One-Time Pancreatic GLP-1 Gene Therapy Prevents Diet-Induced Obesity via Neuronal Pathways in Mice

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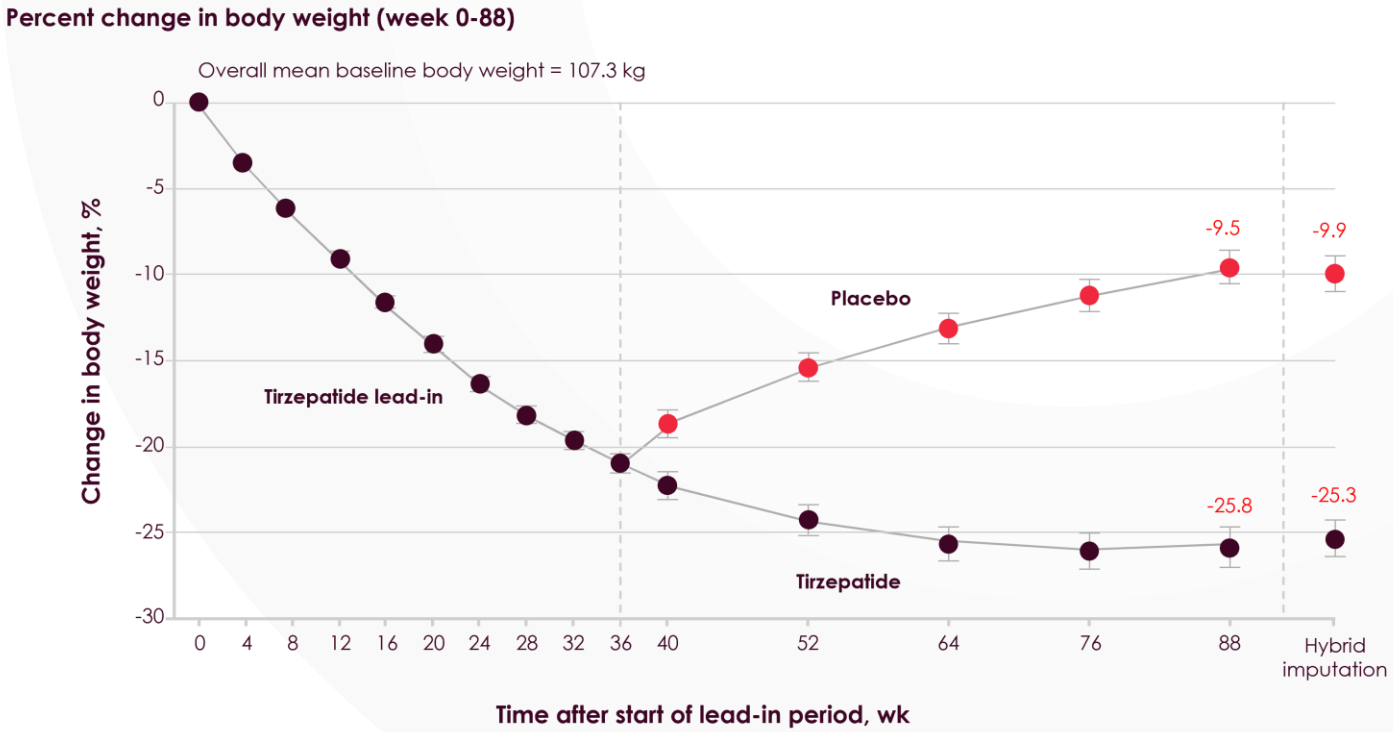
GLP-1 Drugs Do Not Durably Alter Metabolic Setpoint

- GLP-1 therapies **effectively support glycemic control and induce weight loss**[1]
- **Rapid, near total loss of metabolic benefit** upon discontinuation[1]
- **Discontinuation rates are high** with 50% occurring within the first 3 months[2]
- Clear **need for durable, tolerable, and more physiologically relevant** GLP-1-based therapies



1. Aronne et al. JAMA. 2023 Dec 11;331(1):38–48. 2. Blue Health Intelligence, Issue Brief May 2024. Figure adapted from Aronne et al. JAMA. 2023 Dec 11;331(1):38–48. GLP-1=glucagon-like peptide 1.

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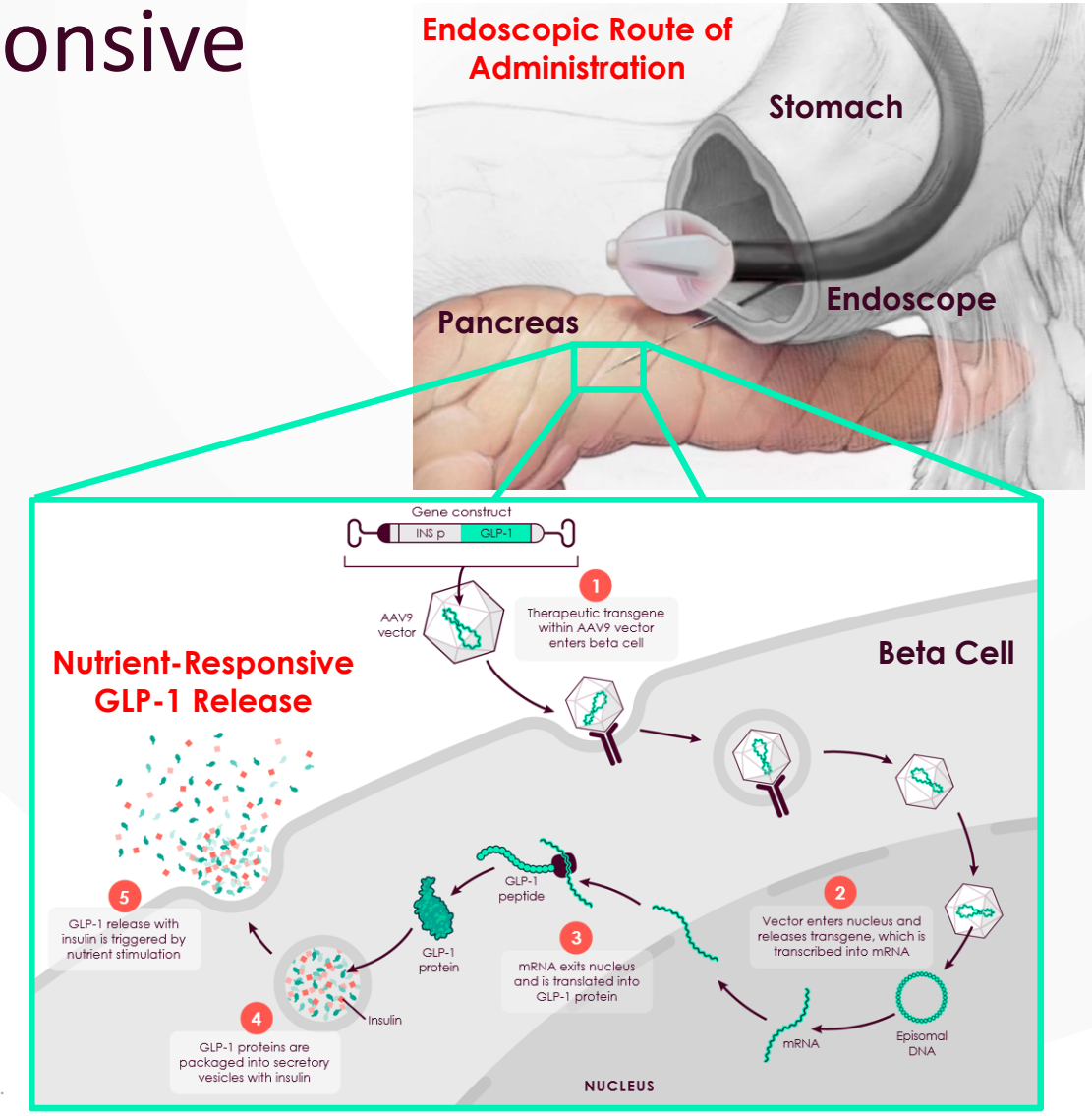
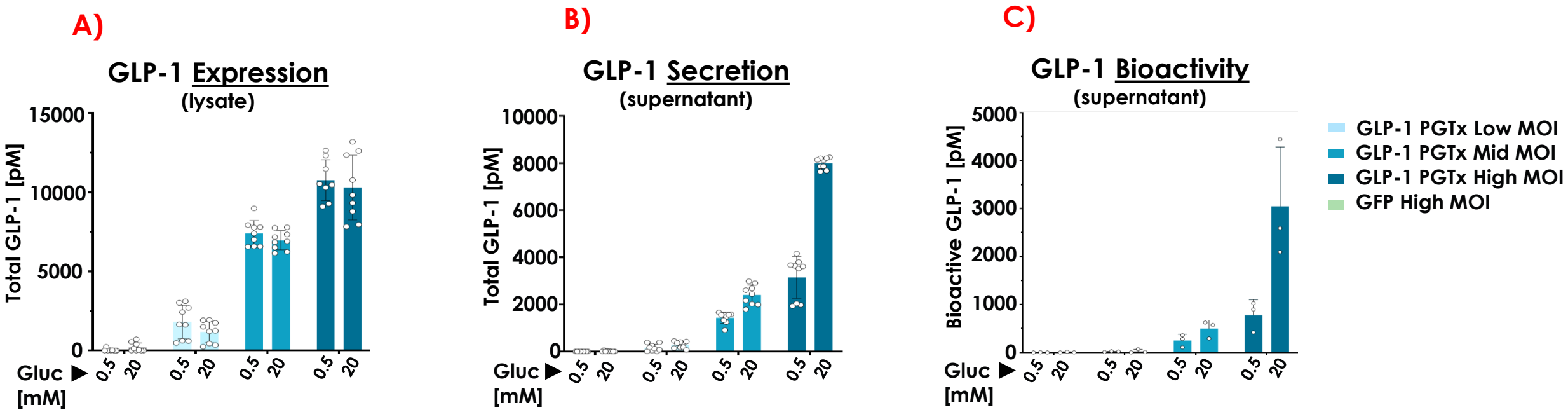
Novel Pancreatic Gene Therapy for Metabolic Disease: Localized, Durable, Nutrient-Responsive

- Adeno-associated virus 9 **(AAV9) vector with human insulin promoter driving human GLP-1 expression**
  - **RJVA-001** – currently in development for type 2 diabetes
- Targeted low-dose **delivery to terminally differentiated beta cells by routine endoscopic ultrasound (EUS)**
- Beta cell machinery leveraged to **produce GLP-1 in response to glucose**
- **GLP-1 Pancreatic Gene Therapy (PGTx) may offer differentiated benefit**



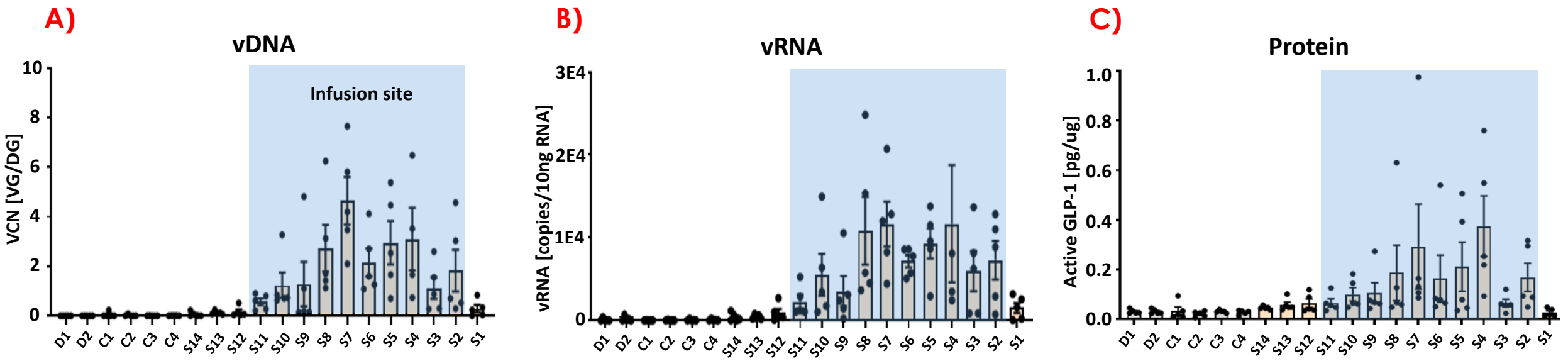
RJVA-001 is in early development and has not been assessed by any regulatory body for investigational or commercial use.
AAV9=adeno-associated virus 9, EUS=endoscopic ultrasound, GLP-1=glucagon-like peptide-1, PGTx=pancreatic gene therapy.

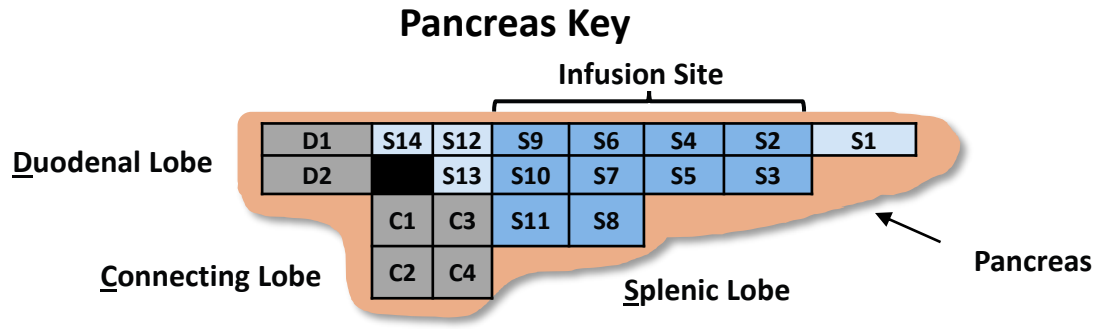
PGTx Shows Nutrient- and Dose-Responsive GLP-1 PGTx Expression and Secretion in Transduced **Human Beta Cell Line**



Fitzpatrick et al. ASGCT 2025 oral presentation. Abstract no. 364. Data are mean ± standard deviation. For GLP-1 expression and secretion, N=3 with 3 technical replicates. For GLP-1 bioactivity, N=1 with 3 technical replicates. GLP-1=glucagon-like peptide 1, Gluc=glucose, GFP=green fluorescent protein, MOI=multiplicity of infection.

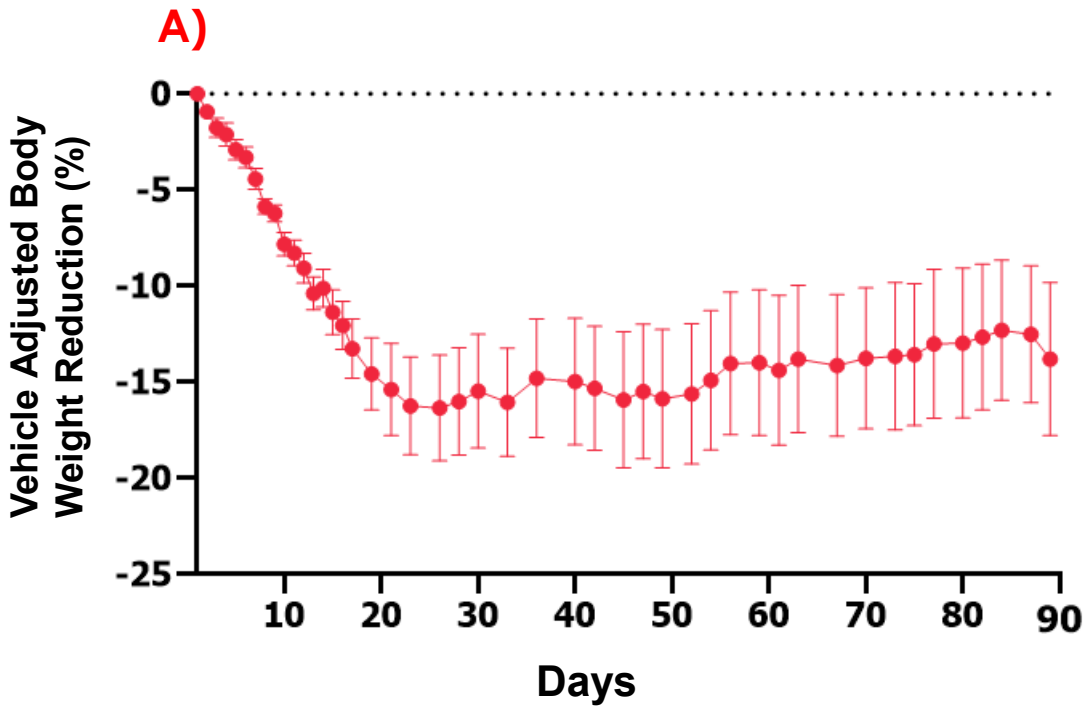
EUS Route of Administration Effectively Delivers GLP-1 PGTx: GLP-1 Enriched in Targeted **Porcine Pancreatic Lobe**

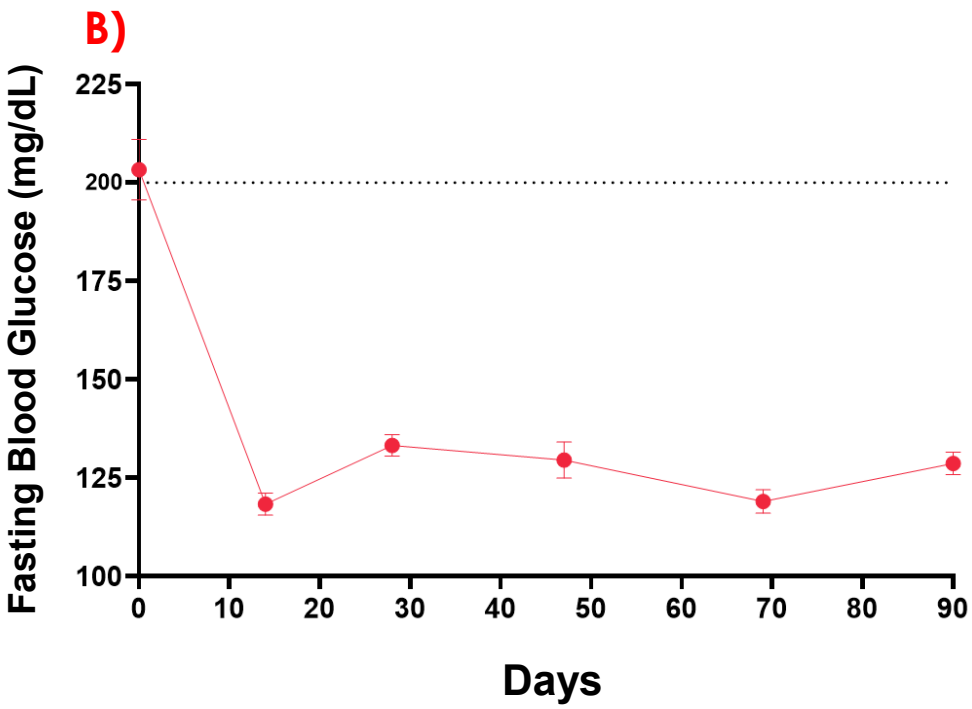




Fitzpatrick et al. ASGCT 2025 oral presentation. Abstract no. 364. Data are mean ± standard error of the mean, N=5 pigs. VCN, RNA, and GLP-1 protein averaged across pancreatic biopsy sections. EUS=endoscopic ultrasound, GLP-1=glucagon-like peptide 1, VCN=vector copy number, VG/DG=vector genome/diploid genome, ROA=route of administration.

Single-Dose GLP-1 PGTx Durably Improves Metabolic Outcomes in **Diet-Induced Obesity Mice**

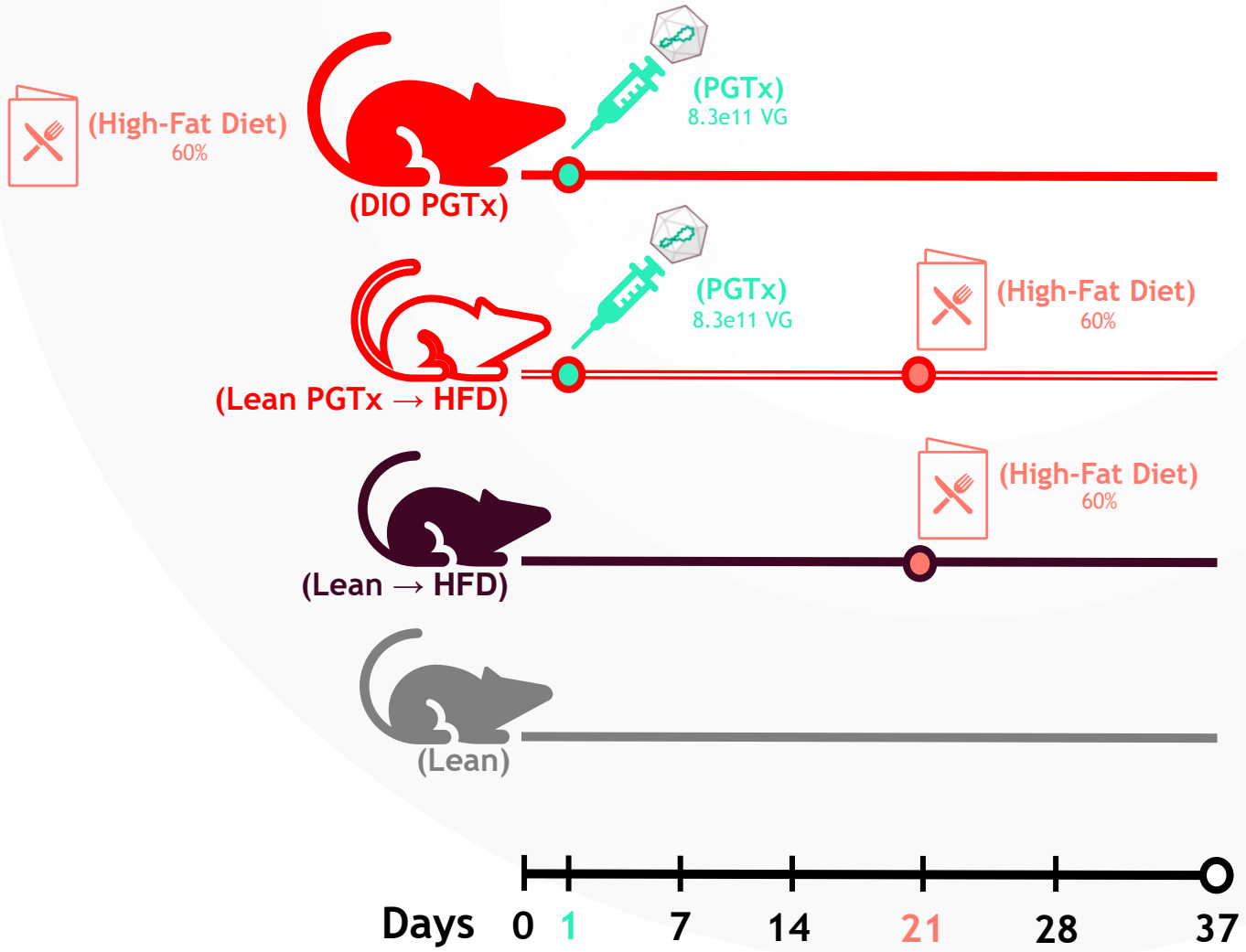




Fitzpatrick et al. OW 2024 oral presentation. Oral no. 081. Mean ± standard error of the mean shown; n=8 per group. GLP-1=glucagon-like peptide 1, PGTx=pancreatic gene therapy.

Can Pancreatic Gene Therapy ***Prevent*** the Development of Metabolic Disease?

- AAV9 vector with **insulin promoter driving Exendin-4 expression**
  - **Tool PGTx** – designed for exploratory studies
- Four murine cohorts:
  1. DIO treated with PGTx (**DIO PGTx**)
  2. Lean treated with PGTx, challenged with HFD (**Lean PGTx→HFD**)
  3. Lean challenged with HFD (**Lean→HFD**)
  4. Lean (**Lean**)



DIO=diet-induced obesity, HFD=high-fat diet, PGTx=pancreatic gene therapy, VG=vector genomes.

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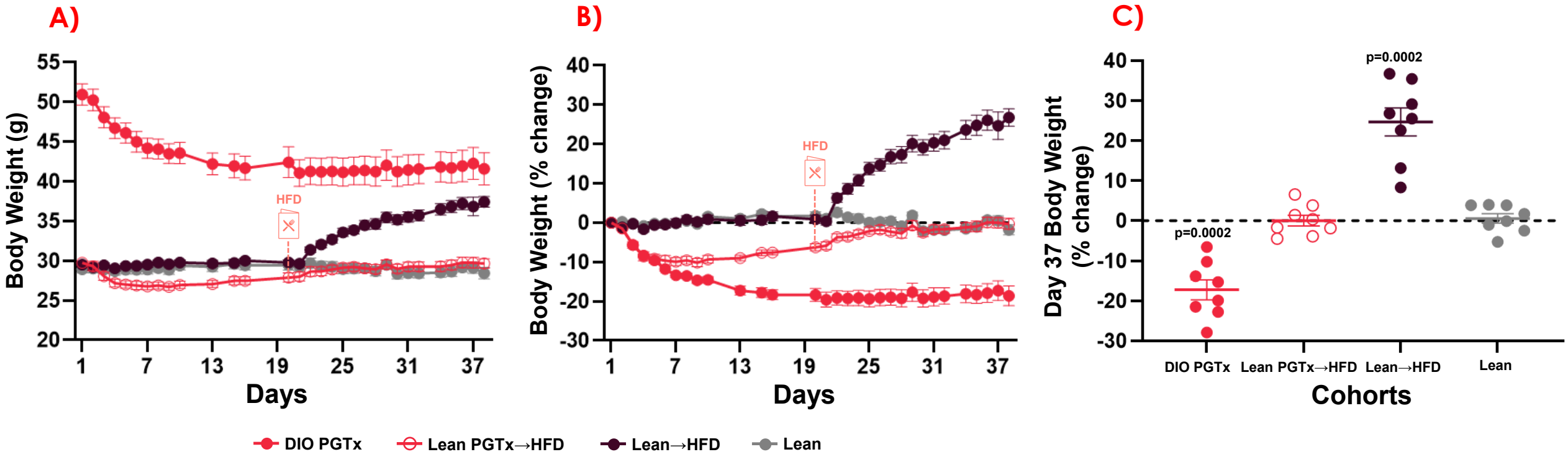
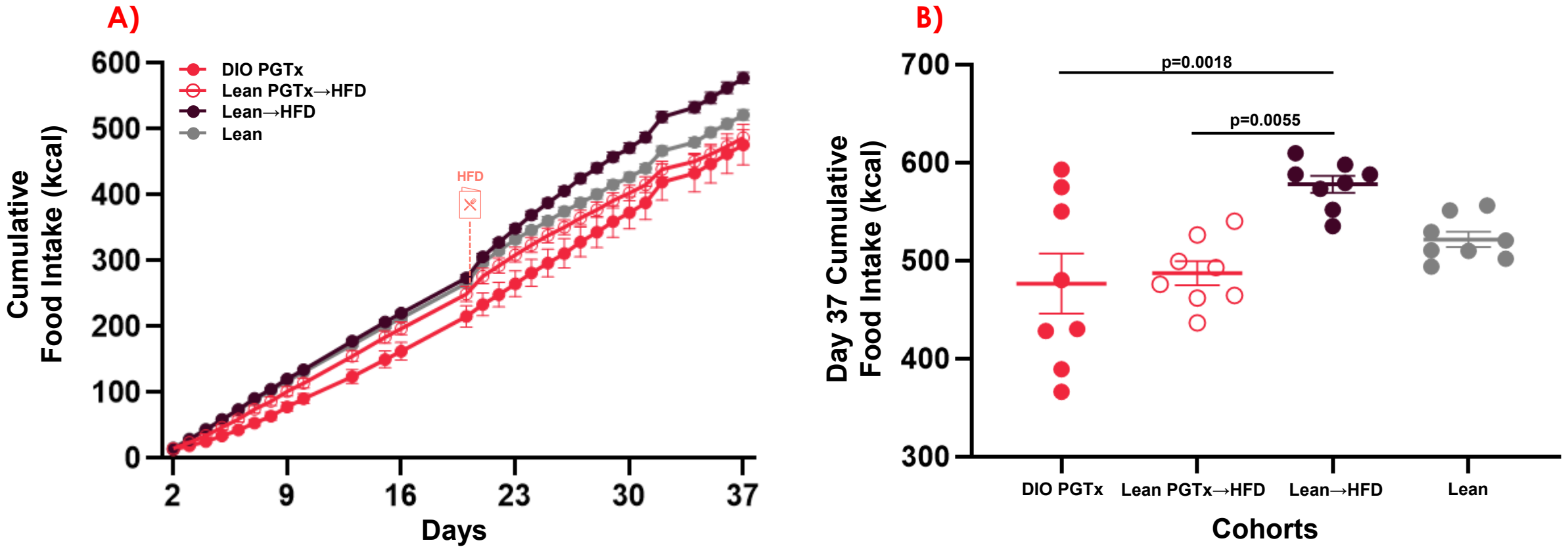
PGTx Reduced Body Weight and *Prevented* Weight Gain in Lean Mice Challenged with HFD



Data are reported as mean absolute and percent change from baseline ± standard error of the mean, n=8 per group. DIO=diet-induced obesity, HFD=high-fat diet, PGTx=pancreatic gene therapy.

Body Weight Changes were Reflected by Alterations in Food Intake



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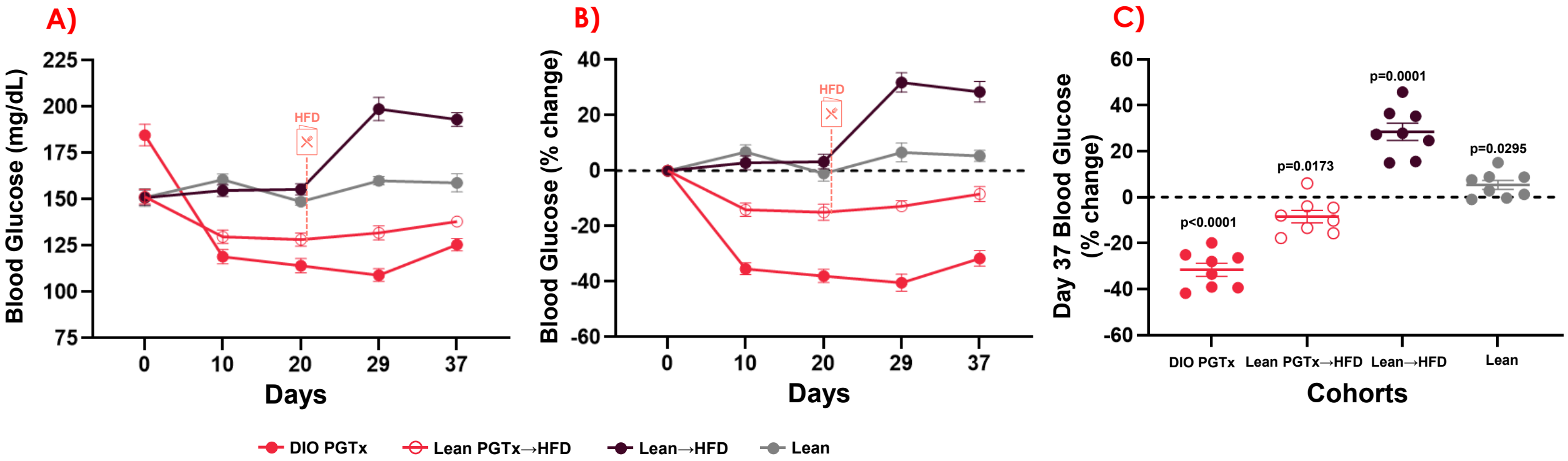
PGTx Reduced Blood Glucose in DIO Mice and *Prevented* Hyperglycemia in Lean Mice Challenged with HFD



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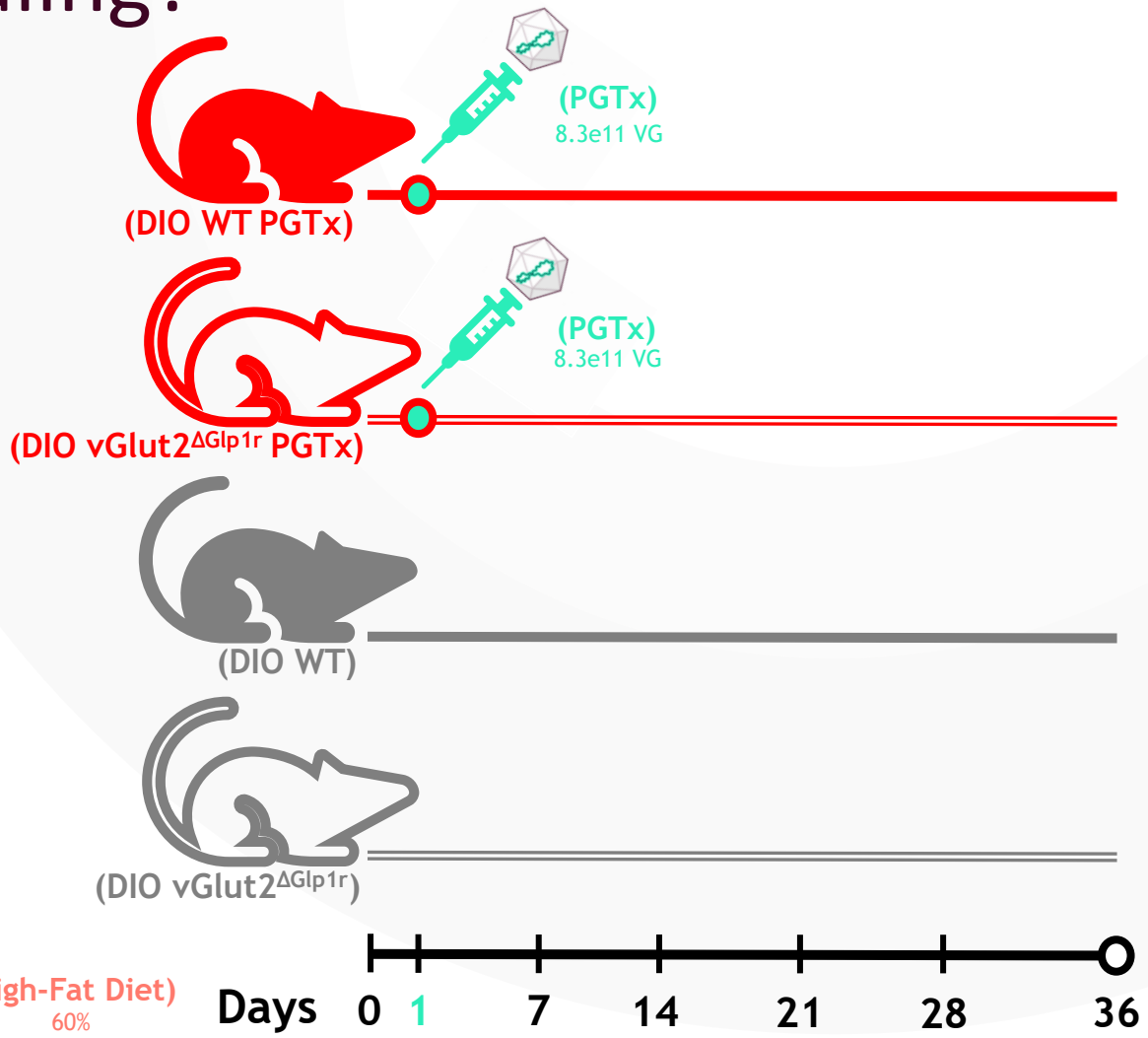
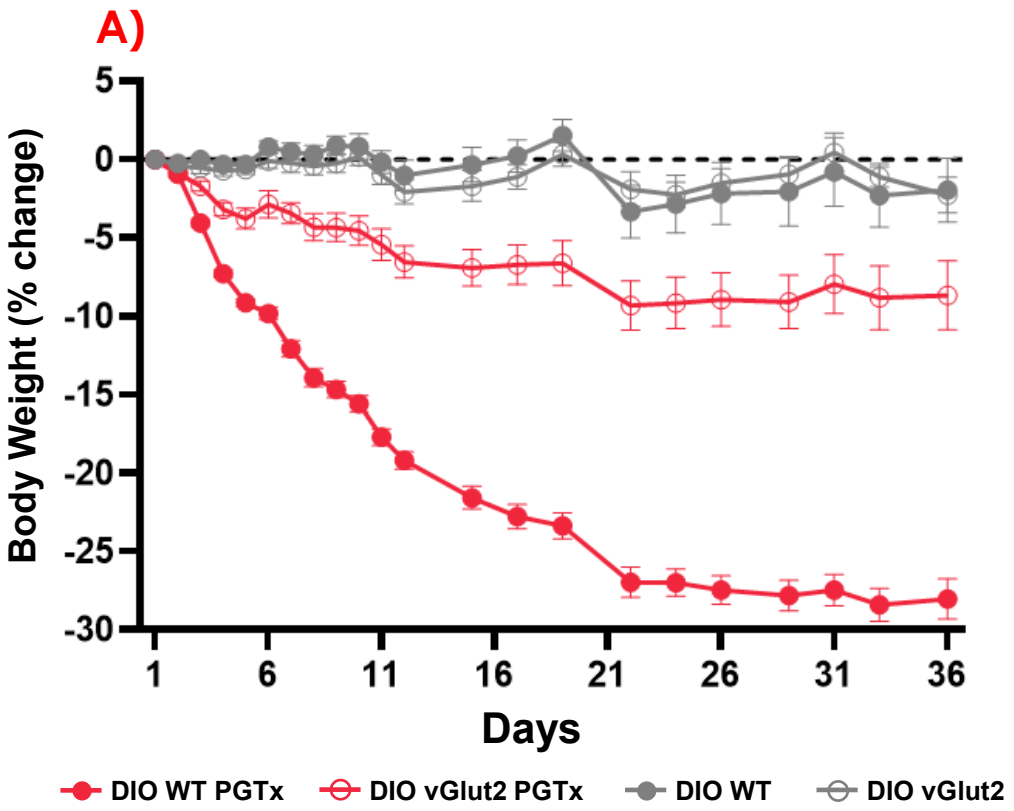
Are PGTx-Driven Metabolic Improvements Mediated by Neuronal GLP-1 Receptor Signaling?

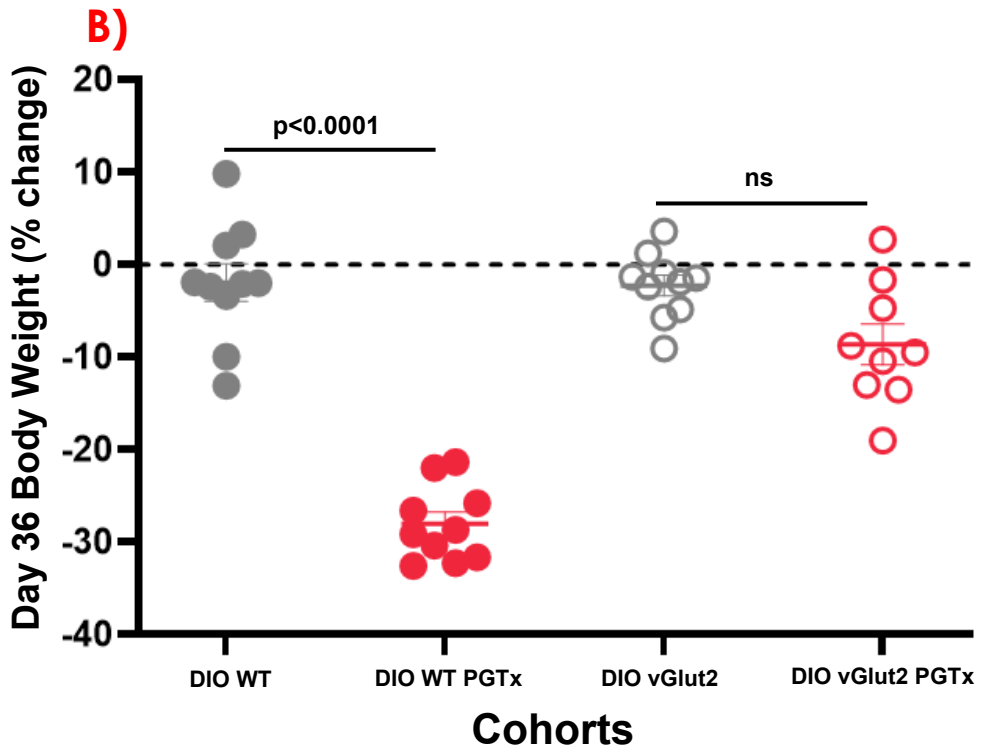
- AAV9 vector with **insulin promoter driving Exendin-4 expression**
  - **Tool PGTx** – designed for exploratory studies
- Four DIO murine cohorts:
  1. Wild-type treated with PGTx (**DIO WT PGTx**)
  2. vGlut2$^{\Delta Glp1r}$ treated with PGTx (**DIO vGlut2 PGTx**)
  3. Wild-type (**DIO WT**)
  4. vGlut2$^{\Delta Glp1r}$ (**DIO vGlut2**)



DIO=diet-induced obesity, HFD=high-fat diet, PGTx=pancreatic gene therapy, VG=vector genomes, WT=wild-type.

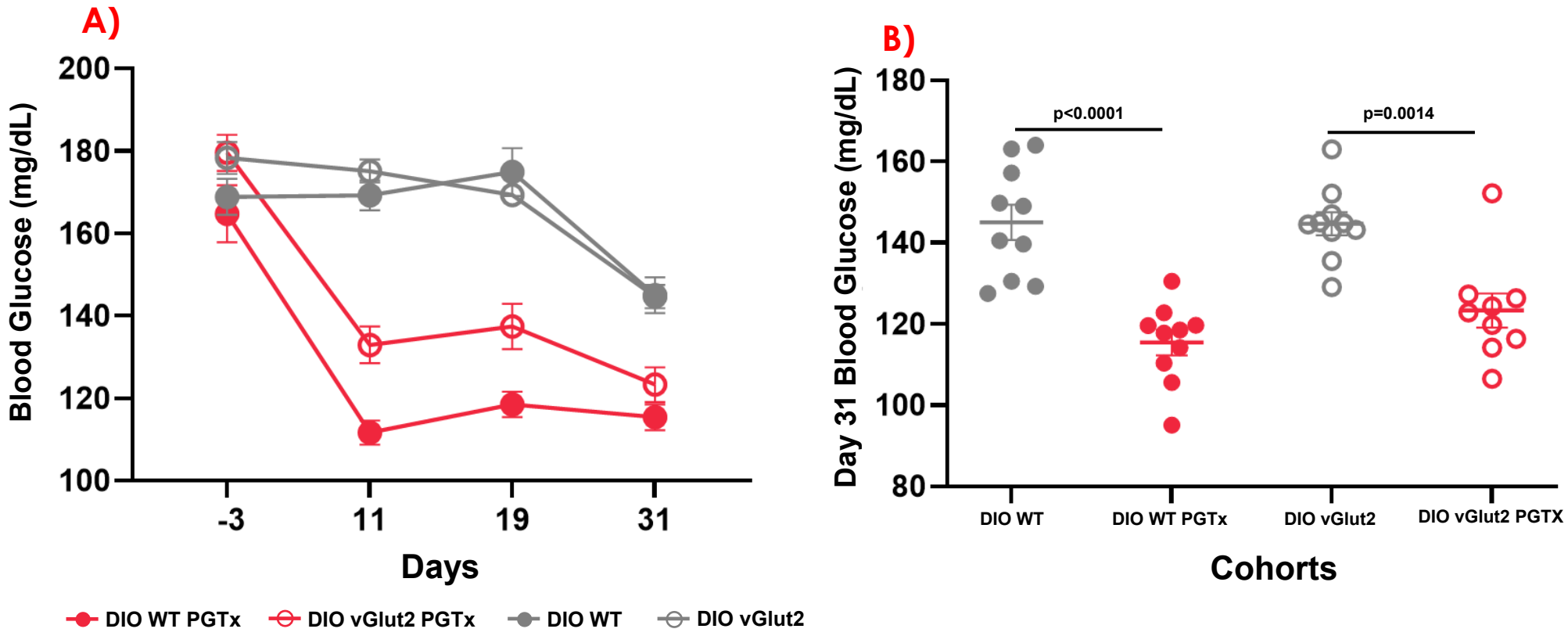
PGTx-Induced Body Weight Reduction was *Blunted* with Glutamatergic Neuron Disruption of GLP-1R Signaling





Data are reported as mean percent change from baseline ± standard error of the mean, n=9-10 per group. DIO=diet-induced obesity, GLP-1R=glucagon-like peptide 1 receptor, ns=non-significant, PGTx=pancreatic gene therapy, WT=wild-type.

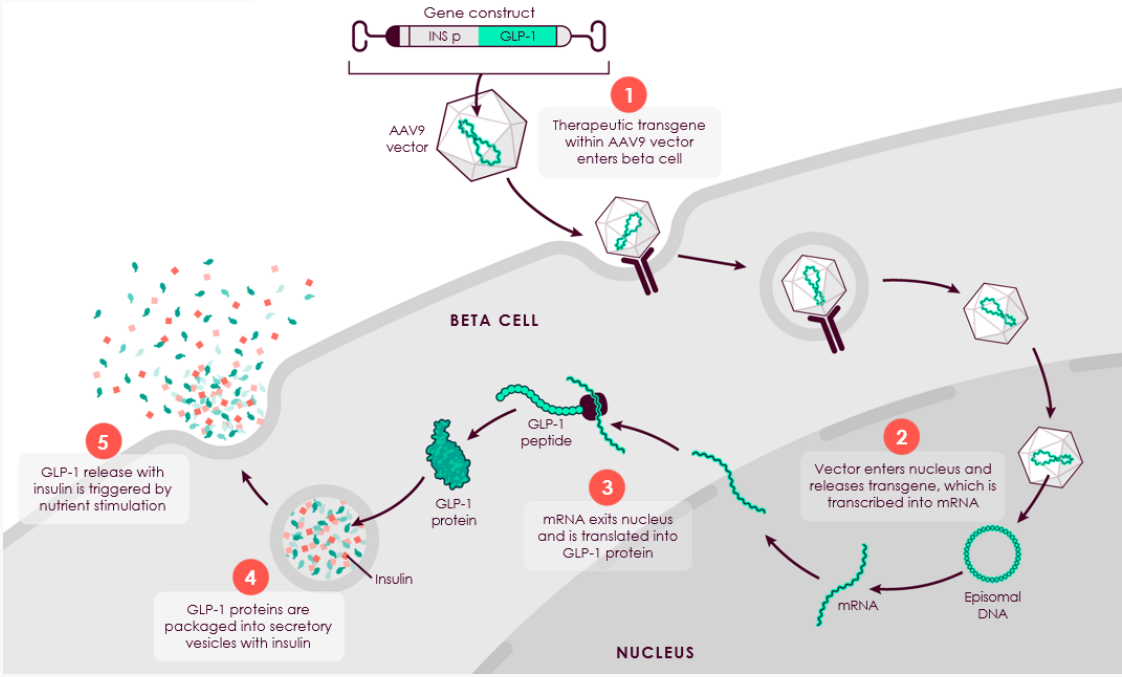
PGTx-Induced Blood Glucose Reduction was *Not* Inhibited by Glutamatergic Neuron Disruption of GLP-1R Signaling



Data are reported as mean absolute and percent change from baseline ± standard error of the mean, n=9-10 per group. DIO=diet-induced obesity, GLP-1R=glucagon-like peptide 1 receptor, HFD=high-fat diet, PGTx=pancreatic gene therapy, WT=wild type.

Summary and Conclusions

- GLP-1-based pancreatic gene therapy:
  - Can **durably reduce weight and glycemia** in DIO mice
  - Can **prevent weight gain and hyperglycemia** when treatment is given prior to HFD challenge
  - **Does not cause excessive weight loss or hypoglycemia in lean mice**
  - May **work partially through neuronal GLP-1 receptors**
- Pancreatic gene therapy **may advance GLP-1 therapies through reversal and prevention of metabolic disease**



DIO=diet-induced obesity, GLP-1=glucagon-like peptide 1, HFD=high-fat diet.

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