Single-dose GLP-1-based Pancreatic Gene Therapy Maintains Weight Loss After Semaglutide Withdrawal in a Murine Model of Obesity

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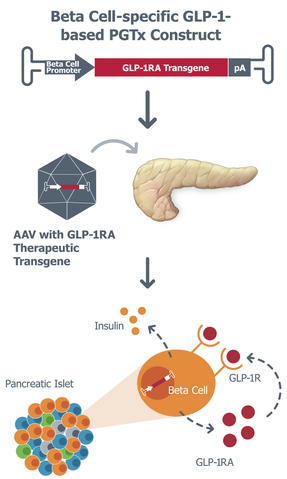
INTRODUCTION

- Glucagon-like peptide 1 (GLP-1)-based therapies demonstrate efficacy in obesity, yet effect durability remains a challenge with most patients regaining weight after treatment discontinuation.
- We developed a novel adeno-associated virus (AAV) pancreatic gene therapy (PGTx) platform enabling durable production of therapeutic proteins by the pancreas.
- **The aim of this study was to assess the efficacy and durability of single-dose GLP-1-based PGTx compared to daily semaglutide (Sema) in a murine model of diet-induced obesity (DIO).**

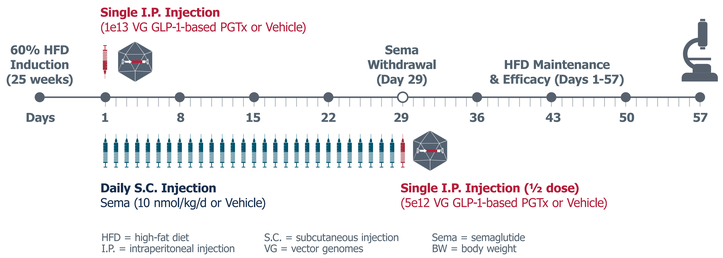
METHODS & RESULTS

Figure 1. GLP-1-based PGTx Transgene Construct and Mechanism of Action. A gene expression cassette containing a beta cell-specific promoter and GLP-1 receptor agonist (GLP-1RA) therapeutic transgene was packaged into AAV vectors to create GLP-1-based PGTx for efficacy analyses in DIO mice. GLP-1-based PGTx transduction of beta cells induces pancreatic production of GLP-1RA protein and glucose-stimulated insulin secretion and improves cellular function.[1]



pA = polyadenylation
AAV = adeno-associated virus
GLP-1 = glucagon-like peptide 1
GLP-1R = GLP-1 receptor
GLP-1RA = GLP-1R agonist
PGTx = pancreatic gene therapy

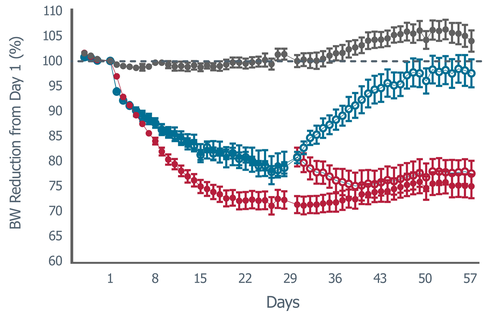
Figure 2. GLP-1-based PGTx and Sema Treatment in Diet-induced Obesity Model. Five-week-old C57BL/6 mice were fed a 60% high-fat diet over 25 weeks to achieve a target body weight (BW) of 50 grams. Mice were then randomized by BW and received either 1) single i.p. injection of GLP-1-based PGTx (1e13 VG, n=10) or vehicle (n=8) or 2) daily s.c. injections of Sema (10 nmol/kg/d x 28 days, n=10) or vehicle (n=8). Sema was subsequently withdrawn on day 29, and mice were given GLP-1-based PGTx at half the dose (5e12 VG, n=5) or vehicle (n=5). Mean BW and food intake were measured daily over 57 days. Treatments were well-tolerated.



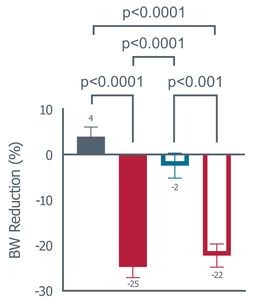
HFD = high-fat diet
I.P. = intraperitoneal injection
S.C. = subcutaneous injection
VG = vector genomes
Sema = semaglutide
BW = body weight

Figure 3. Single-dose GLP-1-based PGTx Durably Reduced Body Weight and Maintained Body Weight Reduction After Sema Withdrawal. On day 28 post-treatment, BW was decreased by 27% with single-dose GLP-1-based PGTx vs. 21% with daily Sema ($p<0.05$). GLP-1-based PGTx-induced BW loss was maintained to 57 days post-treatment ($p<0.0001$) (**A**). Sema withdrawal resulted in regain of BW to -2% below baseline, while treatment of Sema-withdrawn animals with GLP-1-based PGTx stabilized 28-day BW loss at -22% below baseline at day 57 ($p<0.001$) (**A** & **B**). Mean food intake paralleled BW changes in all treatment groups (**C**). All data are represented as mean ± standard error of the mean.

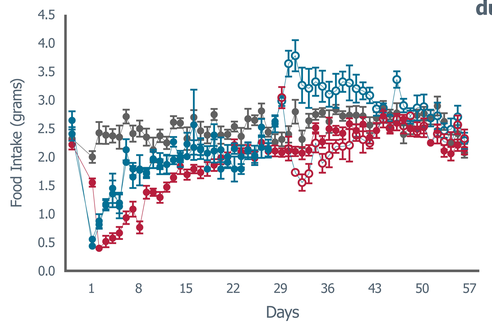
A. Change in BW Over Time



B. End of Study BW Change

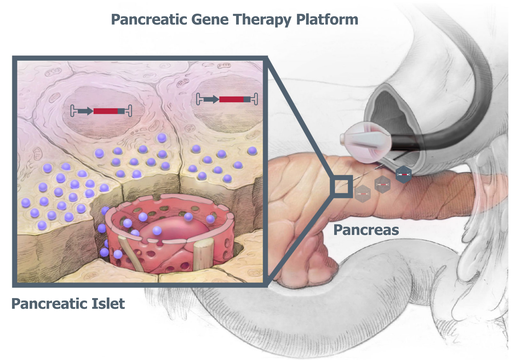


C. Food Intake Over Time



AAV Vehicle
GLP-1-based PGTx (1e13 VG)
Sema (10 nmol/kg/d)
Sema Withdrawal + Vehicle
Sema Withdrawal + GLP-1-based PGTx (5e12 VG)

Pancreatic Gene Therapy Platform



CONCLUSIONS

- **Single-dose GLP-1-based PGTx can durably reduce BW and also maintain BW reduction upon Sema withdrawal.**
- **These data suggest that PGTx has the potential to advance GLP-1-based therapies toward durable efficacy for metabolic diseases.**

Reference: [1]Lubaczeuski et al. 2023 Keystone Symposia. Poster no. 1025.

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

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