



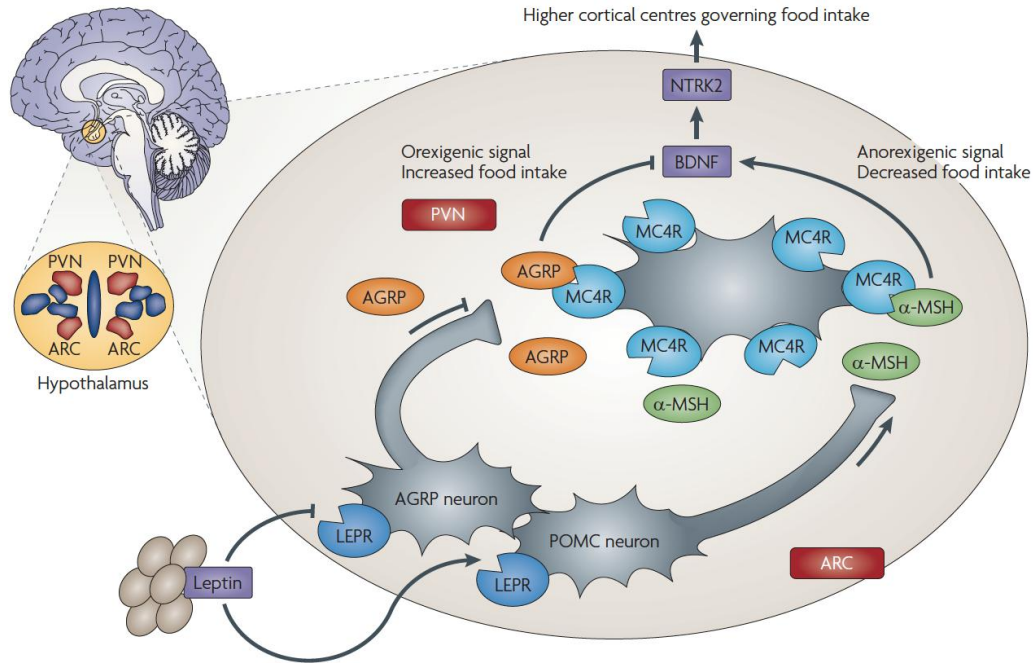
Durable Rescue of Metabolic and Neurobehavioral Phenotypes via Unilateral AAV-BDNF in a Model of Syndromic Obesity

ASGCT 2026
Boston, MA

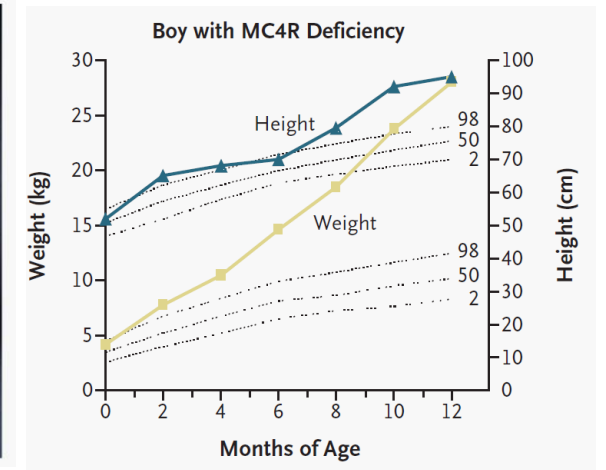
Josefa Sullivan
Senior Director
Vector Design & Optimization

Hypothalamic BDNF signaling controls feeding and satiety

Mutations in the MC4R-> BDNF-> TrkB pathway drive hyperphagia and severe pediatric obesity syndromes



MC4R Deficiency

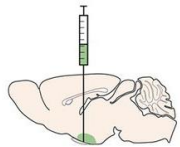


Bespoke BDNF vector optimization increases expression 14-fold *in vivo*

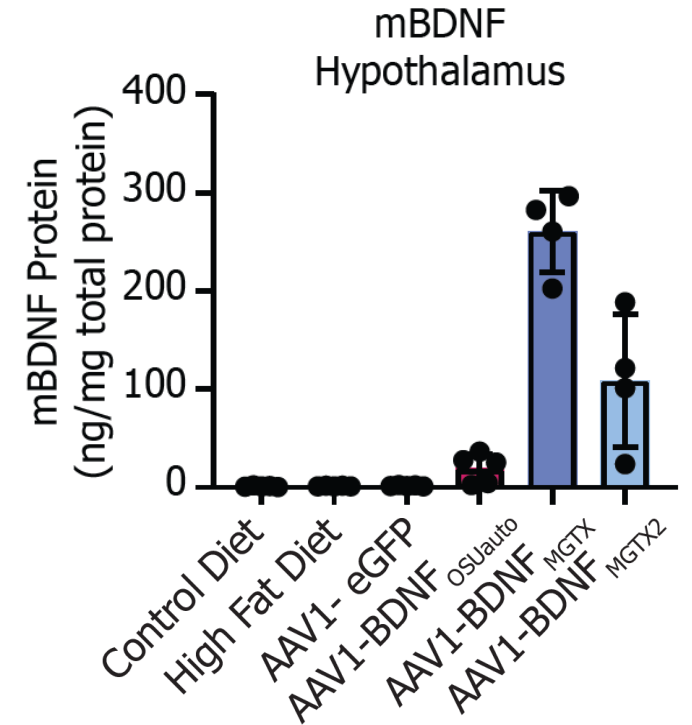
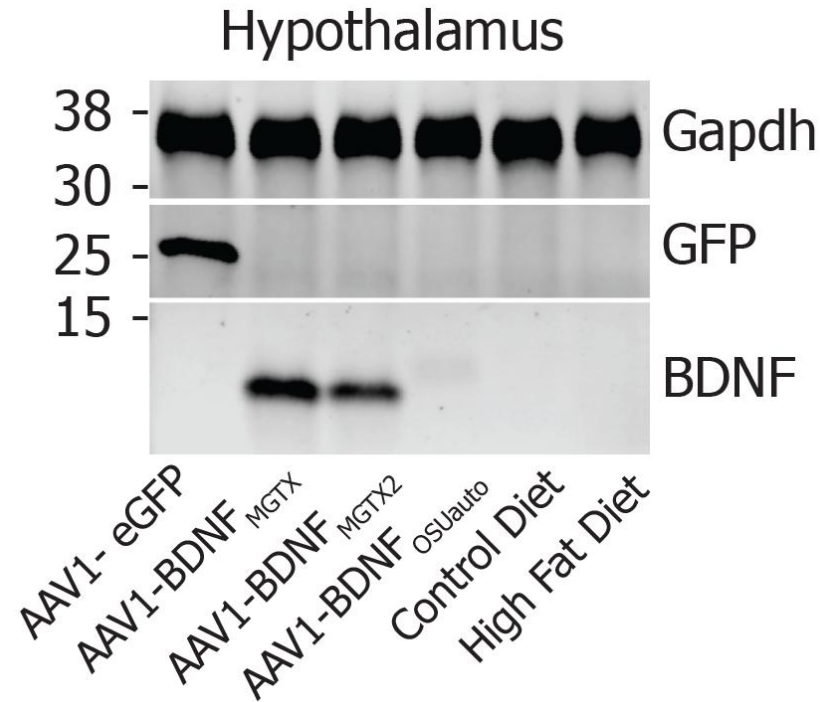
Increasing vector potency may enable therapeutic efficacy at lower doses and improve manufacturability

In-house vector engineering platforms

Extensive in-house vectorology capabilities addressing each element of the vector genome sequence

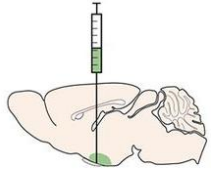


WT ♂ + High Fat Diet (45%)
Bilateral, VmH
2E9 VG/hemisphere

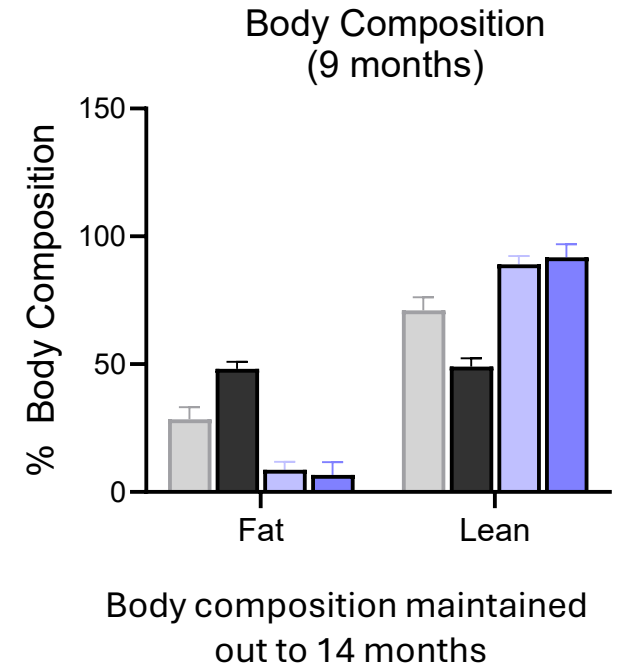
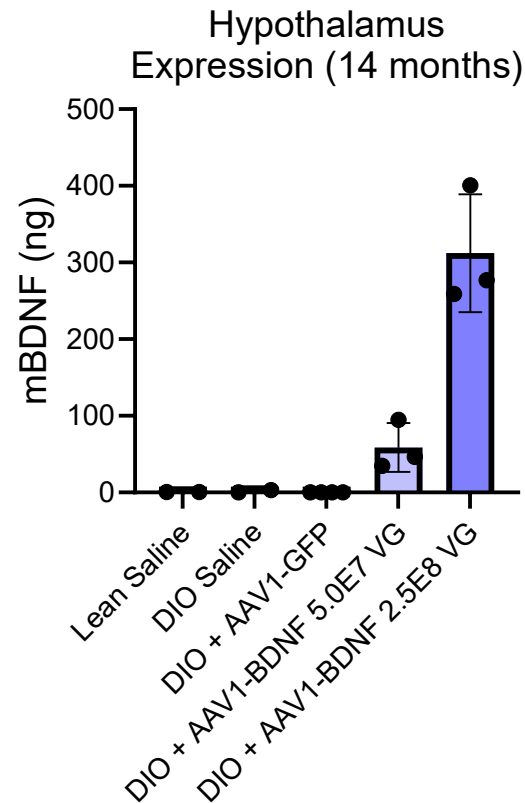
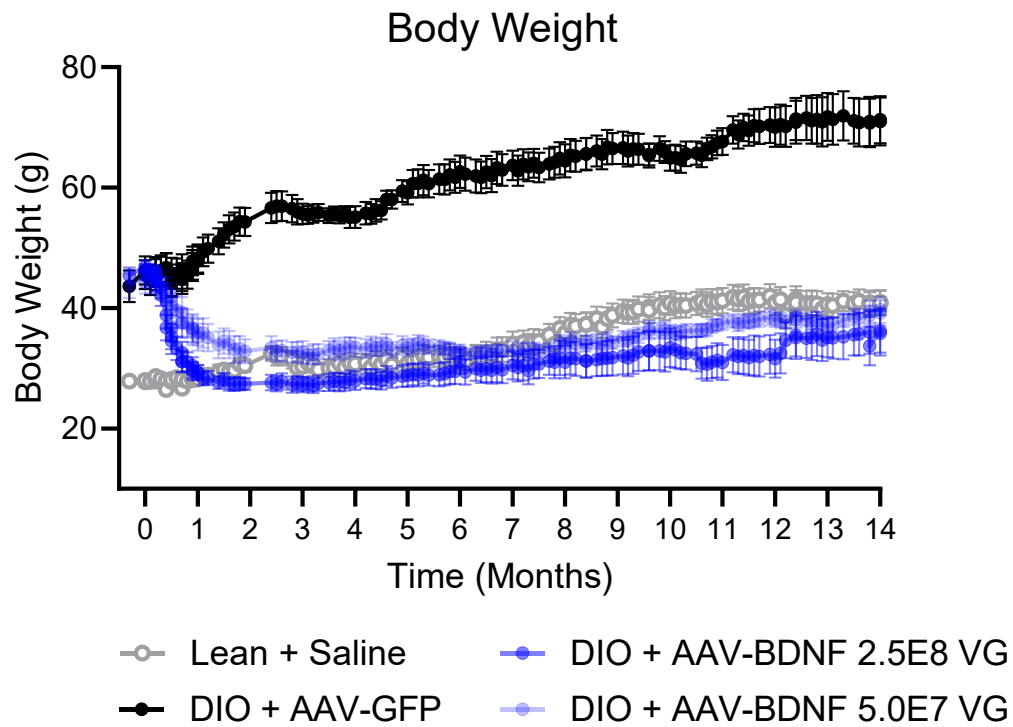


A single unilateral injection causes durable, self-limiting weight loss

Body weight stabilizes at lean-control levels and is maintained for 14 months without cachexia in diet-induced obesity model



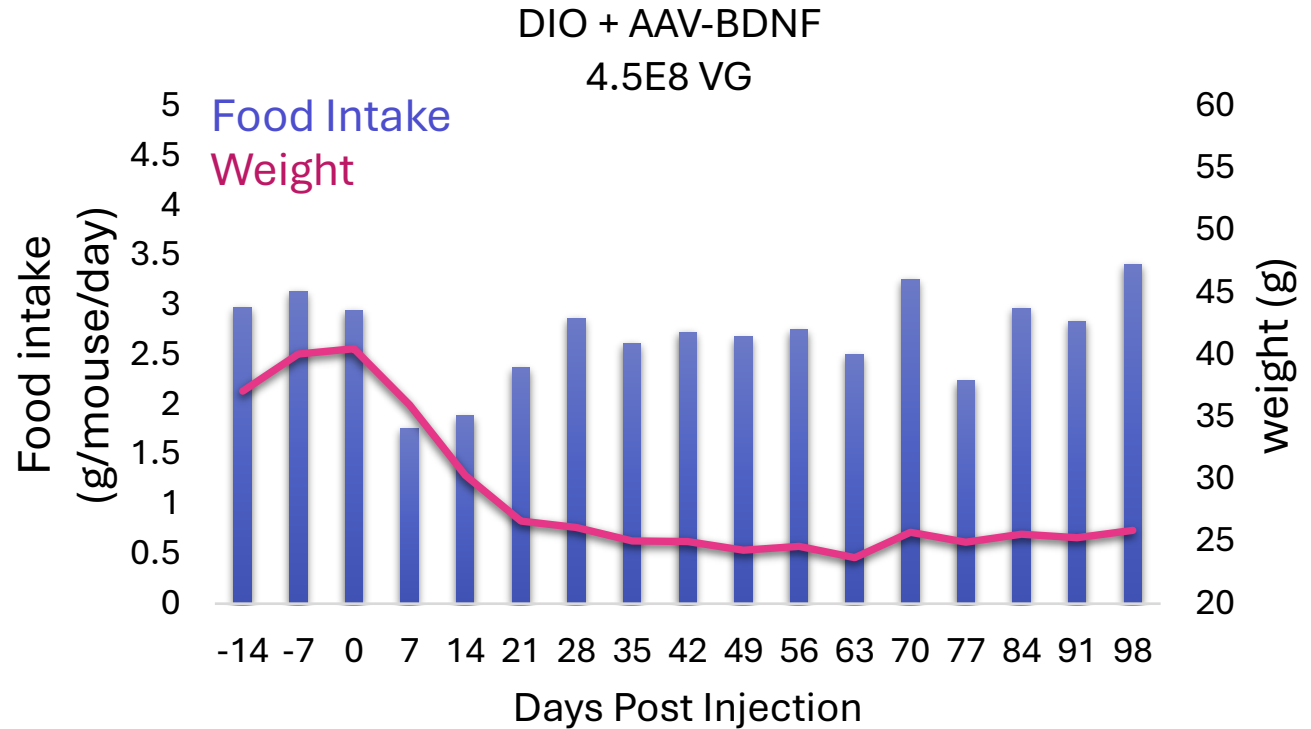
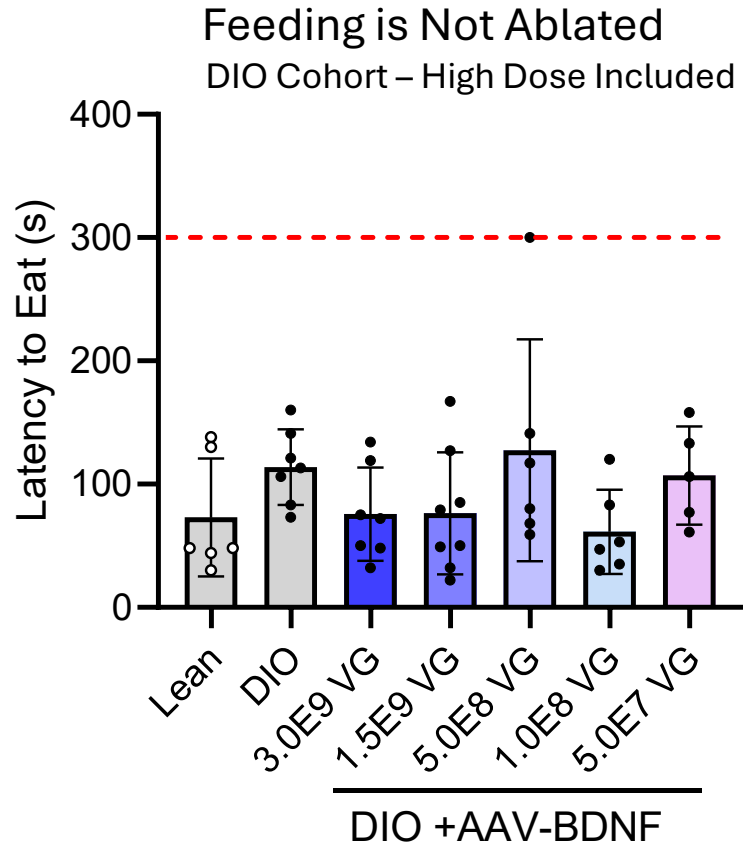
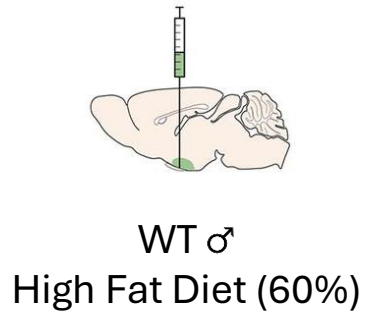
WT ♂ + High Fat Diet (60%)
Unilateral, VmH



Body Weight ****p<0.0001 Two-way RM Anova
Body composition ****p<0.0001 Two-way Anova with multiple comparisons
%Lean Timecourse ****p<0.0001 Two-way RM ANOVA with multiple comparisons

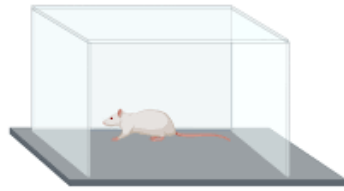
Food intake is transiently reduced after AAV-BDNF treatment in DIO mice

High dose levels of AAV-BDNF does not ablate the ability of animals to consume food

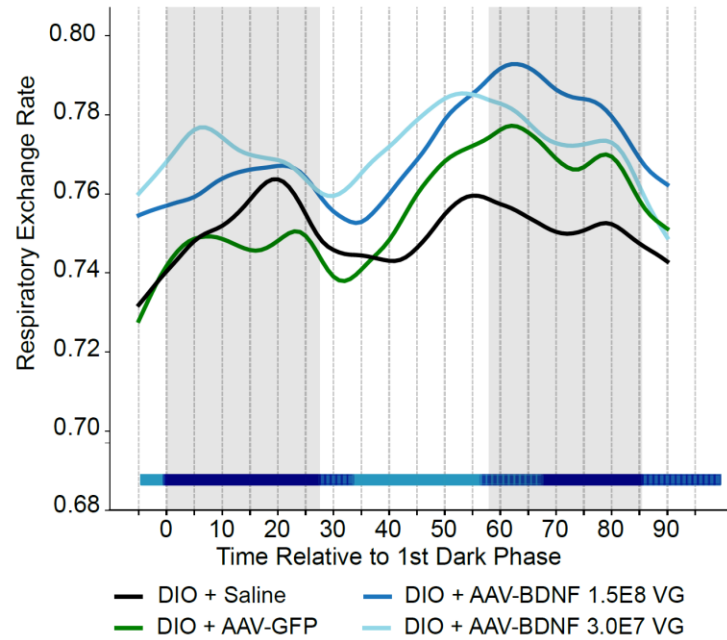
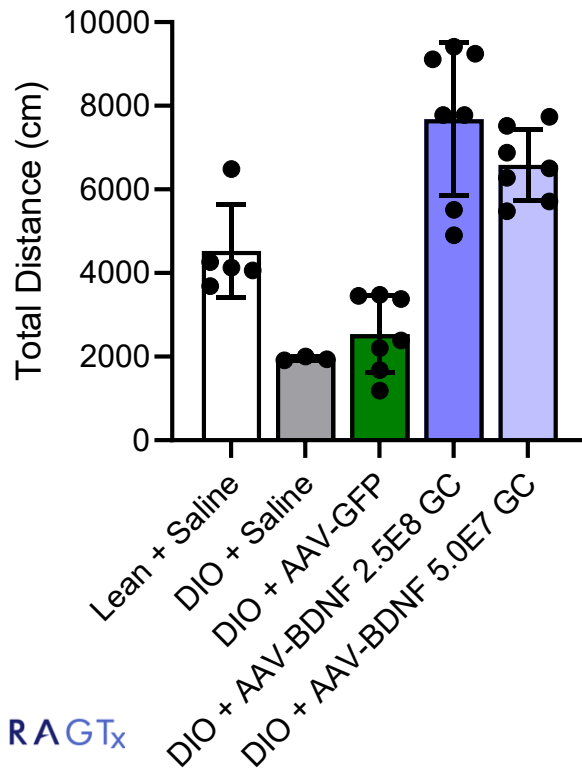
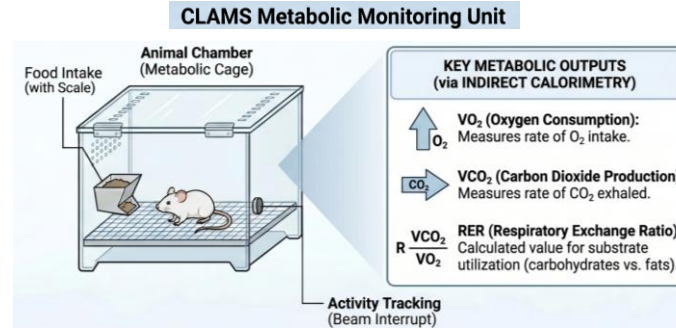


AAV-BDNF treatment increases activity and metabolism in DIO mice

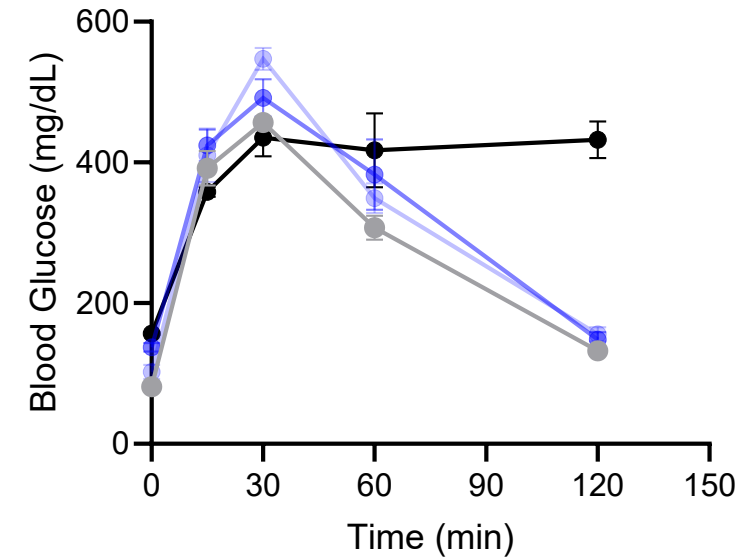
WT ♂
High Fat Diet (60%)
Unilateral



Locomotion

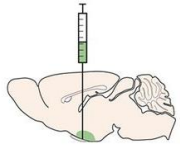


Glucose Tolerance

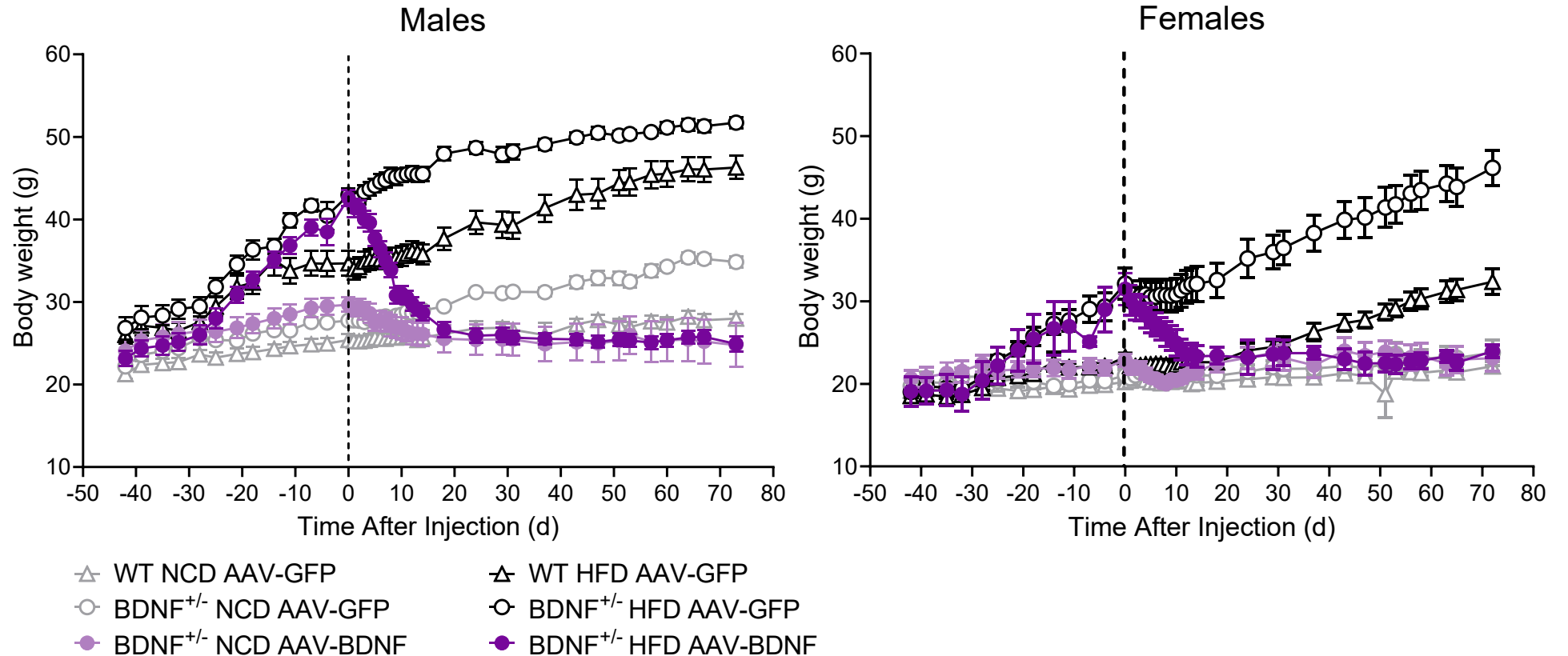


AAV-BDNF reduces weight in a genetic model of BDNF haploinsufficiency

MeiraGTX generated vector is effective in both male and female BDNF heterozygous mice

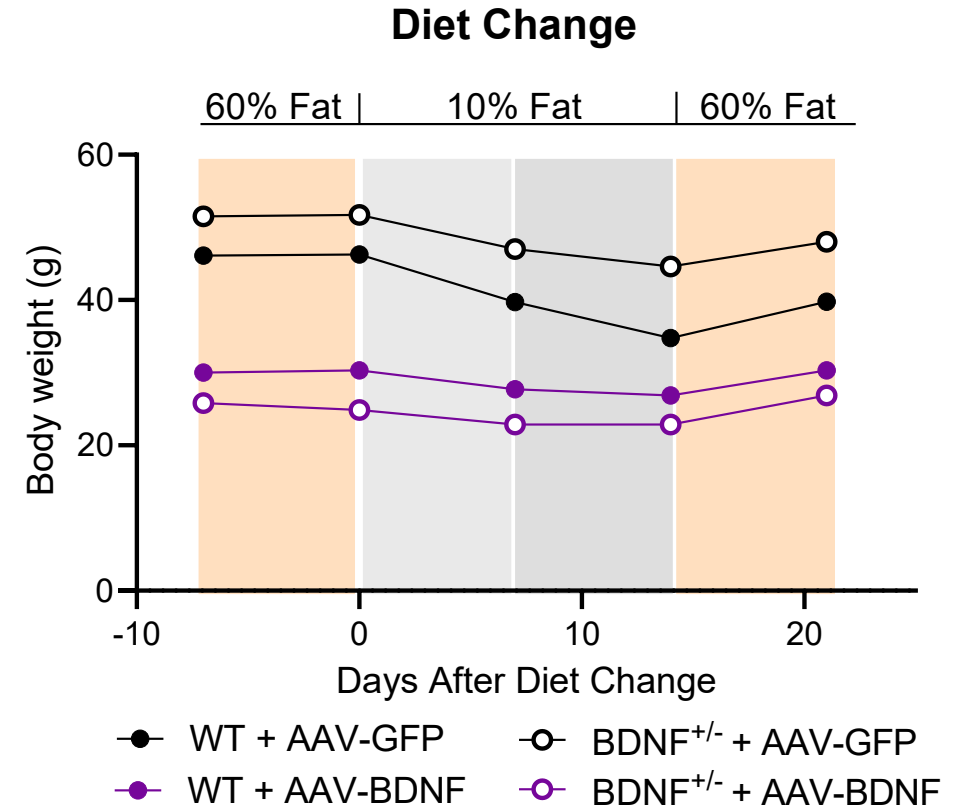
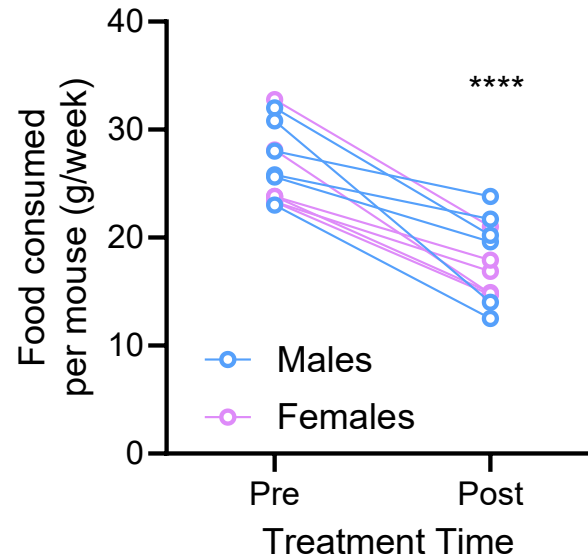
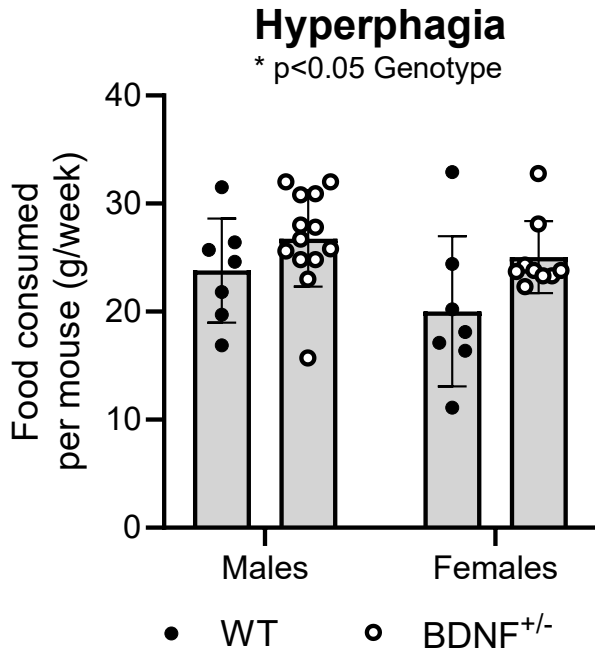


WT & BDNF^{+/-}
♂ & ♀
Control & High Fat Diet (60%)
Unilateral 2.5E8 VG

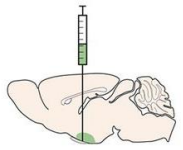


AAV-BDNF suppresses hyperphagia while maintaining metabolic flexibility

Metabolic system remains flexible in context of BDNF over-expression

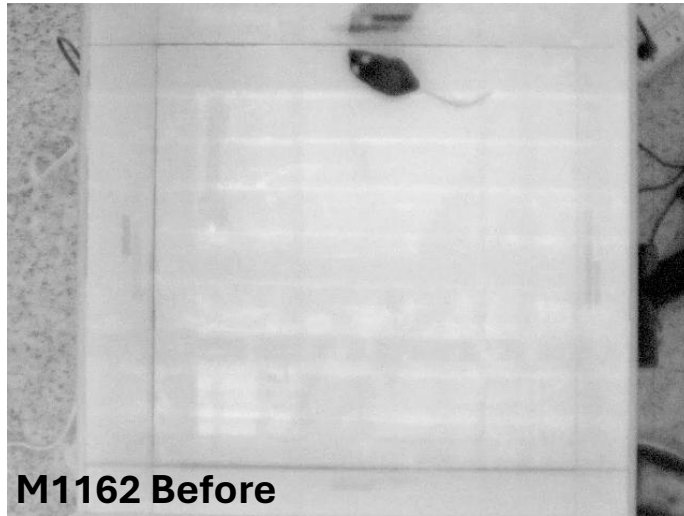


AAV-BDNF reduces aggression in BDNF haploinsufficient mice

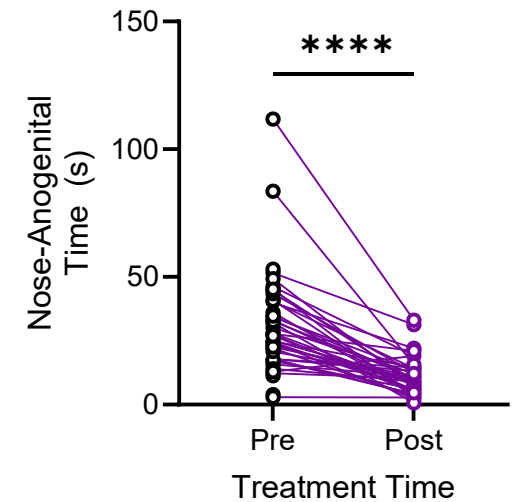
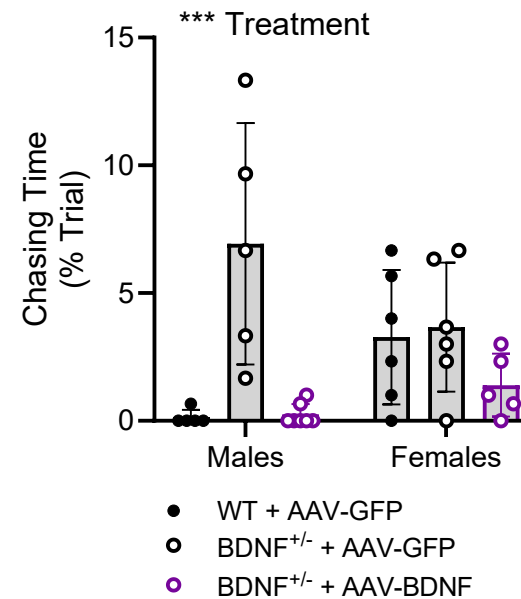
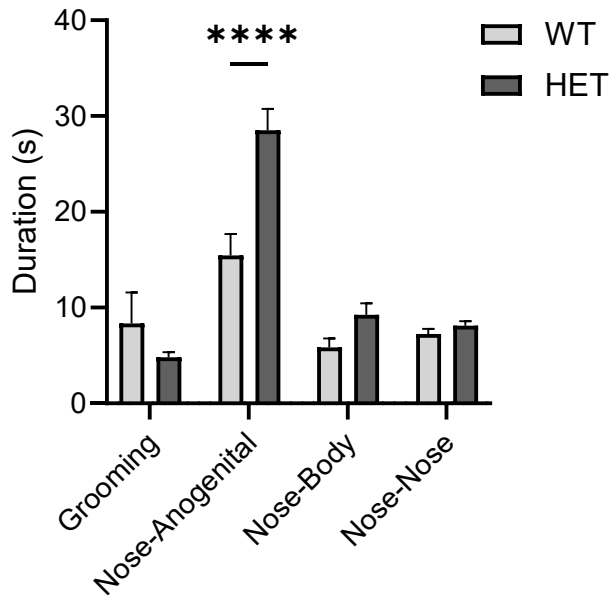
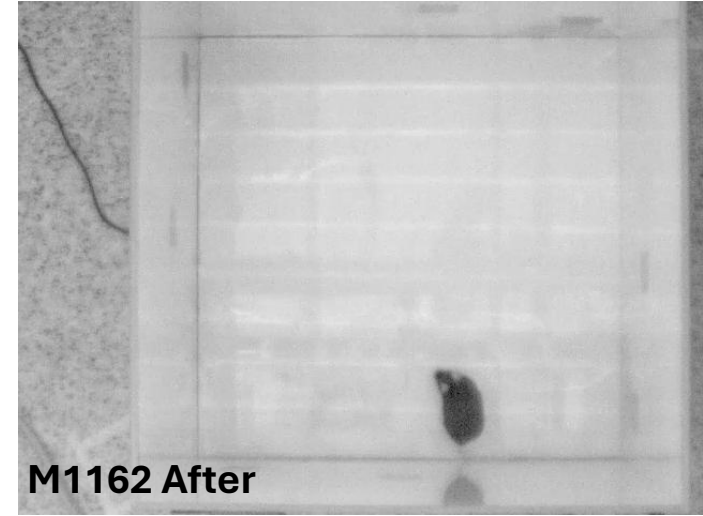


WT & BDNF^{+/-}
 ♂ & ♀
 Control & High Fat Diet (60%)
 Unilateral 2.5E8 VG

BDNF^{+/-} Mouse
 before AAV-BDNF



BDNF^{+/-} Mouse
 after AAV-BDNF



Durable Rescue of Metabolic and Neurobehavioral Phenotypes via Unilateral AAV-BDNF in a Model of Syndromic Obesity

Conclusions

- AAV-BDNF is a potent vector which causes long-lasting weight loss without cachexia in mouse models of obesity at doses as low as $5.0E7$ VG
- AAV-BDNF normalizes body weight, hyperphagia, and aggression in a mouse model of BDNF haploinsufficiency, a rare pediatric obesity syndrome

Future Work

- Refine neural network analysis to better capture behavioral phenotypes in females
- In situ hybridization to understand the localization of BDNF over-expression in the mouse brain

Acknowledgements

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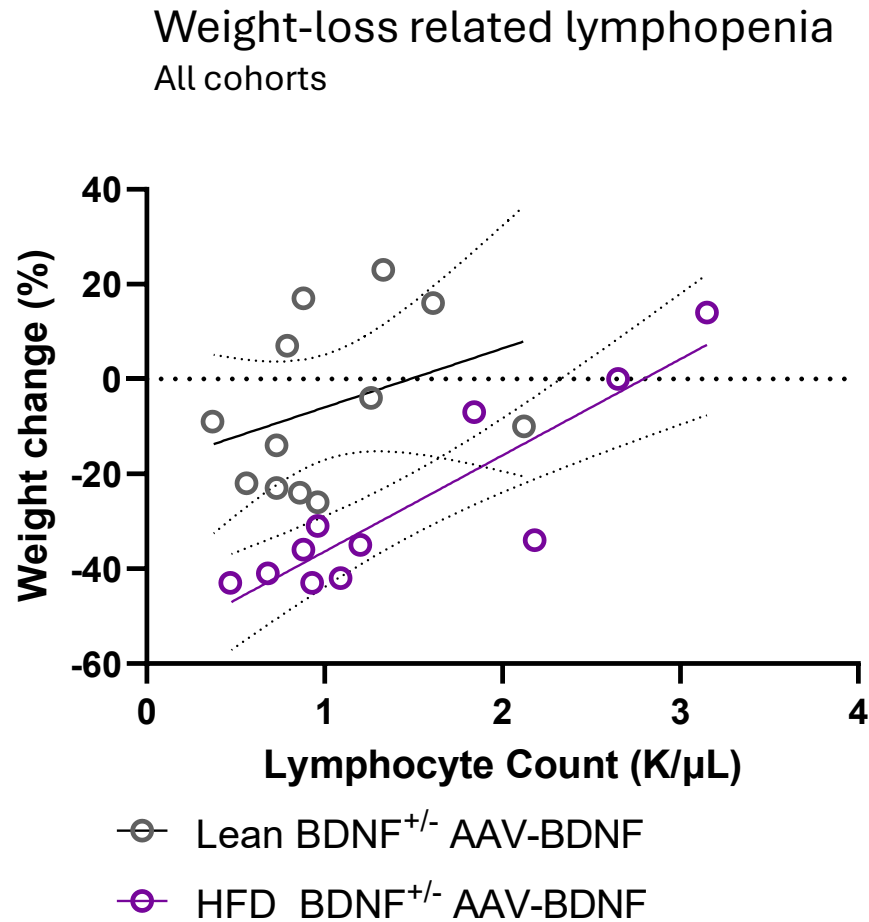
Sadaf Farooqi

Mike Kaplitt



AAV-BDNF is well tolerated in mouse models

Observed lymphopenia has been reported as a consequence of weight loss



Caloric restriction causes transient lymphopenia in mice and humans (PMID: 29804201; PMID: 27410480)

