Islet-Targeted GLP-1 Receptor Agonist Gene Therapy Reduces Fat and Improves Metabolism in Obese Mice

Harith Rajagopalan, Alice Liou Fitzpatrick, Suya Wang, Nicole Picard, Emily Cozzi, Randy Seeley, Timothy Kieffer, Jay Caplan

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GLP-1 Drugs: Weight Rebound is a Significant Problem

Current GLP-1 drugs do not durably alter metabolic setpoint

Discontinuation of therapy leads to **near total loss of metabolic benefit**[1]

GLP-1 therapies support weight loss and glucose control, **but weight maintenance has become a critical challenge**

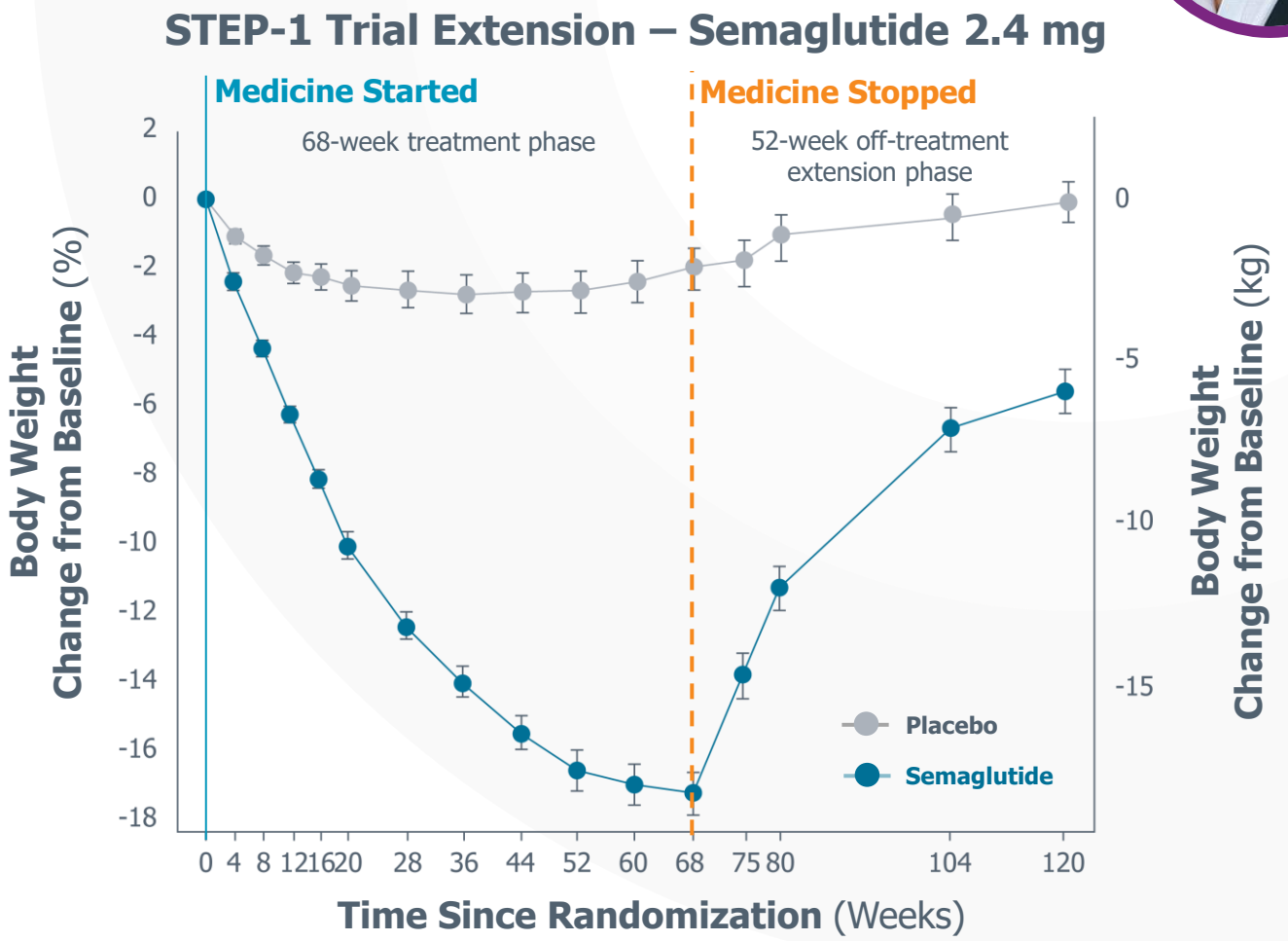

Figure adapted from Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564. 1. Wilding et al. Diabetes Obes Metab. 2022 24:1553-1564. GLP-1=glucagon-like peptide 1

Real-World Evidence Shows High Discontinuation Rates

BCBS data show 50% GLP-1 drug discontinuation within 3 months

Private insurer **survey of ~170K unique GLP-1 drug users** for weight loss from January 2014 to December 2023[1]

Early discontinuation is often due to tolerability, but medium-term discontinuation rates still remain high across a range of tested variables:

- Cost (out of pocket expense)
- Type of prescriber (PCP vs. endocrinologist)
- Age of patient
- Comorbidity index

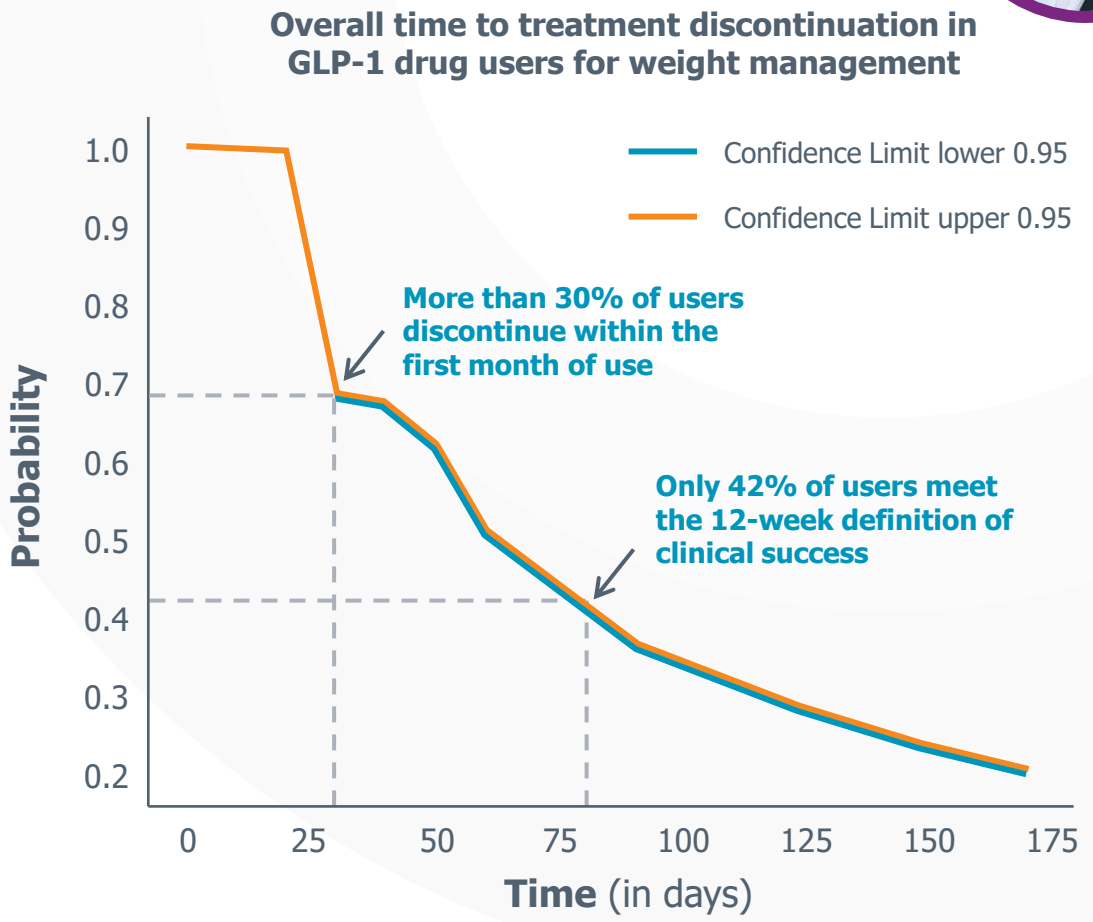

Figure adapted from Blue Health Intelligence, Issue Brief May 2024. 1. Blue Health Intelligence, Issue Brief May 2024. BCBS=Blue Cross Blue Shield, GLP-1=glucagon-like peptide 1, PCP=primary care physician

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Pancreatic Gene Therapy (PGTx) to Modify Islet Function

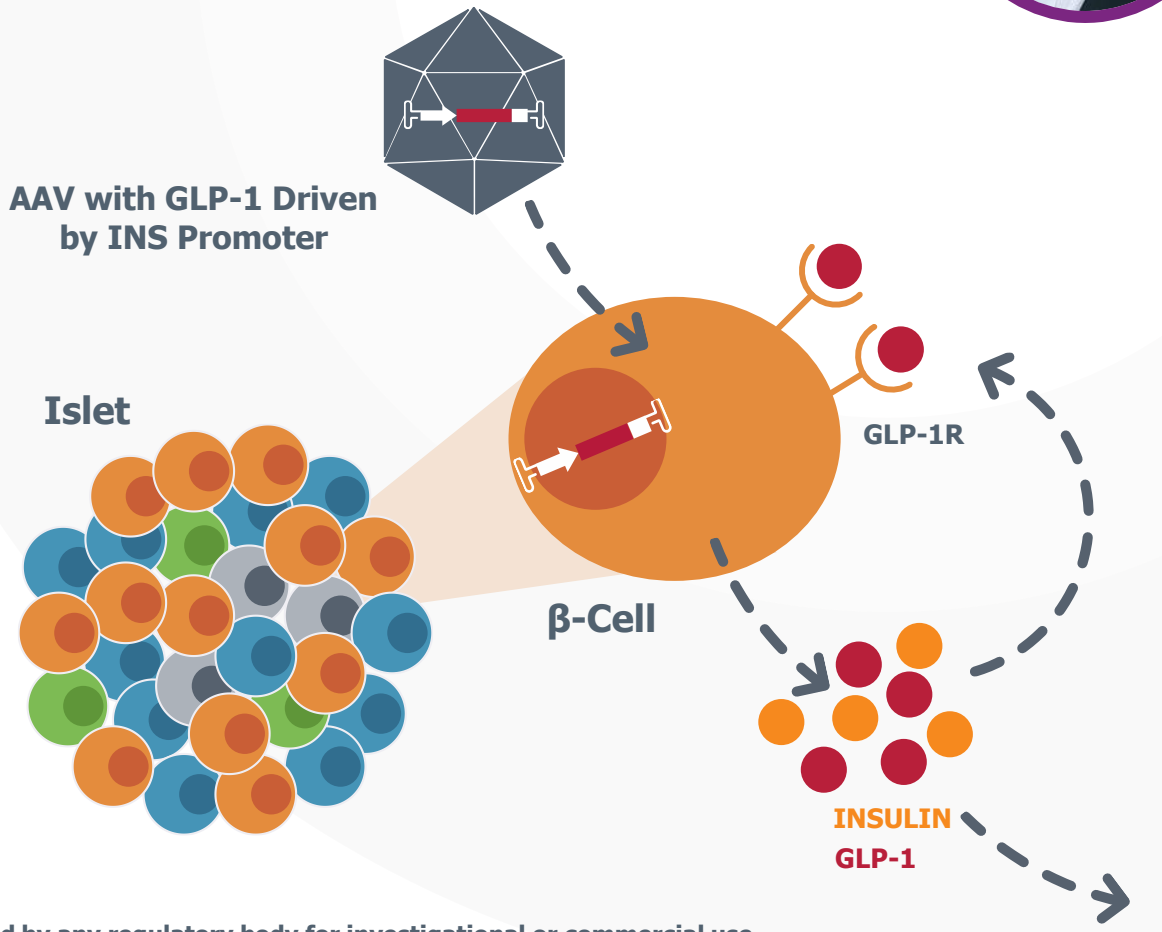
Potential for durable improvement in metabolic health

Smart GLP-1™ gene therapy, targeted to pancreatic islets, may offer differentiated benefit

β-cell machinery can be leveraged to produce nutrient-stimulated hormones[1,2]

Islet cells are terminally differentiated,[3] making adeno-associated virus (AAV) suitable for durable effect

Opportunity to amplify islet GLP-1 signaling to improve β-cell health



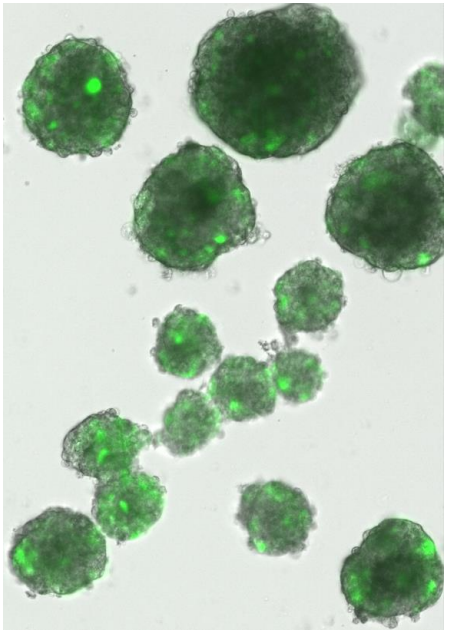
The Pancreatic Gene Therapy (PGTx) platform is in early development and has not been assessed by any regulatory body for investigational or commercial use.

Figure adapted from Saikia et al. JCI Insight. 2021 6:e1418511. 1. Lubaczeuski et al. Keystone 2023 oral presentation. Poster no. 1025. 2. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. 3. Perl et al. J Clin Endocrinol Metab. 2010 95: E234–E239. AAV=adeno-associated virus, GLP-1=glucagon-like peptide 1, GLP-1R=GLP-1 receptor, INS=insulin, PGTx=pancreatic gene therapy

GLP-1RA PGTx in Human Islets and Human β-Cell Line

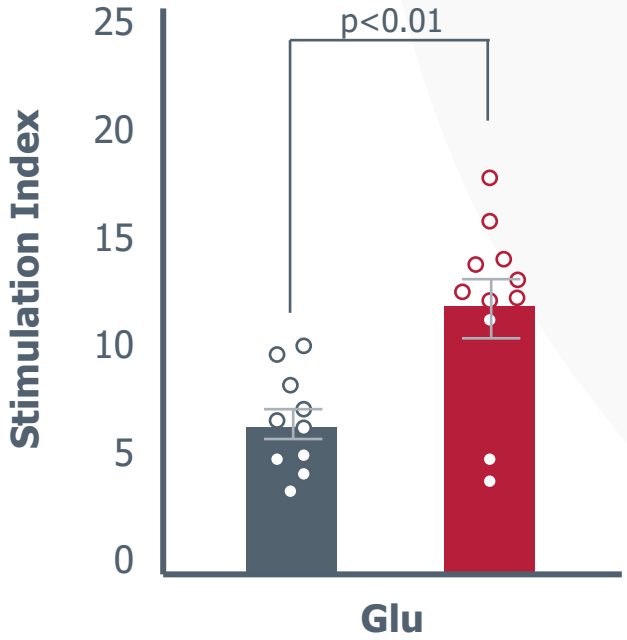
Improves glucose-stimulated insulin secretion via GLP-1R

A) Human Islet Transduction

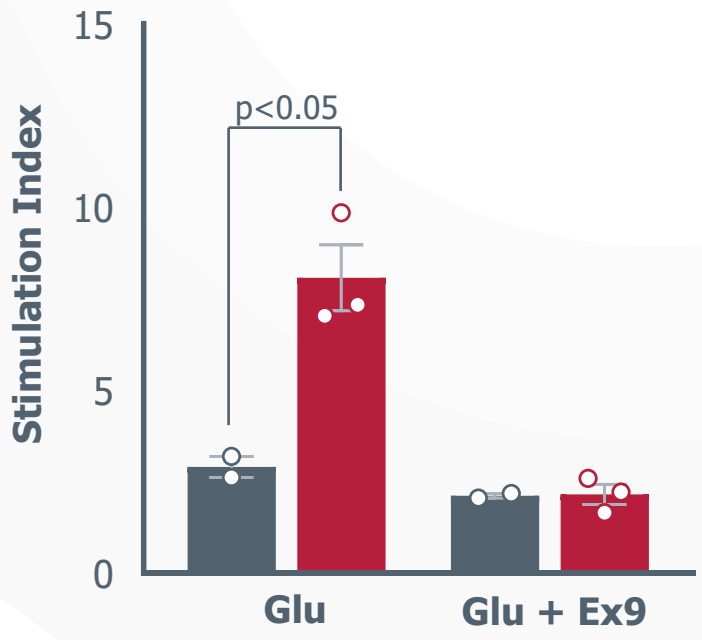


GFP Expression

B) Human Islet GSIS



C) Human β-cell Line GSIS ± Ex9 (GLP-1R Antagonist)



Mean ± SEM shown; n=2-11 per group. B) Glucose stimulation of 16.7 mM from 2.8 mM baseline, C) Glucose stimulation of 11 mM from 0 mM baseline. Rajagopalan et al. ADA 2023 oral presentation. Abstract no. 181-OR. Ex9=Exendin-9, GFP=green fluorescent protein, GLP-1R= glucagon-like peptide 1 receptor, GLP-1RA=GLP-1R agonist, Glu=glucose, GSIS=glucose-stimulated insulin secretion, PGTx=pancreatic gene therapy

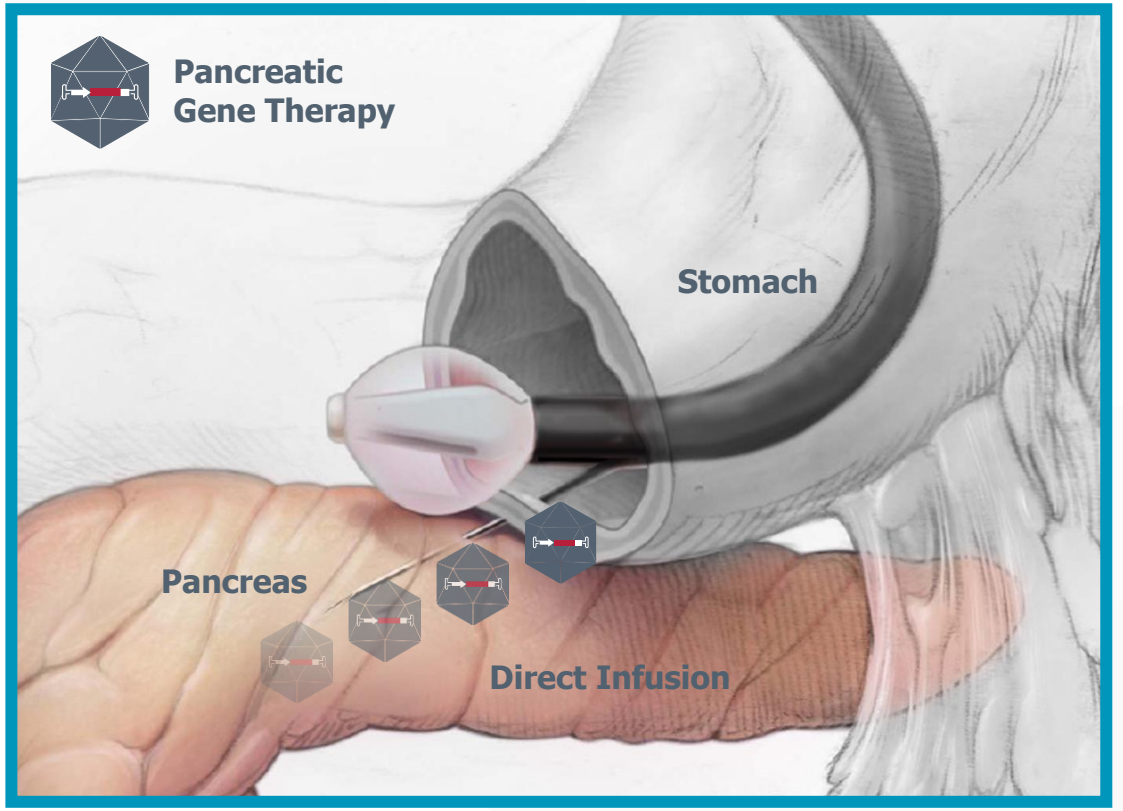
Gene Therapy Route of Administration to Pancreas

Proprietary, automated, endoscopic delivery device

Local delivery enables low viral genome dosing with limited systemic virus exposure[1]

Islets are readily accessible[2,3] via already established, routine, upper endoscopic ultrasound procedures[4] performed in ~300K patients per year in US[5]

Procedural risk is further mitigated with device design (e.g., needle size, volume, controlled infusion rate)



Endoscopic Procedure & PGTx Delivery

1. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191. 2. Docherty & Russ. Encyclopedia of Tissue Engineering and Regenerative Medicine 2019, pg. 367-374. 3. Ravi et al. Medicine (Baltimore). 2021 Apr 30;100(17):e25642. 4. Hasan & Hawes. Gastrointest Endosc Clin N Am. 2012 Apr;22(2):155-67. 5. Peery et al. Gastroenterology 2022 Feb: 162(2):621-644. PGTx=pancreatic gene therapy

Dose-Dependent Viral Transduction in Yucatan Pig Model

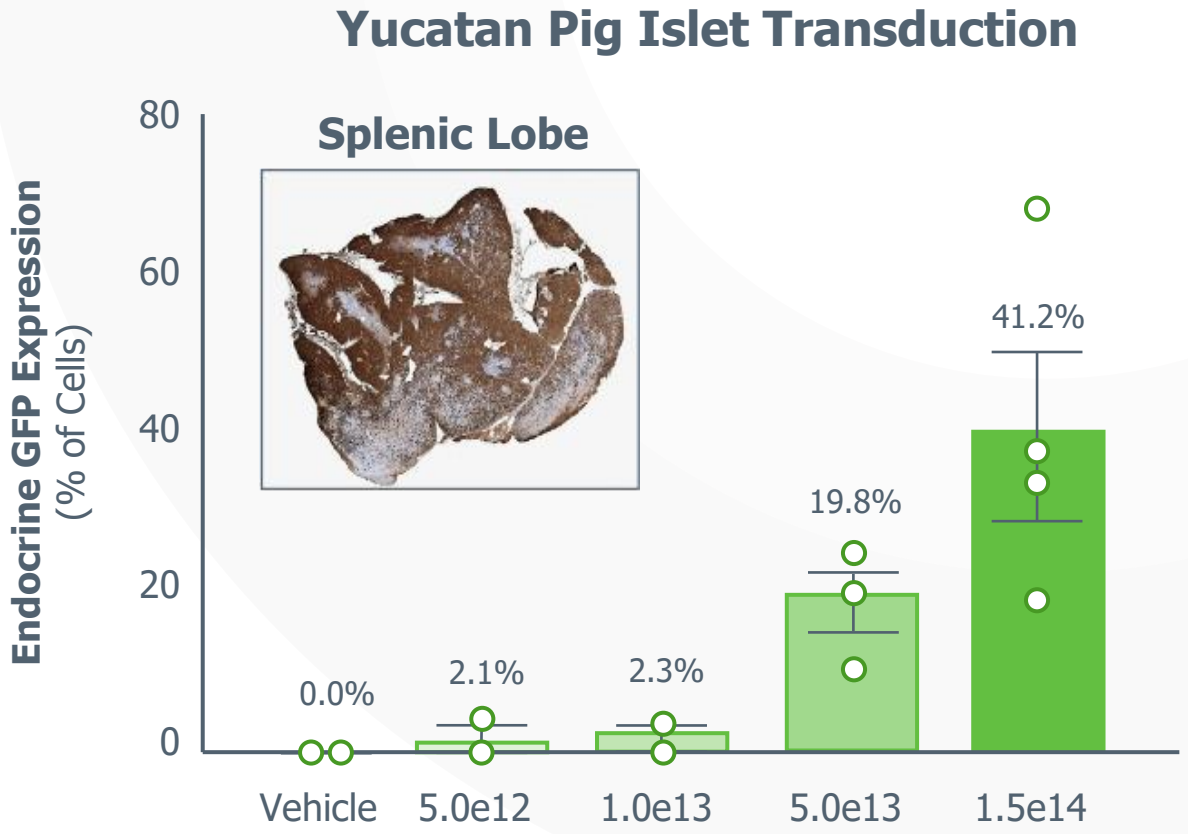
Local delivery effectively and reliably targets islets

Yucatan pig model **anatomy similar to humans**[1]

Dose-dependent AAV-GFP expression in targeted pancreatic lobe[2,3]

>100 animals treated with 100% technical success

No adverse safety signals to date (e.g., pancreatitis)

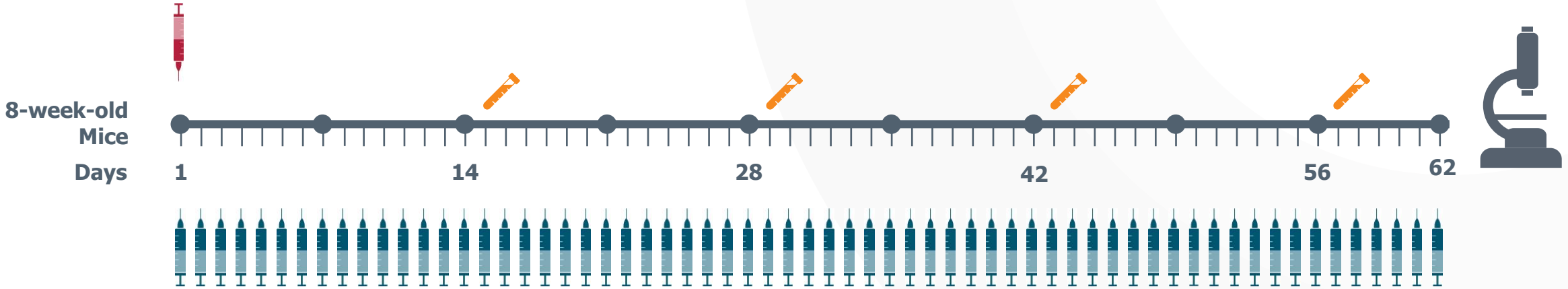


Mean ± SD shown; n=2-4 per group. 1. Walters and Prather. Mo Med. 2013 May-Jun;110(3):212-5. 2. Thompson et al. DDW 2023 poster presentation. Control no. 3862948. 3. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191. AAV=adeno-associated virus, GFP=green fluorescent protein

GLP-1RA PGTx T2D Efficacy Study: Head-to-Head vs. Semaglutide

db/db murine model is *de facto* standard for T2D development

Single I.P. Injection
(5e12 VG PGTx encoding exendin-4 [PGTx-Ex4] or Vehicle)



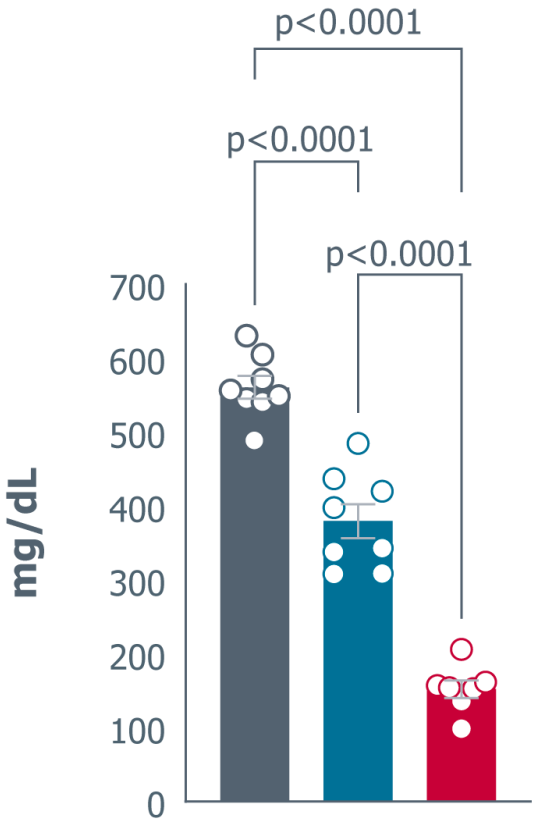
Daily S.C. Injections
Semaglutide (10 nmol/kg/d) or Vehicle

Ex4=exendin-4, GLP-1RA=glucagon-like peptide 1 receptor agonist, I.P.=intraperitoneal, PGTx=pancreatic gene therapy, S.C.=subcutaneous, T2D=type 2 diabetes, VG=vector genomes

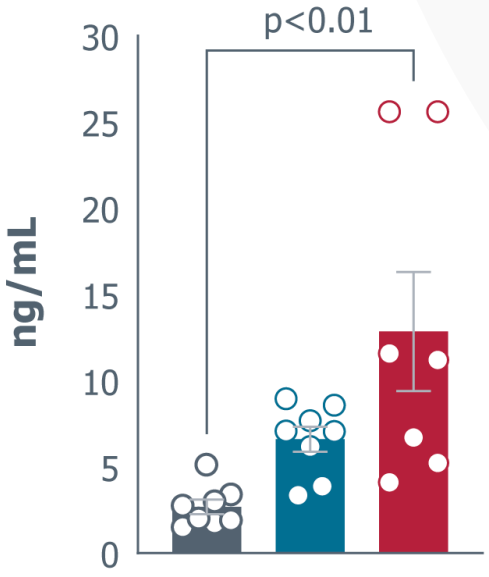
Glucose-Lowering Efficacy in *db/db* Murine Model

GLP-1RA PGTx improves glucose, insulin, and weight vs. daily semaglutide

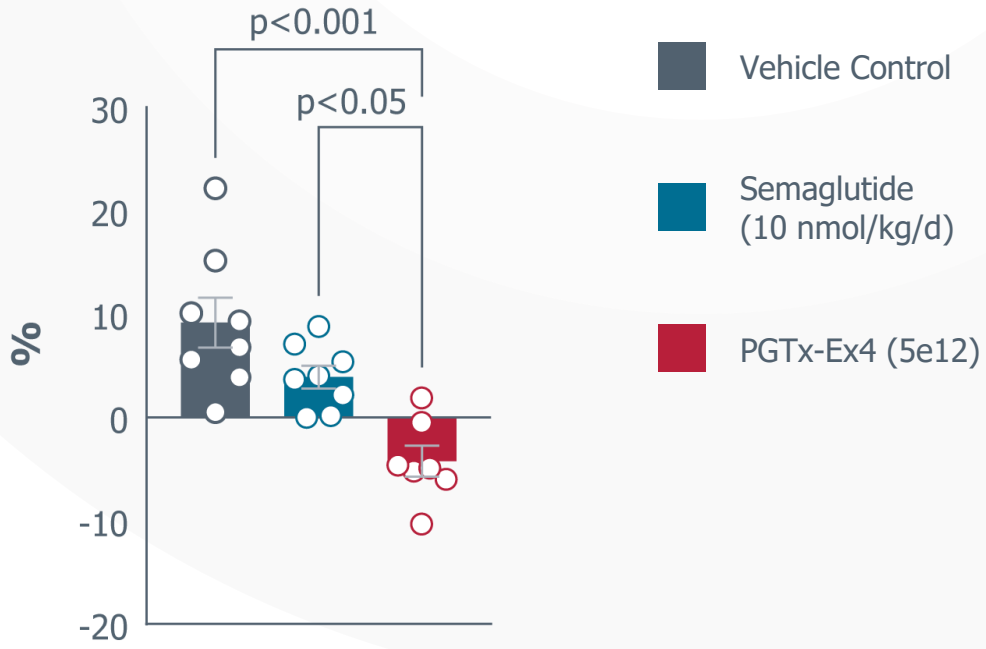
A) Fasting Blood Glucose



B) Fasting Plasma Insulin



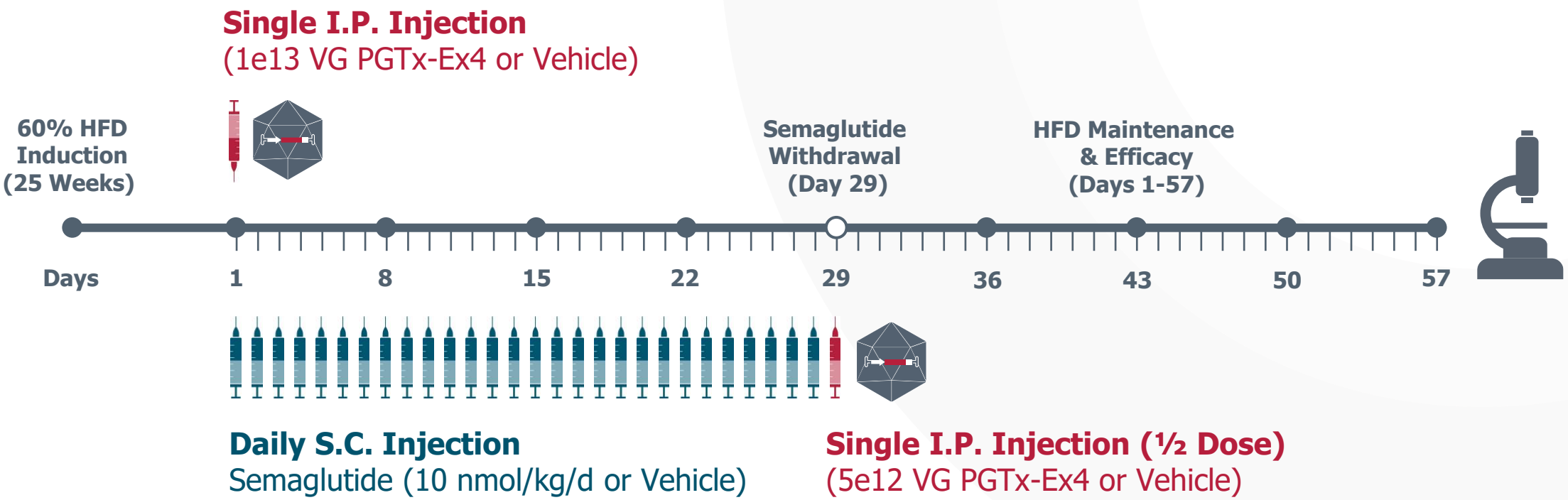
C) Body Weight Change from Baseline



Mean ± SEM shown; n=7-8 per group, day 29 shown, Rajagopalan et al. DDW 2024 oral presentation. Abstract no. 4029196. Ex4=exendin-4, GLP-1RA=glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy

GLP-1RA PGTx Obesity Efficacy Study: Head-to-Head vs. Semaglutide

DIO murine model is *de facto* standard for obesity development

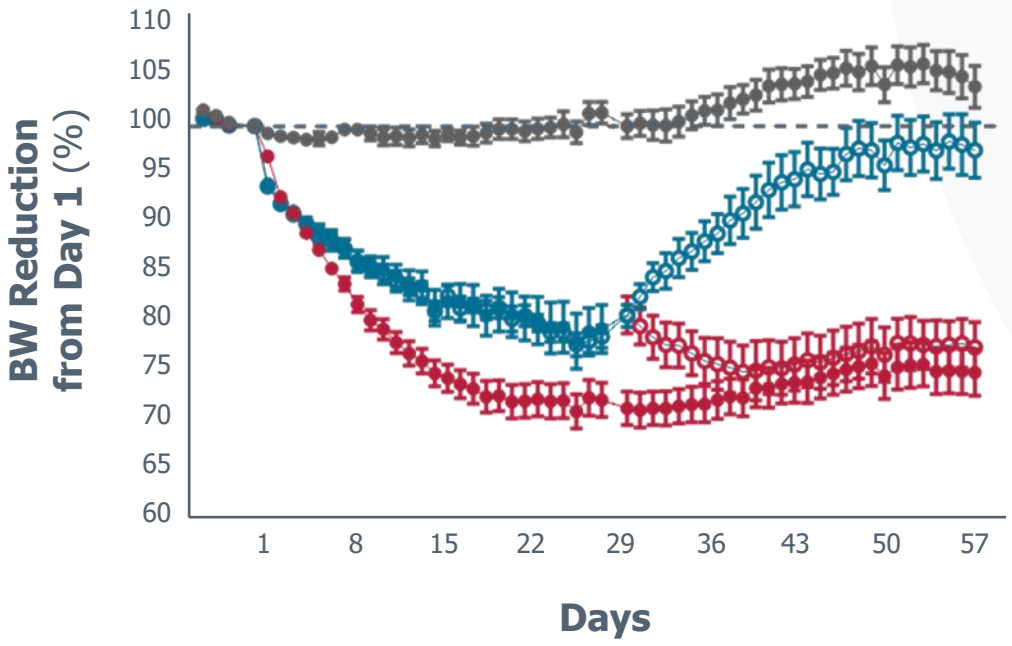


DIO=diet-induced obesity, Ex4=exendin-4, GLP-1RA=glucagon-like peptide 1 receptor agonist, HFD=high fat diet, I.P.=intraperitoneal, PGTx=pancreatic gene therapy, S.C.=subcutaneous, VG=vector genomes

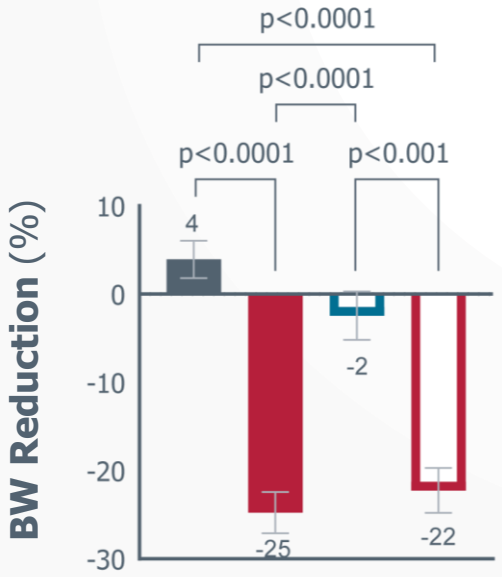
Body Weight Change in DIO Murine Model

Single-dose GLP-1RA PGTx sustains weight loss after semaglutide withdrawal

A) Change in BW Over Time



B) End of Study Change in BW



Vehicle Control

Sema (10 nmol/kg/d)

PGTx-Ex4 (1e13 VG)

Sema Withdrawal + Vehicle

Sema Withdrawal + PGTx-Ex4 (5e12 VG)

Mean ± SEM shown; n=5-10 per group. Fitzpatrick et al. WCIRDC 2023 oral presentation. Abstract no. 0077. BW=body weight, DIO=diet-induced obesity, Ex4=exendin-4, GLP-1RA=glucagon-like peptide 1 receptor agonist, PGTx=pancreatic gene therapy, Sema=semaglutide, VG=vector genomes

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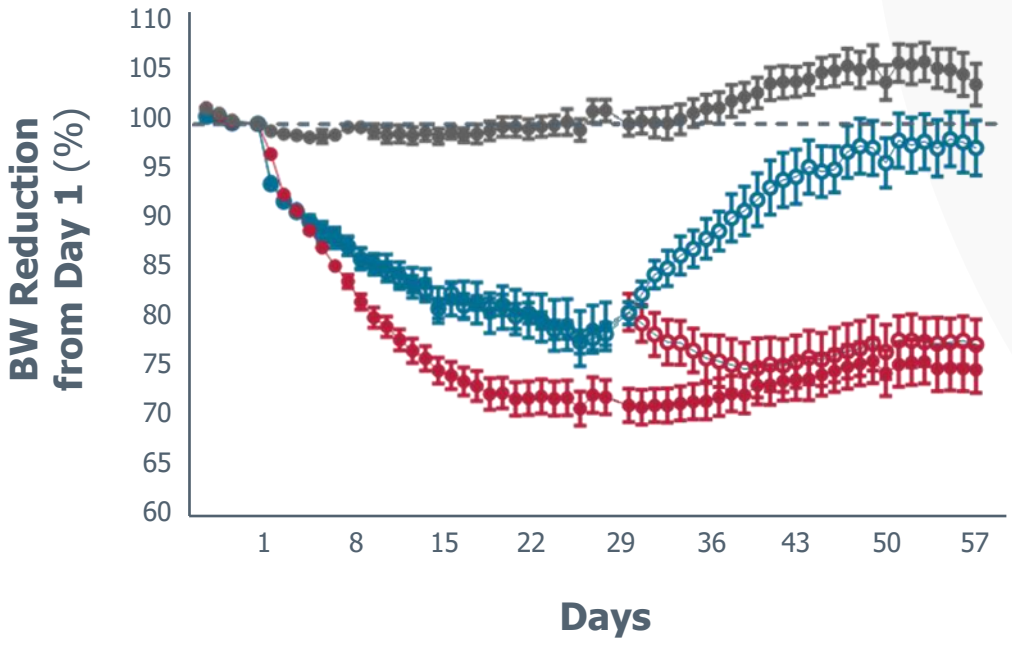
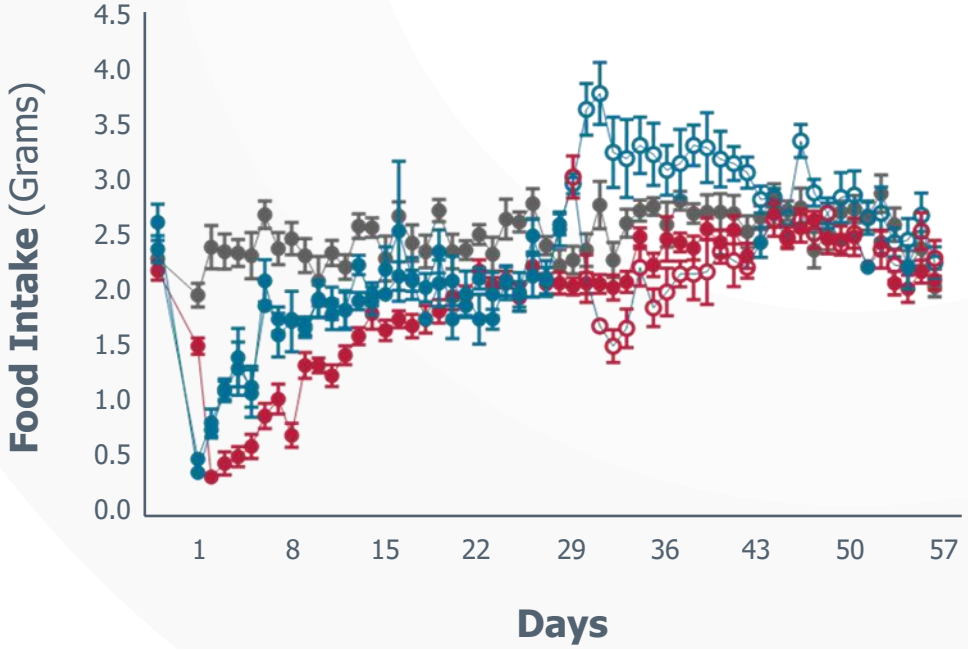
Food Intake Change in DIO Murine Model

Body weight changes are reflected by alterations in food intake

A) Change in BW Over Time



B) Food Intake Over Time



Vehicle Control

Sema (10 nmol/kg/d)

PGTx-Ex4 (1e13 VG)

Sema Withdrawal + Vehicle

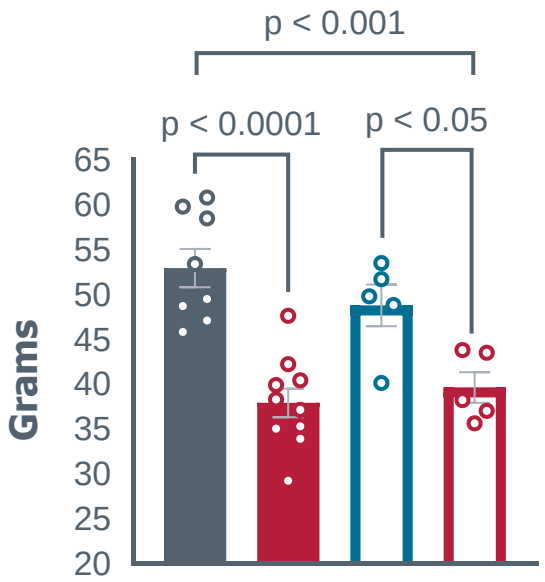
Sema Withdrawal + PGTx-Ex4 (5e12 VG)

Mean ± SEM shown; n=5-10 per group. Fitzpatrick et al. WCIRDC 2023 oral presentation. Abstract no. 0077. BW=body weight, DIO=diet-induced obesity, Ex4=exendin-4, PGTx=pancreatic gene therapy, Sema=semaglutide, VG=vector genomes

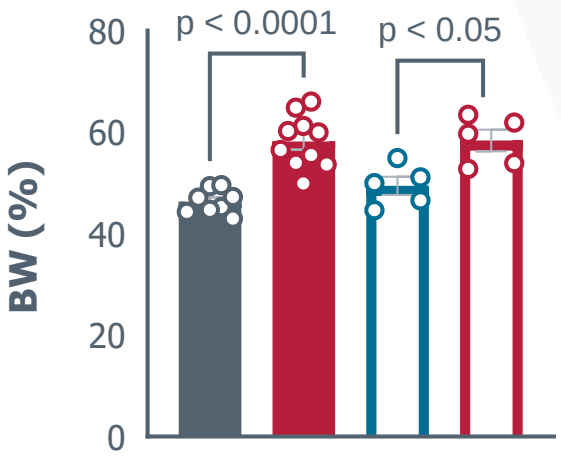
Body Composition Change in DIO Murine Model

Preservation of lean mass: body weight loss primarily from fat mass

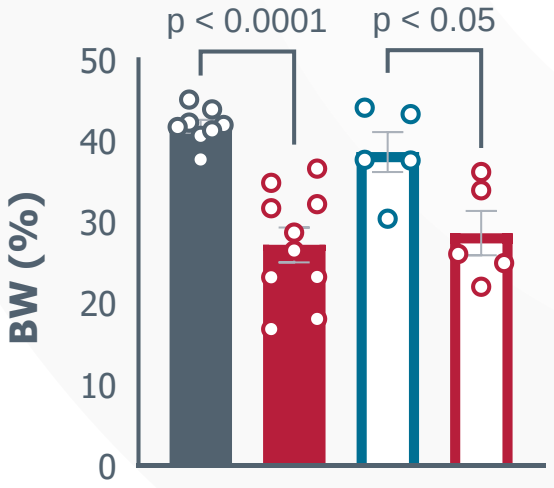
A) Body Weight



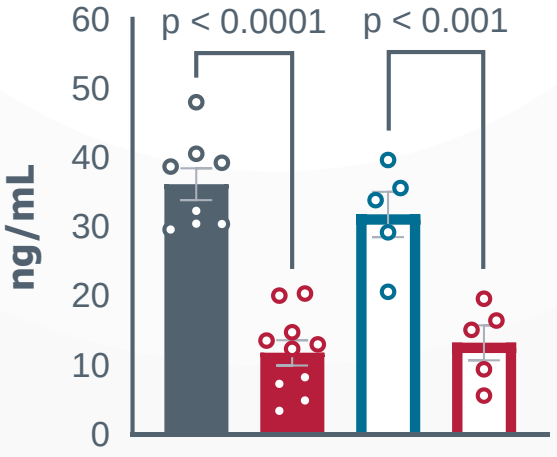
B) Lean Mass



C) Fat Mass



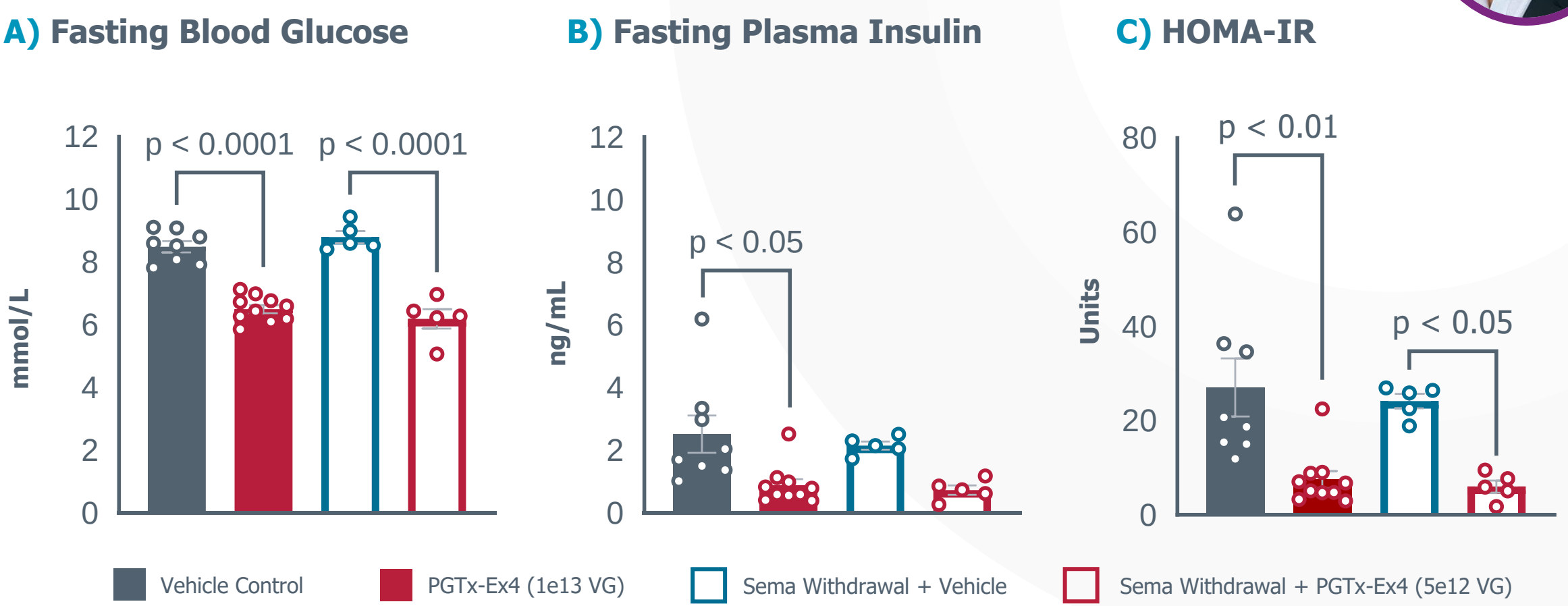
D) Plasma Leptin



Mean ± SEM shown; n=5-10 per group, 8 weeks post-treatment. BW=body weight, DIO=diet-induced obesity, Ex4=exendin-4, PGTx=pancreatic gene therapy, Sema=semaglutide, VG=vector genomes

Fasting Blood Glucose and Insulin Changes in DIO Murine Model

Single-dose GLP-1RA PGTx improves FBG, insulin, HOMA-IR at 8 weeks

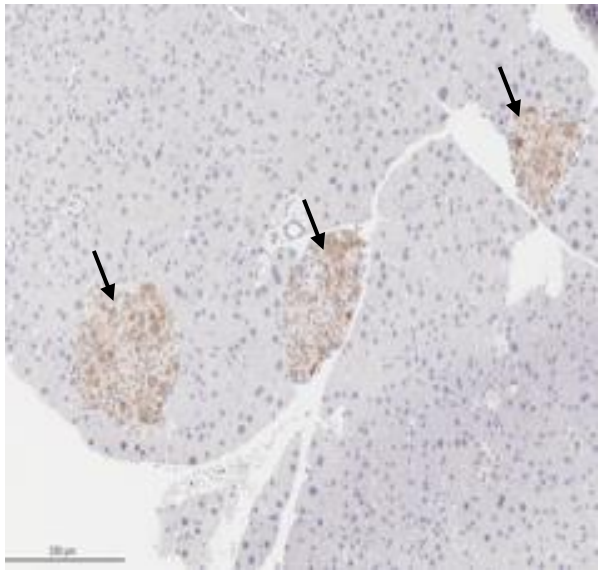


Mean ± SEM shown; n=5-10 per group. DIO=diet-induced obesity, Ex4=exendin-4, FBG=fasting blood glucose, GLP-1RA=glucagon-like peptide 1 receptor agonist, HOMA-IR=homeostatic model assessment of insulin resistance, PGTx=pancreatic gene therapy, Sema=semaglutide, VG=vector genomes

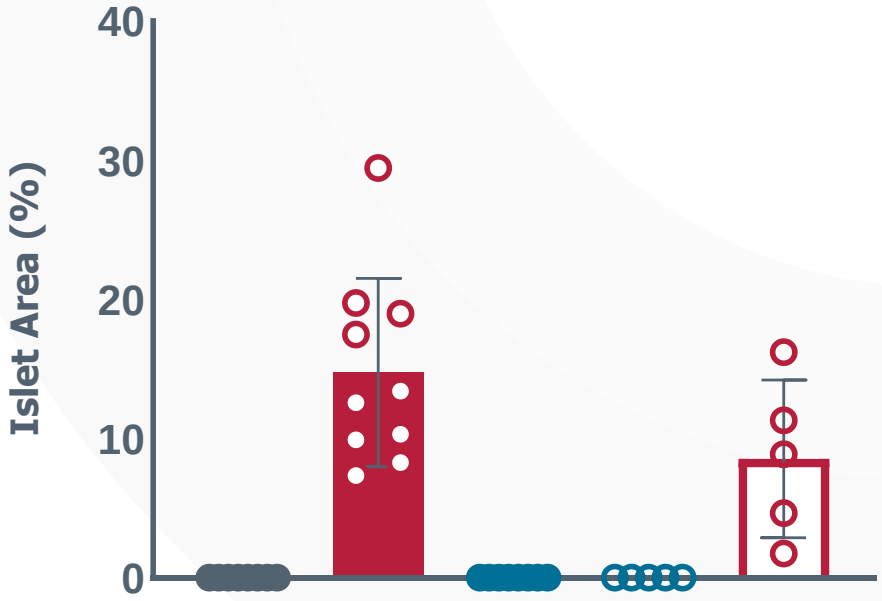
GLP-1RA PGTx Islet Expression in DIO Model

Islet-targeted transduction increases pancreatic expression of GLP-1RA

A) Islet PGTx-Ex4 Transduction



B) Islet Ex4 Expression



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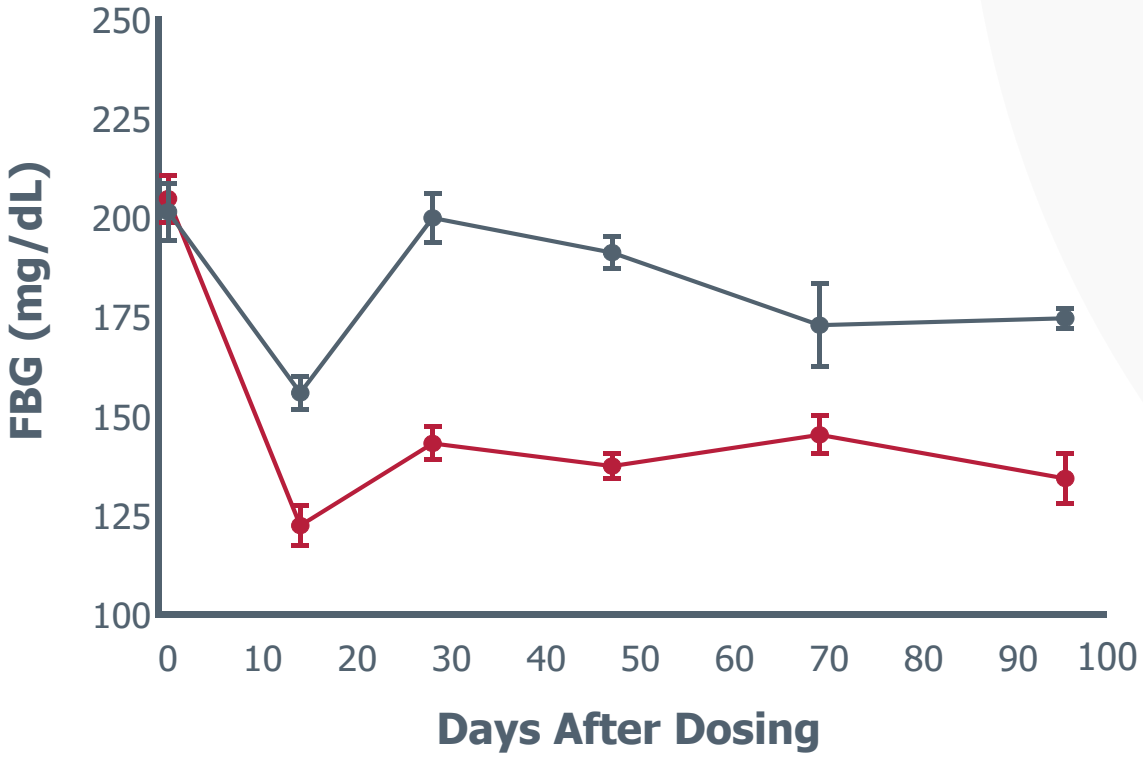
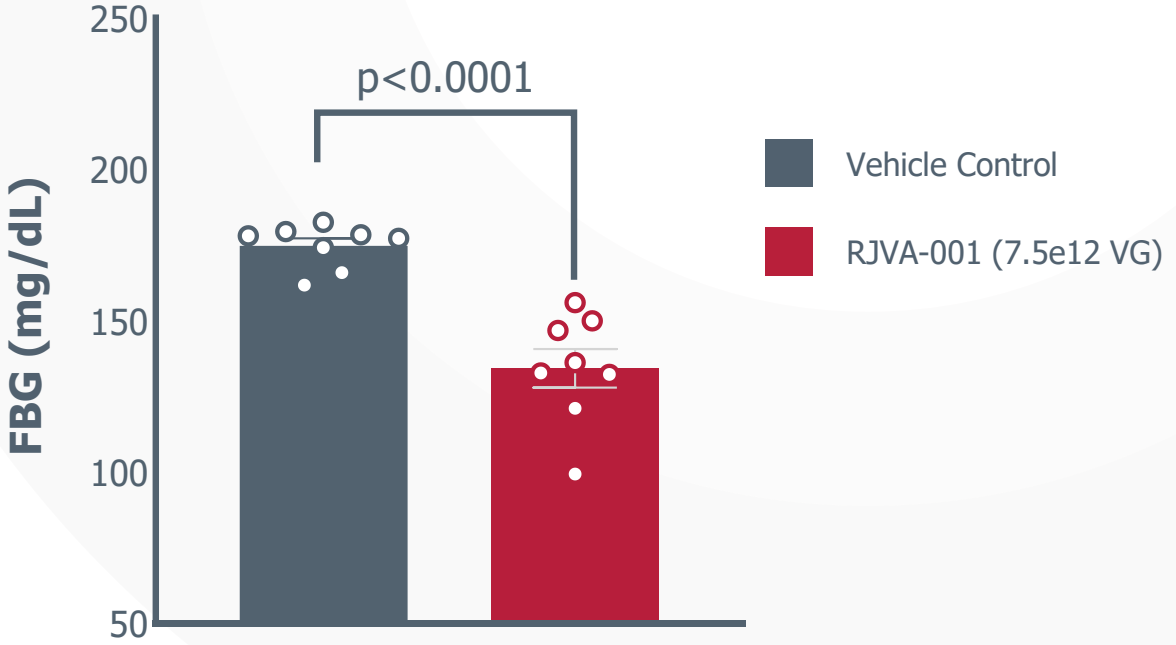
RJVA-001 PGTx Encoding Human GLP-1 Sequence in DIO

Single-dose RJVA-001 durably reduces FBG in mice continued on HFD

A) Change in FBG Over Time



B) FBG (day 95)



Special thanks to Chelsea R Hutch, PhD (R. Seeley Lab) for data generation and analysis.

Mean ± SEM shown; n=8 per group. DIO=diet-induced obesity, FBG=fasting blood glucose, GLP-1=glucagon-like peptide 1, HFD=high fat diet, PGTx=pancreatic gene therapy, VG=vector genomes.

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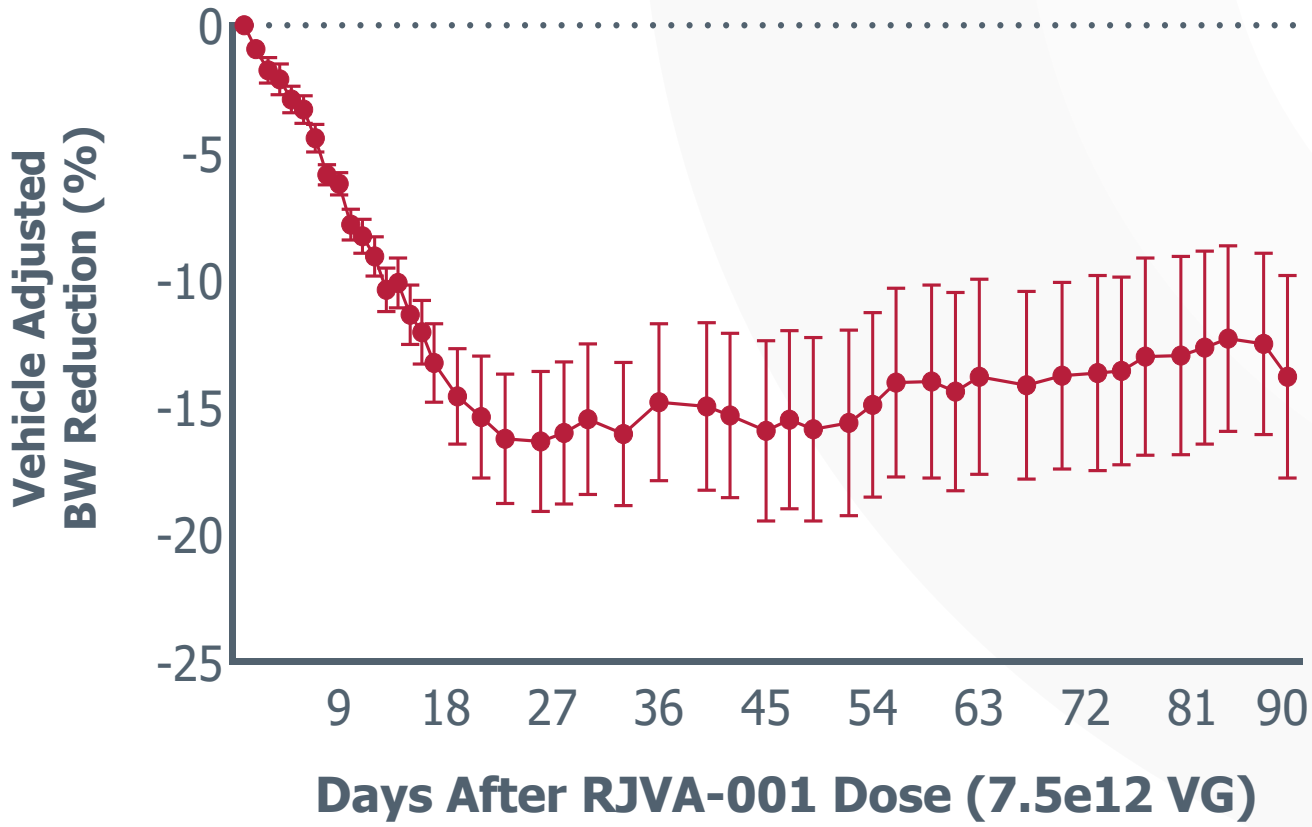
RJVA-001 PGTx Encoding Human GLP-1 Sequence in DIO

Single-dose RJVA-001 durably reduces weight in mice continued on HFD



Special thanks to Chelsea R Hutch, PhD (R. Seeley Lab) for data generation and analysis.

Mean ± SEM shown; n=8 per group. BW=body weight, DIO=diet-induced obesity, GLP-1=glucagon-like peptide 1, HFD=high fat diet, PGTx=pancreatic gene therapy, VG=vector genomes

GLP-1 PGTx Safety and Feasibility Studies in Model Systems

Summary and next steps

Islet-targeted Smart GLP-1™ PGTx in the DIO model:

- Improves **fasting glucose, insulin**, and **HOMA-IR**
- Leads to **durable weight loss** and **weight** and **body composition maintenance** after semaglutide withdrawal

Safety and feasibility observations in pigs and mice have led to **RJVA-001 (PGTx encoding human GLP-1) candidate nomination** and IND-enabling studies

RJVA-002 (Smart GIP/GLP-1™ dual agonist) now nominated for obesity

DIO=diet-induced obesity, GIP=gastric inhibitory polypeptide, GLP-1=glucagon-like peptide 1, HOMA-IR=homeostatic model assessment of insulin resistance, IND=investigational new drug, PGTx=pancreatic gene therapy

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JungHun Lee, PhD
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Suya Wang, PhD
Scientist II

Keiko Ishida, BS
Sr. Assoc. Scientist

Abdul Alhamood, MS
Sr. Assoc. Scientist

ex vivo and animal studies

Alice Fitzpatrick, DVM, PhD
Director

Camila Lubaczeuski, PhD
Scientist II

Joan Sabadell-Basallote, PhD
Scientist I

Rebecca Reese, Assoc.
Scientist I

Lindsay Schulman, MS
Sr. Assoc. Scientist

Nicole Picard, BS
Assoc. Scientist II

Device Engineering

Mike Biasella, BS
Sr. Engineer Manager

Jake Wainer, BS
Sr. Biomedical Engineer

Tech Ops and Research Ops

Eric Horowitz, PhD
Exec. Director, Head of Tech Ops

Bill Monahan, BS
Assoc. Director

Project Management

Madison Hubbard, BS
Project Manager

Advisors

Alan Cherrington, PhD
Vanderbilt University School of Medicine

Geltrude Mingrone, MD, PhD
King's College, London; Catholic University of Rome

Randy Seeley, PhD
Michigan School of Medicine

Dave D'Alessio, MD
Duke University School of Medicine

Jon Campbell, PhD
Duke University School of Medicine

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