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

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Abstract Word Limit: 248/250 words

Abstract

Background: GLP-1-based therapies demonstrate clinical efficacy in obesity, yet durability of effect remains a challenge with most patients regaining weight post-treatment discontinuation. We've developed a novel AAV gene therapy platform enabling durable production of therapeutic proteins by the pancreas. Here, we assessed the efficacy and durability of a single-dose, GLP-1-based, pancreatic gene therapy (PGTx) compared to daily semaglutide (Sema) in a murine, diet-induced, obesity model.

Methods: C57BL/6 mice were fed a 60% high-fat diet for 25 weeks and then randomized by body weight (BW) into groups: single-dose i.p. PGTx (1e13 VG, n=10), daily s.c. Sema (10 nmol/kg/d x 4 weeks, n=10), i.p. PGTx vehicle control (n=8), and daily s.c. Sema vehicle control (n=8). Sema was subsequently withdrawn on day 29, and mice were given PGTx (5e12 VG, n=5) or vehicle (n=5). Mean BW and food intake were measured daily over 57 days.

Results: Treatments were well-tolerated. On day 28 post-treatment, BW was reduced by 27% with single-dose PGTx vs. 21% with daily Sema ($p<0.05$). PGTx-induced BW loss was maintained to 57 days post-treatment ($p<0.0001$). Sema withdrawal resulted in regain of BW to -2% below baseline, while treatment of Sema-withdrawn animals with PGTx stabilized 28-day BW loss at -22% below baseline at day 57 ($p<0.01$). Mean food intake paralleled BW changes in all treatment groups.

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

Keywords* (5 maximum):
gene therapy
pancreas
adeno-associated virus
GLP-1

Abbreviations (5 maximum):**
i.p.: intraperitoneal injection
s.c.: subcutaneous injection
GLP-1: glucagon-like peptide-1
AAV: adeno-associated virus
VG: vector genomes