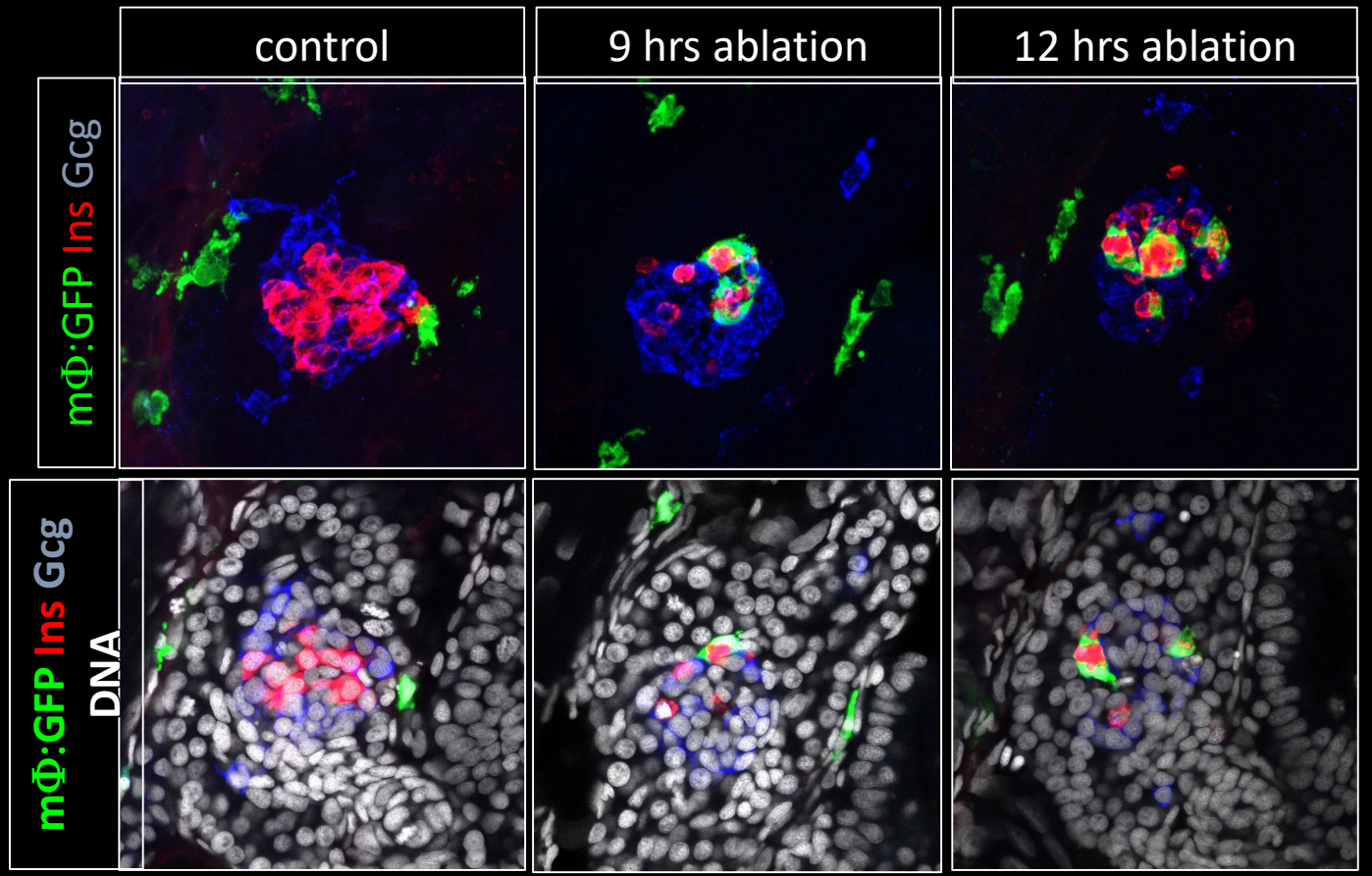
β-Cell Death



Kulkarni, et al. Ox Med Cell Longev 2018

Immune Cell Infiltration in the Zebrafish T1D Model

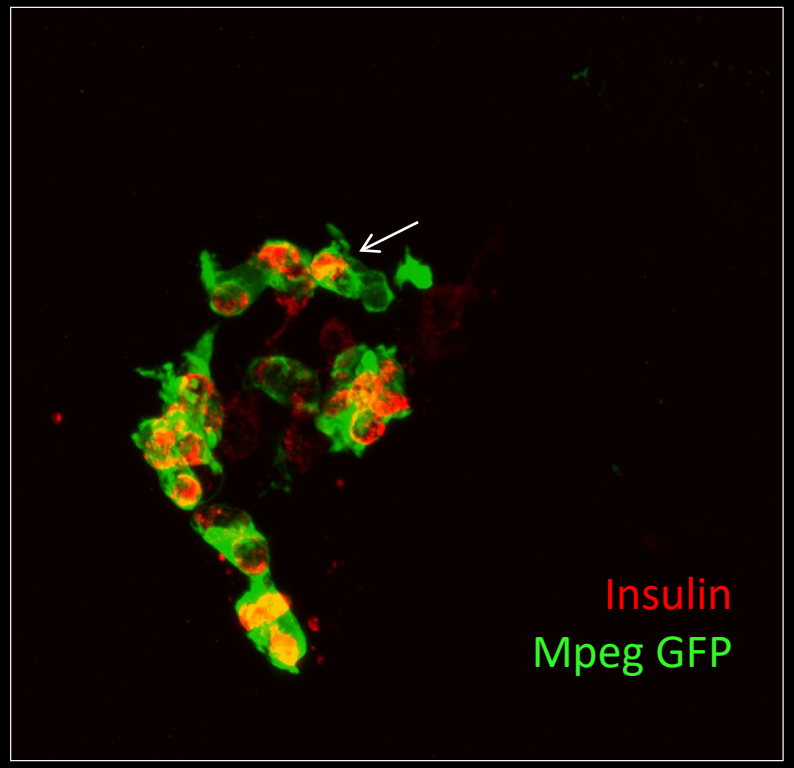
Tg(mpeg:GFP)^{gl22} x Tg(insulin:NTR)^{s950} fish



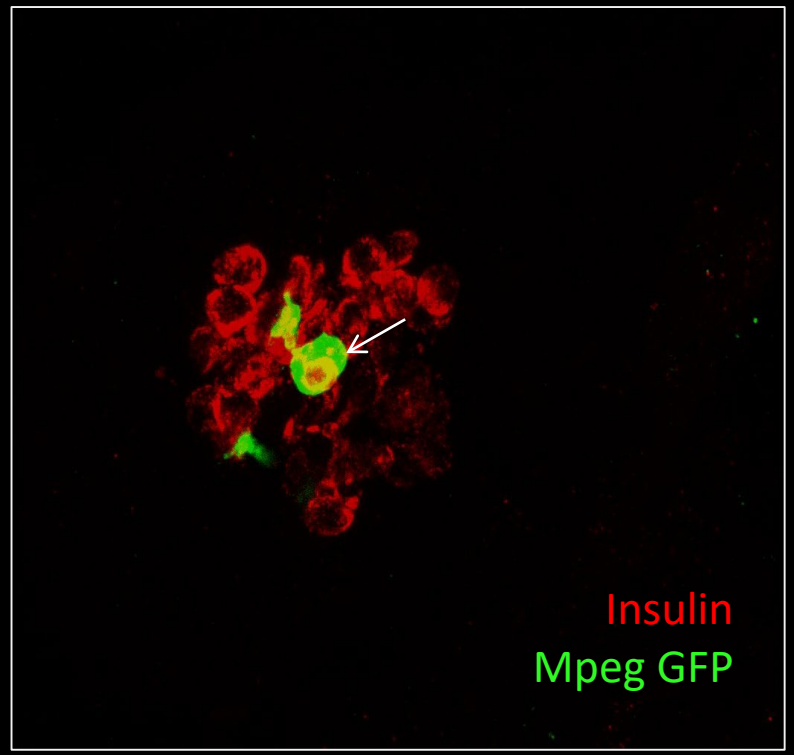
Kulkarni, et al. Unpublished

The Effect OF ML-355 on Immune Cell Homing in the Zebrafish T1D Model

Control (6hrs)

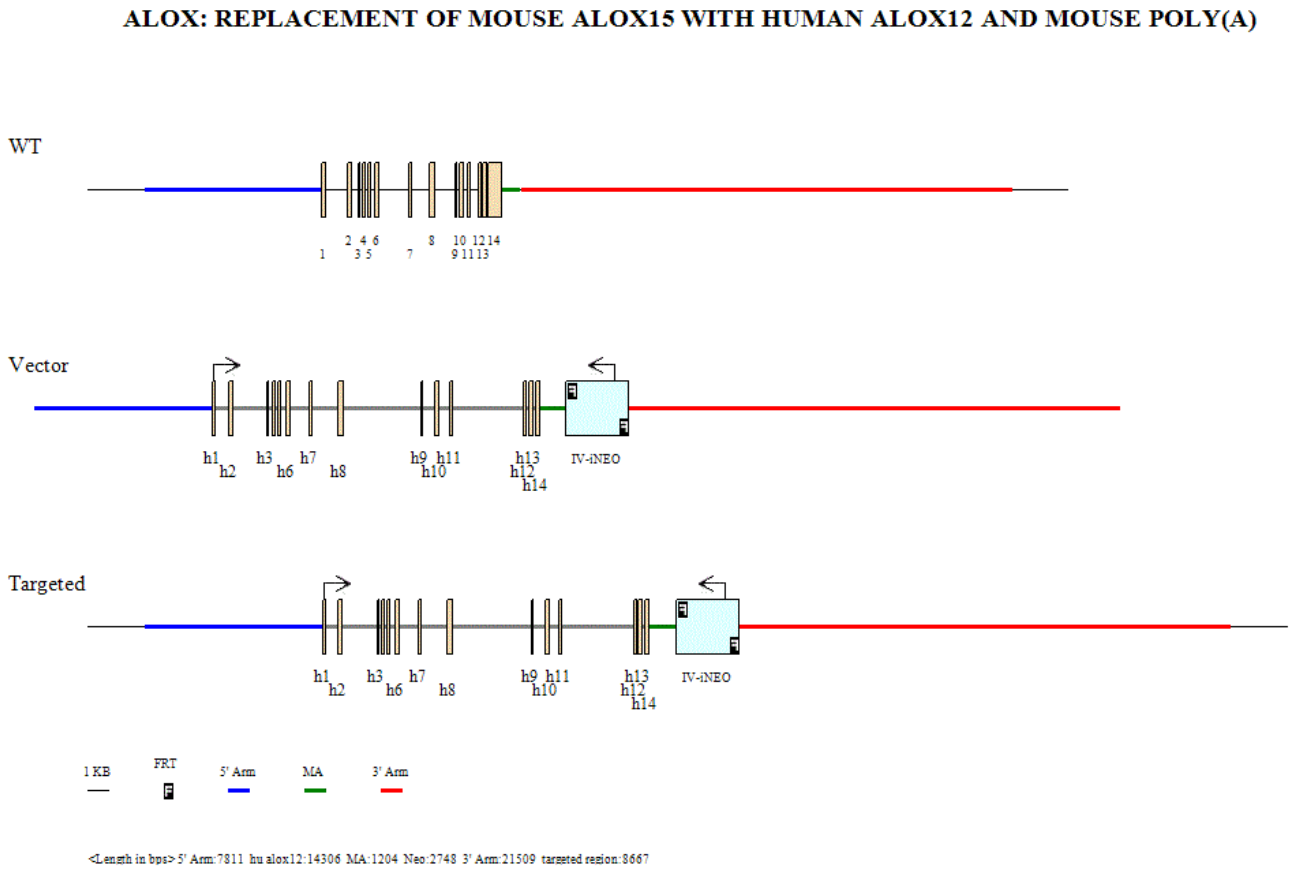


ML-355 (6hrs)



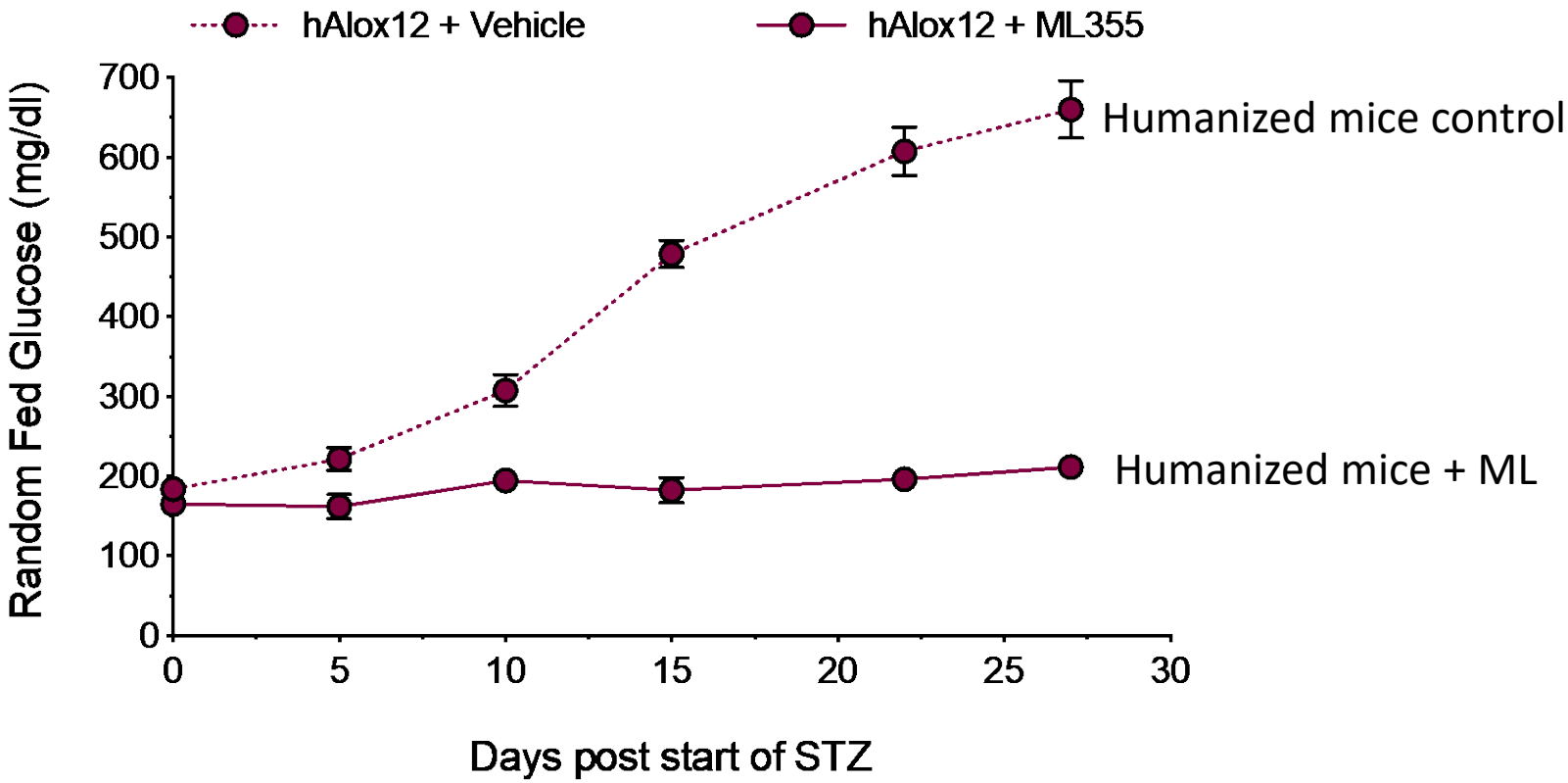
Kulkarni, et al. Unpublished

“Humanized” mice to test human 12-LOX inhibitors



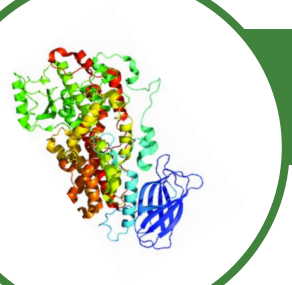
Tersey, et al. *Unpublished*

ML355 protects against diabetes in humanized *ALOX12* mice



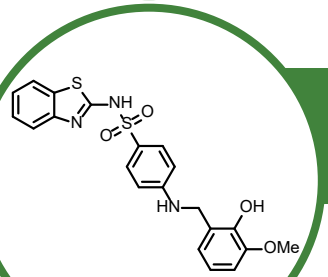
Tersey, et al. *Unpublished*

Where do we go from here? Building a 12-LOX Company (Veralox Therapeutics)



12-LOX - Chemical equity for previously undruggable target

Product of multiyear, multi-institution collaboration leading to a first-in-class, potent and selective 12-LOX inhibitor



Lead molecule in IND-enabling, next-gen work underway

On track to deliver IND at YE 2020, pipeline expansion through 2nd generation drug products in development

Initial work in HITT and T1D with future pipeline in a target

Attracted top tier strategic investors and key opinion leaders for both HITT and T1D, with future expansion into additional indications

HITT: Heparin-induced Thrombocytopenia and Thrombosis
T1D: Type 1 Diabetes

Lab members, collaborators, funding

Mirmira Lab
Sarah Tersey
Marimar Hernandez
Farooq Syed
Marisa Fisher
Ryan Anderson
Kara Benninger
Jennifer Nelson
Karishma Randhave
Esther Levasseur
Chris Reissaus
Annie Pineros-Alvarez
Abhishek Kulkarni
Cody Sorrell

IUSM
Emily Sims
Carmella Evans-Molina
Linda DiMeglio
Amelia Linnemann
Kieren Mather

EVMS
Jerry Nadler
Maggie Morris-Fears

PNNL
Tom Metz
Ernesto Nakayasu
BobbieJo Webb-Robertson

ULB
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IBRI
Teresa Mastracci

Mt. Sinai
Adolfo Garcia-Ocana
Donald Scott

Weill-Cornell
Laura Alonso

National Institute of Diabetes and Digestive and Kidney Diseases

UC4 DK104166
R01 DK060581
R01 DK105588
P30 DK097512

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

IIDP Integrated Islet Distribution Program

nPOD Network for Pancreatic Organ Donors with Diabetes

Mirmira Lab