Poster 507



An ultra-low dose of a localized CNS gene therapy for severe pediatric obesity

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Developing AAV-BDNF gene therapy for severe pediatric obesity syndromes

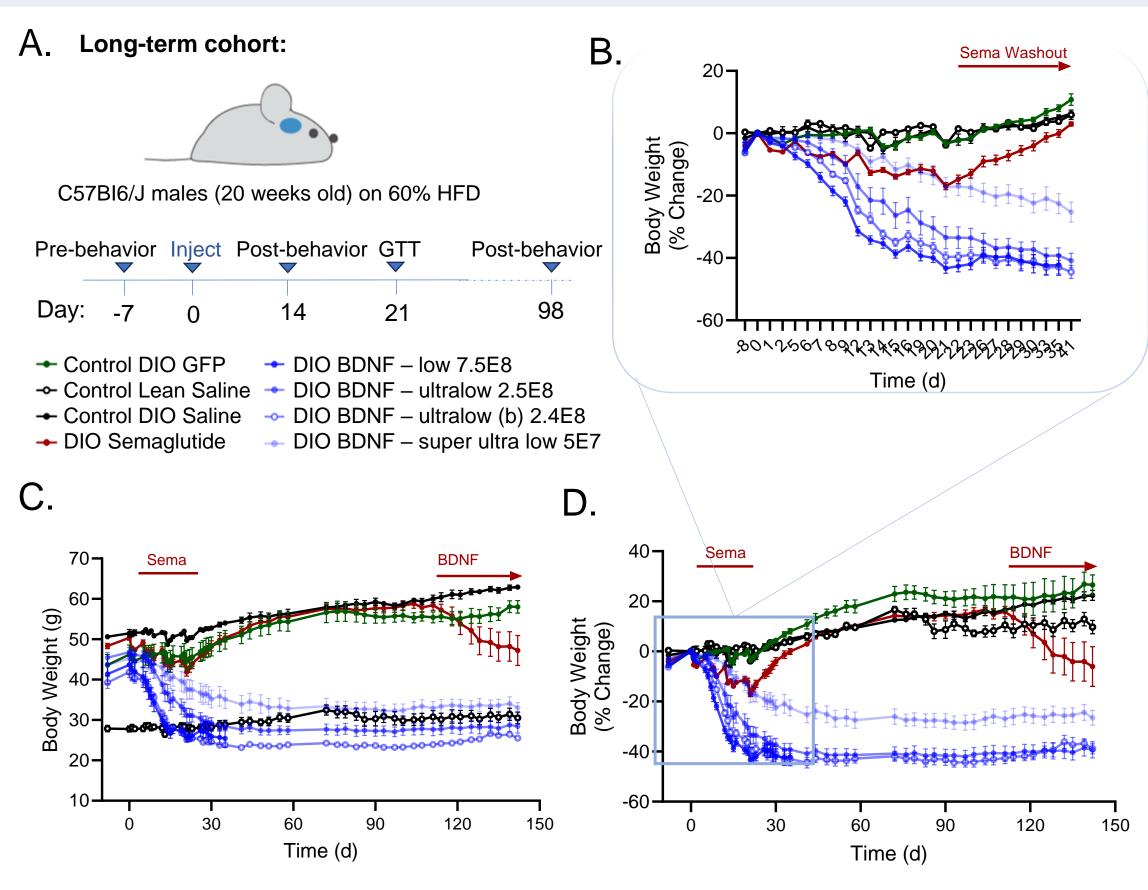
Elevated leptin signals melanocortin 4 receptor (MC4R) expressing neurons to release brain-derived neurotrophic factor (BDNF). BDNF signals through its receptor TrkB and leads to decreased food intake

> Mutations in BDNF (haploinsufficiency) and MC4R (loss of function) cause **severe pediatric obesity syndromes** in humans.

> > Overexpression of BDNF in various genetic and environmental obesity mouse models can rescue a wide range of obesity-related phenotypes.

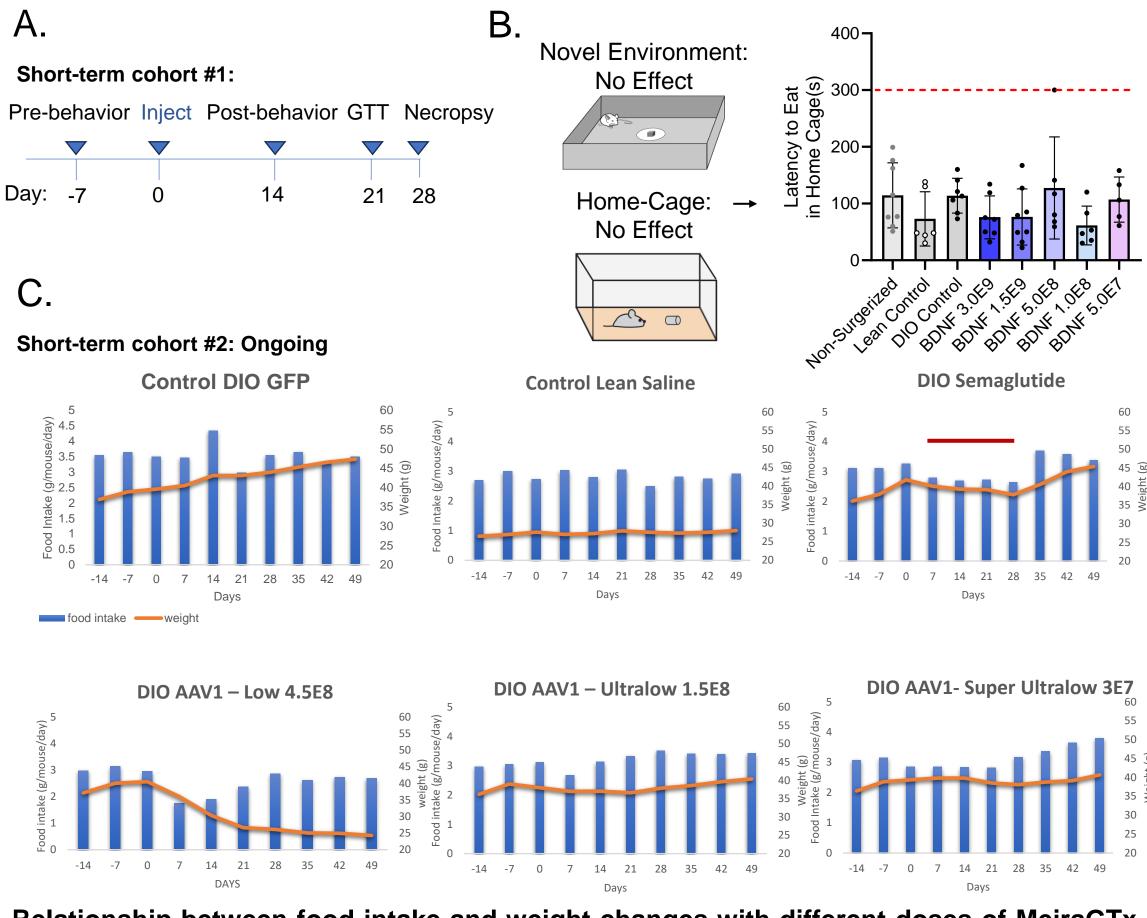
In the ventromedial hypothalamus, the leptin-proopiomelanocortin pathway initiates feeding or fasting through two opposing neuronal populations. In a fed state, elevated leptin signals a decrease in food intake via the release of BDNF from MC4R expressing neurons¹. BDNF haploinsufficiency or de novo mutations in MC4R can cause severe obesity in human patients²⁻⁴. Compared to current therapeutic approaches such as glucagon-like peptide 1 (GLP1) agonists and MC4R agonists, using an adeno-associated virus (AAV)-based gene therapy to deliver BDNF provides more durable and significant effects on patients with MC4R deficiency, including patients with homozygous mutations. We previously optimized the BDNF gene therapy cassette which expresses BDNF protein 19-fold higher than the published construct⁵ in vivo and over 143fold higher than endogenous levels. Here, we investigate the minimum effective dose of this highly potent vector. With such a high-expressing construct, we aim to achieve therapeutic efficacy at a lower viral vector dose which may improve manufacturing and safety outcomes.

A single dose of MeiraGTx-BDNF in the VMH induces rapid and long-lasting weight loss in diet-induced obesity (DIO) mice



Efficacy of MeiraGTx-BDNF in a DIO mouse model. Animals were placed on 60% high-fat or sucrose-matched control diet. Animals were weighed daily for the first four weeks post surgery and then biweekly thereafter. (A) Long term cohort: Different doses of AAV1-BDNF were unilaterally injected into the hypothalamus of DIO C57Bl6 male mice at around 20 weeks of age (B) Percent body weight change after AAV1-BDNF delivery in the first 41 days post surgery. (C) (D) Long-term weight change and percent body weight change after AAV1-BDNF delivery in DIO mouse model is durable up to 5 months. Observations are still ongoing.

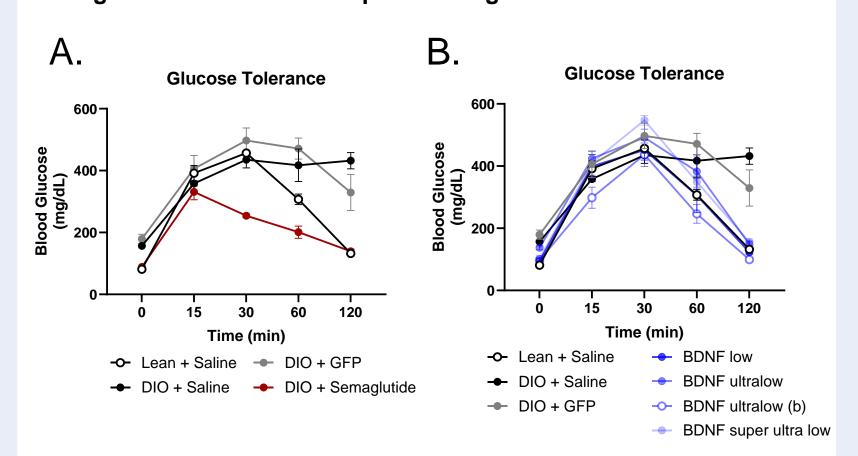
Dose-dependent reduction in daily food intake in MeiraGTx-**BDNF** treated DIO mice



Relationship between food intake and weight changes with different doses of MeiraGTx-BDNF. (A) Experimental timeline for short-term cohort 1. (B) Illustration of novelty suppressed feeding assay. Latency to eat in home-cage is shown for all dosing groups and control groups (C) Combination charts show the temporal dynamics between food intake and weight by group. The red bar on the DIO Semaglutide graph indicates the four-week period of daily dosing (9.7)

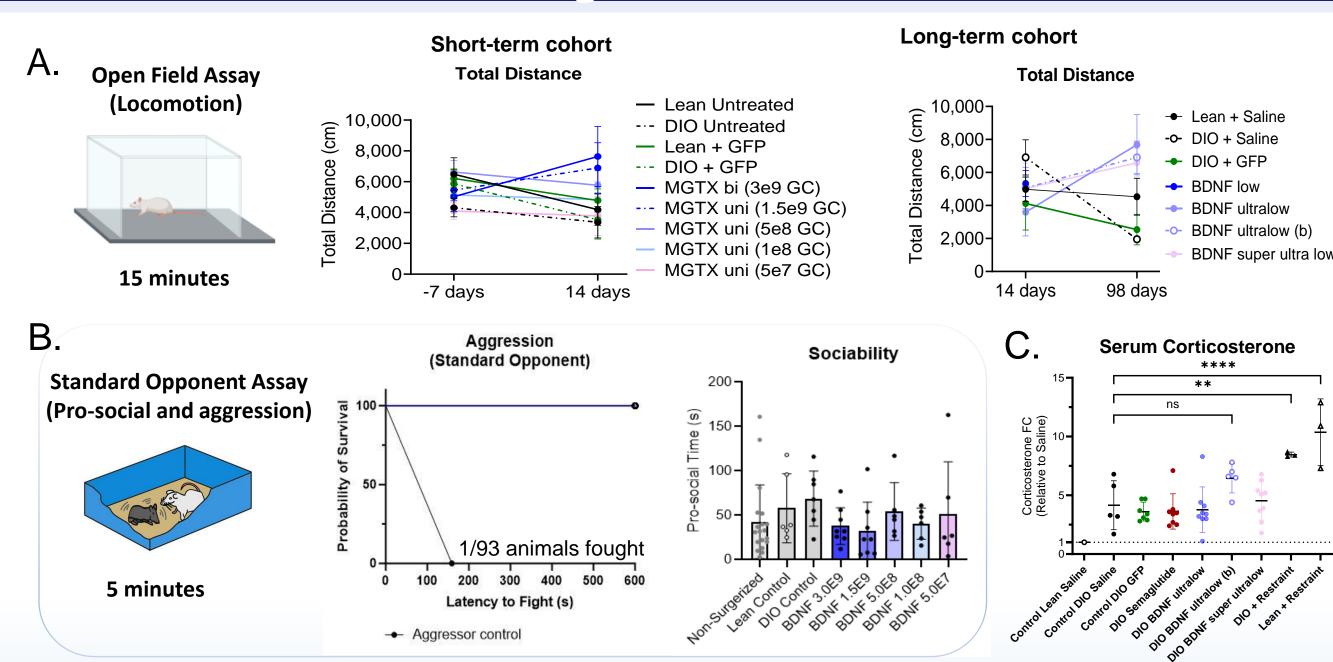
Improved glucose tolerance after **MeiraGTx-BDNF** treatment

Long-term cohort: 3 weeks post-dosing



Effect of MeiraGTx-BDNF treatment on glucose tolerance. Animals were fasted overnight, then injected the next day with 2g/kg glucose intraperitoneally. Blood glucose was measured at baseline and 15, 30, 60, and 120 minutes after glucose injection. All doses of MeiraGTx-BDNF treatment show improved glucose tolerance compared to control AAV-GFP-expressing obese mice. (A) Effect of Semaglutide (9.7 nmol/kg, daily) treatment on glucose tolerance. (B) Impact of different doses of MeiraGTx-BDNF on glucose tolerance.

Increased locomotion but no deficits in aggression or social behaviors following MeiraGTx-BDNF treatment



Social behavior assessments before and after MeiraGTx-BDNF treatment. (A) Open field assay for locomotion measures total distance travelled pre-surgery, 14- and 98-days post-surgery. (B) Standard opponent assay for aggression and social behaviors measures the latency to fight and pro-social time of treated animals. (C) Serum corticosterone levels were measured by ELISA 85 days after surgery.

Conclusions

Our highly potent gene therapy, MeiraGTx-BDNF, has significant potential to be a safe, effective, and durable therapeutic strategy for patients suffering from severe early-onset pediatric obesity syndromes.

- Unilateral delivery of MeiraGTx-BDNF to the ventromedial hypothalamus of obese mice on high-fat diet reduced food intake and increased locomotion.
- Treated animals lost up to 40% of their body weight, plateauing at the level of wild-type lean controls.
- Weight loss was durable for over five months at the time of this poster and will be monitored for the natural lifespan of the animals.
- Glucose tolerance was also improved in mice treated with MeiraGTx-BDNF indicating a return to a healthy metabolic state despite the chronic consumption of a high-fat diet.
- MeiraGTx-BDNF treatment did not disrupt other behaviors controlled by the hypothalamus such as pro-social interactions and did not heighten aggression.

References

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