A first-in-class Activin E Antibody decreases body weight and fat mass in diet-induced obesity mice

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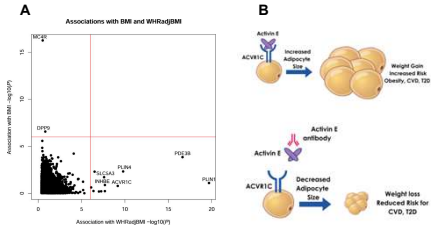
INTRODUCTION

Activin E, a hepatokine, suppresses adipose lipolysis in response to elevated serum fatty acids. A loss-of-function mutation in the inhibin E gene in humans is linked to lower abdominal fat and reduced cardiometabolic disease risk. Using a patented AI/ML platform, we developed a first-in-class Activin E Antibody with high neutralization potency, making it a promising therapeutic candidate for obesity and related metabolic disorders.



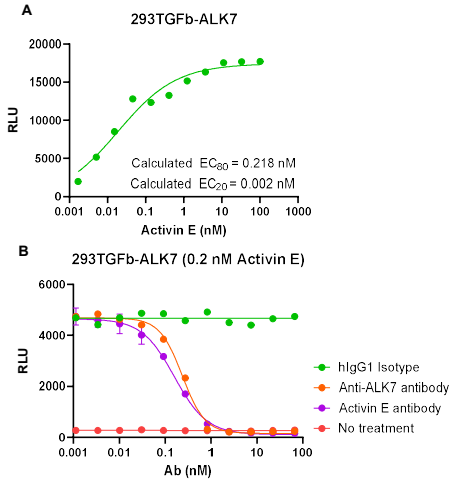
(A) Results of gene-based association tests for WHRadjBMI and BMI in 362,679 European ancestry individuals performed using a generalized linear model. Genes associating with WHRadjBMI are distinct from those associating with BMI, demonstrating that WHRadjBMI reflects fat distribution rather than overall adiposity (Deaton, A.M. et. al. *Nat. Commun* 13, 4319 (2022)-8) . (B) Schematic shows the mode of action of the Activin E antibody

RESULTS

FIGURE 1: Binding kinetics of the Activin E Antibody

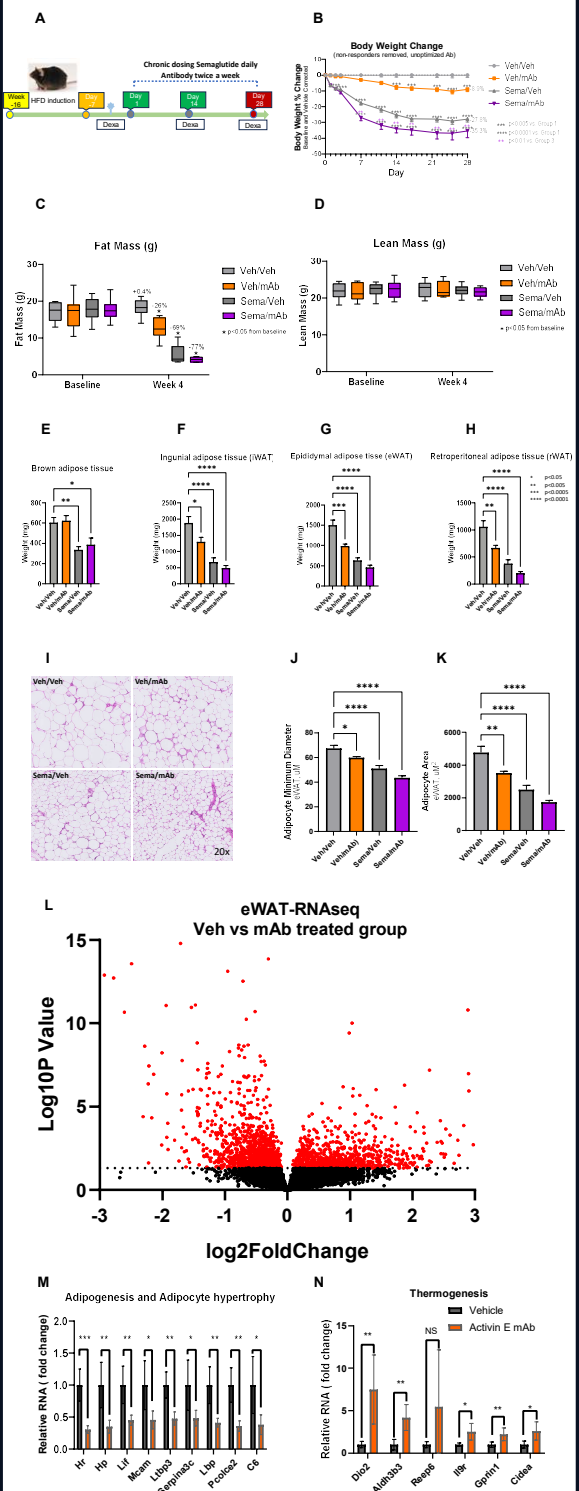
(A) The binding of Activin E antibody was characterized using a Carterra LSA.

FIGURE 2: Activin E Antibody strongly blocks Activin E – induced pSmad2 in 293TGFβ-ALK7 reporter cells.



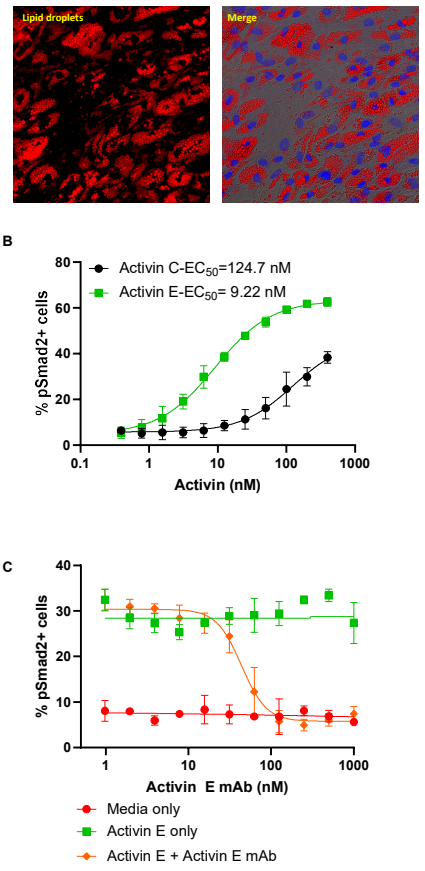
(A) Activin E induced pSmad2 signaling in a dose-dependent manner in 293TGFβ-ALK7 reporter cells. (B) The Activin E antibody blocked Activin E-induced pSmad2 signaling in a dose-dependent manner, as effectively as the anti-ALK7 antibody.

FIGURE 3: Activin E Antibody alone and in combination with GLP-1 causes fat-specific weight loss



(A) Schematic of the in vivo study design. (B) Effect of the treatment on mouse body weight, (C) fat mass, (D) lean mass, (E-H) different adipose tissue depots in DIO mice. Treatment with Activin E antibody significantly reduced adipocyte diameter and adipocyte area. (I) Representative image of H&E staining from different treatment groups. (J, K) Quantitative data from (I), bar graph shows mean ± SE, *p < 0.05,p<0.005, ***p<0.0005,****p<0.0001, statistically using two-way ANOVA. (L) RNAseq from eWAT in vehicle and Activin E antibody treated group. Treatment with Activin E antibody significantly downregulated the genes that induce adipogenesis and adipocyte hypertrophy (M) but potentiated thermogenic and browning adipocyte genes (N). Bar graph shows mean ± SD, *p < 0.05,**p<0.005, ***p<0.0005, statistically using Student's t-test.**

FIGURE 4: Activin E Antibody strongly blocks Activin E – induced pSmad2 in human adipocytes.



(A) Representative image of the lipid droplet in an adipocyte differentiated for 8 days from a human visceral pre-adipocyte. (B) Activin E induced pSmad2 signaling in a dose-dependent manner. (C) The Activin E Antibody blocked Activin E-induced pSmad2 signaling in a dose-dependent manner in human differentiated adipocytes.

CONCLUSION

Our data has shown the first-in-class Activin E Antibody exhibits sub-nanomolar binding potency and demonstrates a strong blockade of Activin E-induced pSmad2 in both reporter cells and human differentiated adipocytes. In a diet-induced obesity mouse model, treatment with the Activin E antibody alone reduced body weight and fat mass. Combining the Activin E antibody with GLP-1 significantly enhanced weight loss and fat reduction compared to GLP-1 alone. These results highlight the therapeutic potential of targeting Activin E with an antagonist antibody in treating obesity and related metabolic disorders.