

A novel anti-amyloid-beta oligomer antibody reduces plaque burden more efficiently than Lecanemab in 5xFAD mice

Yubin Wang, Lei Huang, Matthew Bujold, Lingyun Tang, and Xin Du (xdu@mabwell-therapeutics.com)

Mabwell Therapeutics, Inc. www.mabwell-therapeutics.com

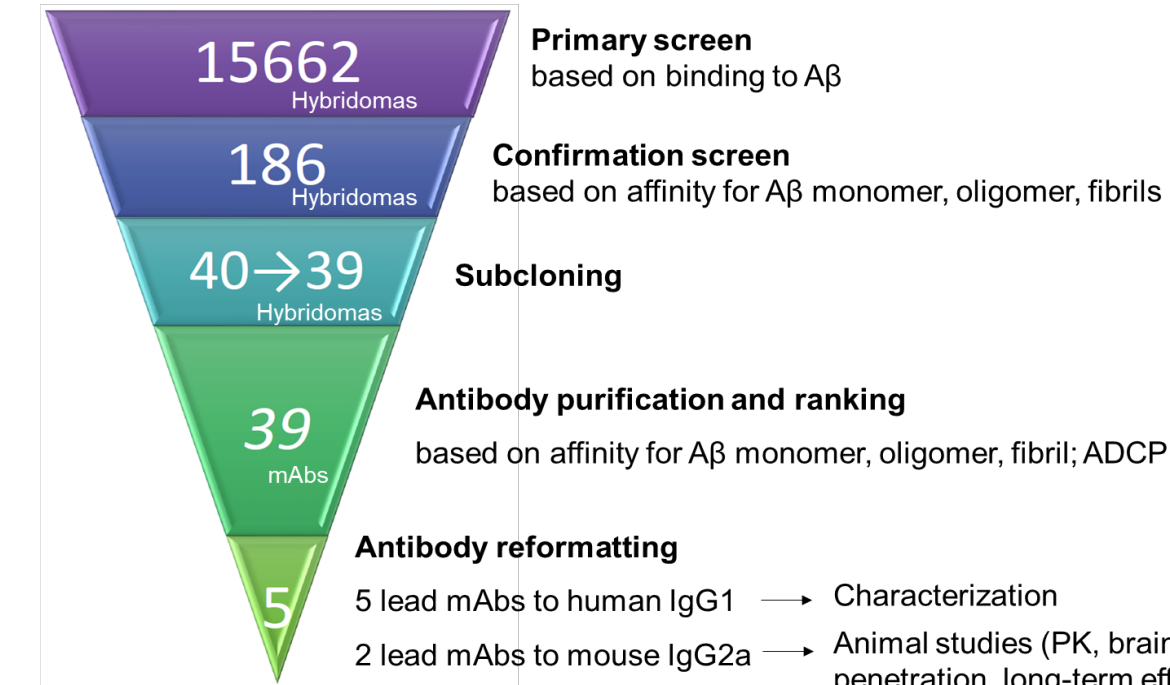
Introduction

The amyloid-beta (A β) oligomers and protofibrils are the more toxic form of A β as compared with monomers and plaque fibrils. Lecanemab, a humanized monoclonal antibody (mAb) with high affinity for A β oligomers and protofibrils, reduced cognitive decline in patients with early Alzheimer's disease in a phase 3 clinical trial and was granted accelerated approval in the US. Here we report a novel fully-human anti-A β oligomer mAb with profiles similar to Lecanemab.

Methods

AlivaMab human F(ab')₂ transgenic mice were immunized with A β oligomers to generate A β oligomer selective mAbs. The antibodies were screened for, and ranked, based on their selectivity for A β oligomer over monomer and ability in mediating the uptake of A β oligomers by microglia. Pharmacokinetics (PK) and brain penetration of lead mAb candidates was determined in mice. In vivo efficacy was evaluated in 7-month old 5xFAD mice with weekly intraperitoneal injection of antibody lead at 1, 3, or 10 mg/kg dose levels for 4 months. After completion of dosing, open field test was performed on the treated mice and amyloid plaque burden in the brain was measured by Campbell-Switzer stain and ELISA.

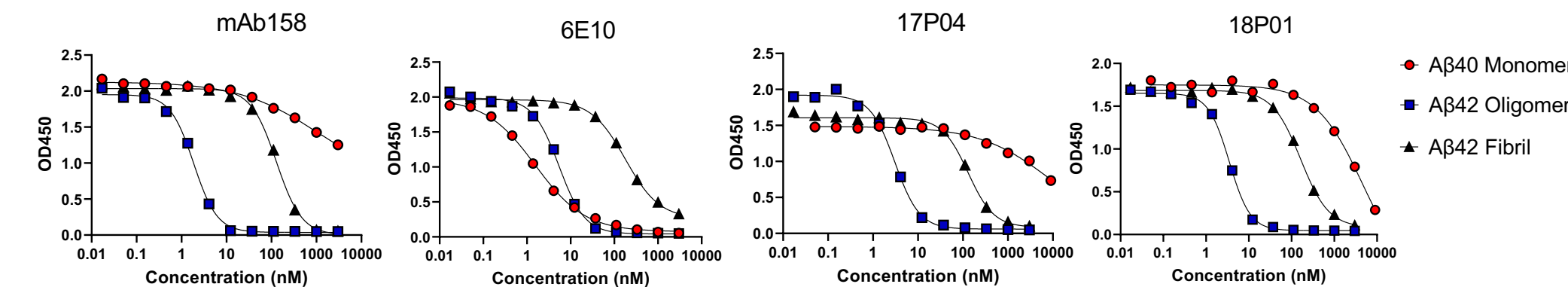
Immunization in AlivaMab human F(ab')₂ transgenic mice with A β oligomer



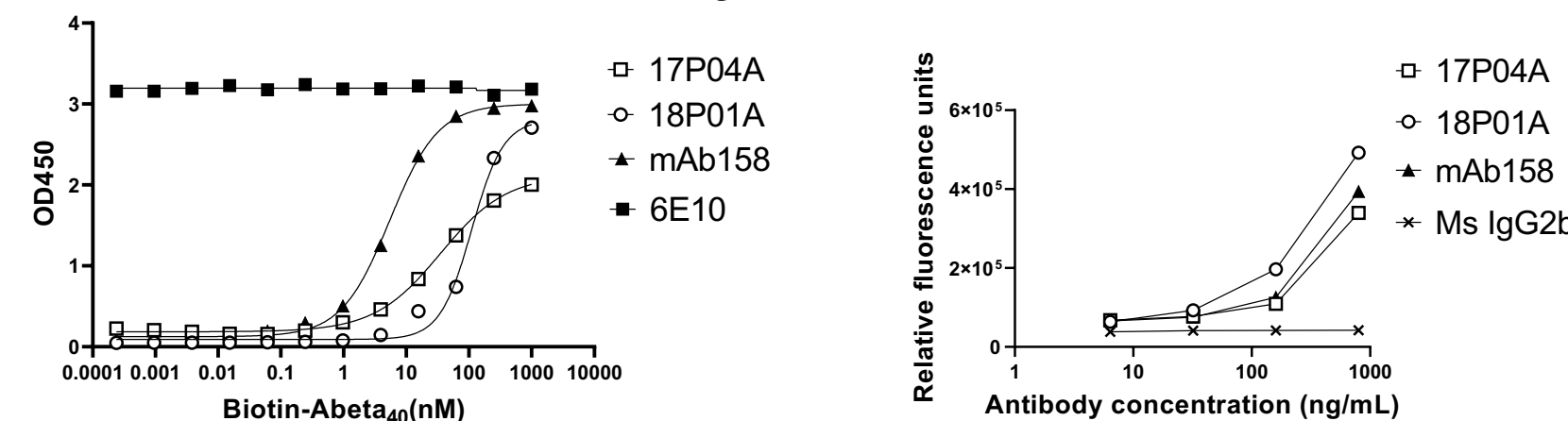
Characterization of lead mAbs

ID	Direct ELISA		Competitive ELISA				Capture ELISA	ADCP
	EC50 Abeta 1-42 (nM)	EC50 Abeta p3-42 (nM)	IC50 oligomer (nM)	IC50 monomer (nM)	IC50 fibril (nM)	IC50 monomer / IC50 oligomer	EC50 monomer (nM)	
18P01A	0.062	UND	3.5	4601.0	162.8	1311.2	67.00	1.36
17P04A	0.045	UND	3.1	8433.0	130	2758.6	35.19	0.79
mAb158	0.043	21.6	2.0	4124.0	116.9	2062.0	7.72	1.00
20O07A	0.050	UND	3.0	934.9	67.3	313.3	2.57	1.05
22D04A	0.035	UND	2.5	UND	111	UND	1.05	1.39
06E17A	0.052	UND	4.5	2579	38.6	569.4	0.02	0.95

Profiles of lead mAbs and mAb158 (mouse version of Lecanemab). The list was sorted by ratios of EC50 monomer (capture ELISA) to IC50 oligomer (competitive ELISA). mAb158 is the reference antibody of this study. The top 2 lead mAbs 18P01 and 17P04 have higher oligomer selectivity than that of mAb158. UND, undetermined value.

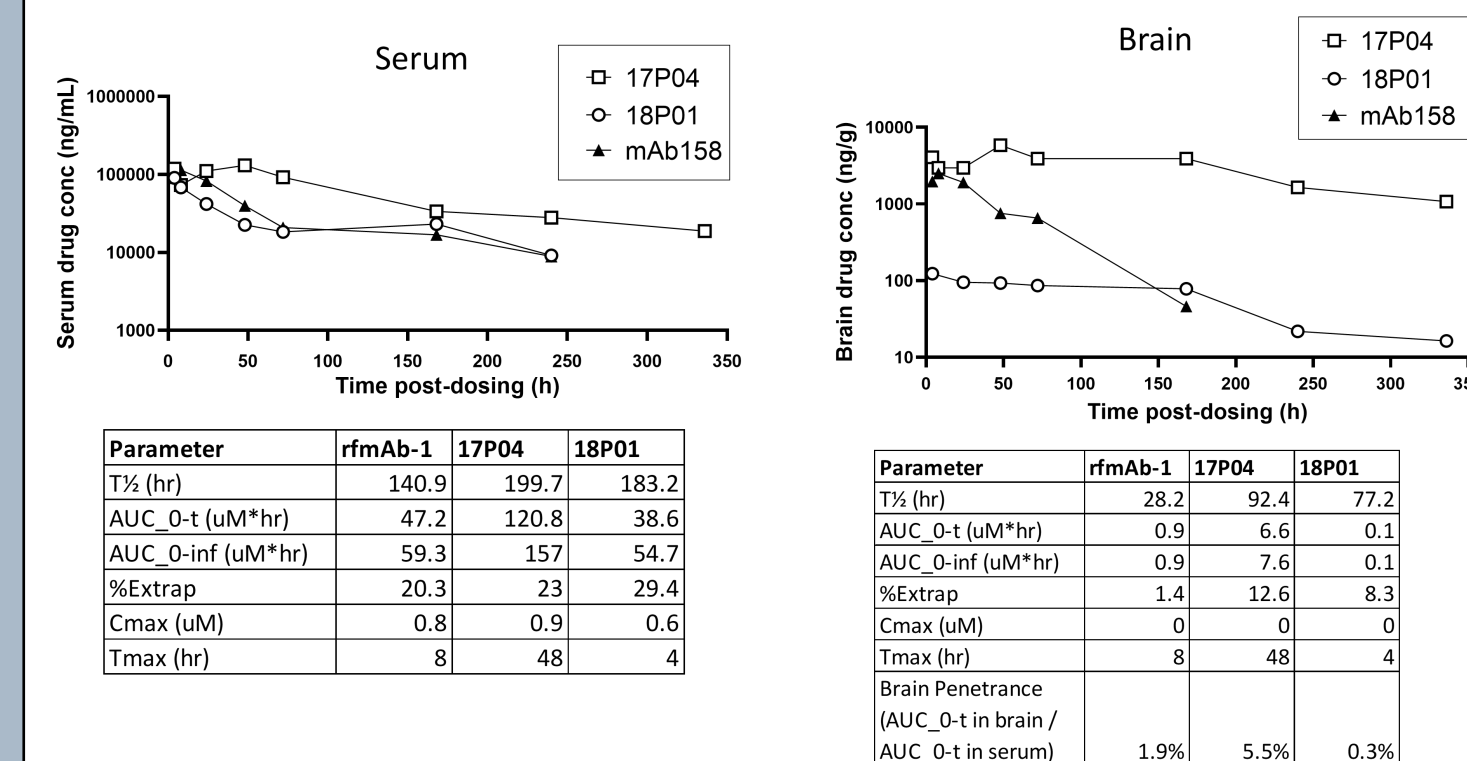


Competitive ELISA was used to evaluate the relative affinities of antibodies for A β monomer, oligomer and fibril. The antibodies were subjected to monomer, oligomer or fibril competition on monomer coated plates. mAb158, 17P04 and 18P01 exhibited similar profiles with high affinities for oligomer and low affinities for monomer. 6E10 had high affinities for both monomer and oligomer.



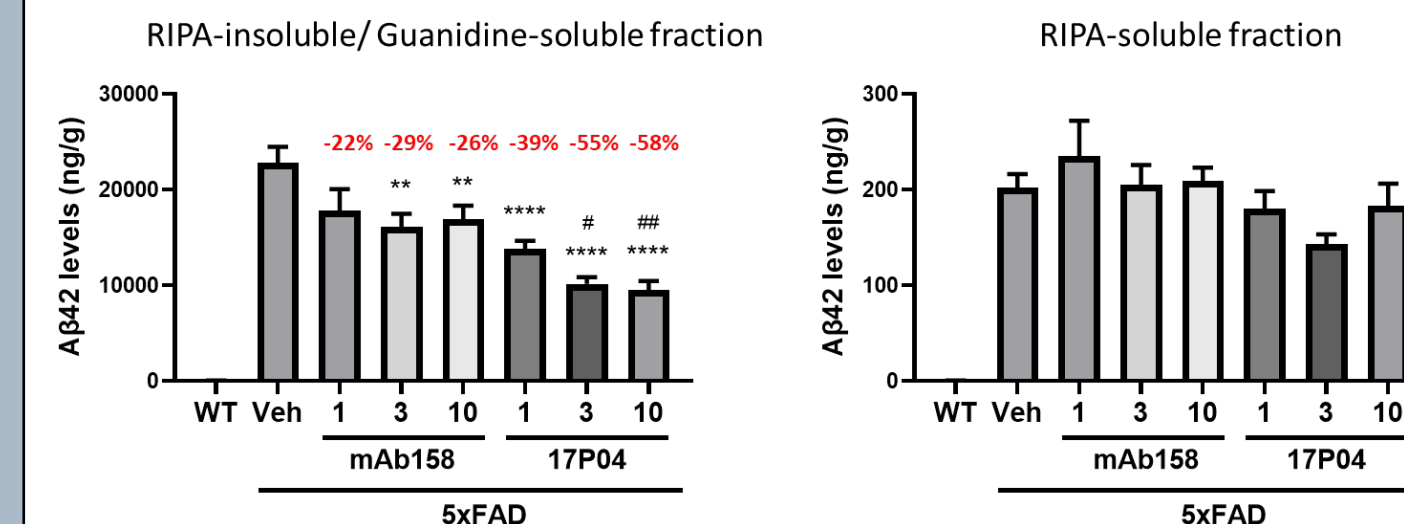
Left, capture ELISA was used to measure the affinities of mAbs for A β monomer. 17P04, 18P01, and mAb158 had low affinity while 6E10 had high affinity for monomer. **Right**, the ability of lead antibodies to mediate the phagocytosis of HiLyte488 labeled A β oligomer by microglia (ADCP) was evaluated in BV-2 cells.

Pharmacokinetic study

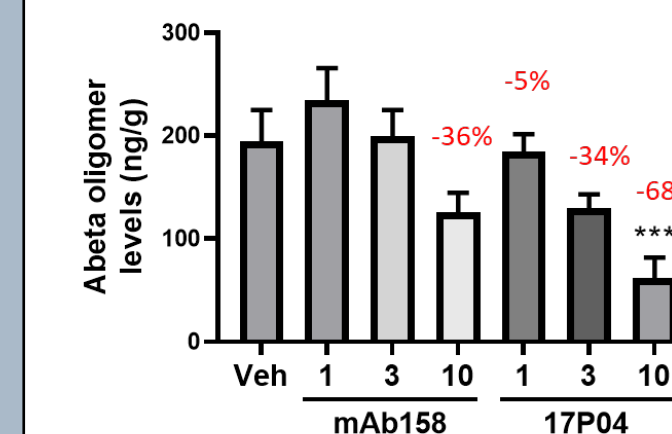


PK of 17P04, 18P01, and mAb158 in the serum (left) and brain (right) of B6SJLF1 mice. 17P04 had a longer half-life in serum and brain and better brain penetration than mAb158. Despite long half-life in serum and brain, 18P01 demonstrated poor brain penetration.

In-vivo efficacy study

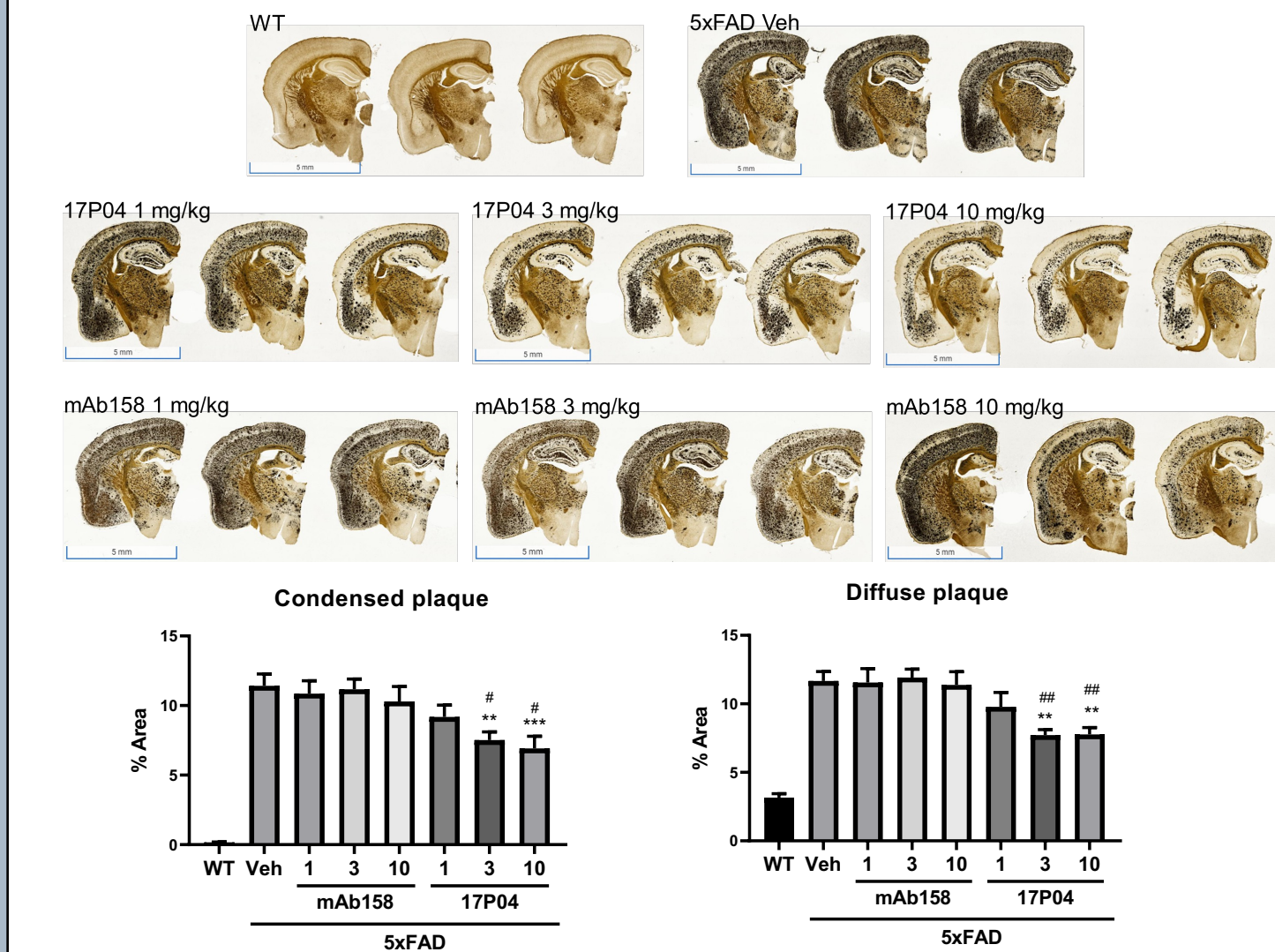


17P04 removed insoluble Abeta₁₋₄₂ more efficiently than mAb158 in the brain of 5xFAD mice. N = 8 - 14.

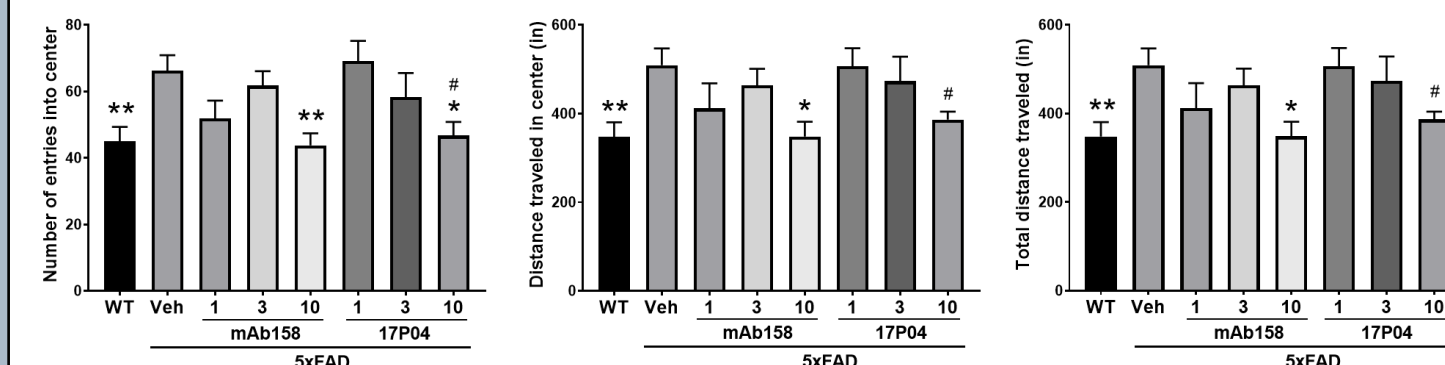


17P04 removed soluble Abeta oligomer more efficiently than mAb158 in the brain of 5xFAD mice. N = 8 - 14.

In-vivo efficacy study



17P04 but not mAb158 significantly reduced condensed and diffuse plaque in the brain of 5xFAD mice. N = 8 - 13.



In Open Field test, 5xFAD mice demonstrated an anxiolytic effect (**Left and middle**) and increased locomotor activity (**right**), when compared to WT mice. The anxiolytic effect and increased locomotor activity was significantly reduced by 17P04 or mAb158 treatment at 10 mg/kg of dose. N = 7 - 25.

Conclusion

We identified a novel fully-human anti-A β oligomer mAb with superior oligomer selectivity, half life, brain exposure, and plaque removal efficacy in comparison with Lecanemab.