FRACTYL health

American Society of Gene + Cell Therapy

# A Pancreatic Gene Therapy Delivery Platform for the Treatment of Type 2 Diabetes

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# Disclosure Statement

**Authors:** Harith Rajagopalan, Jacob Wainer, Alice Liou, Rebecca Reese, Suya Wang, Keiko Ishida, Nicole Picard, Camila Lubaczeuski, Emily Cozzi, and Jay Caplan are employees and shareholders of Fractyl Health, Inc. Jason A. West and Nidhi Khanna are former employees of Fractyl Health, Inc. Christopher C. Thompson, Linda S. Lee, and Rob P. Trasolini are employees of Brigham and Women's Hospital and Harvard Medical School.

**Revita® is for investigational use only in the United States.**
**The Rejuva® platform is in early development and not approved by any regulatory body for investigational or commercial use.**

# Fractyl Health, Inc.

## Pioneering new treatment approaches for type 2 diabetes (T2D)

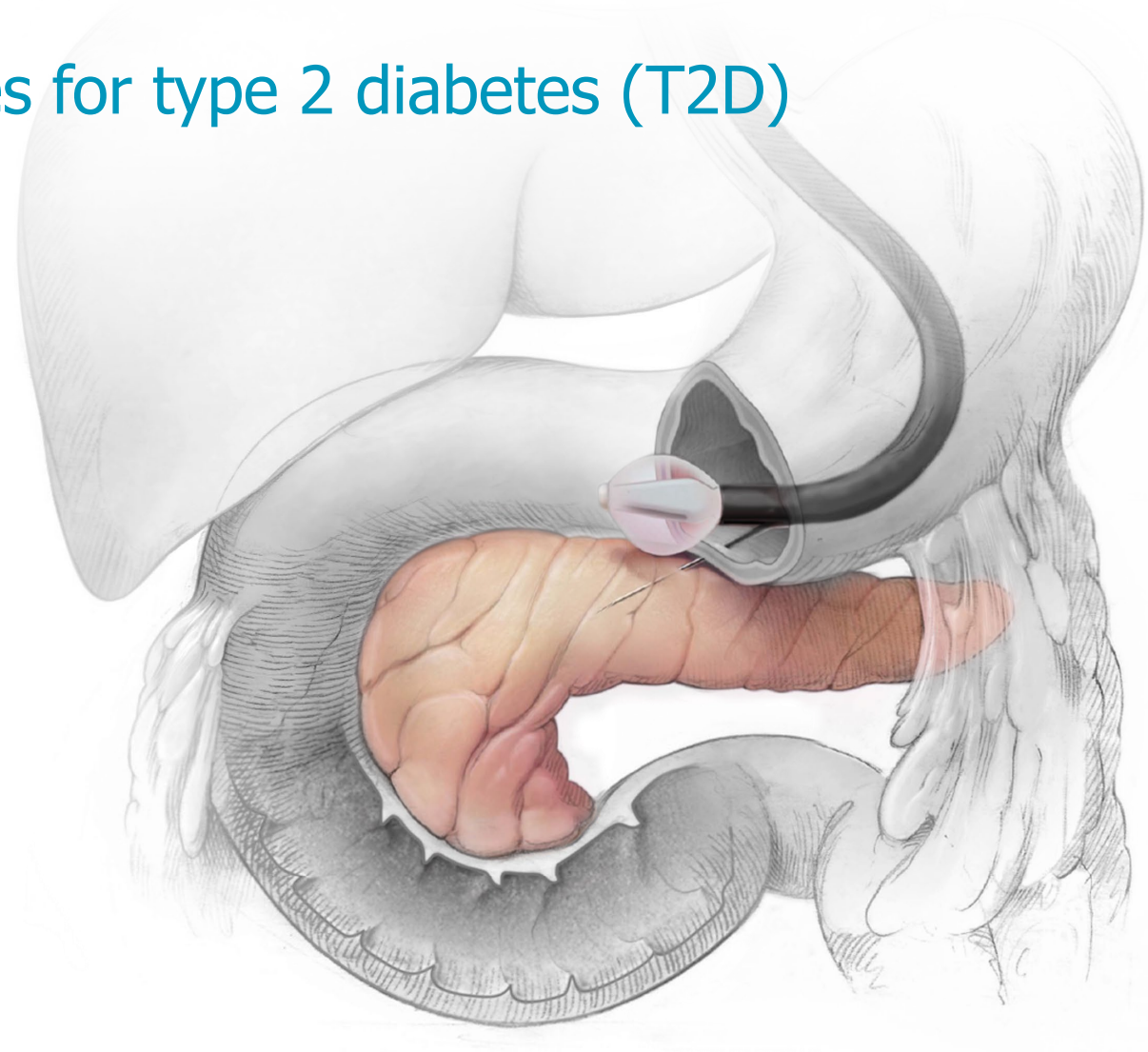
**Complementary development programs targeting key organs in T2D**

**Revita®** (targeting the duodenum)

Endoscopic procedure using hydrothermal ablation in the duodenum

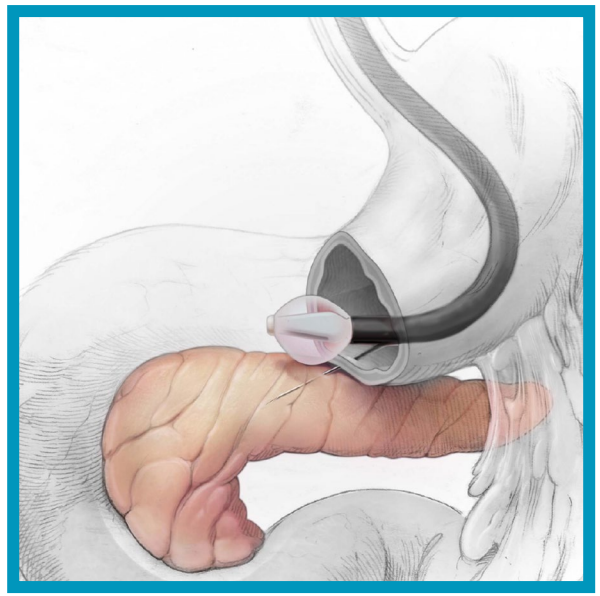
**Rejuva®** (targeting the pancreas)

Adeno-associated virus (AAV)–based pancreatic gene therapy platform

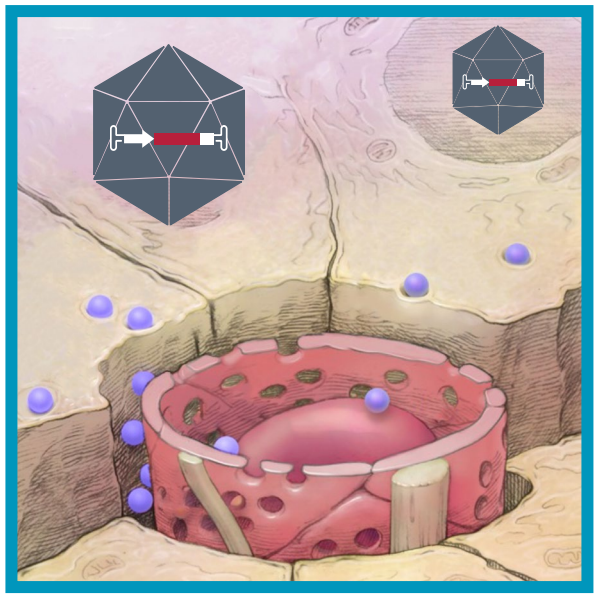


# Rejuva Directly Targets the Pancreas with Gene Therapy

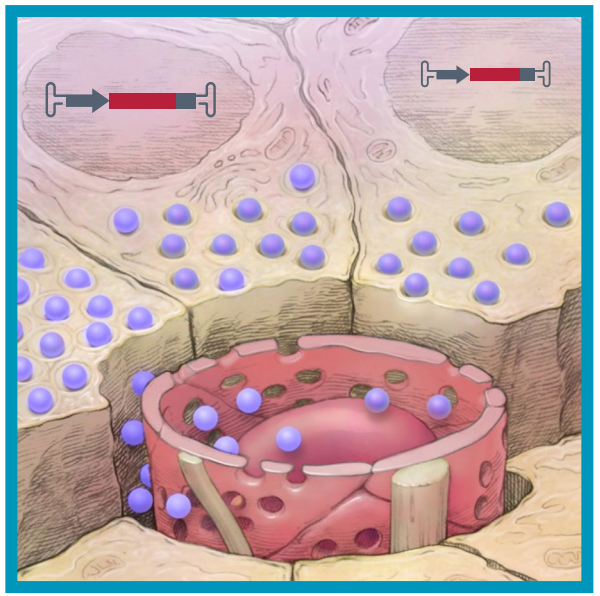
## Key therapeutic elements



**Endoscopic device and procedure**



**AAV Gene Therapy Delivery Vehicle**



**Tissue-Restricted Transgene Expression**

# GLP1RAs for T2D Have Proven Clinical Benefit But Are Limited

## Opportunity to advance GLP1RA field with local gene therapy approach

Glucagon-like peptide 1 receptor agonists (GLP1RAs) have proven clinical efficacy

Limited by adherence and tolerability of systemic delivery[2,3,4]

In the US, 50% of patients discontinue therapy within 330 days[1,3,4]

Discontinuation of GLP1RA therapy is associated with total loss of metabolic benefit[5]

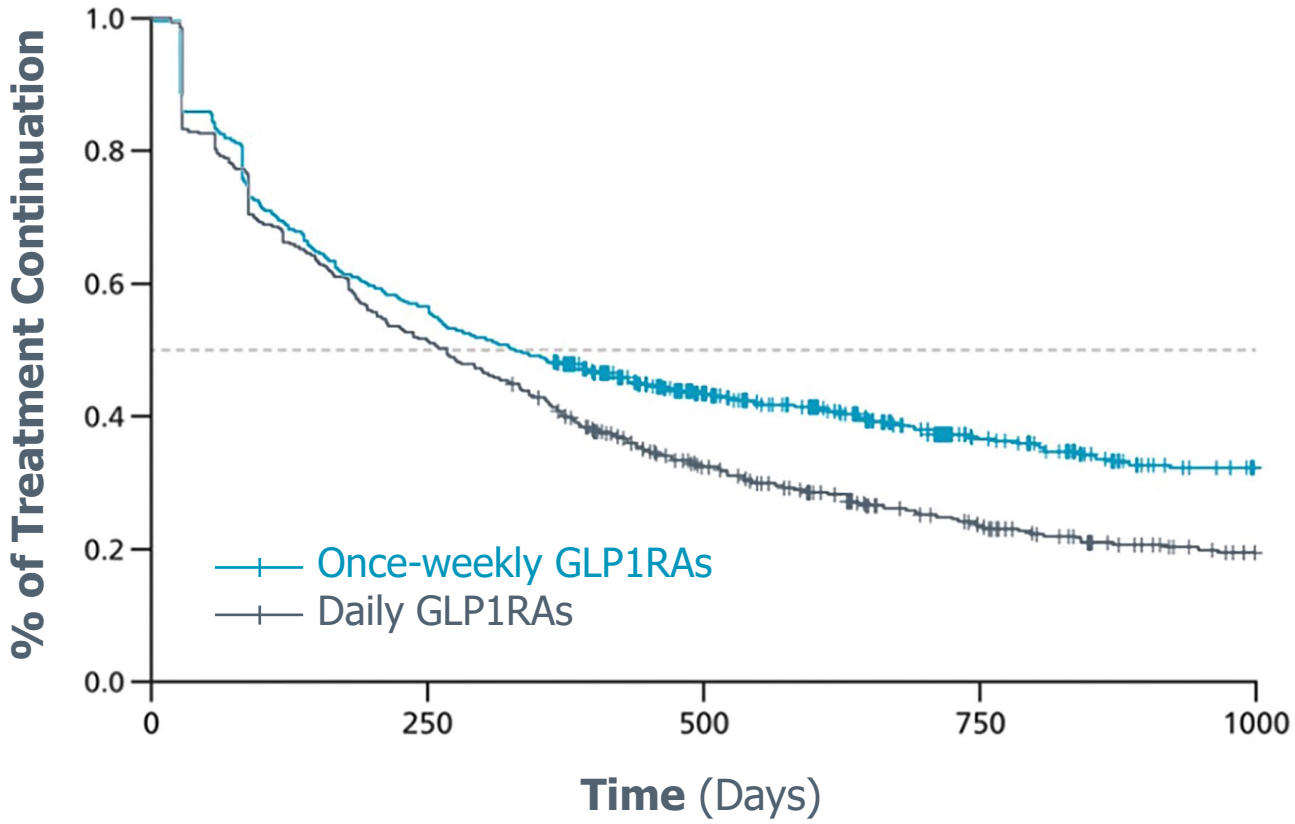





Figure adapted from: 1. Polonsky et al. Diabetes Ther (2022) 13:175–1871. 2. Campbell and Drucker. Cell Metabolism 17, June 4, 2013 3. Weiss 2020 Patient Pref Adherence 14:2337-2345. 4. Polonsky 2021 Diabetes Spectr 34(2):175-183. 5. RISE Consortium Diabetes Care. 2019;42(9):1742-1751.

# Rationale for AAV-GLP1RA Gene Therapy to Improve Islet Function

## Declining islet health is an early driver of T2D progression

T2D islet:

- β-cell loss of insulin
- α-cell excess glucagon

GLP1RAs reverse both and improve islet cell health[1]

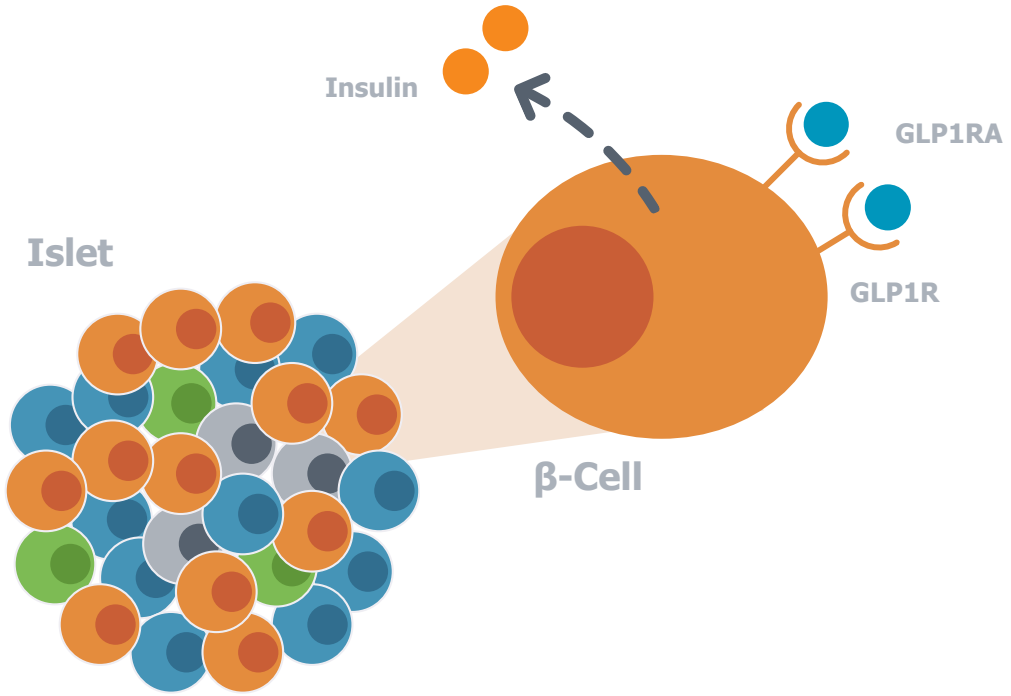





Figure adapted from: Saikia et al. JCI Insight 2021;6(3):e1418511. 1. Campbell and Drucker. Cell Metabolism 17, June 4, 2013.
AAV=adeno-associated virus, GLP1RA=GLP-1 receptor agonist

# Rationale for AAV-GLP1RA Gene Therapy to Improve Islet Function

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T2D islet:

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- α-cell excess glucagon

GLP1RAs reverse both and improve islet cell health[1]

**AAV-GLP1RA gene therapy may address limitations by driving local, durable production of GLP1RA to improve islet function**

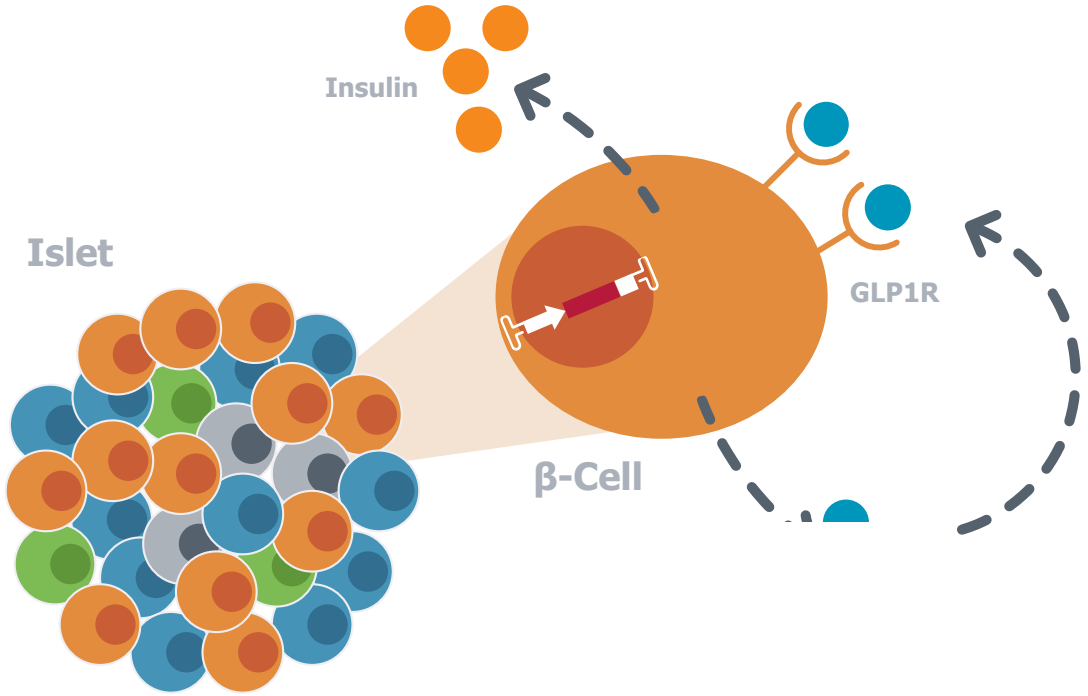





Figure adapted from: Saikia et al. JCI Insight 2021;6(3):e1418511. 1. Campbell and Drucker. Cell Metabolism 17, June 4, 2013.
AAV=adeno-associated virus, GLP1RA=GLP-1 receptor agonist

# Rationale for AAV-GLP1RA Route of Administration & Islet Targeting

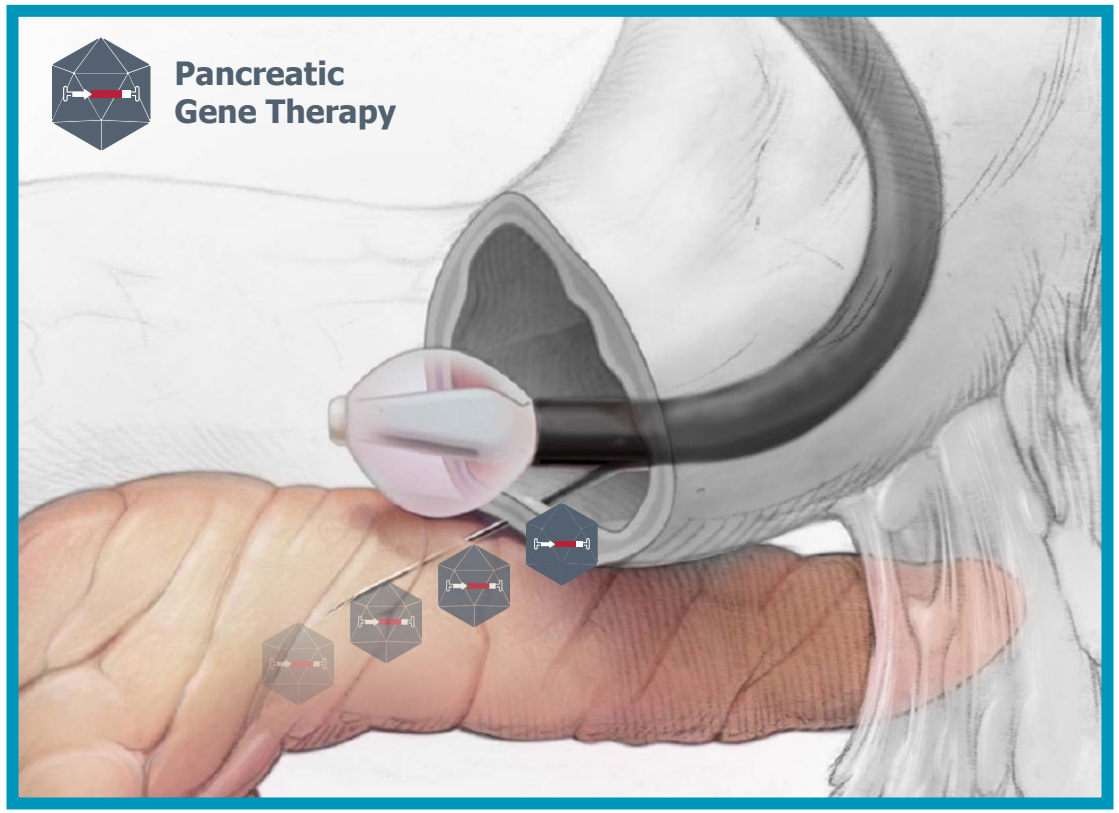
## Islets are most easily accessed via endoscopic ultrasound

Endoscopic ultrasound (EUS) is routine (~300K cases per year)[1]

EUS via stomach provides direct access to pancreatic body and tail

Islets are 1-2% of total pancreas mass,  predominantly in tail, and mostly terminally differentiated[2,3,4]

Risk of procedural pancreatitis can be mitigated with device and procedure steps



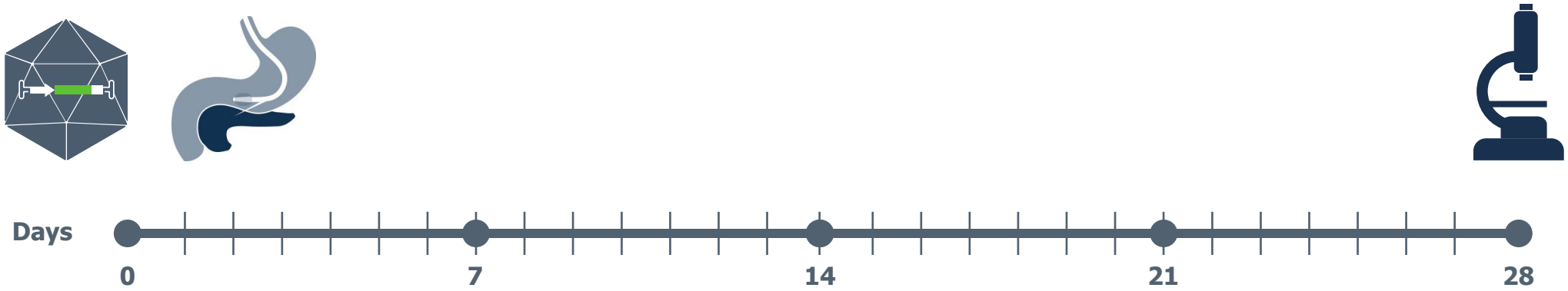

**Endoscopic Procedure & AAV Delivery**



1. Peery et al. Gastroenterology 2021 Oct 19. 2. Docherty et al. Encyclopedia of Tissue Engineering and Regenerative Medicine. 2019. 3. Ravi et al. Medicine (Baltimore). 2021 Apr 30;100(17):e25642. 4. Perez-Frances et al. Cell Rep. 2022;38(7):110377.

# EUS-Guided AAV ROA Feasibility in Yucatan Pig

## Porcine model approximates human GI tract and pancreas anatomy




**EUS-guided Pancreatic Infusion**
AAV9-CMV-GFP (Ubiquitous)*
AAV9-INS-GFP (β-cell Restricted)

**Routine Safety**
ALT
Lipase
NF-L

**Sacrifice (days 21-28)**
ALT
Lipase
NF-L
Vector Biodistribution
Organ Histology

*AAV9-CMV-GFP used to assess on target efficacy and acute safety

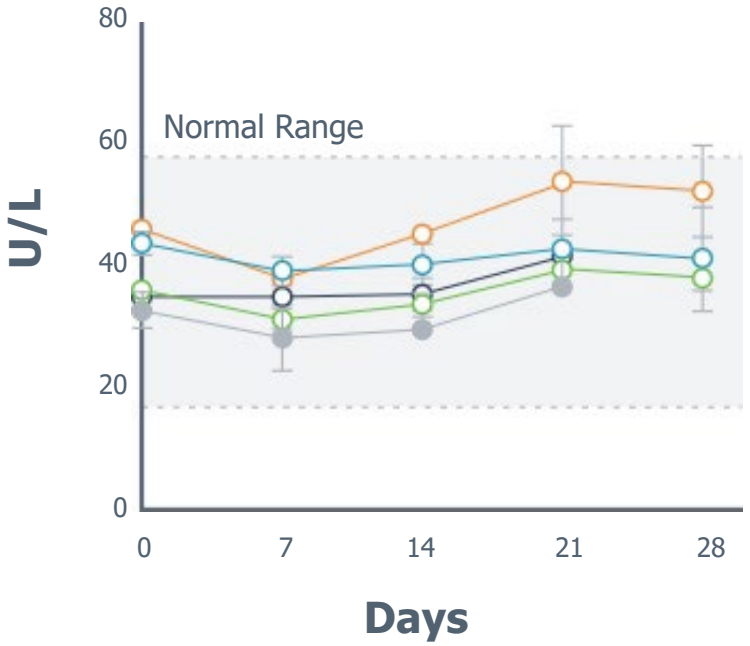


EUS=endoscopic ultrasound, ROA=route of administration, GI=gastrointestinal, ALT=alanine aminotransferase, NF-L=neurofilament light chain, AAV=adeno-associated virus, GFP=green fluorescent protein, CMV=cytomegalovirus, INS=insulin

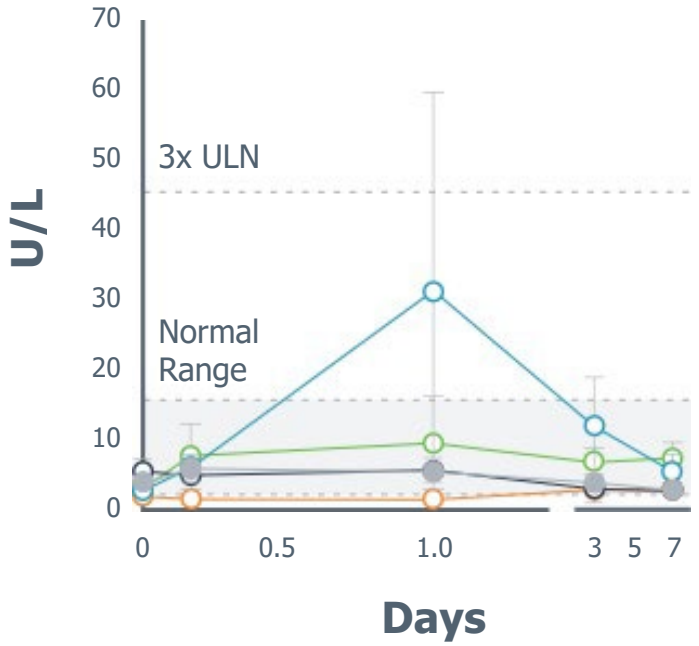
# EUS-Guided AAV ROA in Yucatan Pig

## Serum ALT and lipase remained in the normal range across most timepoints

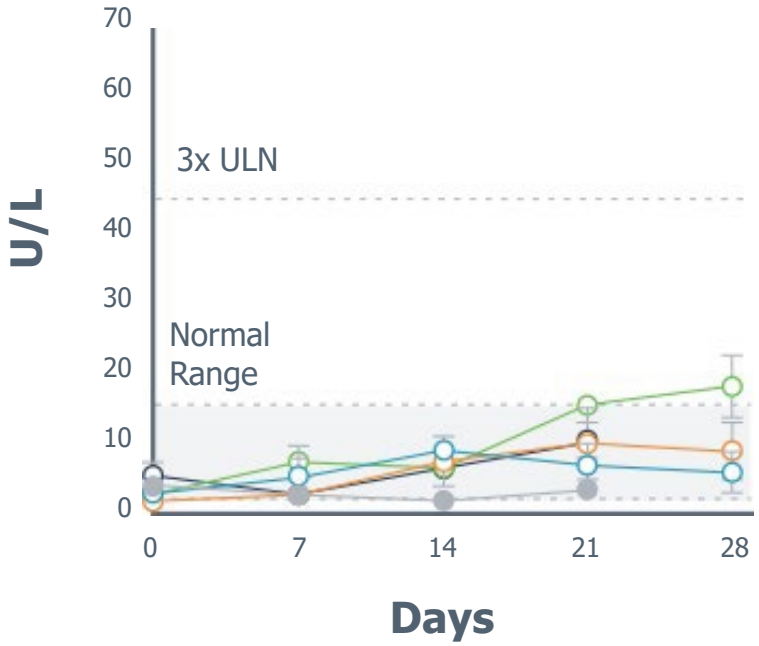
### A) 28-day ALT




### B) 7-day Lipase




### C) 28-day Lipase





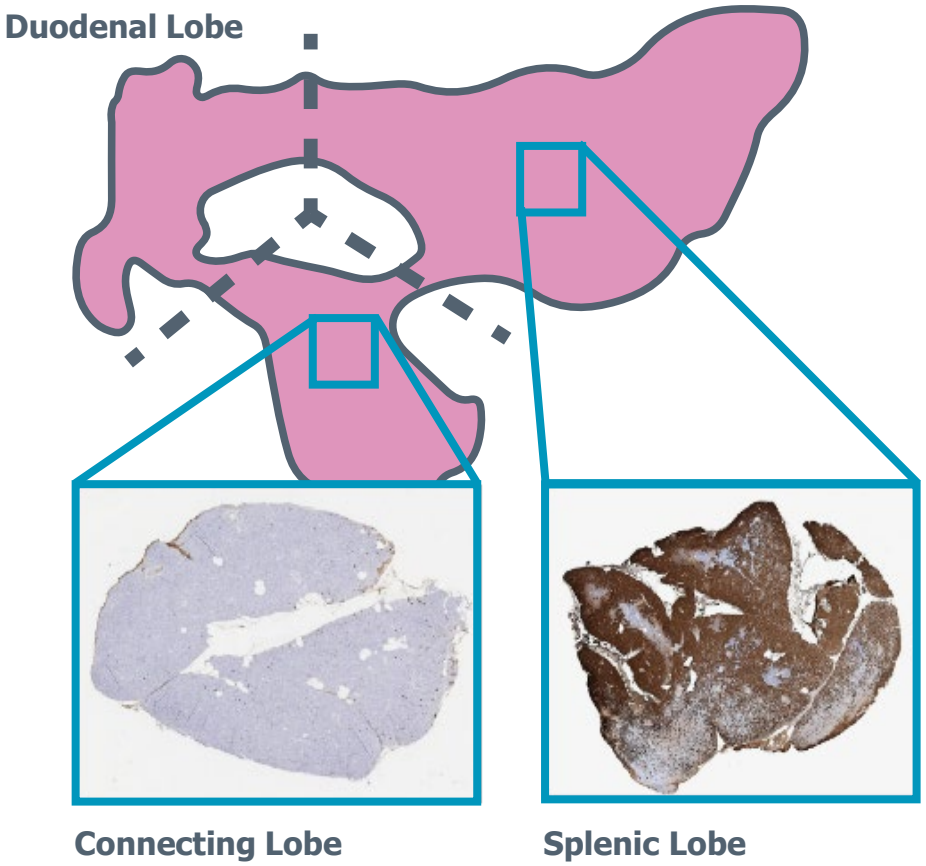


Mean ± SEM shown; n=2-4 per group. ALT=alanine transaminase, EUS=endoscopic ultrasound, ROA=route of administration, AAV=adeno-associated virus

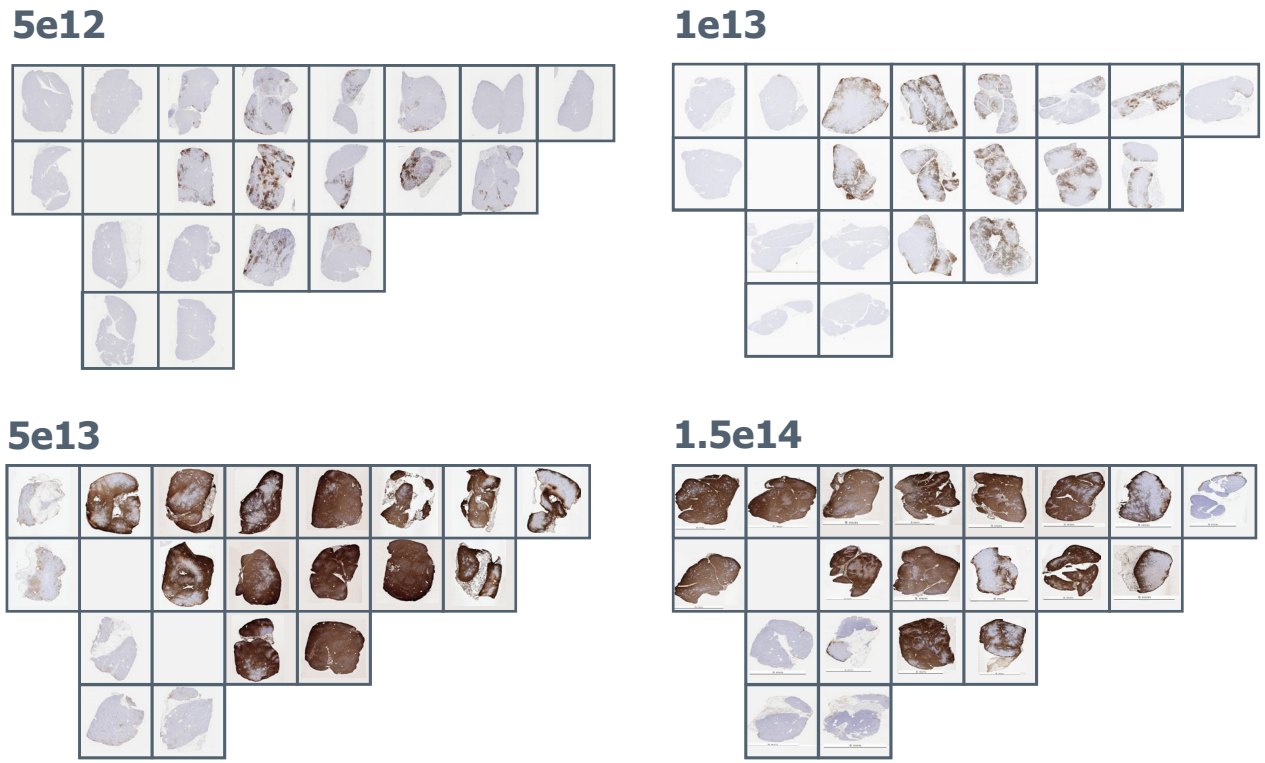
# EUS-Guided AAV ROA in Yucatan Pig

## Dose-dependent expression of GFP throughout targeted splenic lobe

### A) Extensive GFP in Splenic Lobe




### B) VG Dose-Dependent GFP in Pancreas



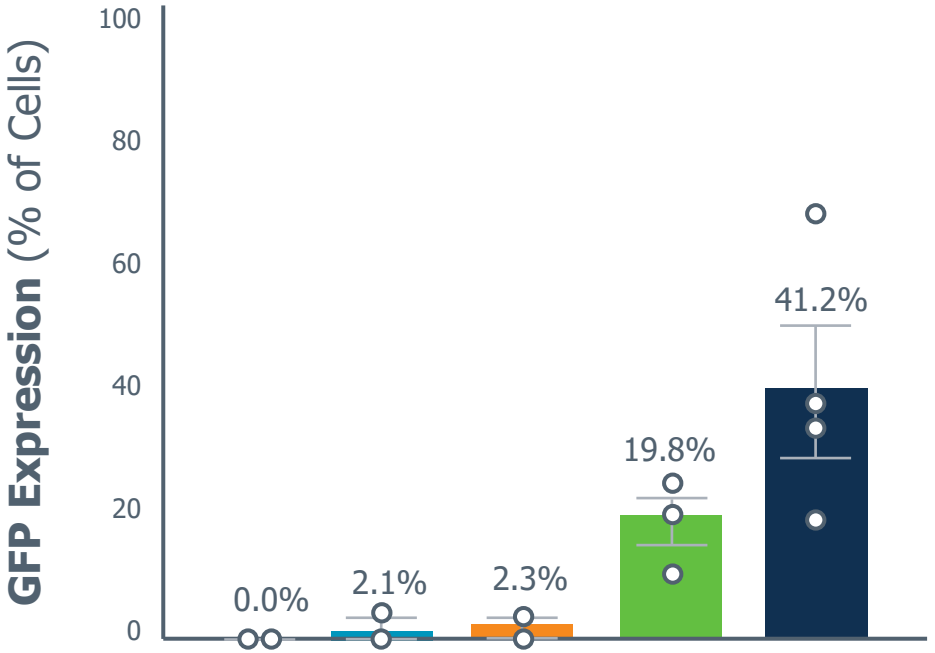



EUS=endoscopic ultrasound, ROA=route of administration, AAV=adeno-associated virus, GFP=green fluorescent protein, VG=vector genomes

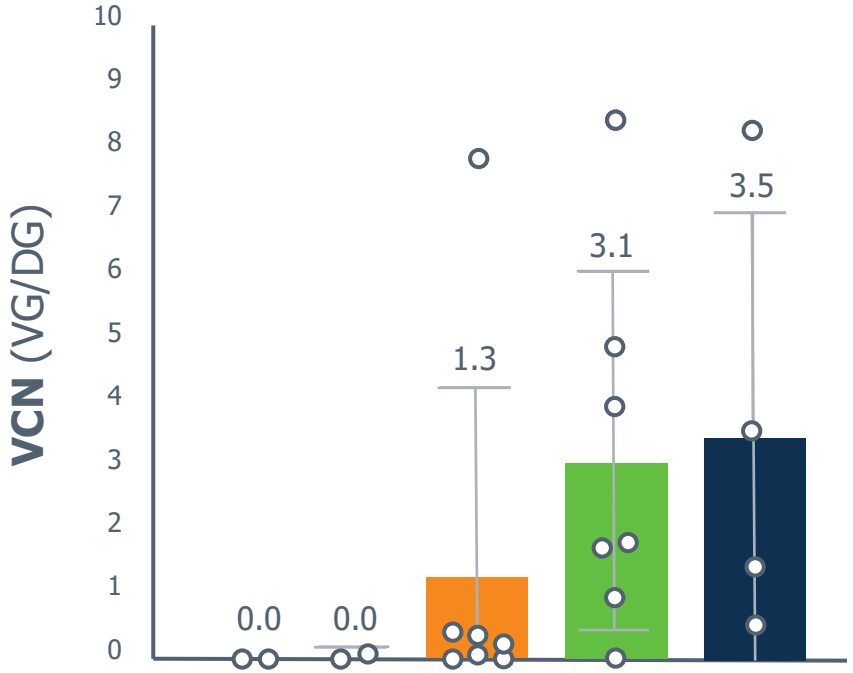
# EUS-Guided AAV ROA in Yucatan Pig

## ~ 40% of splenic lobe islet cells express GFP transgene at highest dose

### A) Islet GFP Expression




### B) On-target VCN



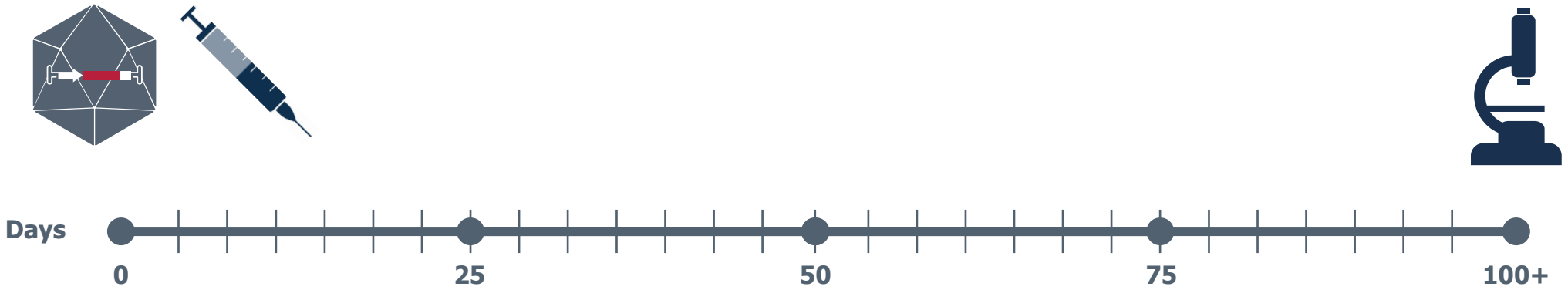




Mean ± SD shown; n=2-7 per group; EUS=endoscopic ultrasound, ROA=route of administration, AAV=adeno-associated virus, GFP=green fluorescent protein, VCN=vector copy number, VG=vector genomes, DG=diploid genomes

# *In Vivo* and *In Vitro* AAV-GLP1RA Efficacy Proof of Concept

## Murine model of T2D progression and islet analyses




**I.P. Injection**
**(35-day-old db/db mice)**
AAV9-INS-GLP1RA
Vehicle

**Efficacy/MOA**
Weekly Fasting Blood Glucose
Biweekly Insulin
IPGTT

**Sacrifice (days 42-100+)**
Organ Histology
Pancreatic GLP1RA Protein
Serum GLP1RA
Islet Isolation



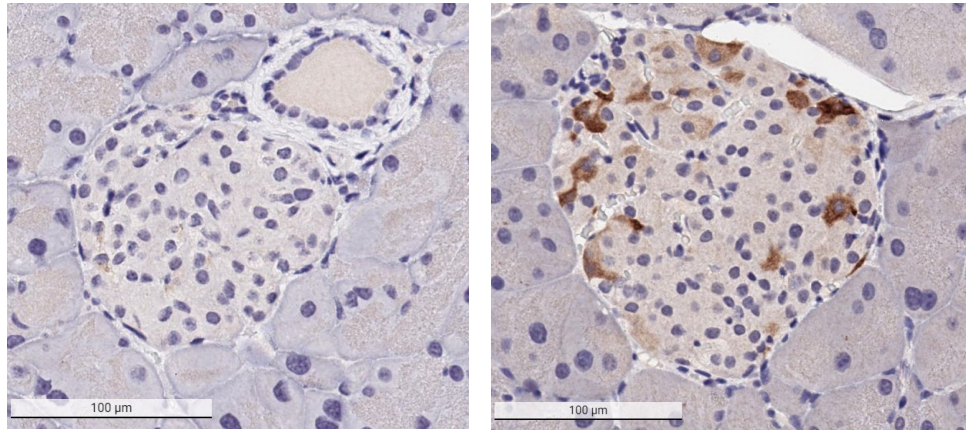
AAV=adeno-associated virus, INS=insulin, GLP1RA=GLP-1 receptor agonist, I.P.=intraperitoneal, IPGTT=intraperitoneal glucose tolerance test

# *In Vivo* AAV-GLP1RA Efficacy Proof of Concept in Db/db Mouse

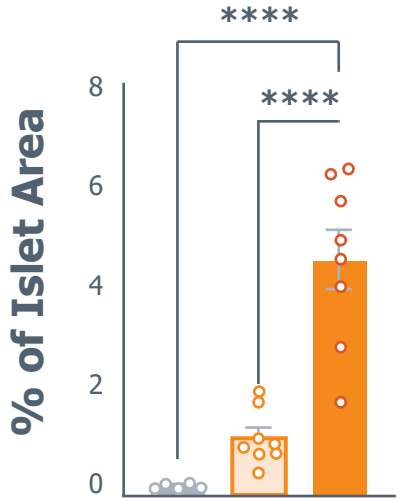
## AAV-GLP1RA targets pancreas with ~4% of islet cells transduced

### A) Pancreatic Islets 10 Weeks Post I.P. Injection

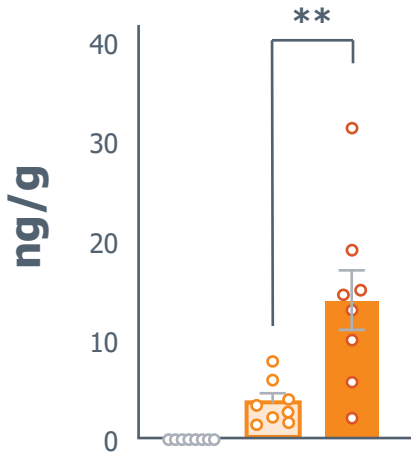
**Vehicle** **AAV-GLP1RA**




### B) Islet GLP1RA Protein Expression




### C) Whole Pancreas GLP1RA Protein Expression





**Note:** **GLP1RA expression restricted to islet and below limit of quantification in serum**

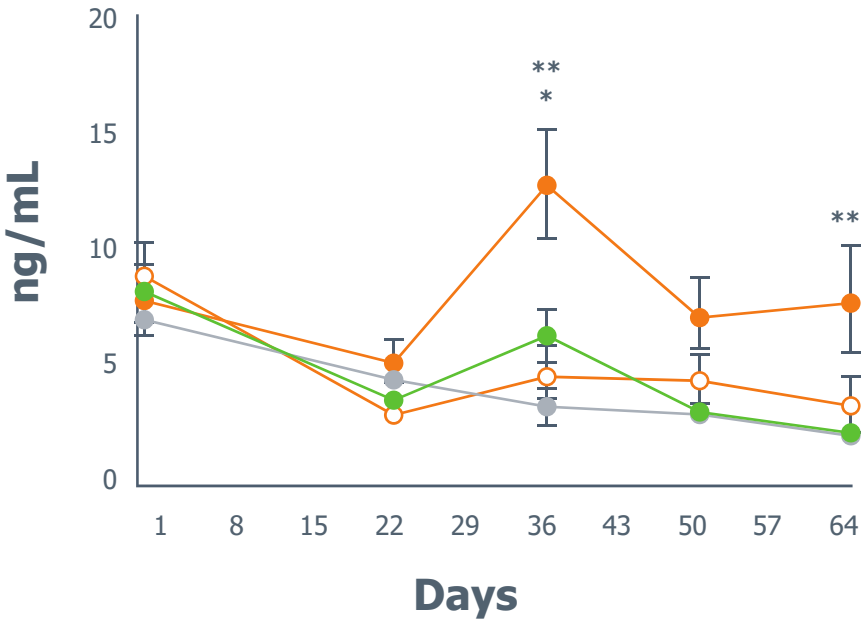


Mean ± SEM shown; **p<0.01, ****p<0.0001; n=5-8 per group; AAV=adeno-associated virus, GLP1RA=GLP-1 receptor agonist, I.P.=intraperitoneal, VG=vector genomes

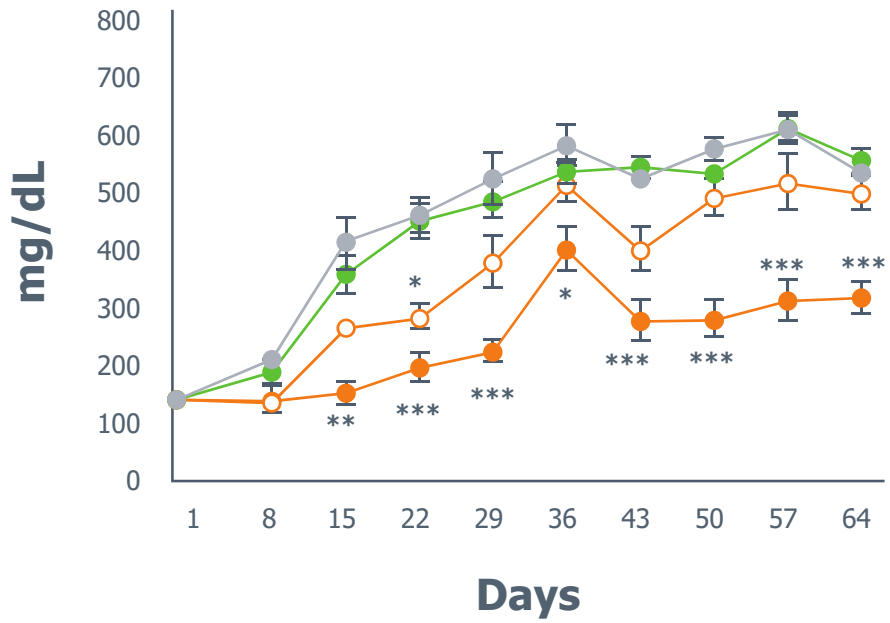
# *In Vivo* AAV-GLP1RA Efficacy Proof of Concept in Db/db Mouse

## AAV-GLP1RA increases fasting insulin and reduces fasting blood glucose

**A) Biweekly Insulin** (4–6 hour fasted)




**B) Weekly FBG** (4–6 hour fasted)



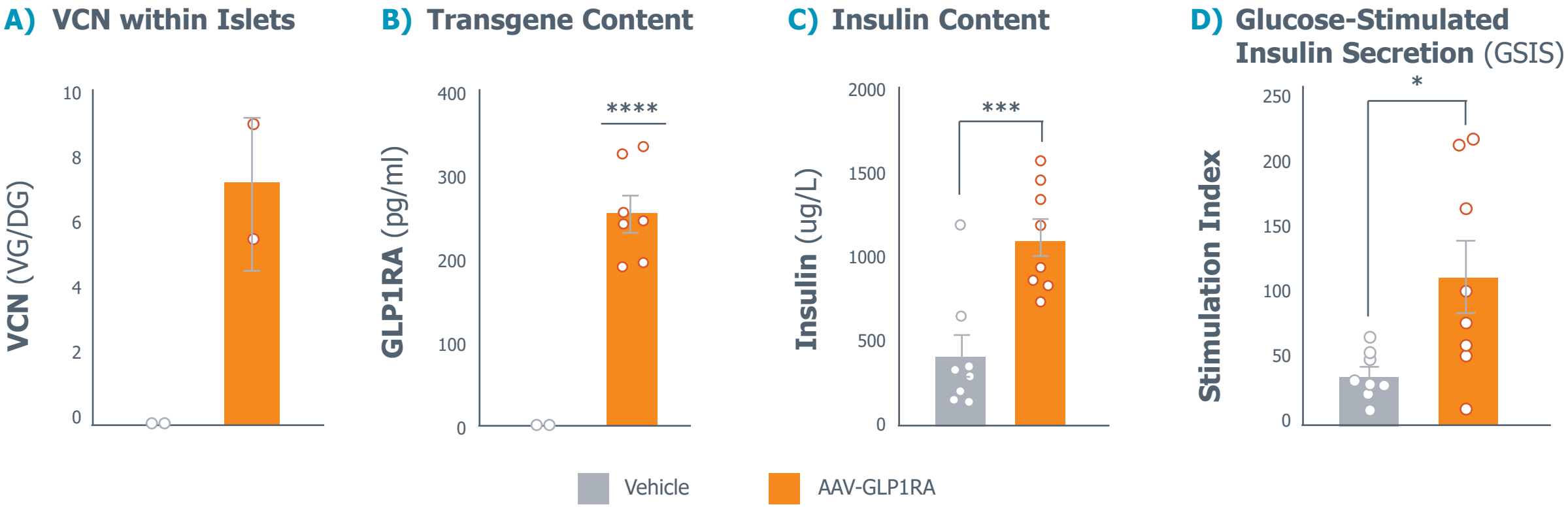




Mean ± SEM shown; *p<0.05, **p<0.01, ***p<0.001; n=8 per group; AAV=adeno-associated virus, GLP1RA=GLP-1 receptor agonist, GFP=green fluorescent protein, FBG=fasting blood glucose

# *In Vitro* AAV-GLP1RA Efficacy – Isolated Islets from Treated Mice

## AAV-GLP1RA increases db/db islet GLP1RA, insulin, and subsequent GSIS



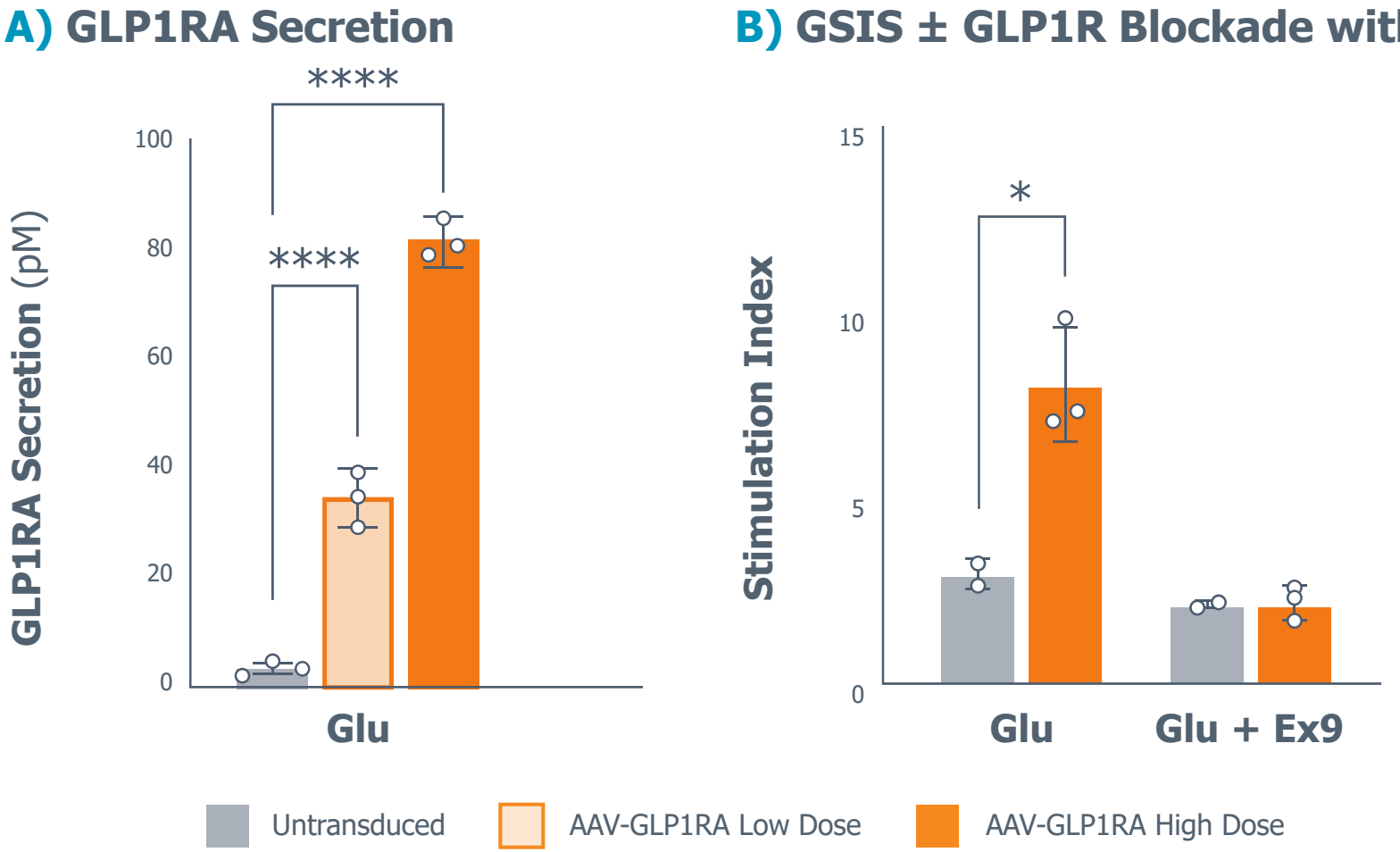

**Islet Transduction** → **GLP1RA Expression** → **Insulin Production** → **Glucose Stimulation**



Mean ± SD shown; *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001; n=2-8 per group; AAV=adeno-associated virus, GLP1RA=GLP-1 receptor agonist, VCN=vector copy number, VG=vector genome, DG=diploid genome

# *In Vitro* AAV-GLP1RA Efficacy Proof of Concept in Human β-cell Line

## AAV-GLP1RA induces GLP1RA protein secretion and improves β-cell function



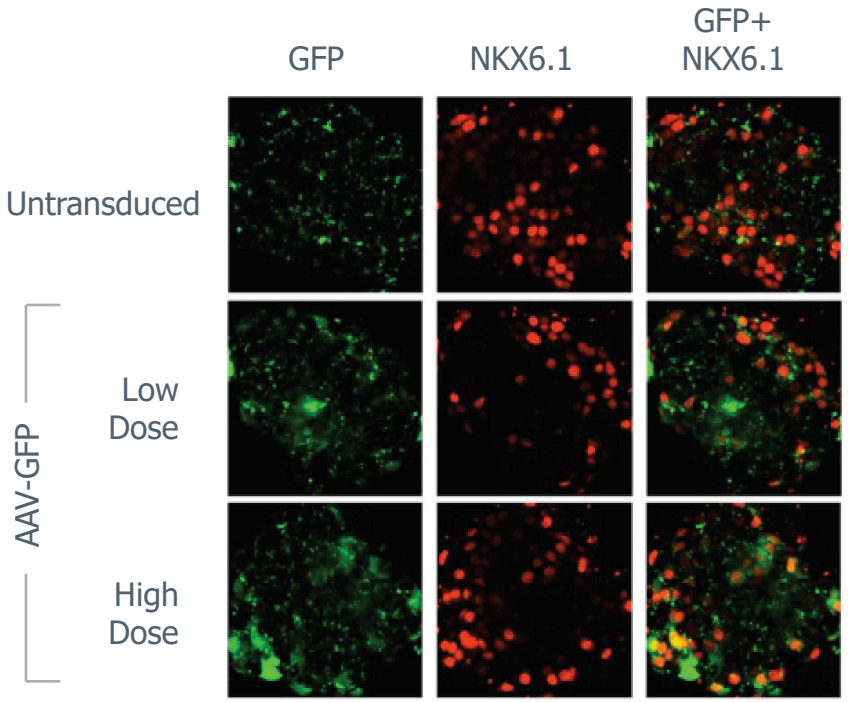



Mean ± SEM shown; *p<0.05, ****p<0.0001; n=2-3 per group. AAV=adeno-associated virus, Ex9=Exendin-9, GLP1RA=GLP-1 receptor agonist, Glu=glucose

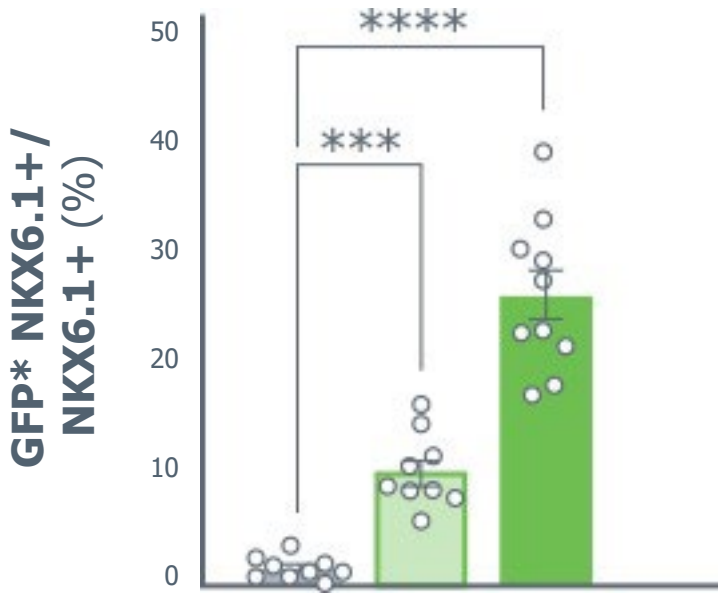
# *In Vitro* AAV-GLP1RA POC Efficacy in Human Islet

## AAV-GLP1RA targets up to 30% of human islet β-cells and improves function

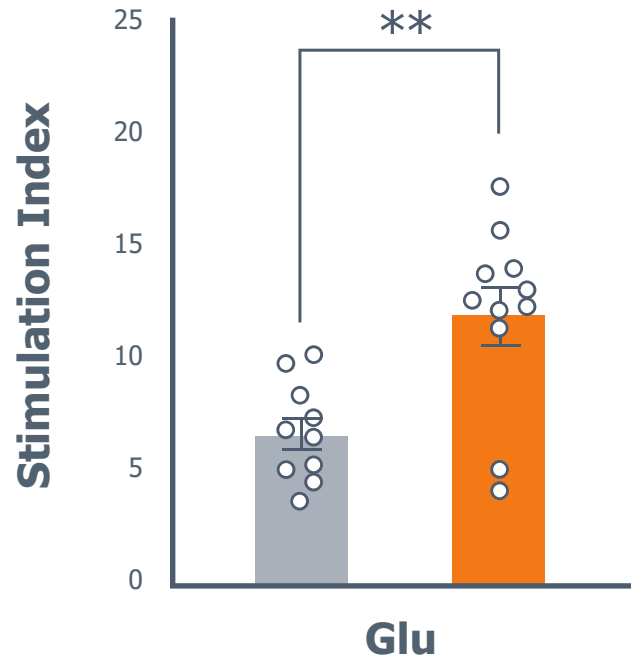
### A) β-cell Transduction




### B) Transduction Efficiency




### C) GSIS







Mean ± SEM shown; **p<0.01, ***p<0.001, ****p<0.0001; n=9-11 per group. AAV=adeno-associated virus, GFP=green fluorescent protein, GLP1RA=glucagon-like peptide 1 receptor agonist, Glu=glucose, NKX6.1=NK6 Homeobox 1, POC=proof of concept,

# Conclusions

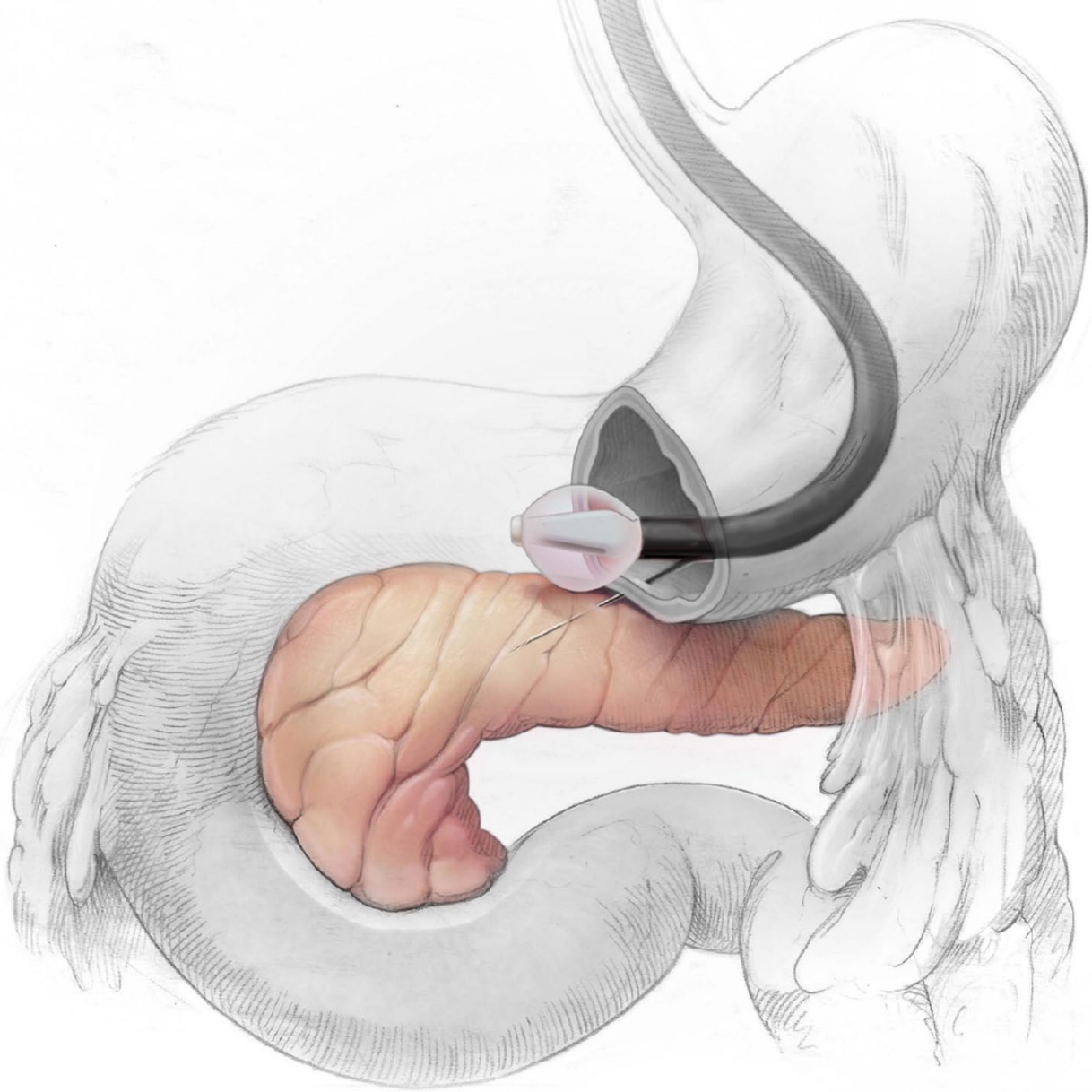
EUS-guided ROA is a feasible and novel platform for pancreatic gene therapy

AAV9 can dose-dependently target the pancreatic islet and drive transgene expression

POC efficacy for GLP1RA-based gene therapy to restore β-cell function and improve glycemic control in rodents and human cells

No unexpected safety signals observed in models studied to date

Expanded biodistribution and safety analyses will be presented on May 20th, 8:00 AM, Petree Hall C (Abstract 312)





POC=proof of concept, EUS=endoscopic ultrasound, ROA=route of administration, AAV=adeno-associated virus, GLP1RA=glucagon-like peptide 1 receptor agonist

# Thank You For Your Attention

## Acknowledgements

### Fractyl Health

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Lin Quek


Gary White


Suya Wang


Keiko Ishida

#### Device Engineering


Jake Wainer


Mike Biasella

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