Activin E-Blocking Antibody for Treatment of Metabolic Diseases

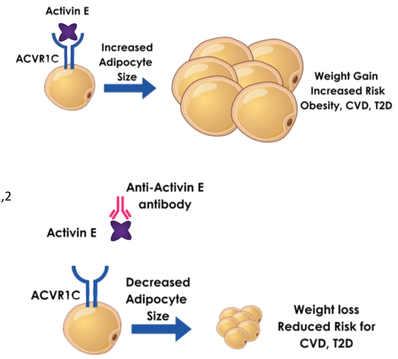
Cory Schwartz[1], Cody Moore[1], Alexander Taguchi[1], Hongyu Zhang[1], Tam Phuong[1], Tom Hsu[1], Matthew Dent[1], Courtney Wood[1], Patrick Crutcher[2], Justin DiMartino[2], Martin B. Brenner[1]

1. iBio, Inc., 11750 Sorrento Valley Rd. Suite 200, San Diego, CA, 92121; 2. AstralBio Inc., 867 Boylston St., Boston, MA, 02116

Therapeutic Targeting of Activin E

Why Target Activin E?

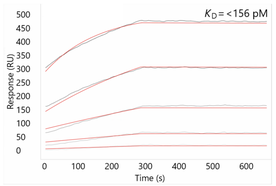
- Activin E: Liver-derived TGFβ-family hepatokine[1,2]
- Strong genetic evidence links Activin E signaling to adiposity, diabetes, and cardiovascular disease[1,2]
- Genetic loss-of-function reduces fat accumulation and disease risk[1,2]
- Validated by preclinical RNA-targeting therapies
- Challenging target for antibody discovery due to difficulties working with active recombinant protein, overcome by iBio AI-enabled discovery platform

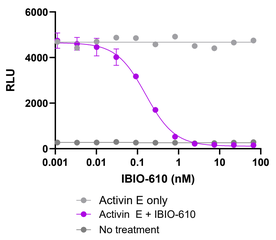


Antibody Testing and Engineering

Lead Activin E antagonist antibody (IBIO-610) has high affinity binding to Activin E

K_D < 156 pM



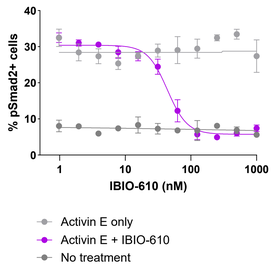


Potent neutralization of Activin E-mediated signaling in cell-based reporter assay

IC_{50} ≈ 150 pM *(treated with 200 pM Activin E)*

Potent neutralization of Activin E-mediated signaling in human adipocytes

IC_{50} ≈ 150 pM *(treated with 200 pM Activin E)*



Clone	ka (1/Ms)	kd (1/s)	KD (M)	Ratio (IgG4/IgG4 HLE)
IBIO-610 WT IgG4	7.02E+05	1.95E-03	2.78E-09	4.3
IBIO-610 (HLE IgG4)	4.09E+05	2.68E-04	6.54E-10	

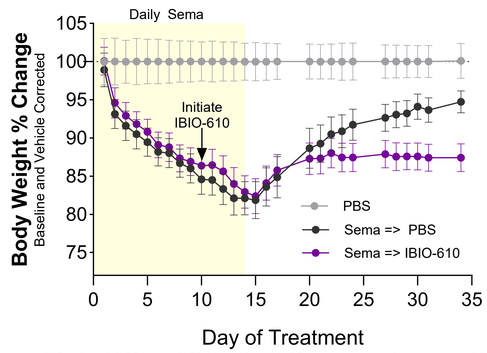
Increased human FcRn binding at low pH

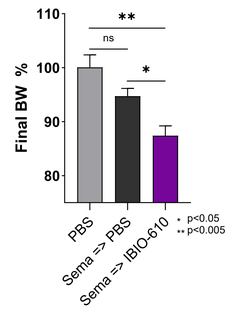
FcRn affinity >4x enhancement over standard IgG

1. Akbari et al. Nat Commun. 2022 Aug 23
2. Deaton et al. Nat Commun. 2022 Jul 27

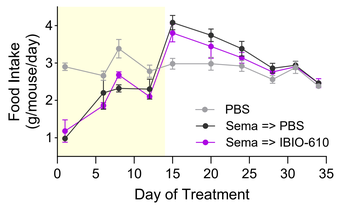
Synergism with GLP-1

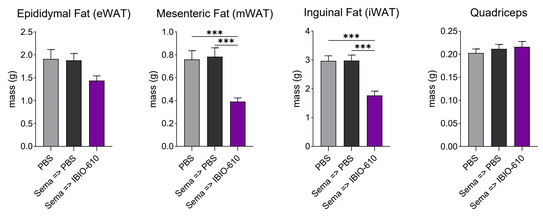
Prevention of Weight and Fat Regain after GLP-1 Cessation



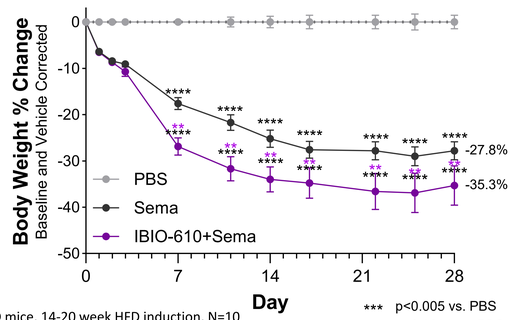


DIO mice, 14-20 week HFD induction, N=10 per group, antibody dosed BIW 10 mg/kg S.C. starting on day 10, semaglutide daily for days 1-14, 10 nmol/kg, 2-way ANOVA



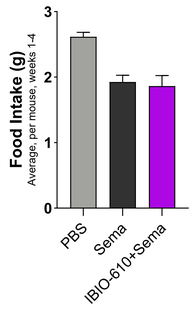


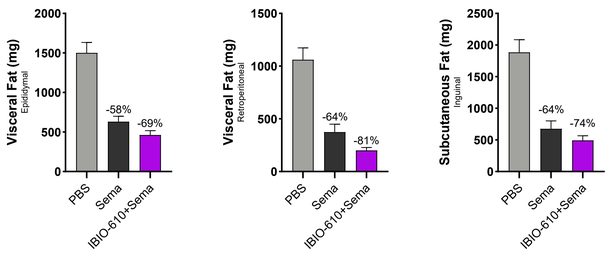
Combination with GLP-1 for Enhanced Weight Loss



DIO mice, 14-20 week HFD induction, N=10 per group, antibody dosed BIW 10 mg/kg S.C., Sema daily 10 nmol/kg, 2-way ANOVA

*** p<0.005 vs. PBS
**** p<0.0001 vs. PBS
** p<0.01 vs. Sema

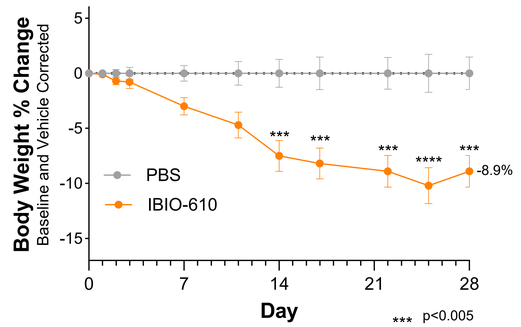




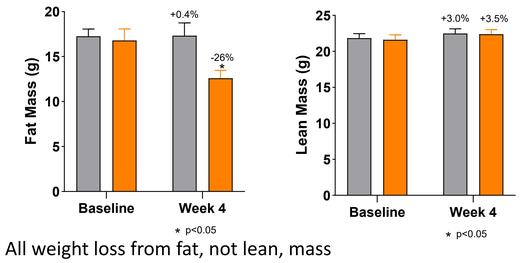
Adipose tissue assessed via necropsy

Monotherapy Weight Loss

Fat-Selective Weight Loss



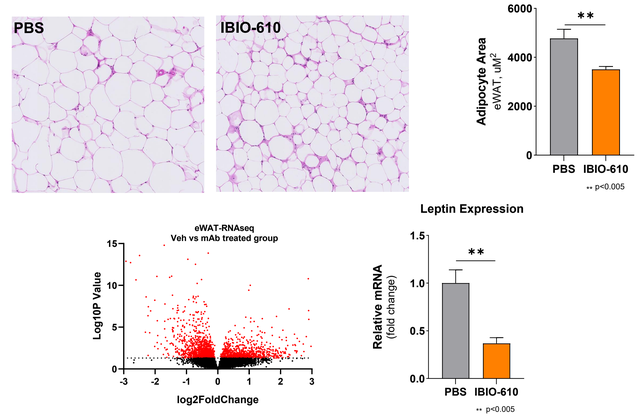
DIO mice, 14-20 week HFD induction, N=10 per group, BIW dosing, 10 mg/kg S.C., Non-responder outlier mice removed from data, 2-way ANOVA



All weight loss from fat, not lean, mass

Body composition measured via DEXA

Impact on Adipose Tissue



Activin E Antagonism represents a potential novel solution for fat selective weight loss as a monotherapy, GLP-1 combination, or as maintenance therapy