

PANCREAS-TARGETED DUAL GIP/GLP-1 GENE THERAPY REDUCES BODY WEIGHT AND HEPATIC STEATOSIS IN A MURINE MODEL OF DIET-INDUCED OBESITY

Alice Liou Fitzpatrick, Lin Quek, Junghun Lee, Jessie Von Stetina, Suya Wang, Lindsay Schulman, Nicole Picard, Abdul Alhamood, Zakir Siddiquee, Keiko Ishida, Rebecca Reese, Camila Lubaczeuski, Joan Sabadell-Basallote, Doug Garrity, Jacob Wainer, Michael Biasella, William Monahan, Eric Horowitz, Emily Cozzi, Shimyn Slomovic, Jay Caplan, Harith Rajagopalan

Fractyl Health, Inc.



DDW2026
Digestive Disease Week®

MAY 2-5, 2026 | CHICAGO, IL
EXHIBIT DATES: MAY 3-5, 2026

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SPEAKER DISCLOSURE

Alice Liou Fitzpatrick

I disclose the following financial relationship(s) with a commercial interest:

I am an employee and shareholder of Fractyl Health, Inc.

Rejuva is an investigational gene therapy program in preclinical development. RJVA-001 is the subject of planned first-in-human clinical studies, pending regulatory and ethics approvals in the Netherlands and Australia. RJVA-002 remains in preclinical development and has not been submitted to any regulatory authority.

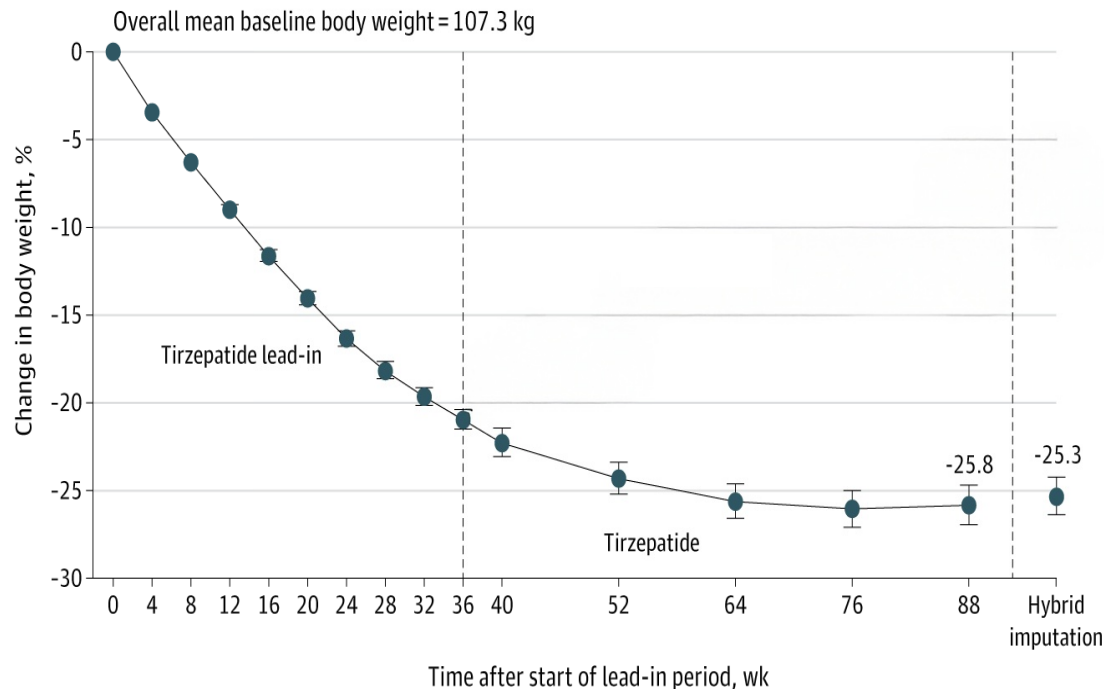
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GLP-1 and Dual Incretin Agonists Induce Substantial Weight Loss and Metabolic Benefit

Chronic Administration Required

Percent change in body weight (week 0-88)¹



- GLP-1RAs have transformed management of obesity and type 2 diabetes resulting in:
 - Significant weight loss³
 - Reduction in HbA1c²
 - Reduced liver fat⁴
 - Other emerging cardiovascular metabolic benefits⁵

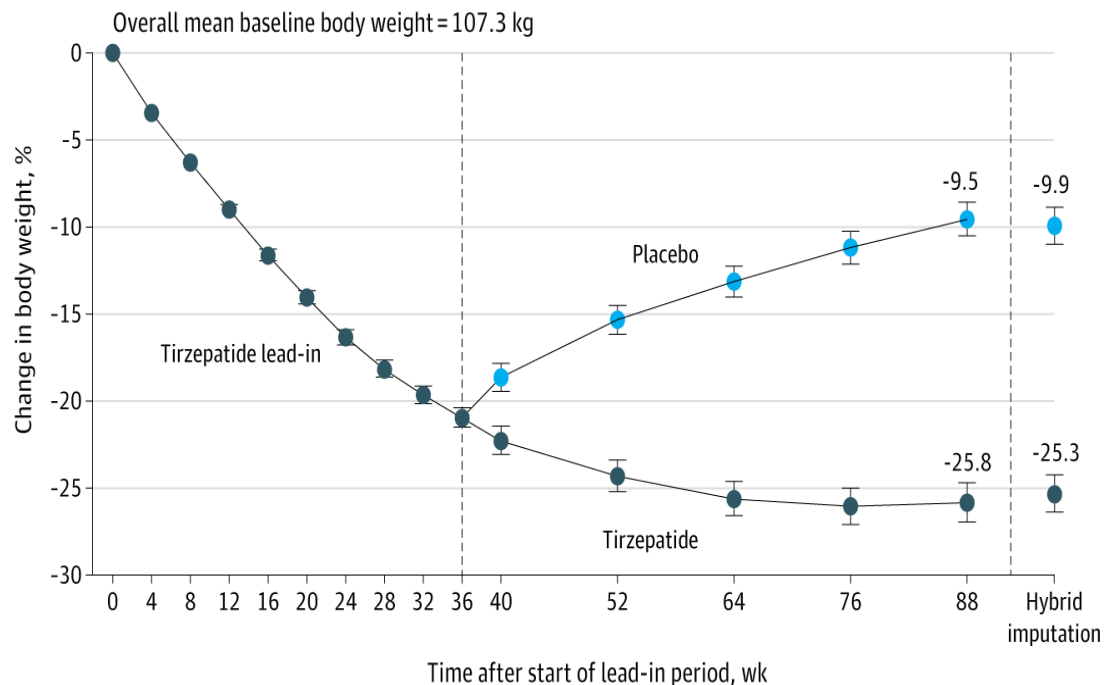
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1. Aronne et al. *JAMA*. Dec 11;331(1):38-48 (2024); 2. Osumili et al. *Diabetes Therapy* 11:16(6): 1279-1311 (2025); 3. Veljii-Ibrahim et al. *J. Obesity*. <https://doi.org/10.1155/job/3897161> (2025) 4. Gastaldelli et al. *Lancet Diabetes & Endocrinology*.10(6):393-406 (2022). 5. Kong et al. *Nature Comm*. 17, 972 (2026). GLP-1=glucagon-like peptide-1, GLP-1RA = glucagon-like-peptide-1 receptor agonist

GLP-1 and Dual Incretin Agonists Induce Substantial Weight Loss and Metabolic Benefit

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- GLP-1RAs have transformed management of obesity and type 2 diabetes resulting in:
 - Significant weight loss³
 - Reduction in HbA1c²
 - Reduced liver fat⁴
 - Other emerging cardiovascular metabolic benefits⁵
- Discontinuation of GLP-1-based therapy leads to weight regain.¹
- Chronic administration required to maintain metabolic benefit.

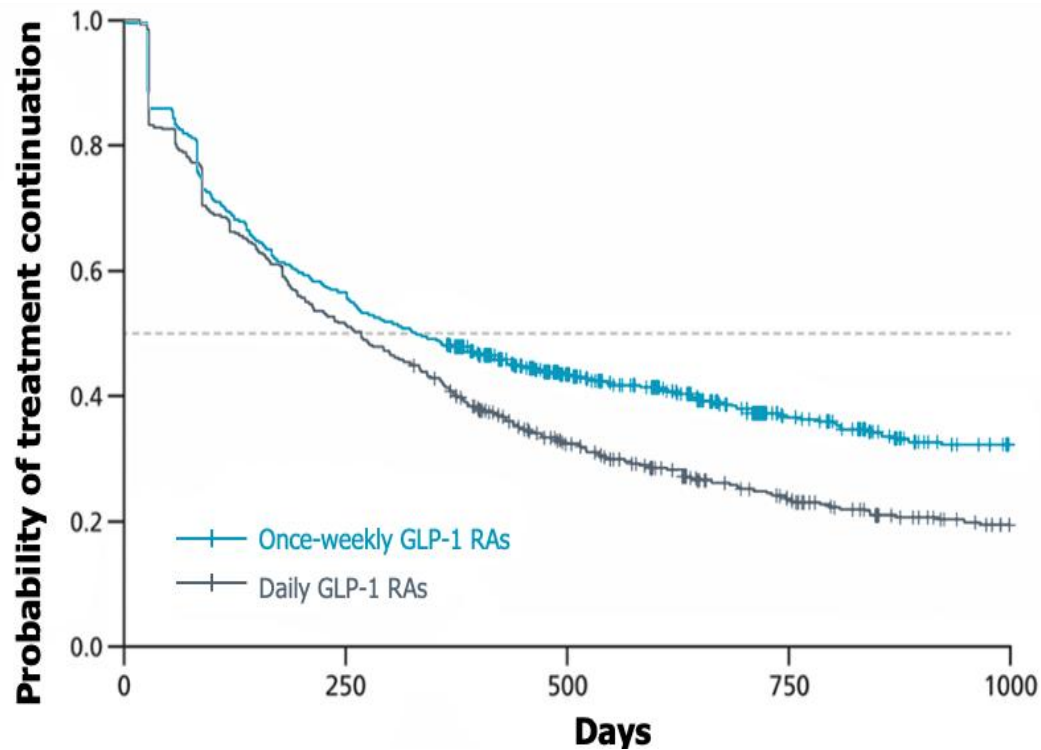
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1. Aronne et al. *JAMA*. Dec 11;331(1):38-48 (2024); 2. Osumili et al. *Diabetes Therapy* 11:16(6): 1279-1311 (2025); 3. Veljii-Ibrahim et al. *J. Obesity*. <https://doi.org/10.1155/job/3897161> (2025) 4. Gastaldelli et al. *Lancet Diabetes & Endocrinology*.10(6):393-406 (2022). 5. Kong et al. *Nature Comm.* 17, 972 (2026). GLP-1=glucagon-like peptide-1, GLP-1RA = glucagon-like-peptide-1 receptor agonist

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Persistence and Durability Limitations Prevent Sustained Metabolic Benefit:

A New Strategy is Needed



- Low real-world persistence, even with modern incretin therapies¹
- Up to 2/3 of patients discontinue within 1 year¹

A durable, one-time interventional approach is needed to achieve and maintain weight loss

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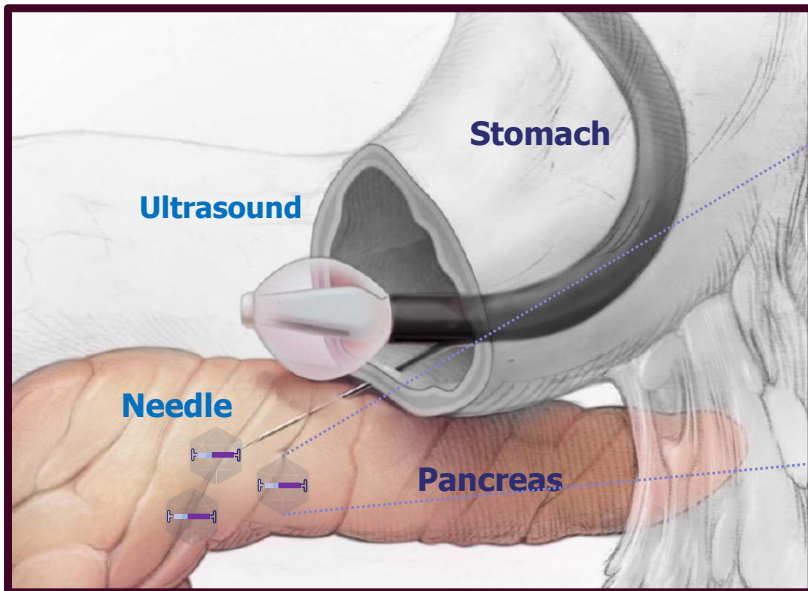
1. Figure adapted from Polonsky et al. Diabetes Ther. 13:175-1871 (2022), GLP-1RAs=glucagon-like-peptide-1 receptor agonists

REJUVA:

An AAV Gene Therapy Platform to Treat Metabolic Disease with a Single Dose

Novel ROA

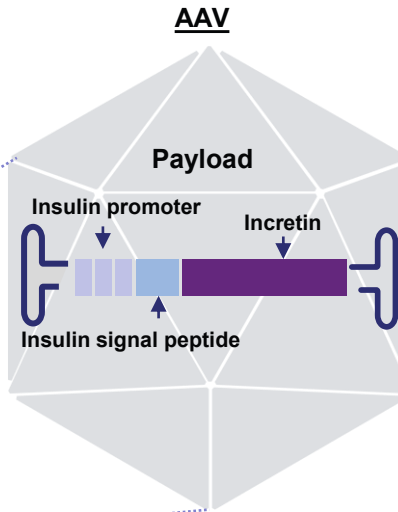
Targeted administration via purpose-built endoscopic ultrasound-guided device



- Targeted AAV delivery
- Low dose
- Restricted biodistribution

Novel MOA

Incretin(s) under Insulin-derived control for beta cell-specific, meal-regulated expression and secretion

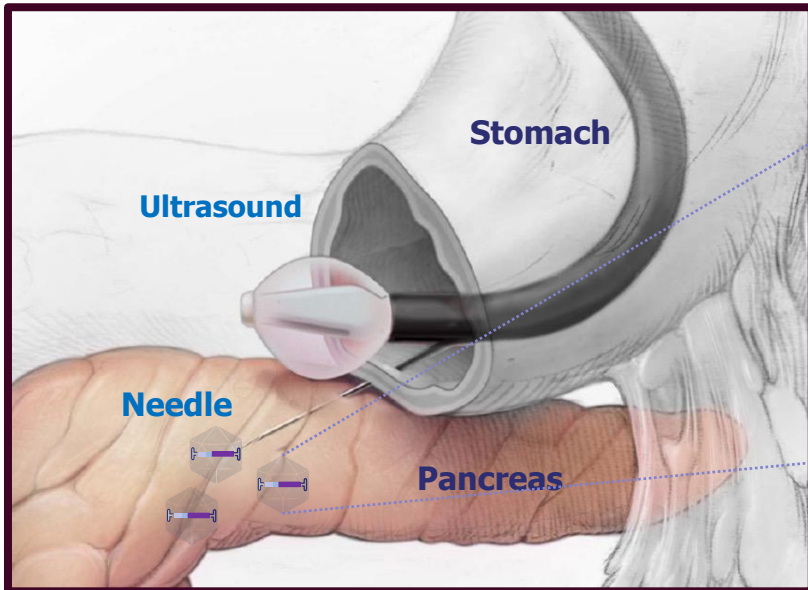


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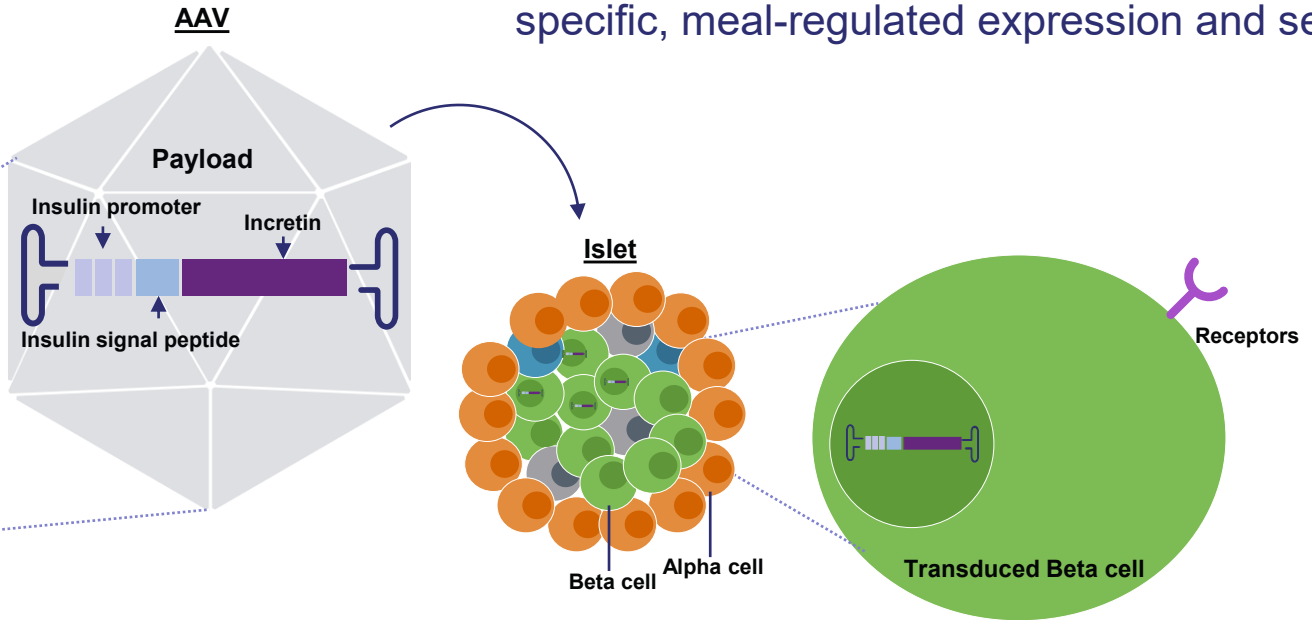
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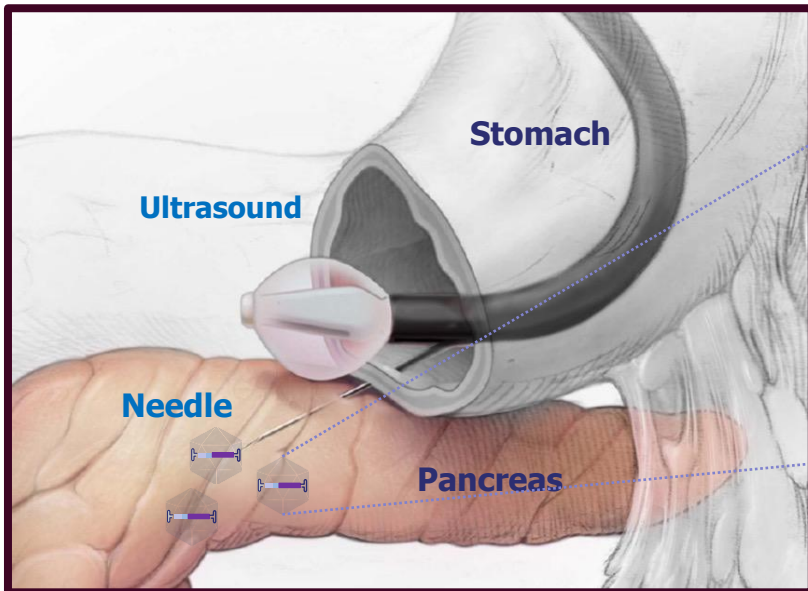
- Beta cell-specific expression

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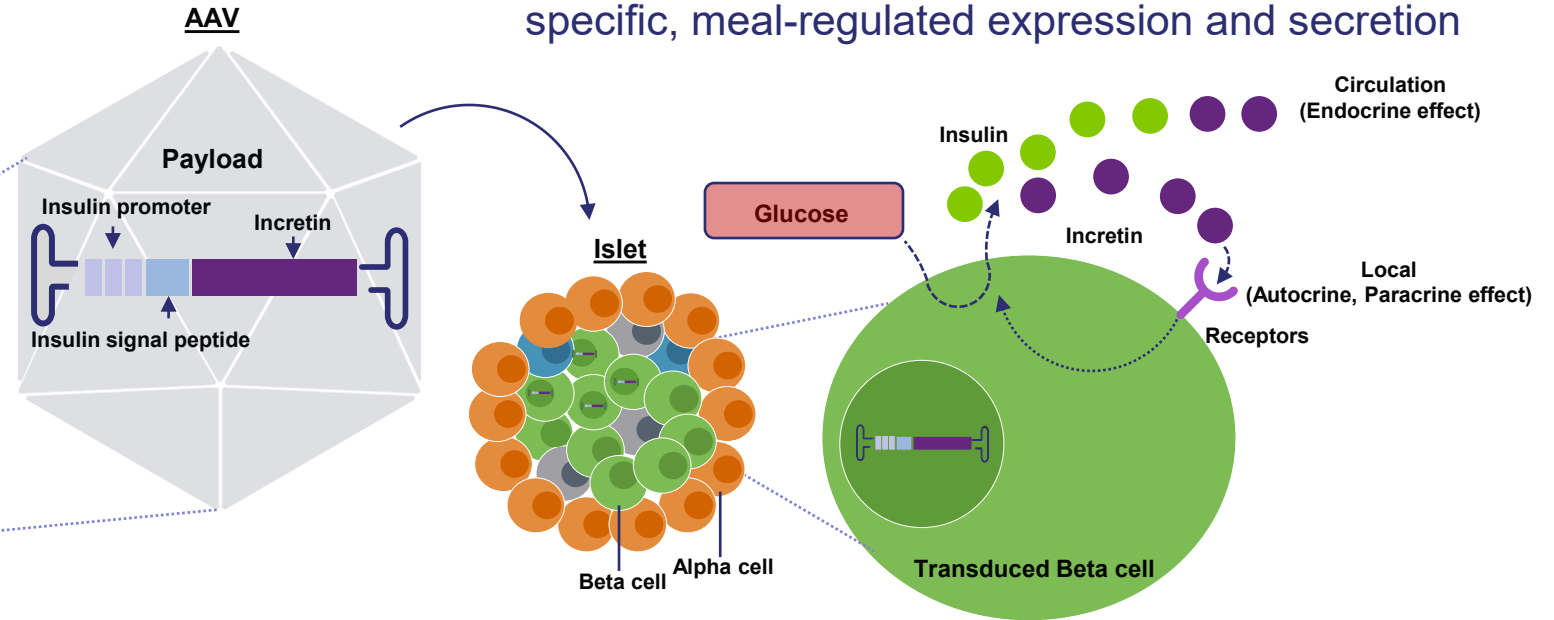
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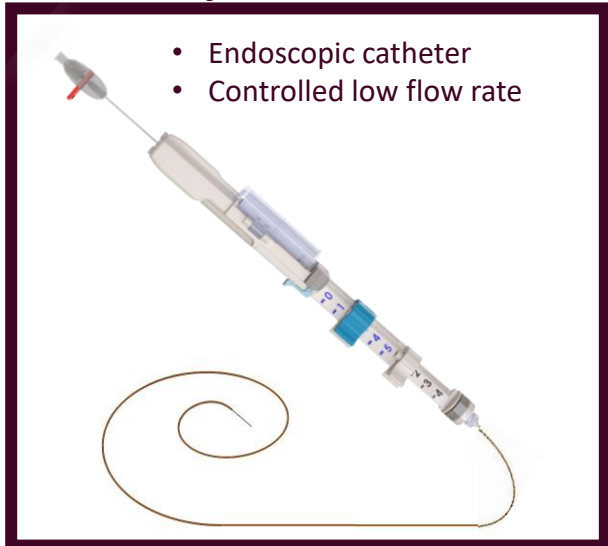
- Beta cell-specific expression
- Leverages insulin pathway
- Glucose-responsive incretin secretion

Rejuva Device Safely Delivers AAV to the Pancreas

Large Animal Safety Model – Yucatan Pig

- Rejuva catheter device introduced directly to pancreas parenchyma via standard endoscopic ultrasound techniques that are already part of standard clinical practice
- Unique features of Rejuva needle and device for enhanced safety and procedural ease
- Routine upper endoscopic procedure conducted in ~ 20 minutes

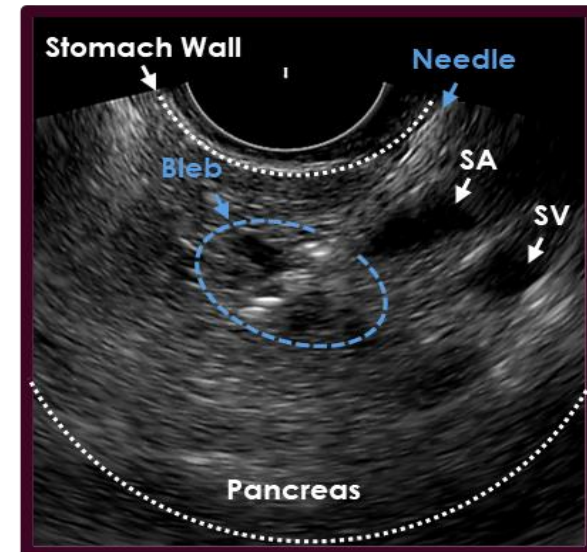
Rejuva Device



Rejuva Needle



Live Ultrasound

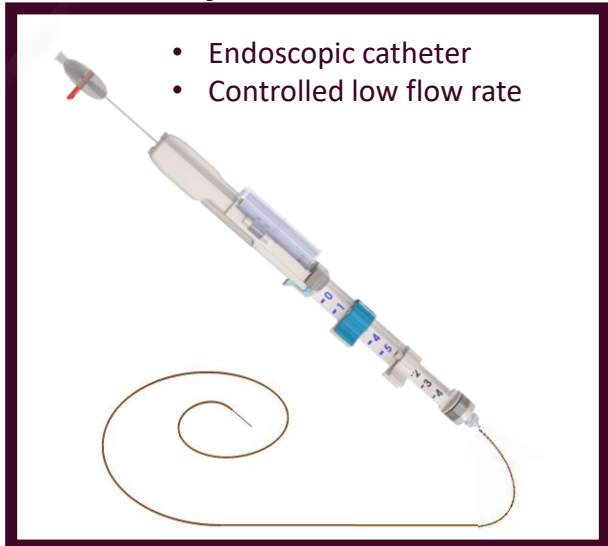


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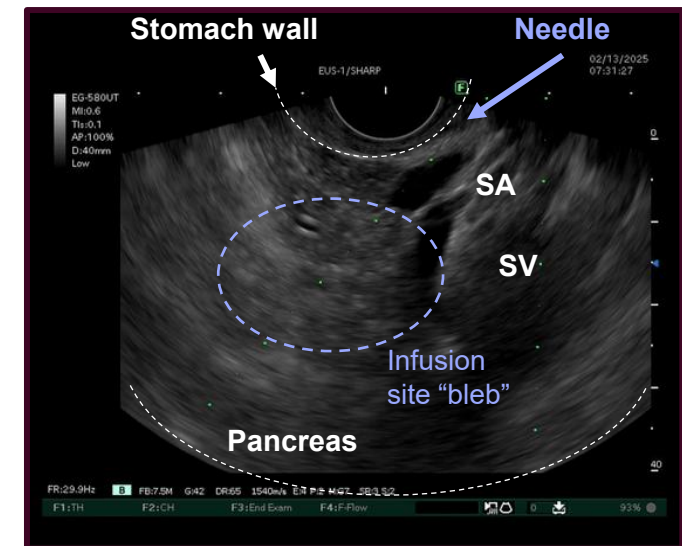
Rejuva Device



Rejuva Needle

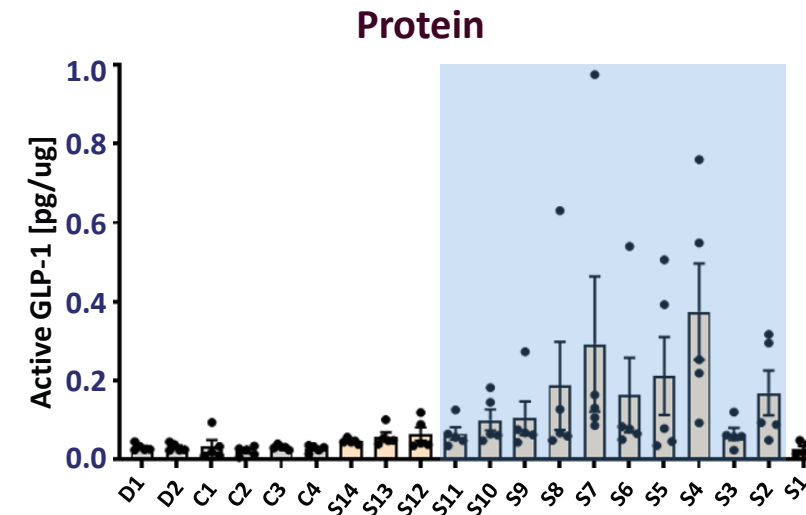
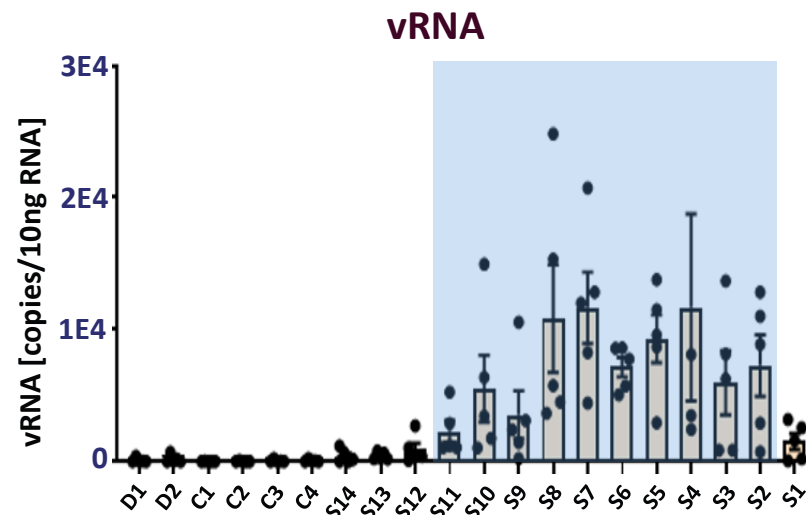
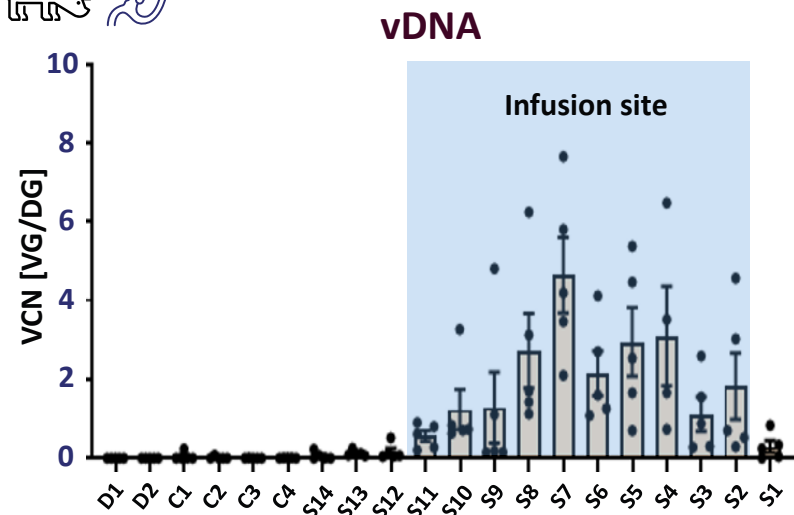


Live Ultrasound

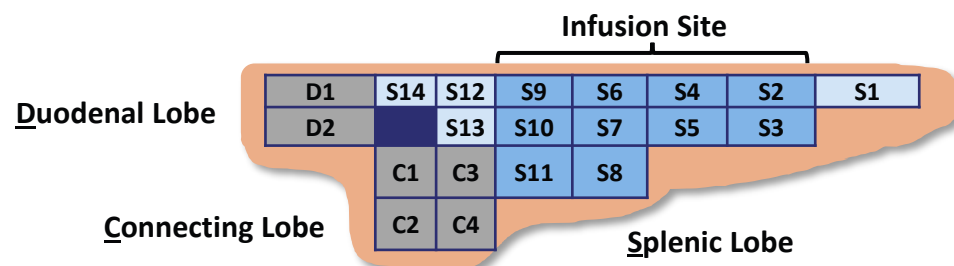


RJVA-001 (AAV-INSp-GLP-1) Effectively Delivered to Pancreas Via Targeted ROA

Transgene DNA, RNA, and active GLP-1 protein enriched in targeted pancreatic splenic lobe



Pancreas Biopsy Key

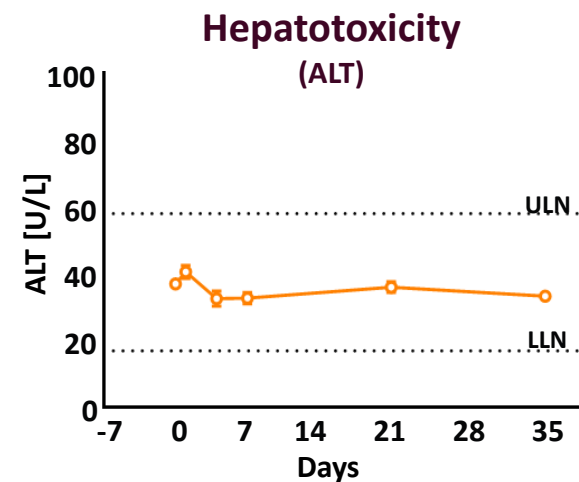
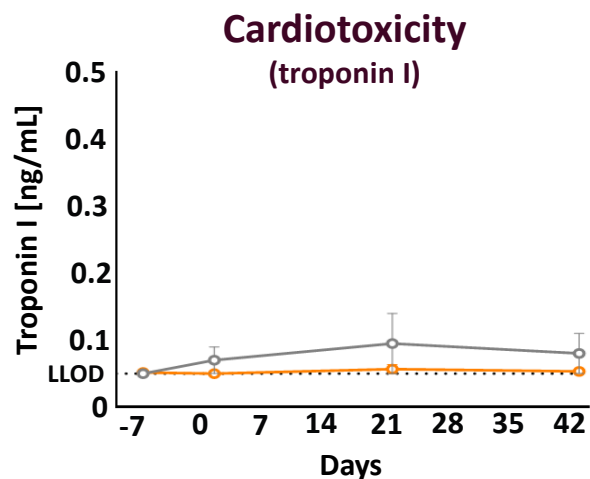
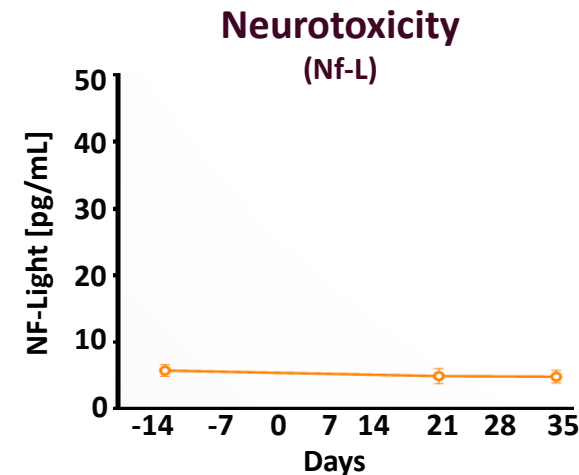
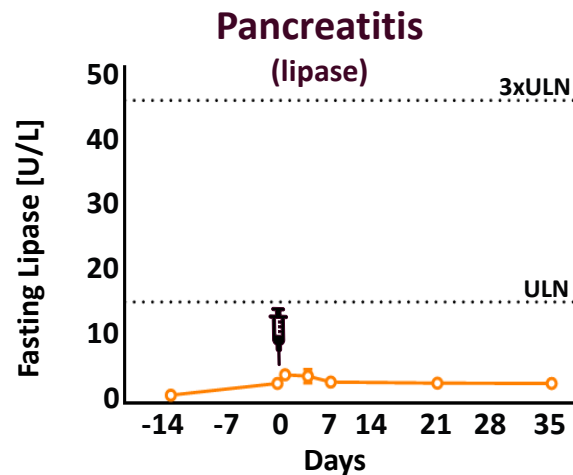
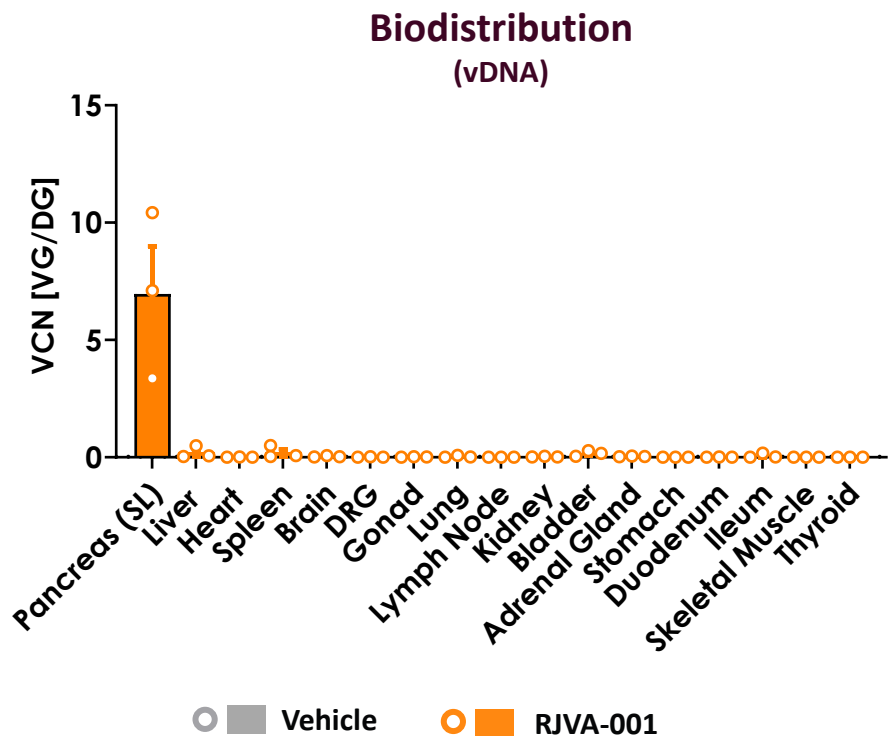


EUS-Guided Pancreatic AAV Delivery is Safe and Effective

Constrained Biodistribution and No Safety Signals



In Vivo: Treated Yucatan Pigs



Data are mean ± SEM, n=2-6 pigs per group.

ALT=alanine transaminase, NF-L=neurofilament light chain, ULN=upper limit of normal, LLN=lower limit of normal, LLOD=lower limit of detection, VCN=vector copy number, VG/DG=vector genome/diploid genome., AAV=adeno-associated virus, INSp=engineered human insulin promoter, GLP-1=glucagon-like peptide 1, EUS=endoscopic ultrasound, DRG=dorsal root ganglion, vDNA= viral DNA

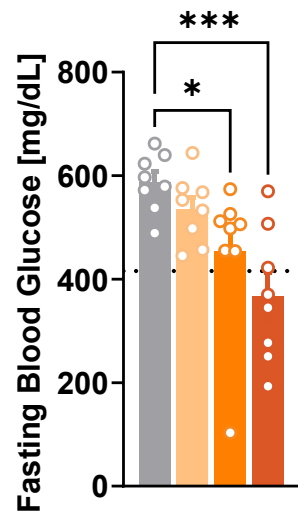
RJVA-001 Improves Glycemia in a Diabetic Mouse Model

Additional Weight Benefit Observed

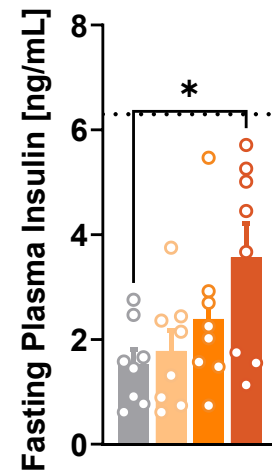


In Vivo: Treated 8-week-old *db/db* Mice, 46 days post single IP AAV injection

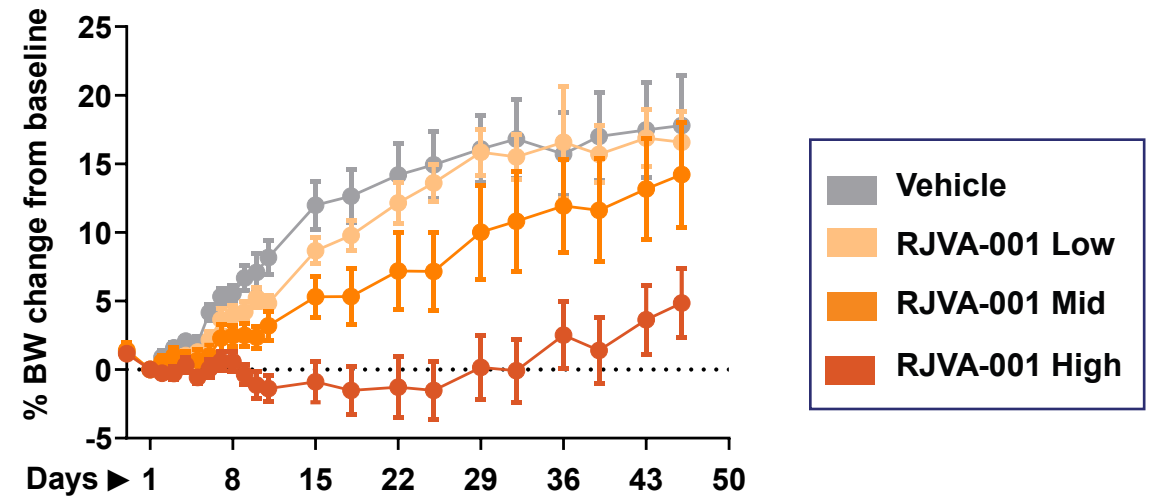
Fasting Blood Glucose



Fasting Plasma Insulin



Body Weight



- Improvement in FBG and plasma insulin in a model of progressive beta-cell dysfunction
- Reduced body weight with increasing dose with an AAV-INSp-GLP-1 gene therapy

Confirmation of MOA from Primary Diabetic Mouse Islets

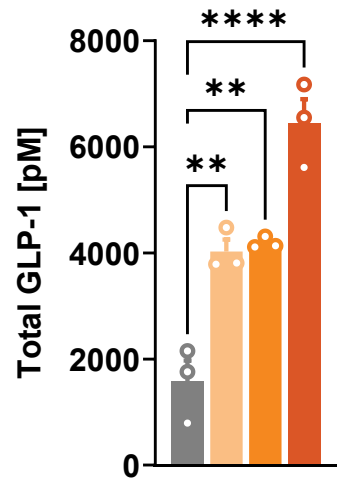
Expression and glucose-responsive incretin secretion



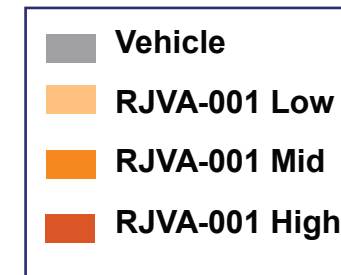
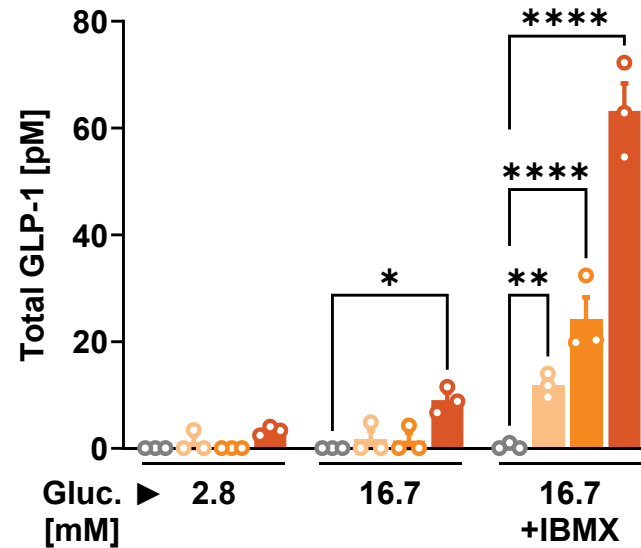
Ex Vivo: Islets Isolated from treated *db/db* Mice, 49 days post single IP AAV injection



GLP-1 Content
(lysate)



GLP-1 Secretion
(supernatant)



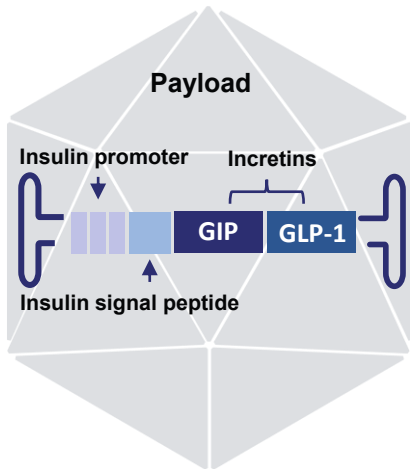
Data are mean \pm SEM. Each data point represents a pool of 40 islets run in triplicate. AAV=adeno-associated virus. Gluc=glucose, GLP-1, GLP1=glucagon-like peptide 1, IBMX=3-isobutyl-1-methylxanthine, INSp=engineered human insulin promoter, IP=intraperitoneal.

RJVA-002 program: Obesity Indication

A Nutrient-Regulated Dual Incretin Design to Improve Body Weight Loss

Dual Incretin transgene construct driven by an engineered human insulin promoter

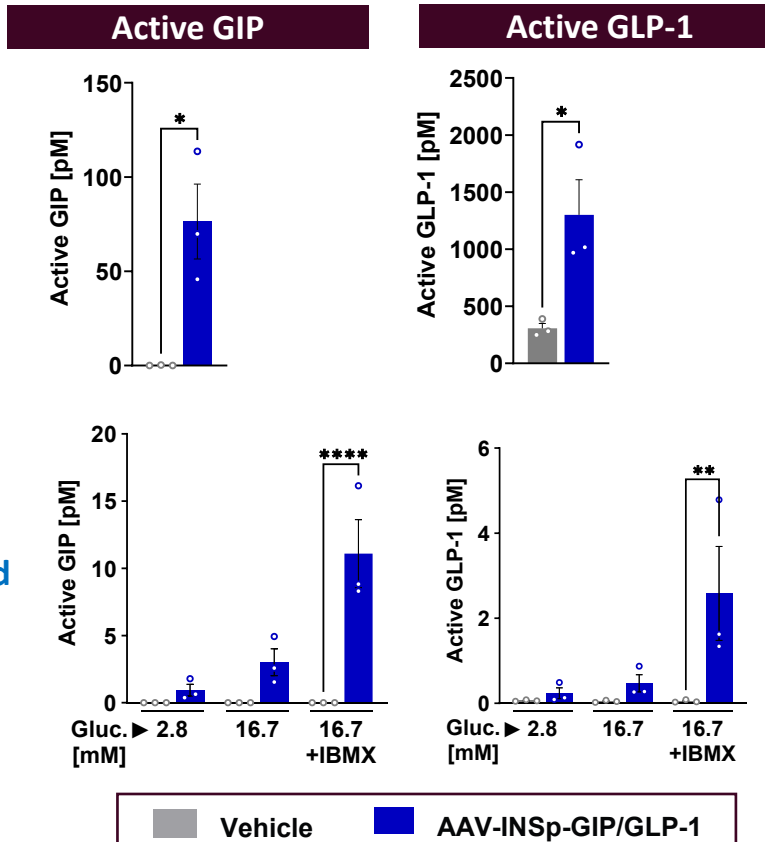
AAV-INSp-GIP/GLP-1



Confirmed expression and nutrient-regulated secretion in Primary Human Islets

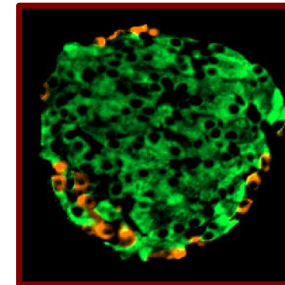
Total Content

Glucose-Stimulated Secretion

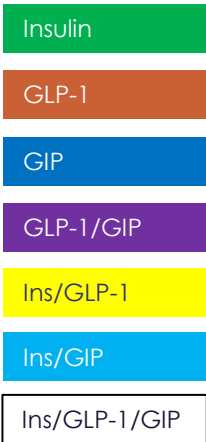
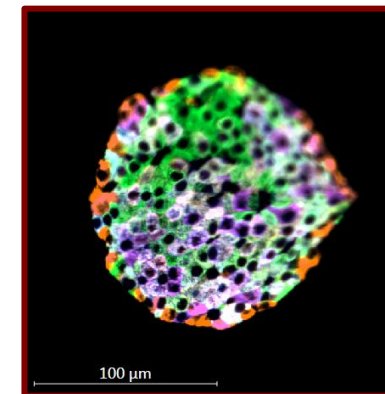


Confirmed dual expression of GIP/GLP-1 in mouse beta cells

Vehicle



AAV-INSp-GIP/GLP-1

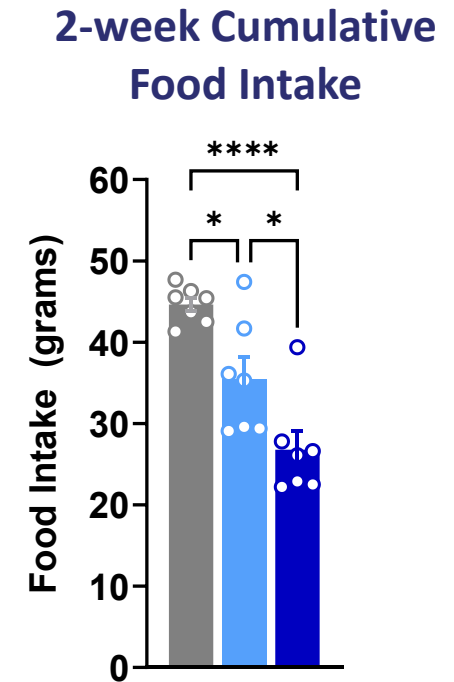
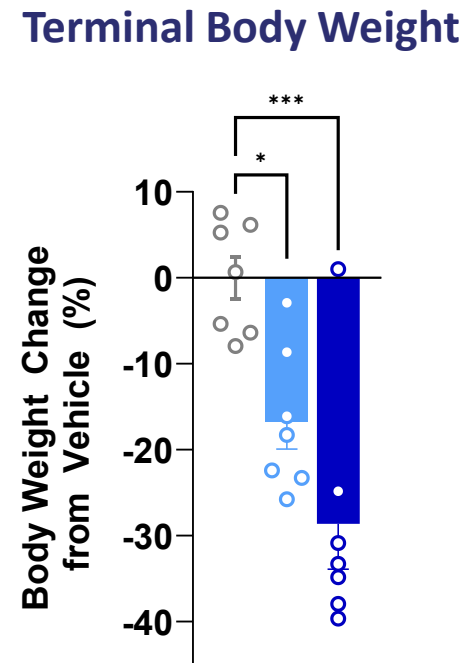
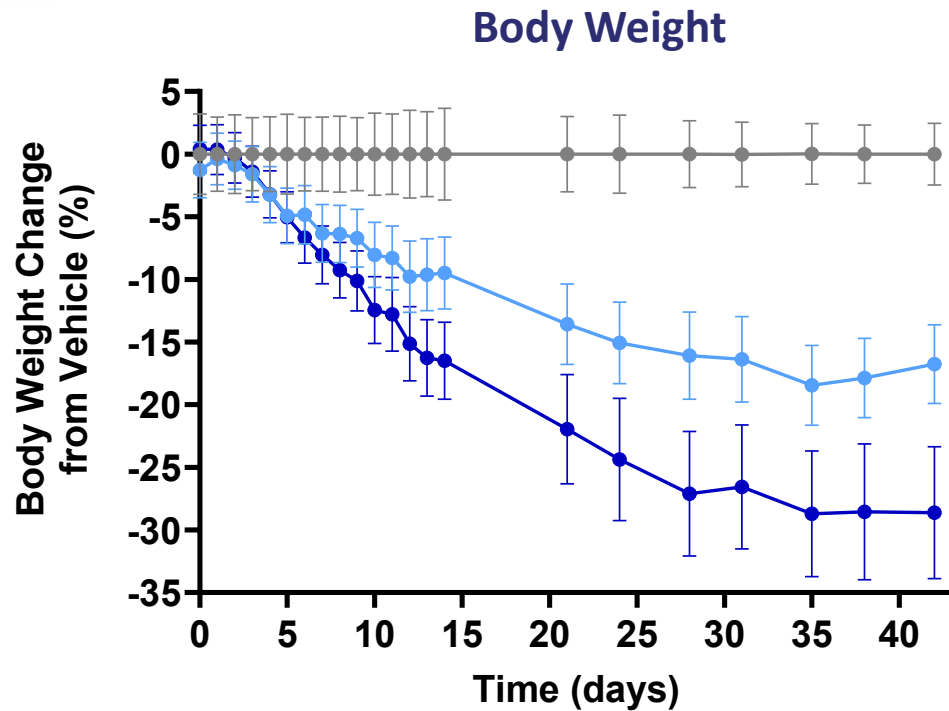


AAV-GIP/GLP-1 Dual Incretin Gene Therapy Effect on Body Weight in a DIO Mouse Model

Single dose durably reduces body weight and food intake



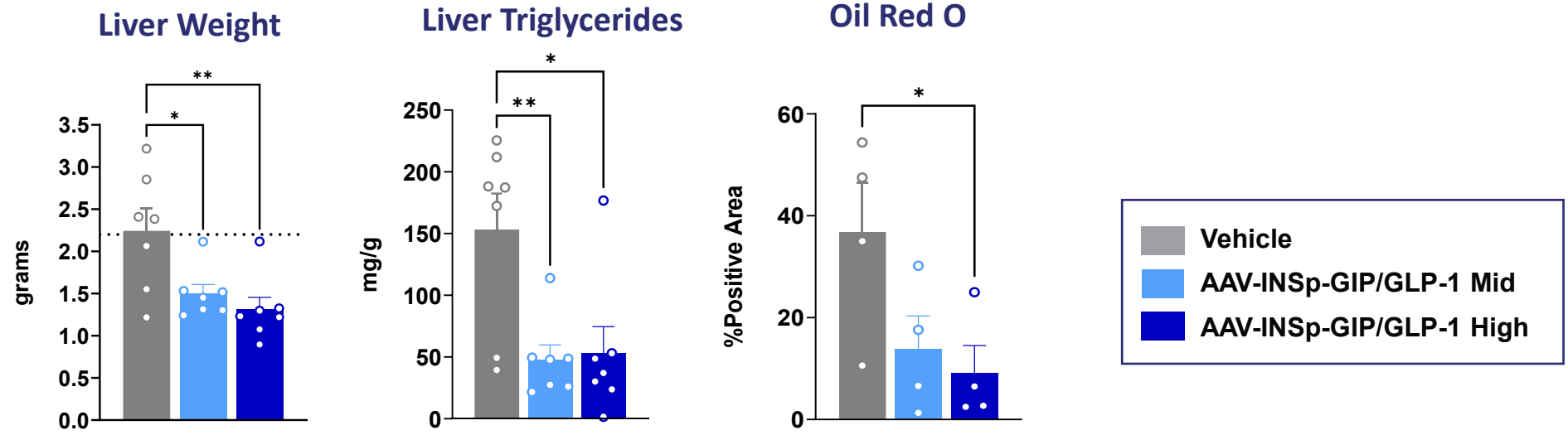
In Vivo: 60% HFD-induced DIO mice
42 days post single IP AAV injection



■ Vehicle ■ AAV-INSp-GIP/GLP-1 Mid ■ AAV-INSp-GIP/GLP-1 High

AAV-GIP/GLP-1 Dual Incretin Gene Therapy Significantly Attenuates Diet-Induced MASLD

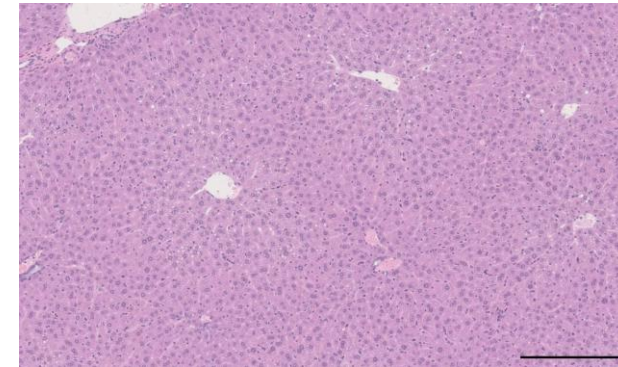
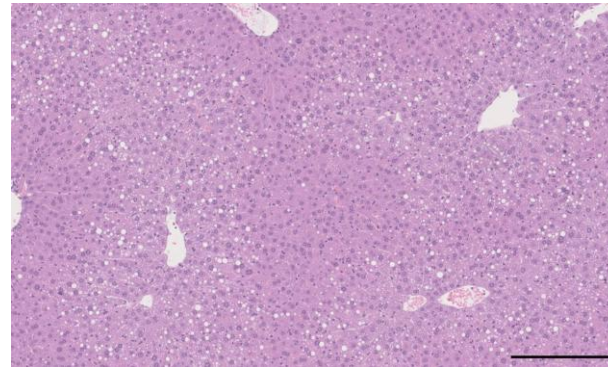
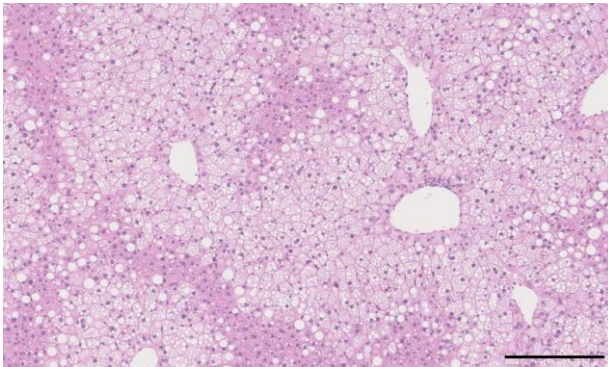
Reduced liver weight, triglycerides, and lipid accumulation



Vehicle

AAV-INSp-GIP/GLP1 Mid

AAV-INSp-GIP/GLP1 High



Summary and Conclusions

- **Single-dose, pancreas-targeted incretin gene therapy delivers durable, incretin expression and glucose-responsive secretion** – eliminating the adherence and persistence limitations of chronic pharmacotherapy
- **EUS-guided pancreatic delivery leverages an established GI procedural approach** - enabling targeted, low-dose administration with restricted biodistribution and acceptable safety outcomes.
- **Dual GIP/GLP-1 construct drives significant weight loss and improvements in diet-induced MASLD** in a DIO mouse model.

Potential to shift treatment paradigm from chronic pharmacotherapy to one-time metabolic reprogramming

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