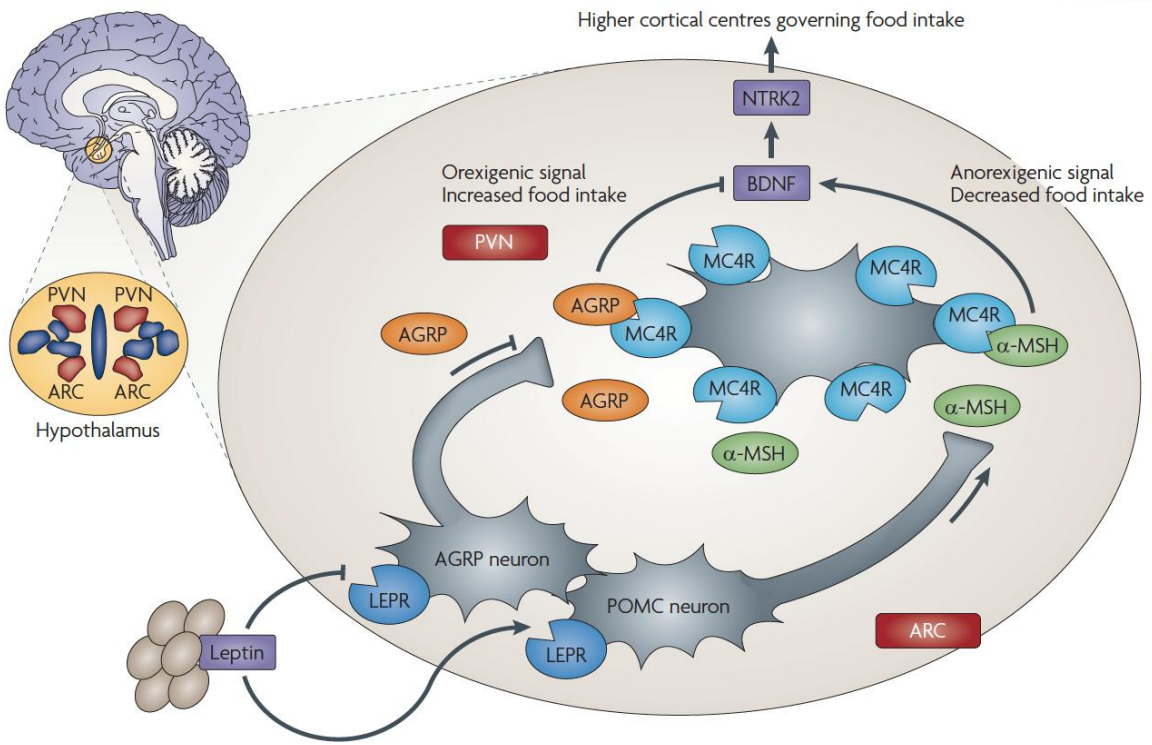


Restoration of the Leptin-Melanocortin Pathway via Hypothalamic AAV-BDNF Rescues Syndromic Obesity

Josefa Sullivan, PhD

BDNF as an Obligate Downstream Node in the Leptin-Melanocortin Satiety Circuit

- Leptin→MC4R→BDNF→TrkB pathway controls feeding and satiety
- Children with BDNF haploinsufficiency experience intractable hyperphagic obesity coupled with severe neurobehavioral comorbidities

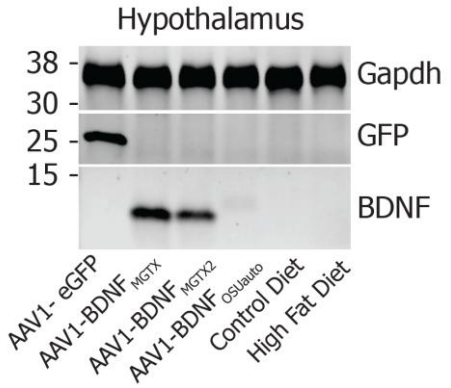


Walley et al. *Nat. Rev. Genetics* 10, 431-442; 2009
Farooqi et al. *N. Engl. J. Med.* 348(12):1085-95; 2003
Dubern et al. *Pharmacol. Res.* 191:106763, 2023

Local, Unilateral Administration Across Environmental and Transgenic Obesity Models

- AAV can deliver high, sustained levels of BDNF to the CNS to rescue metabolic and neurobehavioral phenotypes in monogenic obesity models







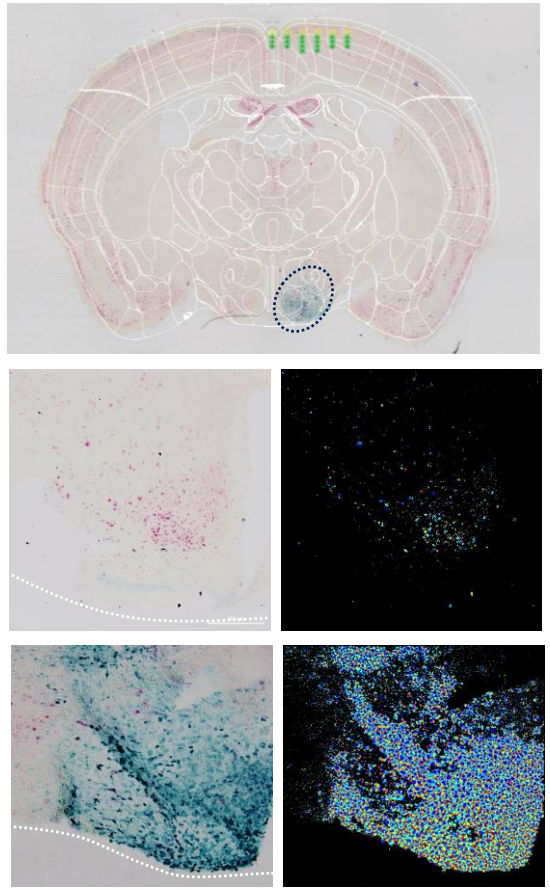
- Diet-Induced Obesity (DIO) Model: Durability, Dosing & Safety Studies

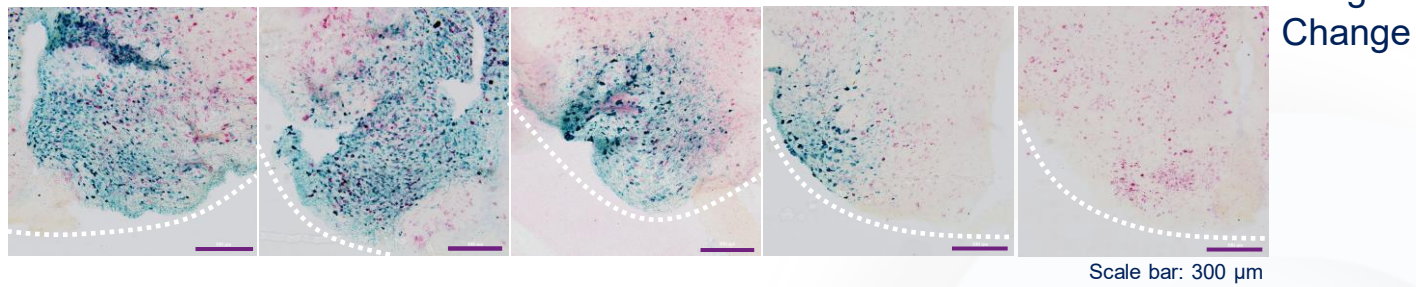
- BDNF Haploinsufficiency Model: Metabolic & Behavioral Efficacy Studies

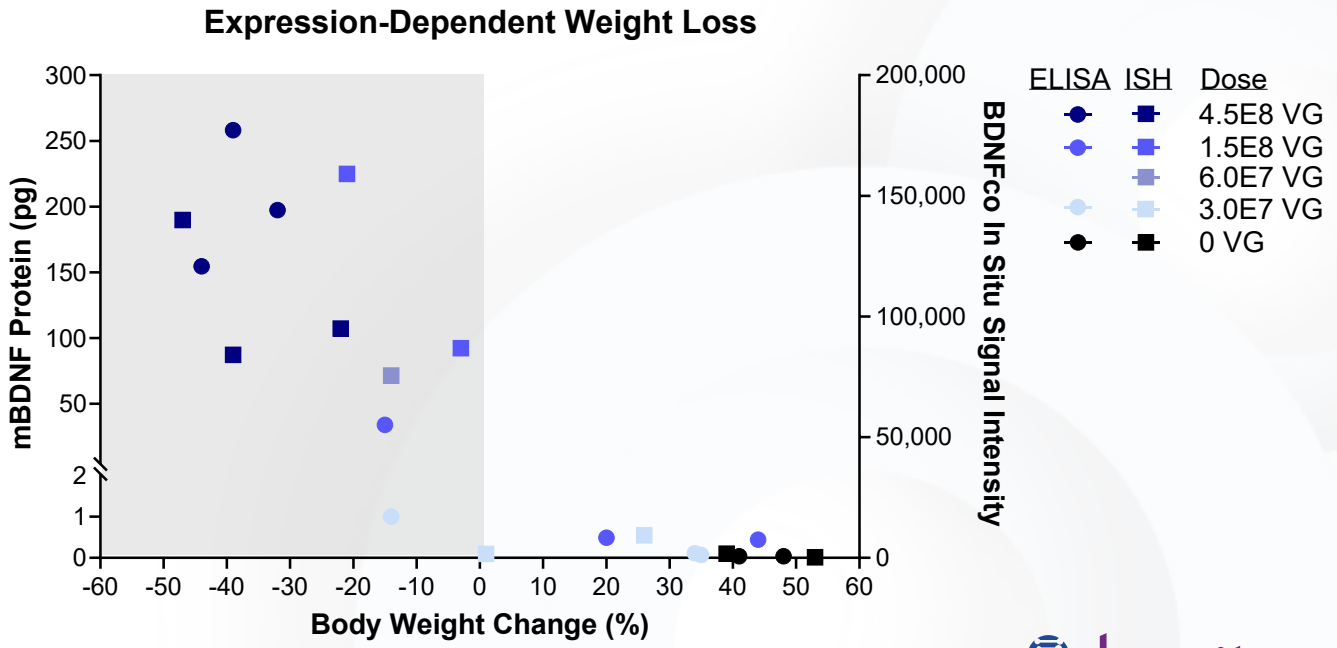
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Hypothalamic BDNF Overexpression Tightly Correlates with Weight Loss

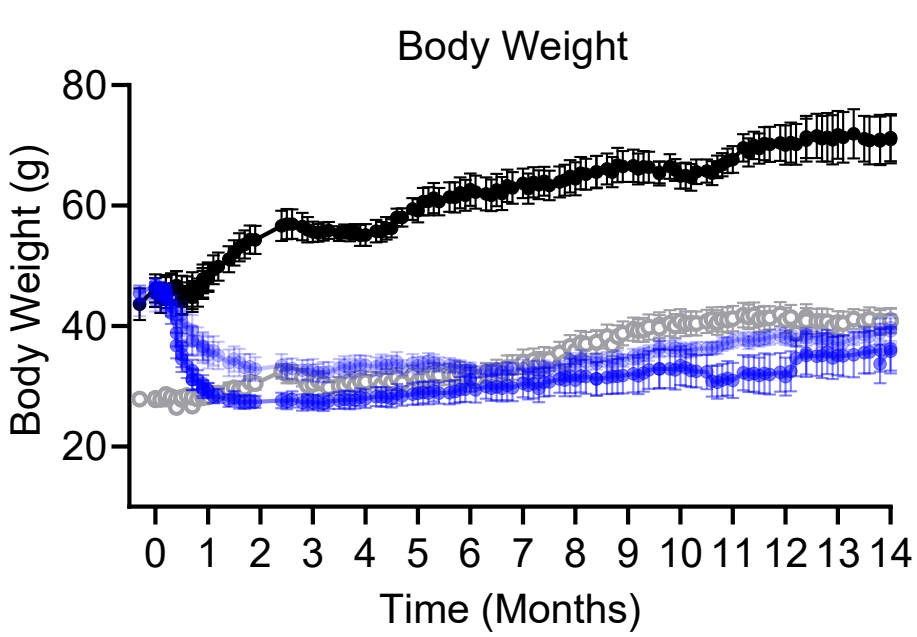
In Situ Hybridization

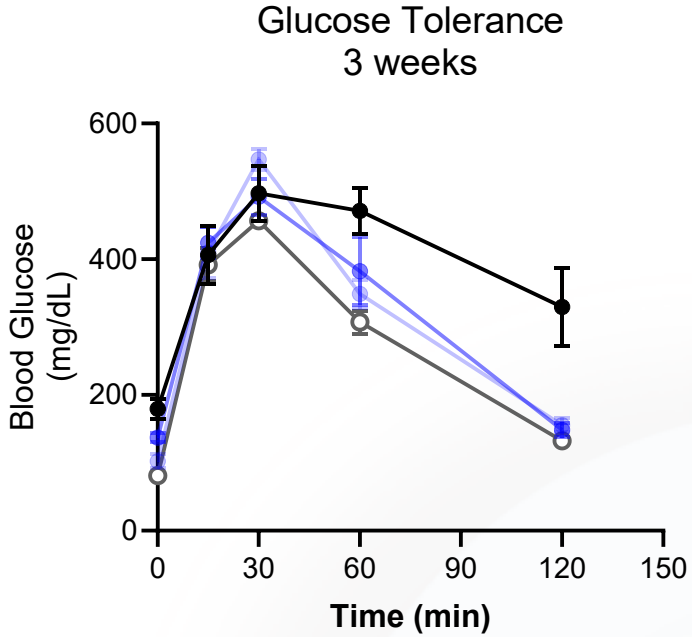


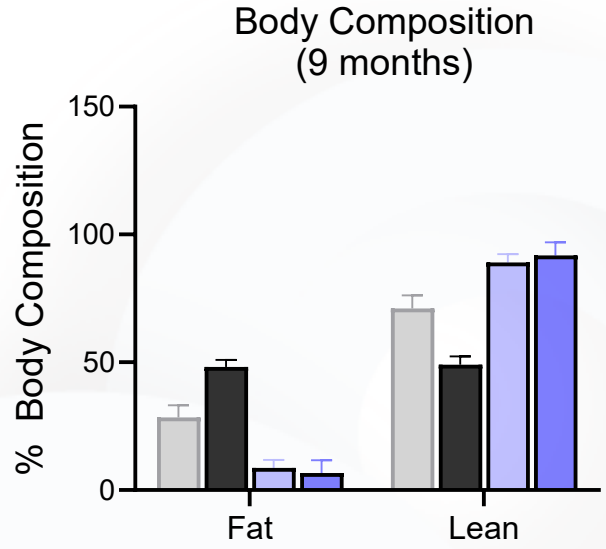




A Single Unilateral Injection Into the VmH Causes Durable, Self-limiting Weight Loss









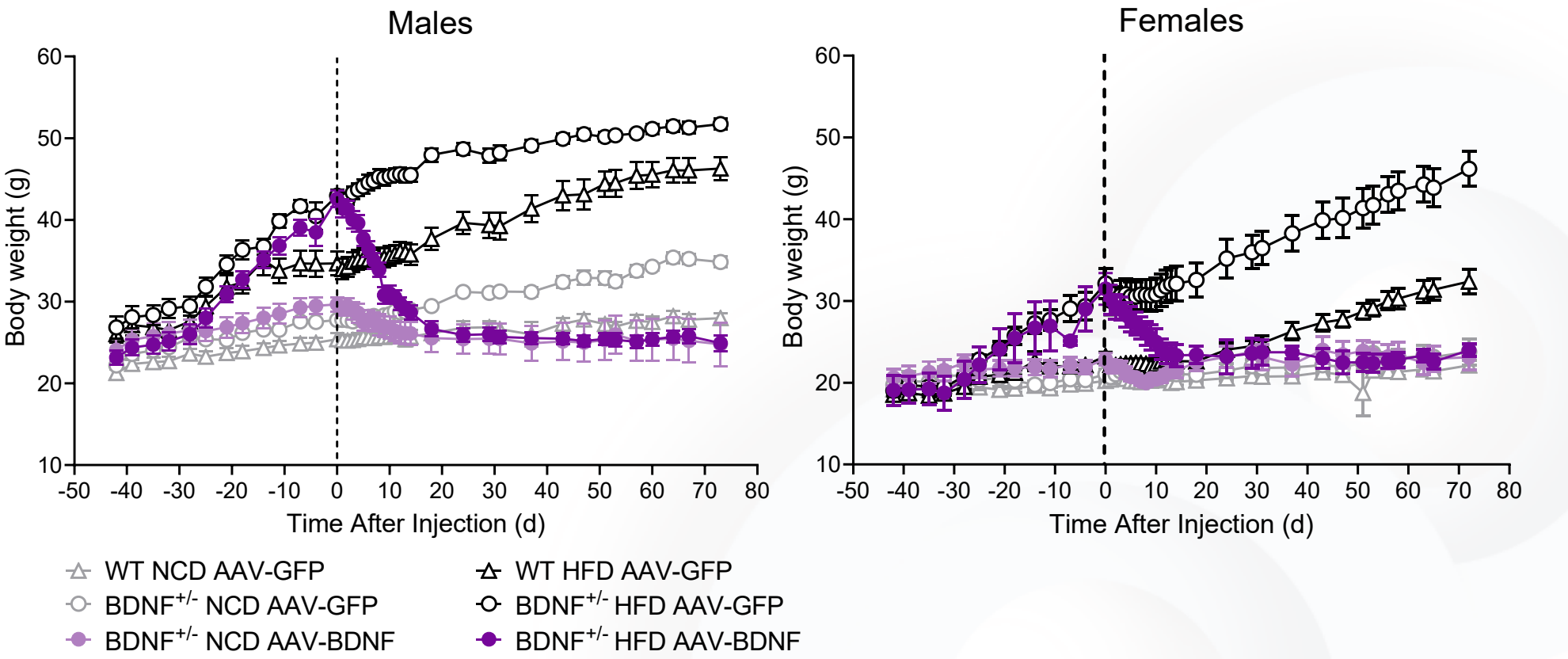
WT ♂ + High Fat Diet (60%)
Unilateral, VmH

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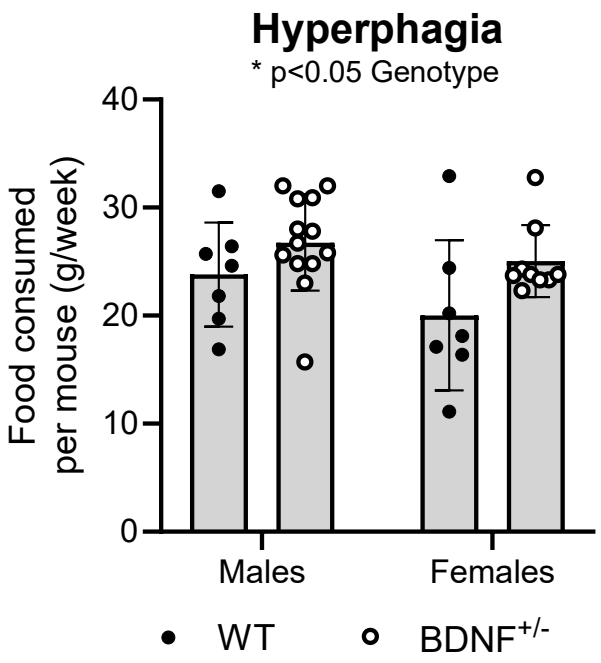
AAV-BDNF Normalizes Weight in a Genetic Mouse Model of BDNF Haploinsufficiency

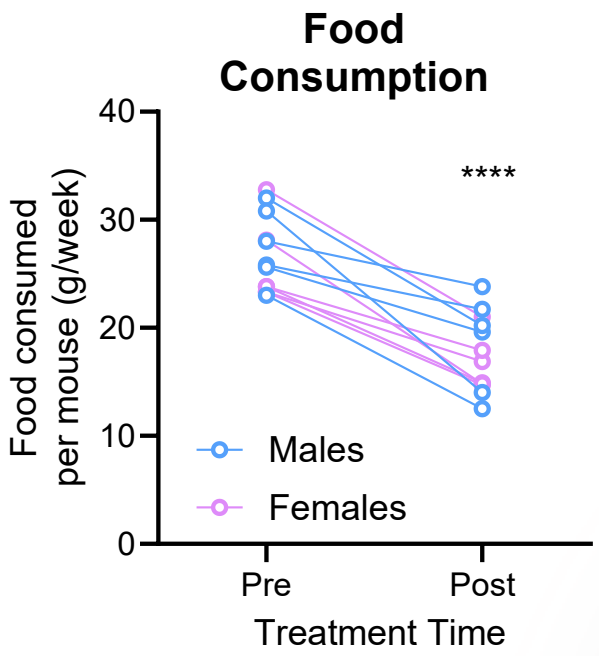


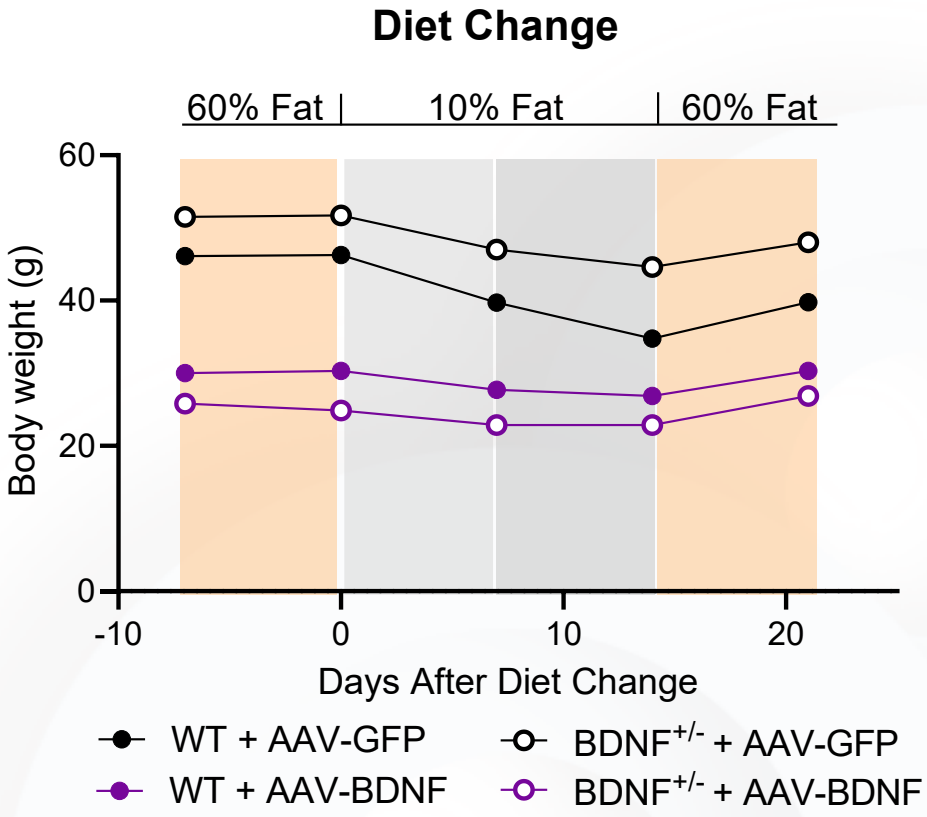
WT & BDNF$^{+/-}$
♂ & ♀
Control & High Fat Diet
Unilateral 2.5E8 VG



Focal Hypothalamic BDNF Restoration Suppresses Hyperphagia While Maintaining Metabolic Flexibility



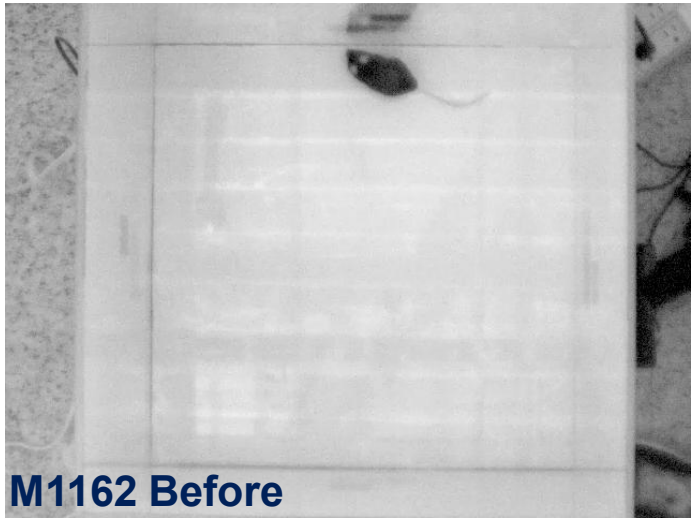




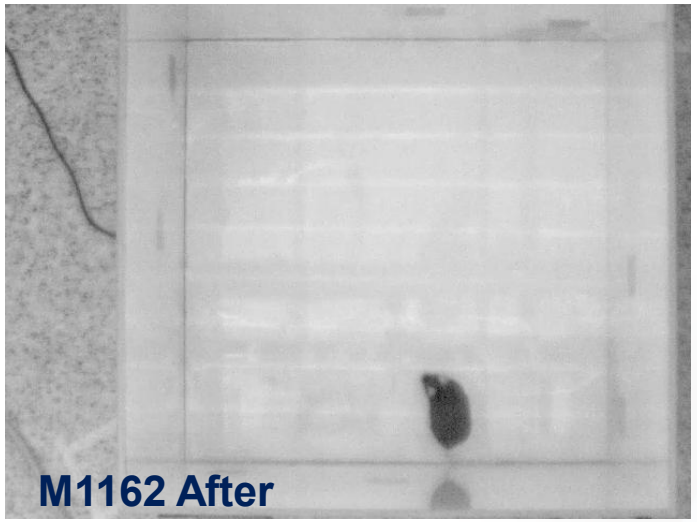
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AAV-BDNF Reduces Aggression in BDNF+/- Haploinsufficient Mice

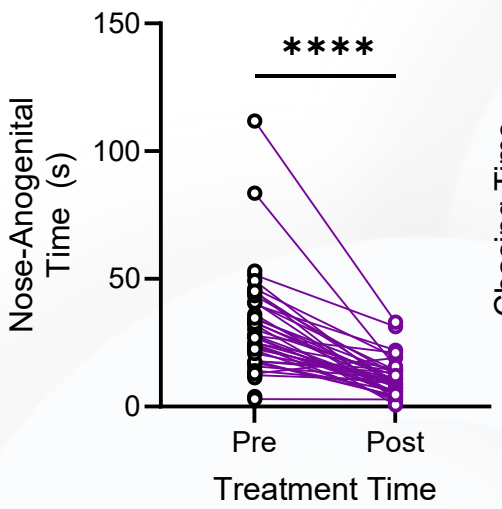
BDNF$^{+/-}$ Mouse before AAV-BDNF



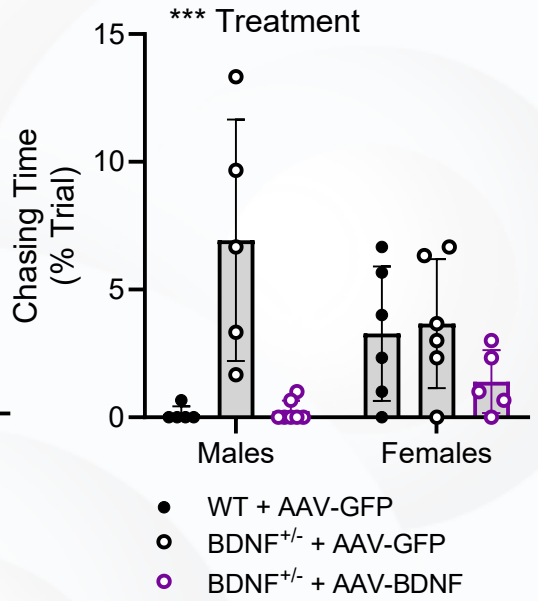
BDNF$^{+/-}$ Mouse after AAV-BDNF



Free Social Assay



Resident Intruder Assay



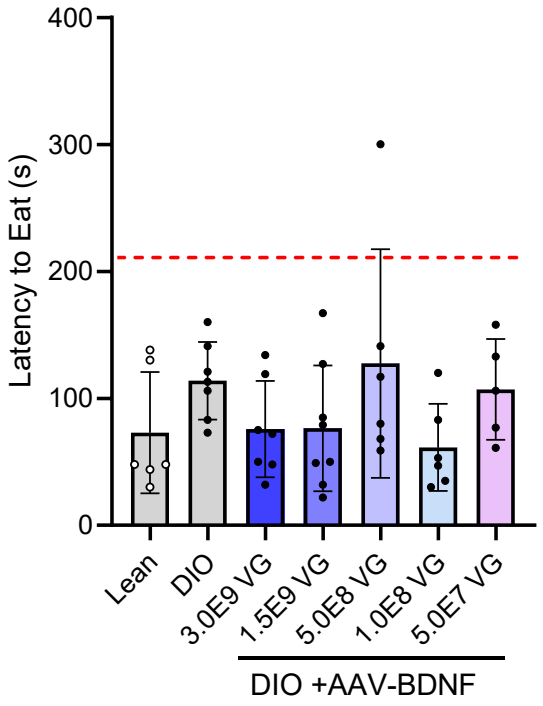


WT & BDNF$^{+/-}$
♂ & ♀
Control & High Fat Diet (60%)
Unilateral 2.5E8 VG

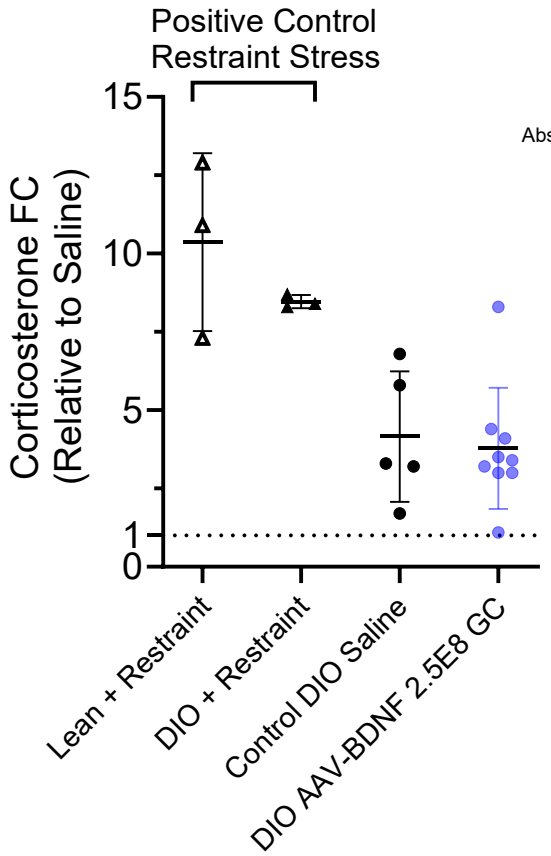
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AAV-BDNF is Well Tolerated Across Mouse Models

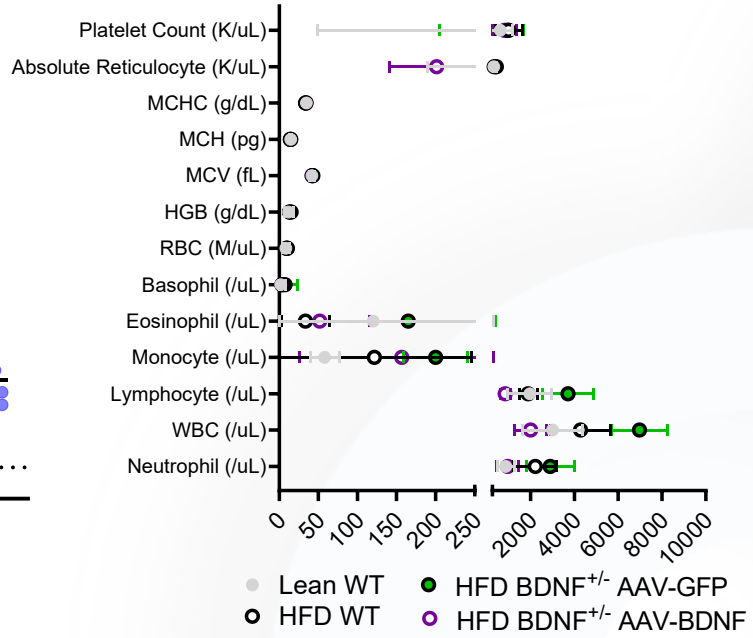
Feeding is Not Ablated
DIO Cohort with High Dose



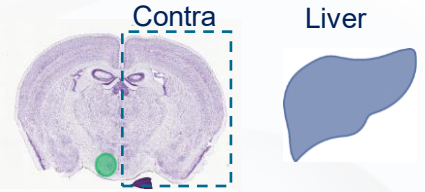
No Excessive Cortisol
DIO Cohort - 6 months



Typical CBC profile
BDNF$^{+/-}$ Cohort



Negligible Biodistribution
DIO Cohort



AAV-BDNF Dose (VG)	Contralateral Brain (Copy #/ ng DNA)	Liver (Copy #/ ng DNA)
4.5 x 10^8	2293	<LOD
2.5 x 10^8	72	<LOD
3.0 x 10^7	<LOD	<LOD

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Conclusions

- Low-dose unilateral hypothalamic AAV-BDNF (local delivery) achieves durable, self-limiting metabolic stabilization
- Simultaneous improvement of metabolic metrics, hyperphagia and behavioral comorbidities in a mouse model of BDNF haploinsufficiency
- De-risked safety and biodistribution profile for clinical translation in rare monogenic obesity

Acknowledgments

Our Collaborators

- Jihye Kim
- Molly Lutolf
- Alisa Panichkina
- Francis S. Lee
- Sadaf Farooqi
- Mike Kaplitt

Our Team

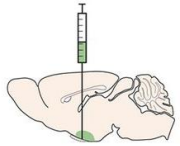
- Chenjin Jin
- Jared Sills
- Betty Bai
- Karen Wei
- Gavin Lagani
- Jeroen Bastiaans
- Barbara T.D. Nguyen-Vu
- Ce Feng Liu



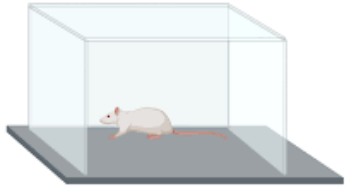


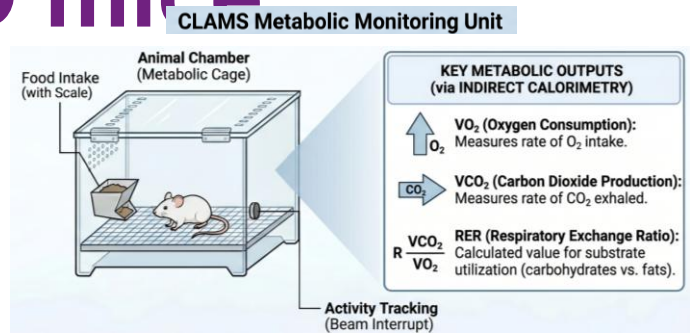
Q A

AAV-BDNF treatment increases activity and metabolic rate in DIO mice

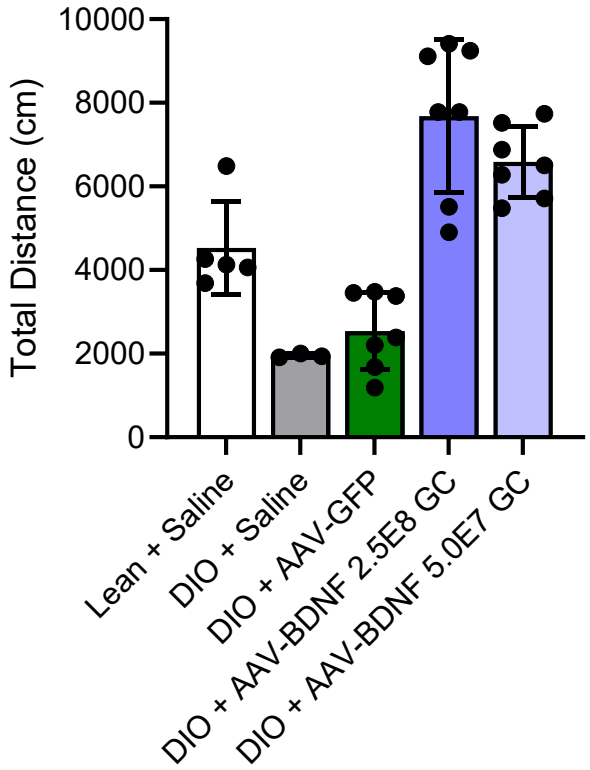


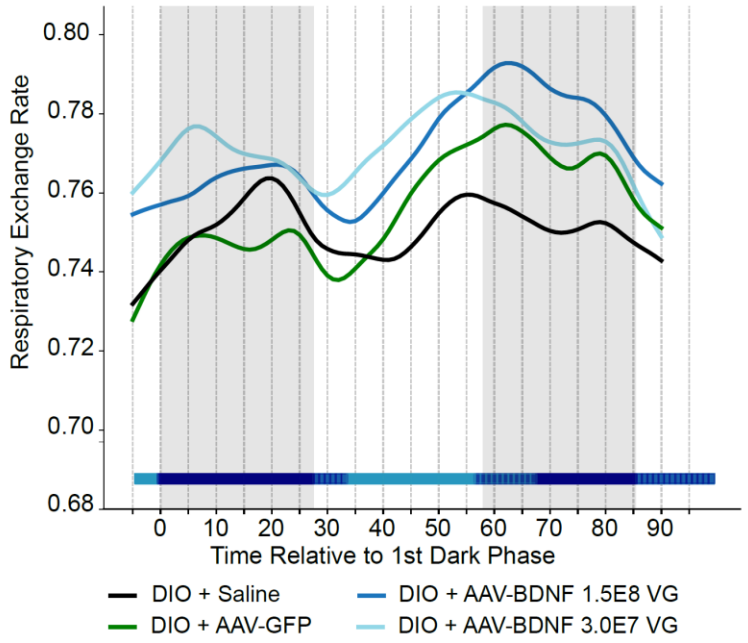
WT ♂
High Fat Diet (60%)
Unilateral



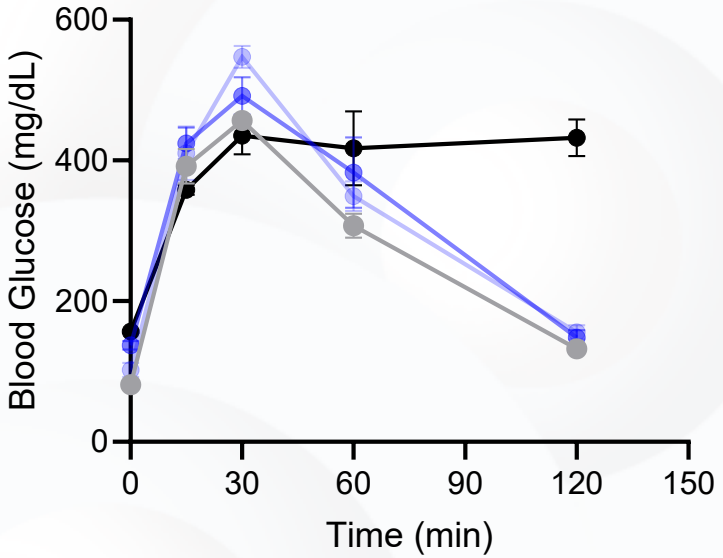


Locomotion

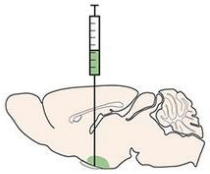




Glucose Tolerance



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



WT ♂
High Fat Diet (60%)

