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Pancreatic Gene Therapy Durably Improves Glycaemia and Delays Disease Progression in a Murine Model of Type 2 Diabetes

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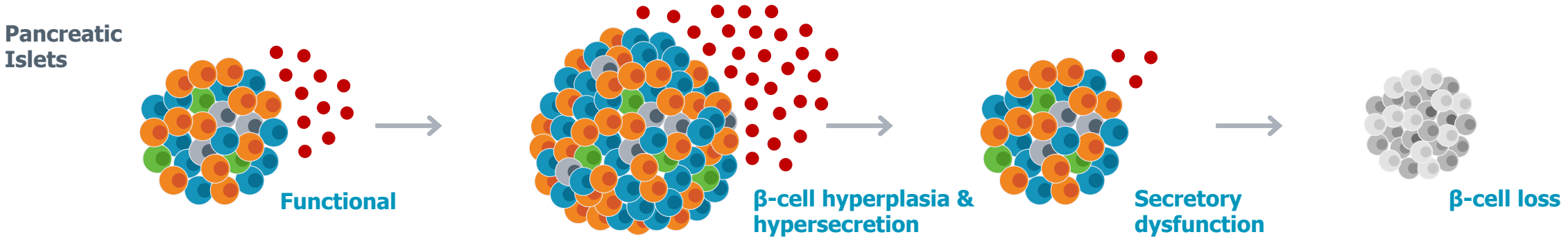
Disclosure Statement

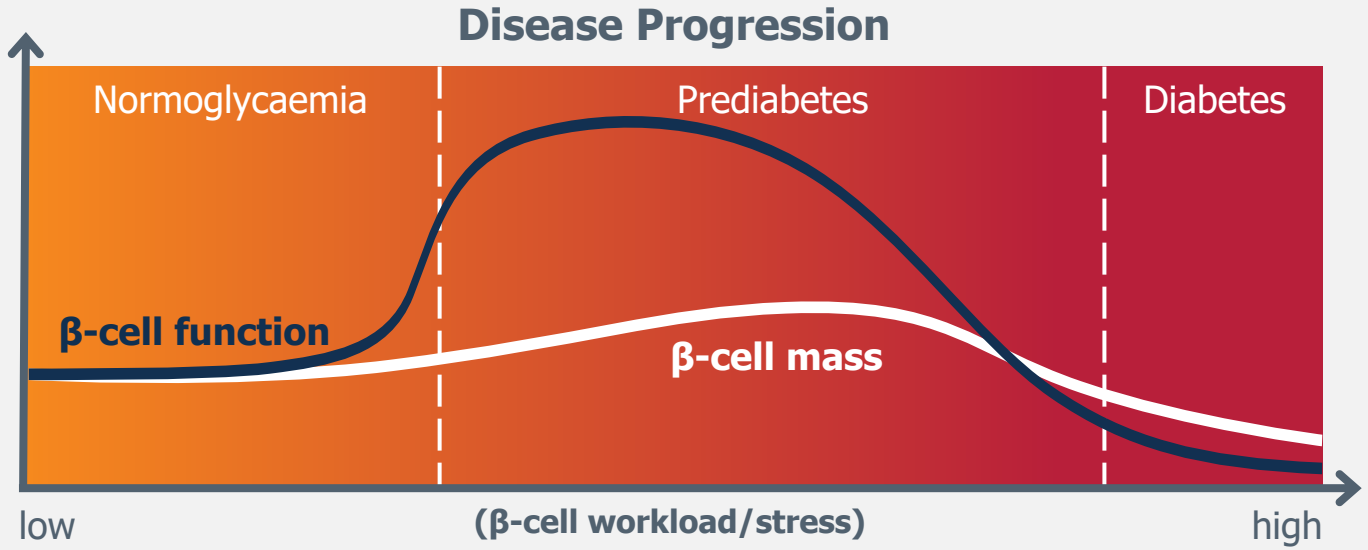
Authors
Harith Rajagopalan, Camila Lubaczeuski, Emily Cozzi, Nicole Picard, Jacob Wainer, Rebecca Reese, Jay Caplan, Alice Liou are employees and shareholders of Fractyl Health, Inc.

Pancreatic Gene Therapy (PGTx) is a preclinical development program which has yet to be assessed by regulatory bodies for investigational or commercial use.

T2D Progression is Driven by Declining Islet Health

Loss of β-cell function is the sine qua non of T2D





Figures adapted from: 1. Chen et al. Mol Metab. 2017 6:943-957. 2. Biondi et al. Int J Mol Sci. 2022 23:5522

Pancreatic Gene Therapy (PGTx) to Improve Islet Function

Potential for durable improvement in β-cell function

Islet cells terminally differentiated, making adeno-associated virus (AAV) a suitable means of durable genetic modification[1,2]

Intra-islet GLP1 signaling can improve β-cell function, health, and survival[3,4]

GLP1-based pancreatic gene therapy (GLP1 PGTx driven by the insulin promoter) may restore islet health in T2D via durable local production of GLP1RA

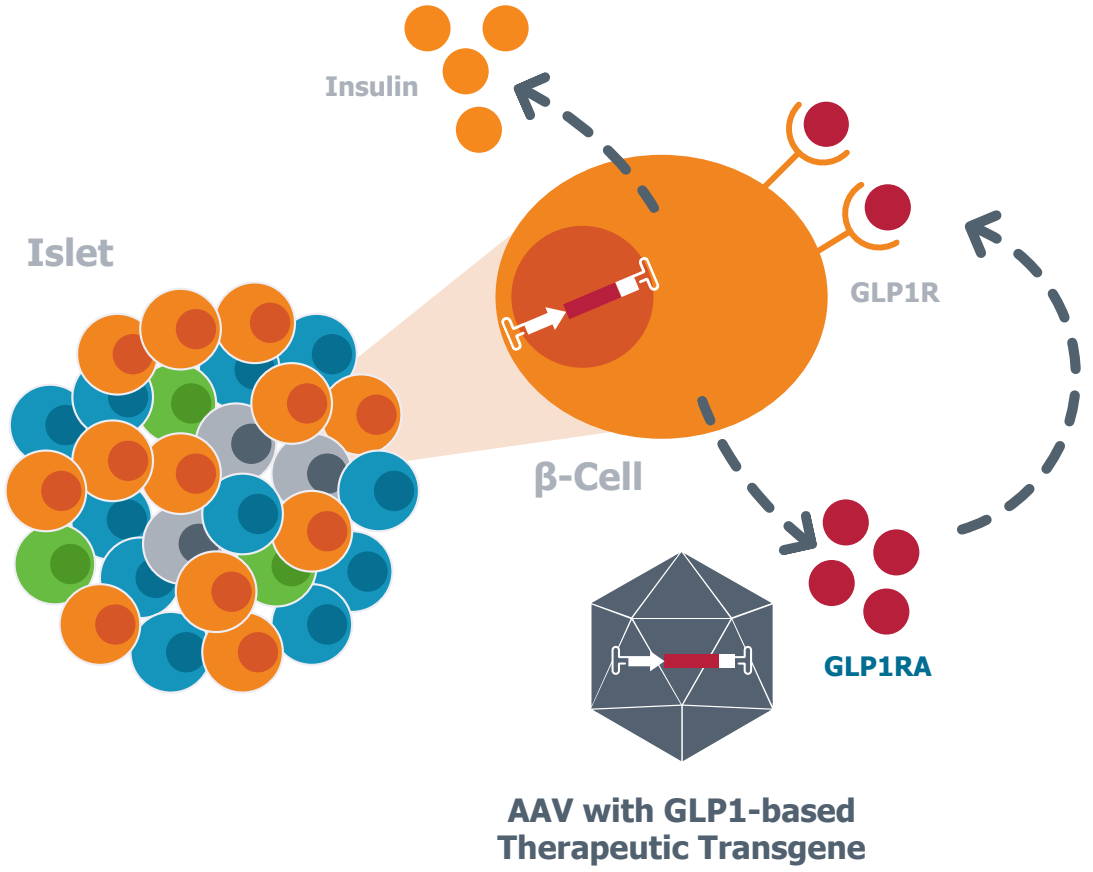
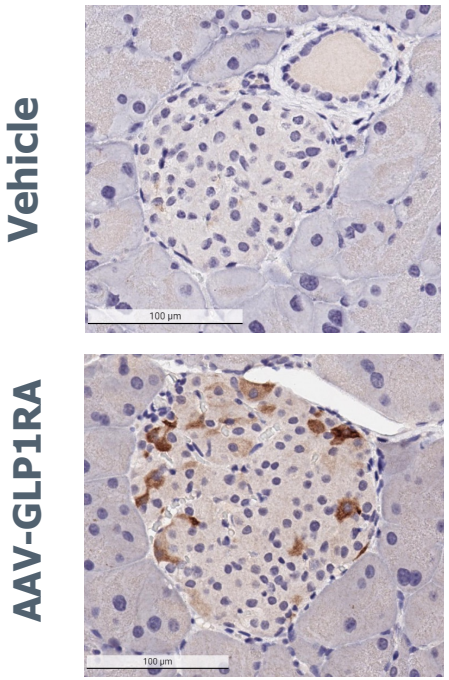


Figure adapted from Saikia et al. JCI Insight. 2021 6:e1418511. 1. Ju et al. Diabetologia. 1998 41:736-739. 2. Kapturczak et al. Mol Ther. 2002 5:154-160. 3. Campbell and Drucker. Cell Metab. 2013 17:819-837. 4. Fava et al. J Diabetes Complications. 2016 30:1651–1658. AAV=adeno-associated virus, GLP1=glucagon-like peptide 1, GLP1R=GLP1 receptor, GLP1RA=GLP1R agonist, PGTx=pancreatic gene therapy

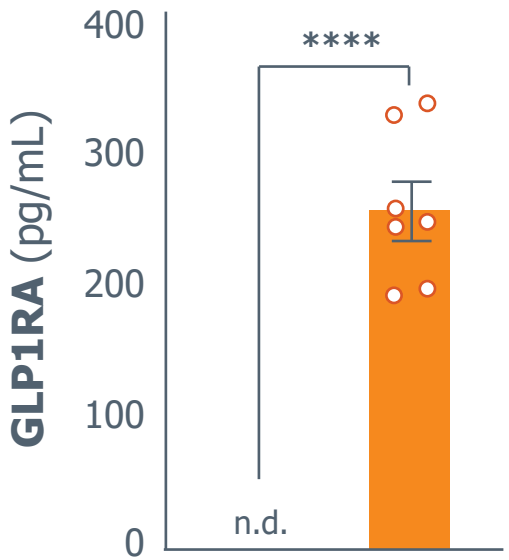
GLP1 PGTx Improves Insulin Production and GSIS in *db/db* Islets

Metabolic improvements in isolated islets 10 weeks after PGTx

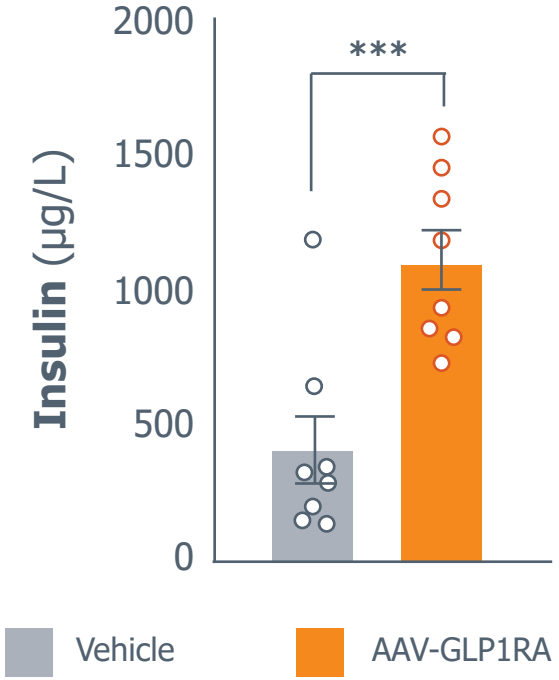
A) Islet Transduction



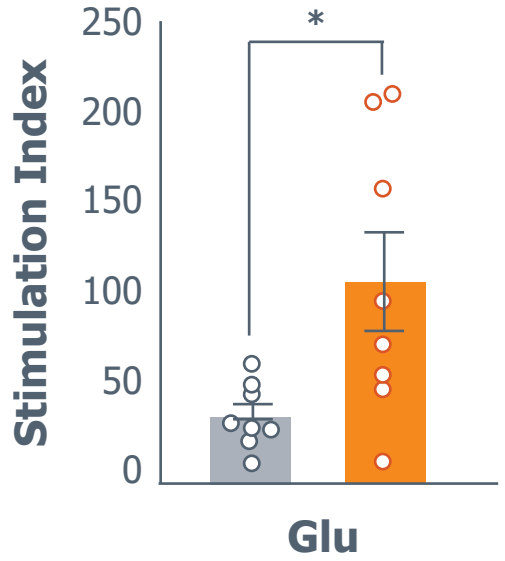
B) GLP1RA Protein Content



C) Insulin Content



D) Glucose-Stimulated Insulin Secretion (GSIS)



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

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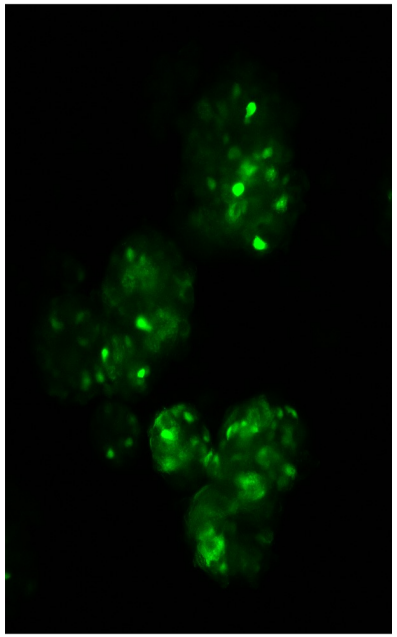
59th Annual Meeting

Mean ± SD shown; *p<0.05, ***p<0.001, ****p<0.0001; n=8 per group. D) Glucose stimulation of 16.7 mM +/- IBMX from 2.8 mM baseline. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191. AAV=adeno-associated virus, GLP1=glucagon-like peptide 1, GLP1RA=GLP1 receptor agonist, Glu=glucose, GSIS=glucose-stimulated insulin secretion, n.d.=not detectable, PGTx=pancreatic gene therapy

GLP1 PGTx Improves GSIS in Human Islets and Human β-cell Line

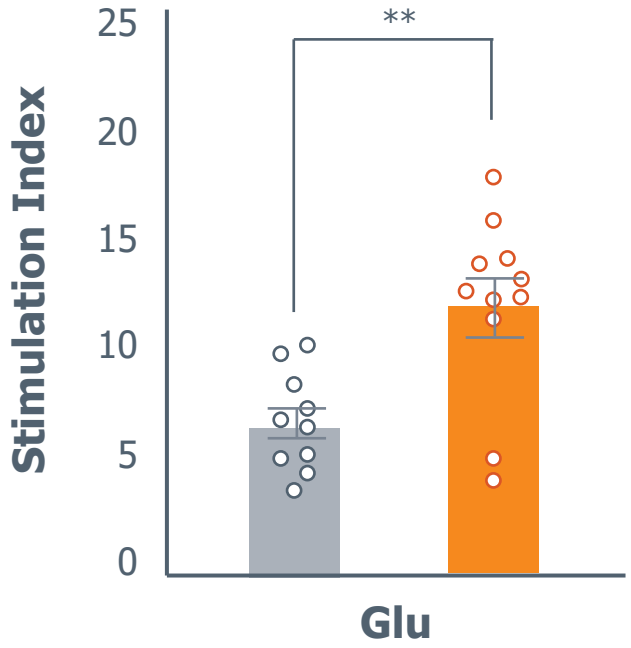
Improved GSIS mediated by GLP1R activation in human cells

A) Human Islet Transduction

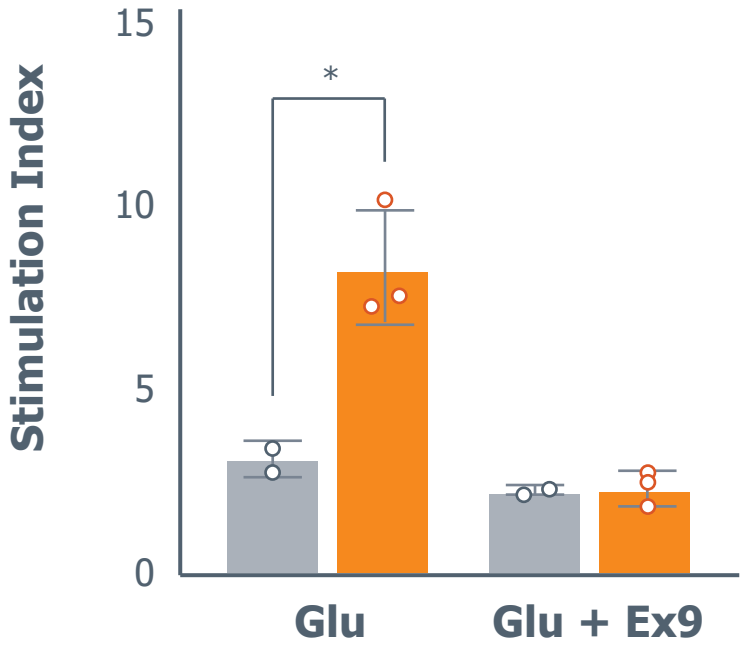


GFP Expression

B) Human Islet GSIS



C) Human β-cell Line GSIS ± Ex9 (GLP1R Antagonist)



Mean ± SEM shown; *p<0.05, **p<0.01; 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. ASGCT 2023 oral presentation. Abstract no. 191.. AAV=adeno-associated virus, Ex9=Exendin-9, GFP=green fluorescent protein, GLP1=glucagon-like peptide 1, GLP1R=GLP1 receptor, GLP1RA=GLP1R agonist, Glu=glucose, GSIS=glucose-stimulated insulin secretion, PGTx=pancreatic gene therapy

Local Delivery of PGTx

Proprietary endoscopic ultrasound-guided infusion device

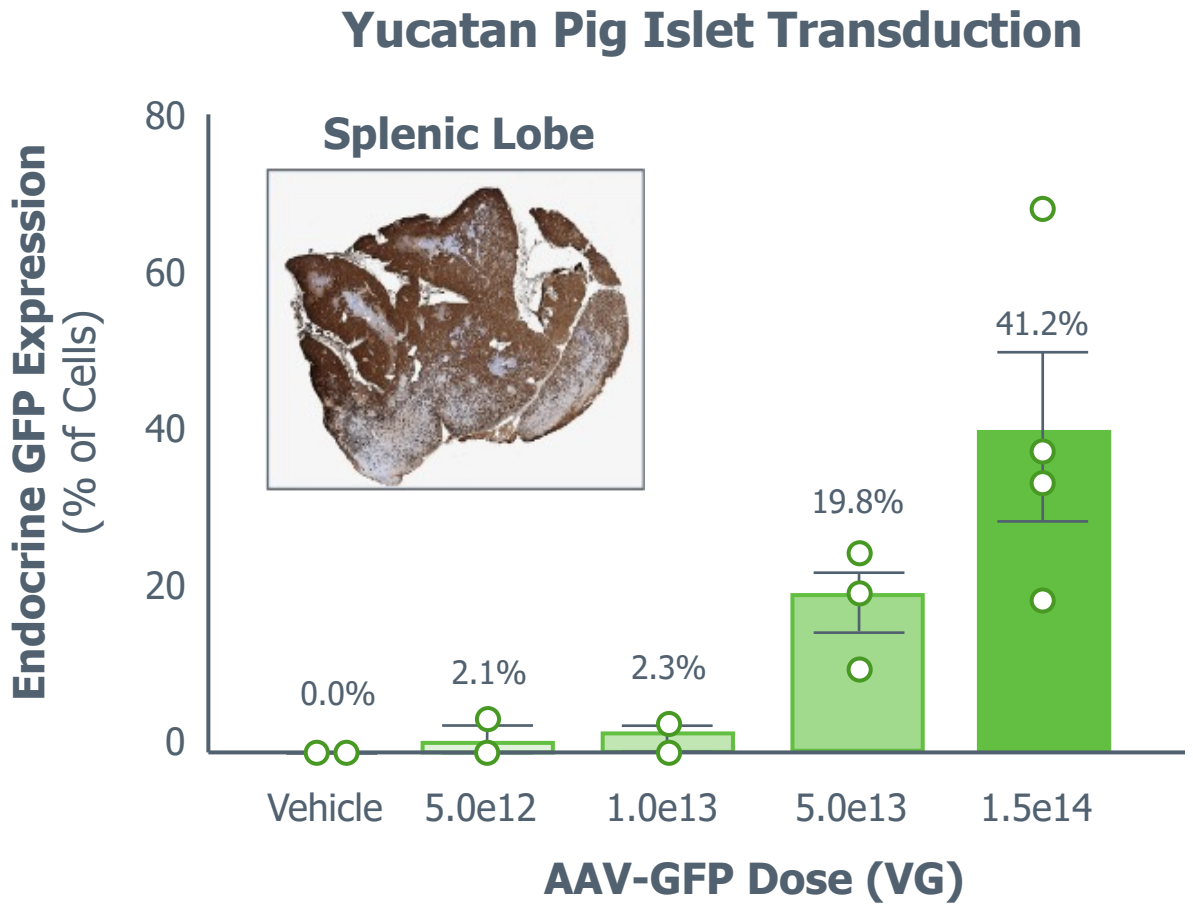
Yucatan pig-model anatomy similar to humans

Proprietary device and endoscopic procedure previously described[1,2]

>50 animals treated with 100% technical success; no adverse safety signals to date

Dose-dependent AAV-GFP expression in targeted pancreatic lobe[1,2]

Low viral genome dose with limited systemic virus exposure – due to local delivery[2]



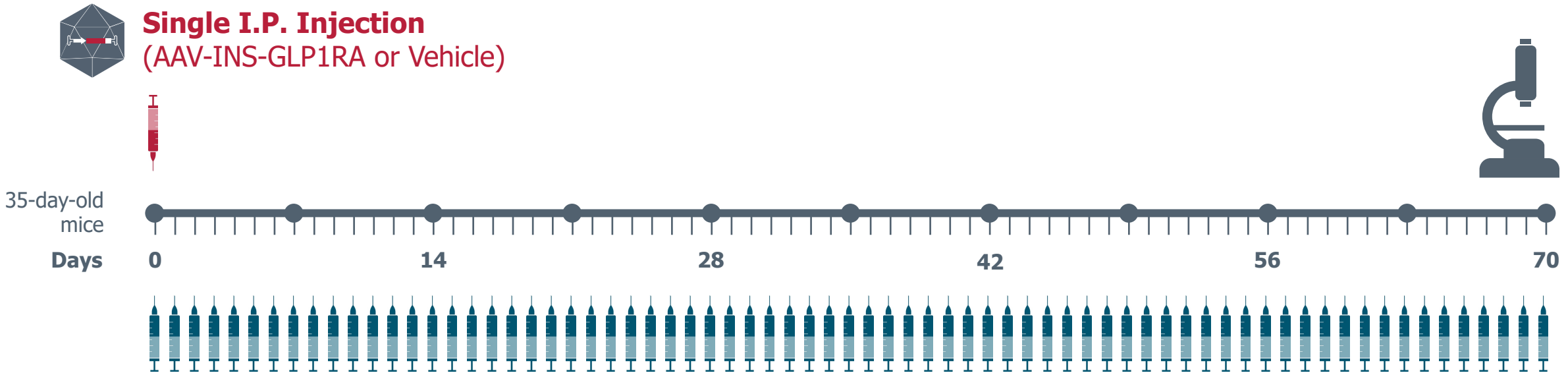
Mean ± SD shown; n=2-4 per group. 1. Thompson et al. DDW 2023 poster presentation. Control no. 3862948. 2. Rajagopalan et al. ASGCT 2023 oral presentation. Abstract no. 191. AAV=adeno-associated virus, GFP=green fluorescent protein, PGTx=pancreatic gene therapy, VG=vector genomes

Compared to Chronic Semaglutide, Can One-Time GLP1 PGTx:

Improve Glycaemia
Delay T2D Progression
and Prevent Weight Gain?

GLP1 PGTx Efficacy Proof of Concept

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



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

*Semaglutide dose selected for glucose-lowering optimization[1]

Efficacy/MOA (day 0-70)
Weekly Fasting Blood Glucose
Biweekly Insulin
Weight

Sacrifice (days 58-70)
Organ Histology
Pancreatic GLP1RA Protein
Serum GLP1RA Protein

1. CDER (2017) Semaglutide NDA Application (209637Orig1s000), Section 4.4 Nonclinical Pharmacology/Toxicology. AAV=adeno-associated virus, GLP1=glucagon-like peptide 1, GLP1RA= GLP1 receptor agonist, INS=insulin promoter, I.P.=intraperitoneal, MOA=mechanism of action, PGTx=pancreatic gene therapy, S.C.=subcutaneous

GLP1 PGTx Expression Restricted to Pancreatic Islets

Safety and feasibility in *db/db* murine model are reassuring thus far

High specificity for pancreas

Insulin promoter effectively restricts transgene expression to pancreatic islets

No detectable expression in off-target tissues (e.g., exocrine pancreas)

Favorable toxicity profile

No abnormal findings in animal behaviour or clinical chemistries thus far

Histopathologic analysis showed no evidence of pancreatitis or pancreatic cancer

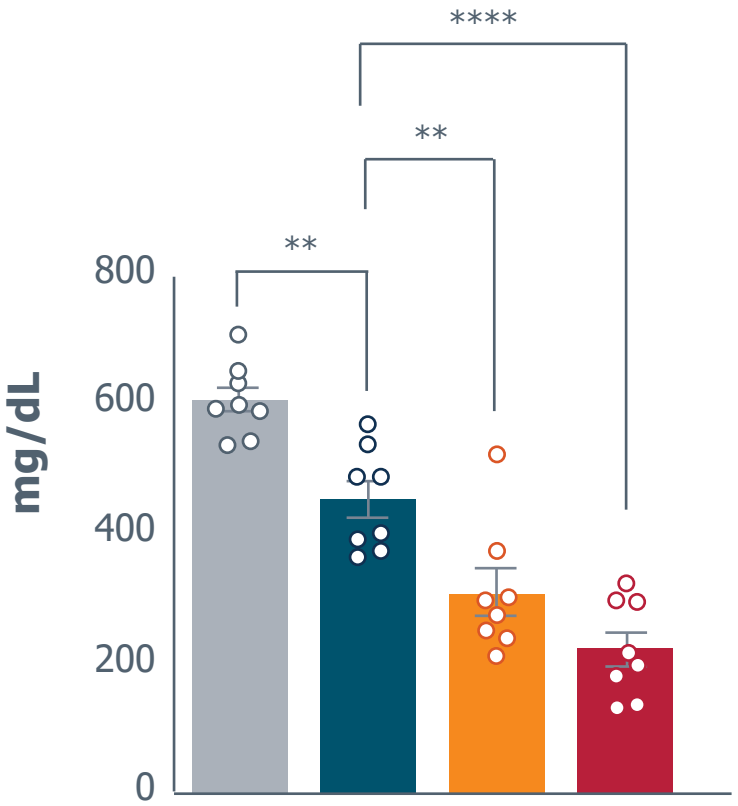
GLP1=glucagon-like peptide 1, PGTx=pancreatic gene therapy

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

GLP1 PGTx improves fasting glucose vs. daily semaglutide

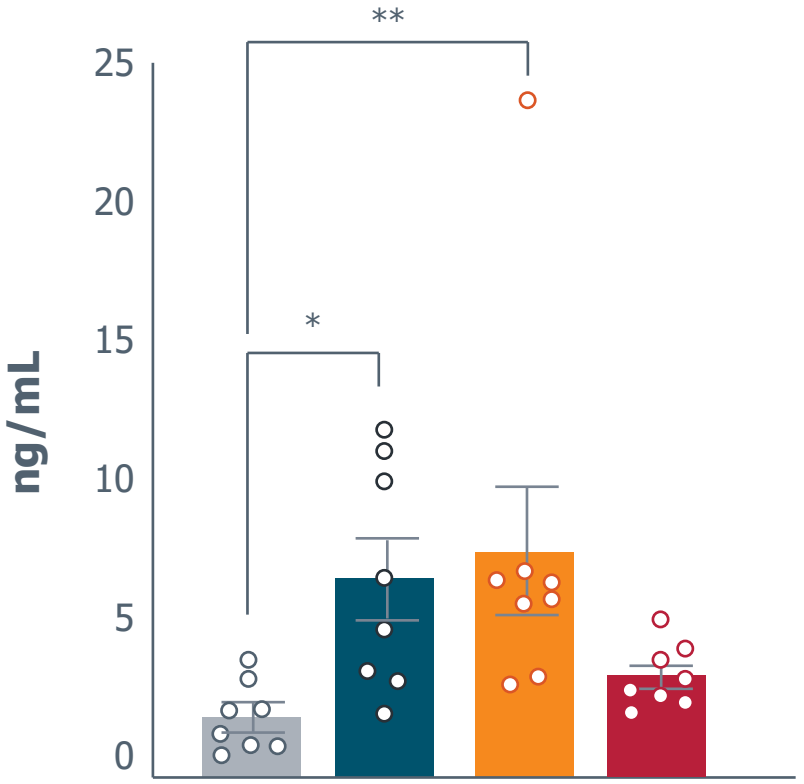
A) Fasting Blood Glucose

(Week 8, 4-6 hours fasted)



B) Fasting Insulin

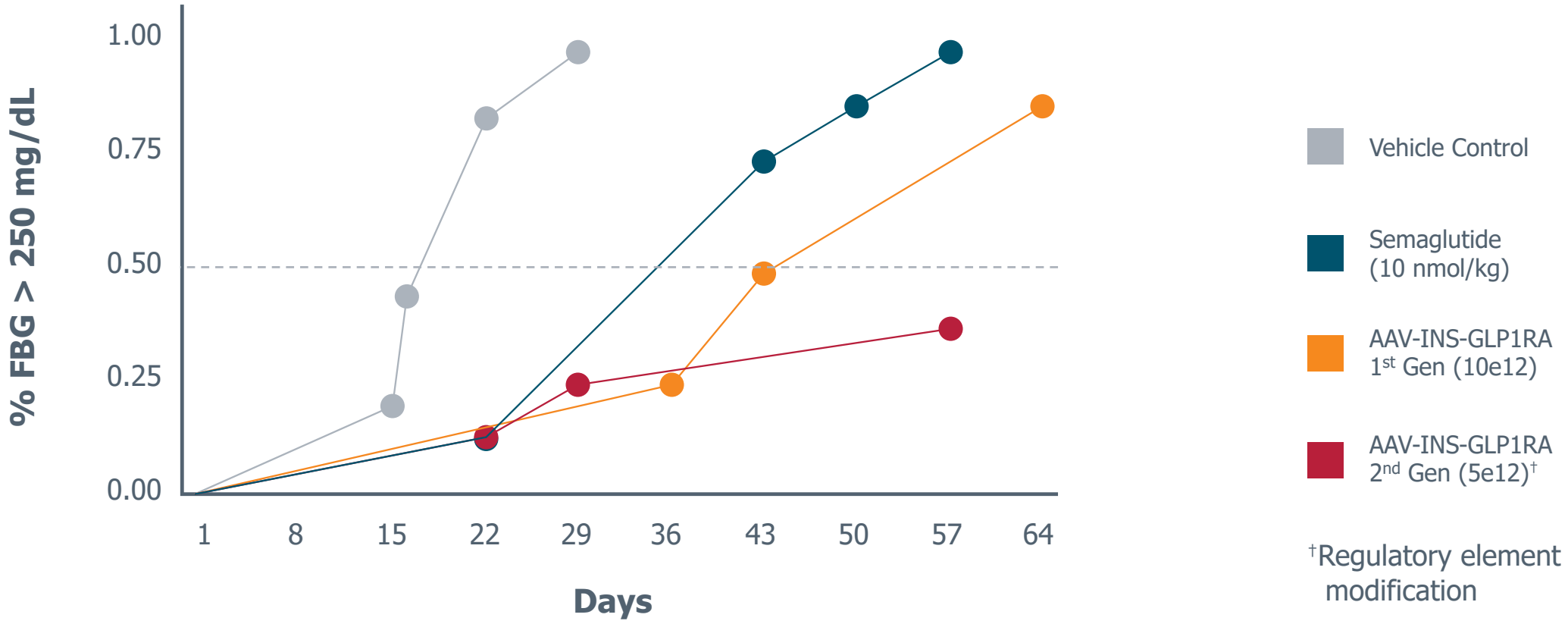
(Week 8, 4-6 hours fasted)



Mean ± SEM shown; *p<0.05, **p<0.01, ****p<0.0001; n=8 per group. AAV=adeno-associated virus, Gen=generation, GLP1=glucagon-like peptide 1, GLP1RA=GLP1 receptor agonist, INS=insulin promoter, PGTx=pancreatic gene therapy

Disease Progression and Durability in *db/db* Murine Model

GLP1 PGTx shifts progression of disease vs. daily semaglutide



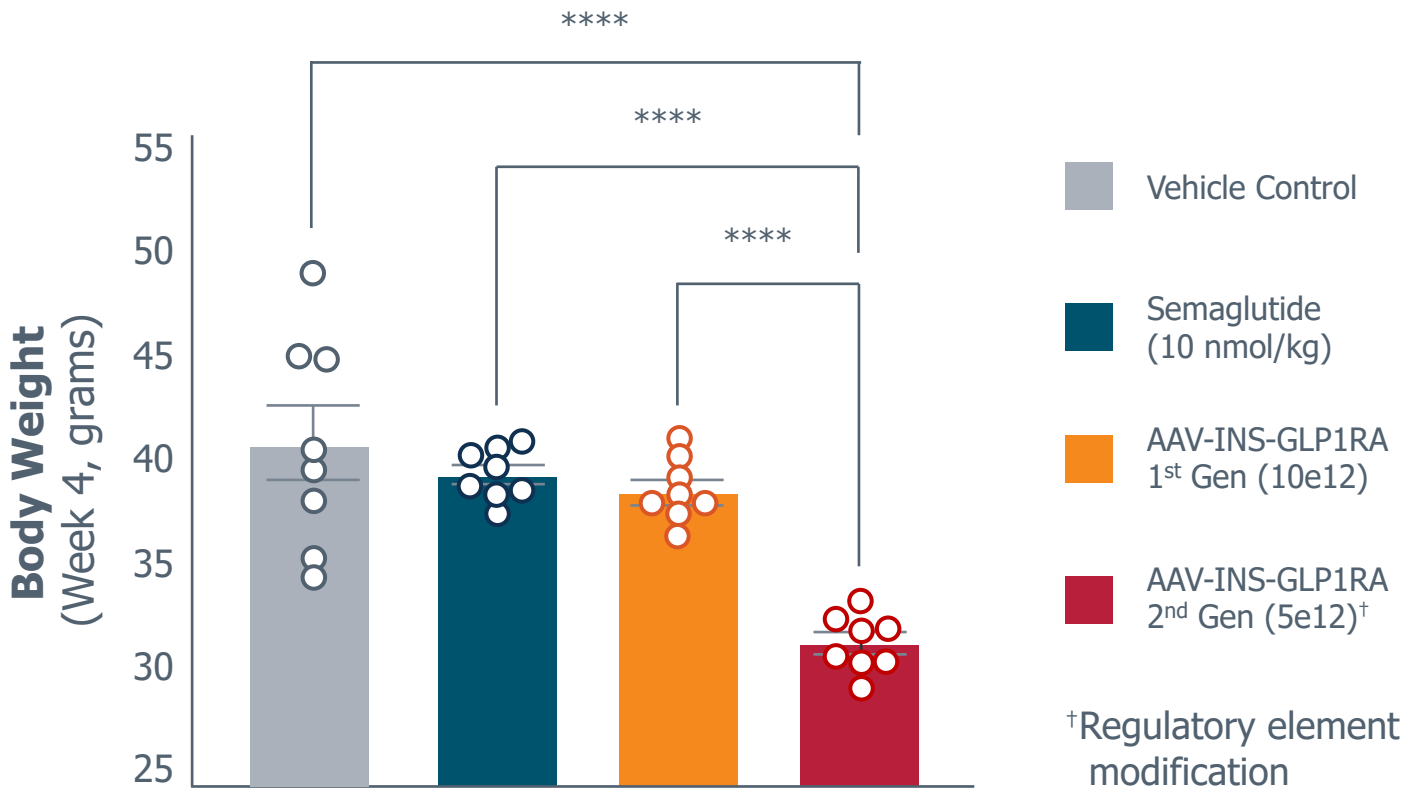
AAV=adeno-associated virus, FBG=fasting blood glucose, Gen=generation, GLP1=glucagon-like peptide 1, GLP1RA=GLP1 receptor agonist, INS=insulin promoter, PGTx=pancreatic gene therapy

Body Weight Change in *db/db* Murine Model

GLP1 PGTx prevents weight gain vs. daily semaglutide

23% lower total body weight with PGTx compared to vehicle

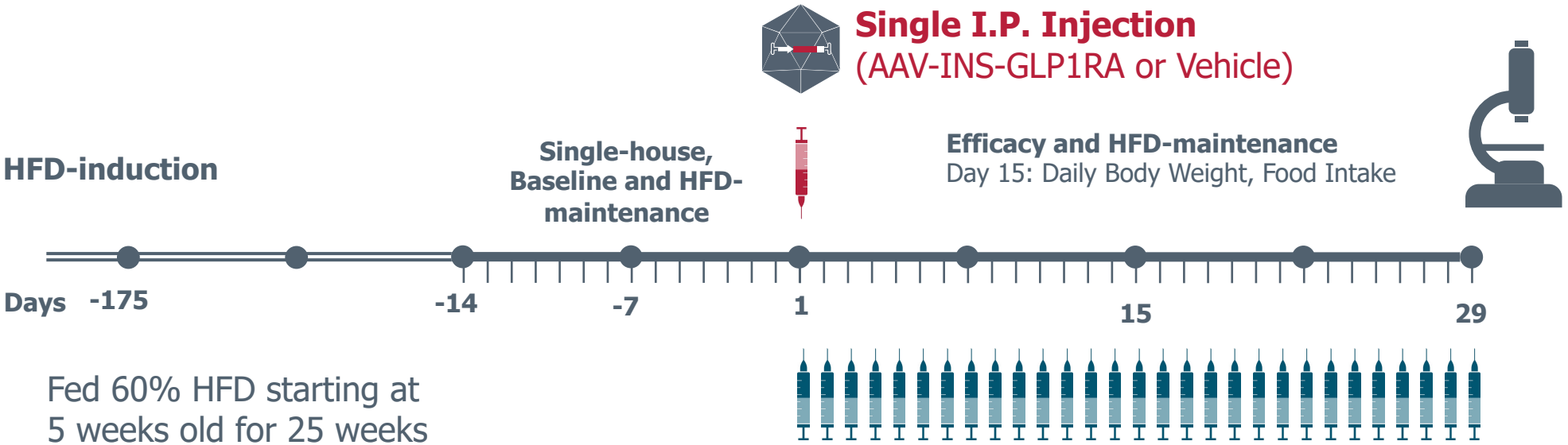
20% lower total body weight with PGTx compared to semaglutide



Mean ± SEM shown; ****p<0.0001; n=8 per group. AAV=adeno-associated virus, Gen=generation, GLP1= glucagon-like peptide 1, GLP1RA=GLP1 receptor agonist, INS=insulin promoter, PGTx=pancreatic gene therapy

GLP1 PGTx Efficacy Proof of Concept

DIO murine model de facto standard for obesity development



Fed 60% HFD starting at 5 weeks old for 25 weeks

Aim 50-gram BW start

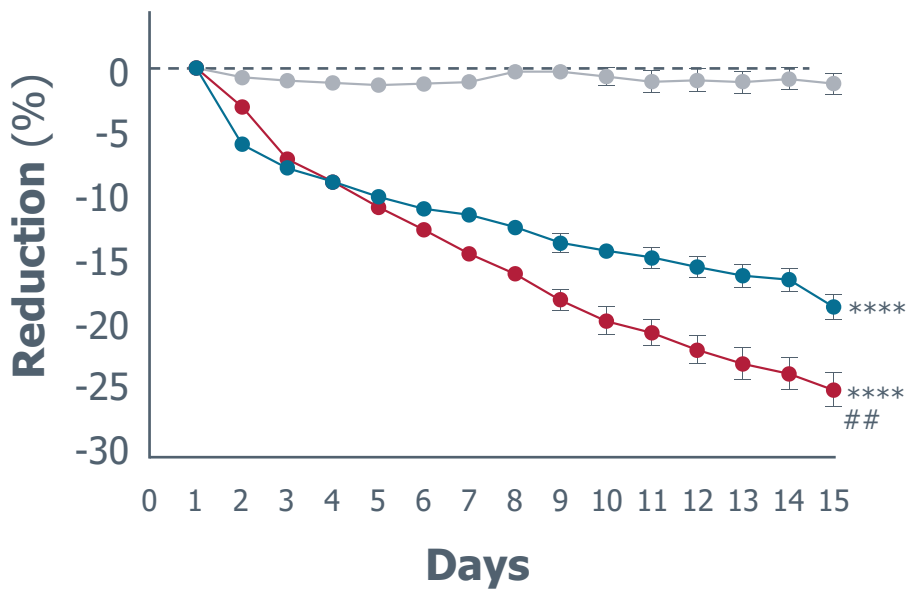
Daily S.C. Injections
Semaglutide (10 nmol/kg*) or Vehicle

*Semaglutide dose targeting 15-20% BWL

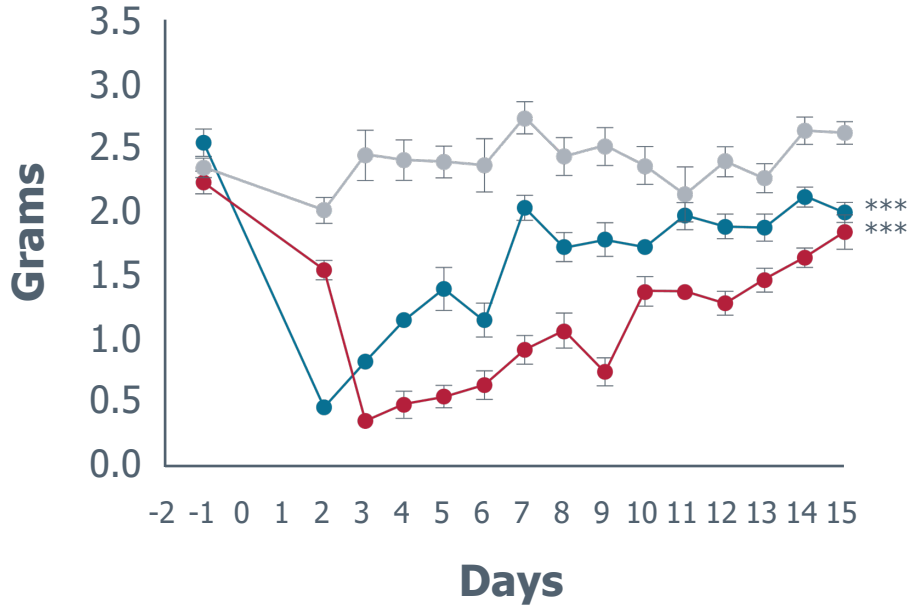
AAV=adeno-associated virus, BW=body weight, BWL=body weight loss, DIO=diet-induced obesity, GLP1=glucagon-like peptide 1, GLP1RA= GLP1 receptor agonist, HFD=high fat diet, INS=insulin promoter, I.P.=intraperitoneal, PGTx=pancreatic gene therapy, S.C.=subcutaneous

Body Weight Change
GLP1 PGTx improves weight loss vs. semaglutide in DIO model

A) Body Weight



B) Food Intake



Vehicle Control

Semaglutide (10 nmol/kg)

AAV-INS-GLP1RA 2nd Gen (1e13)†

†Regulatory element modification

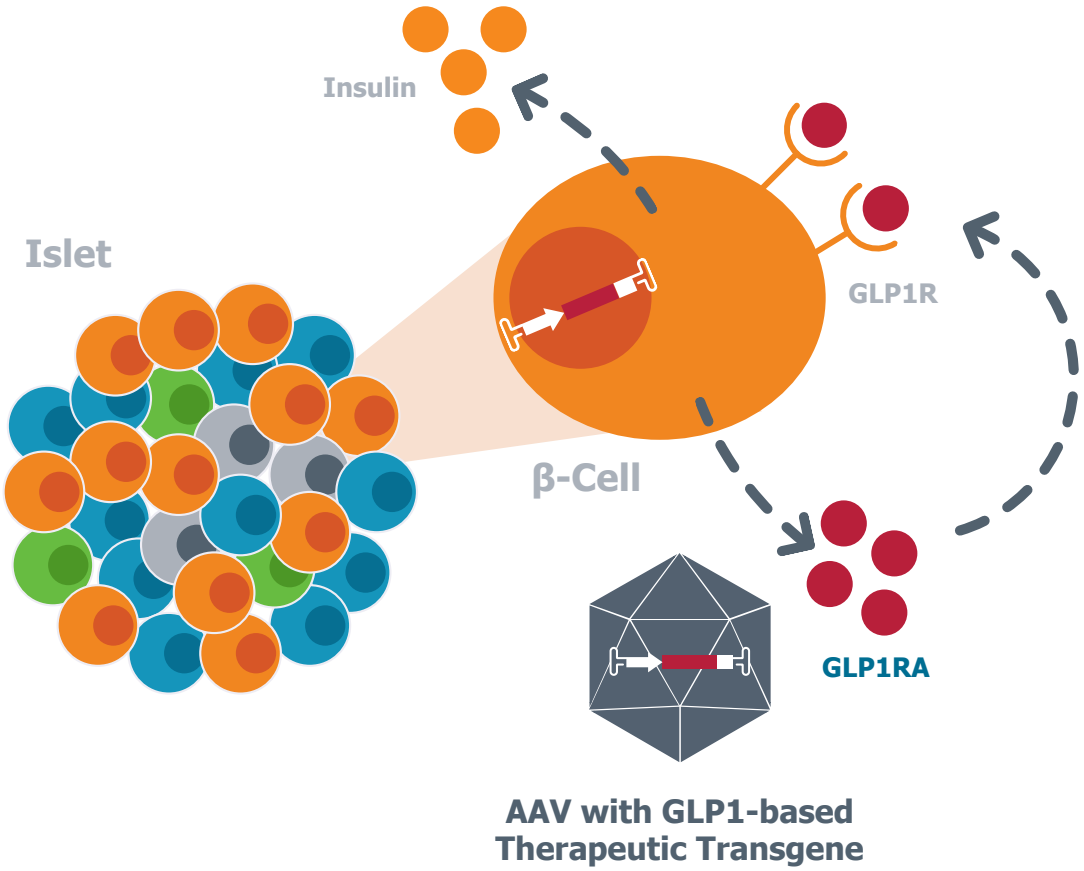
Mean ± SEM shown;***p<0.001, ****<0.0001 treatments vs. vehicle, ##p<0.01 AAV-INS-GLP1RA 2nd Gen vs. semaglutide; n=8-10 per group. AAV=adeno-associated virus, DIO=diet-induced obesity, Gen=generation, GLP1= glucagon-like peptide 1, GLP1RA=GLP1 receptor agonist, INS=insulin promoter, PGTx=pancreatic gene therapy

GLP1 PGTx Safety and Pharmacology Studies in Model Systems

Early feasibility and safety observations in *db/db* mice and Yucatan pigs are encouraging

Compared to chronic semaglutide, single-dose PGTx improves fasting glucose, delays T2D progression, and prevents weight gain in *db/db* model of T2D

PGTx lead optimization demonstrates potential for even greater efficacy in T2D and obesity with low pancreatic dose (ongoing studies in DIO model)



AAV=adeno-associated virus, DIO=diet-induced obesity, GLP1=glucagon-like peptide 1, GLP1R=GLP1 receptor, GLP1RA= GLP1R agonist, PGTx=pancreatic gene therapy

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