850

DEVELOPMENT OF BRAIN SHUTTLE ENABLED AT-04, A NOVEL PEPTIBODY THAT BINDS NEUROPATHOLOGIC FIBRILLAR AGGREGATES

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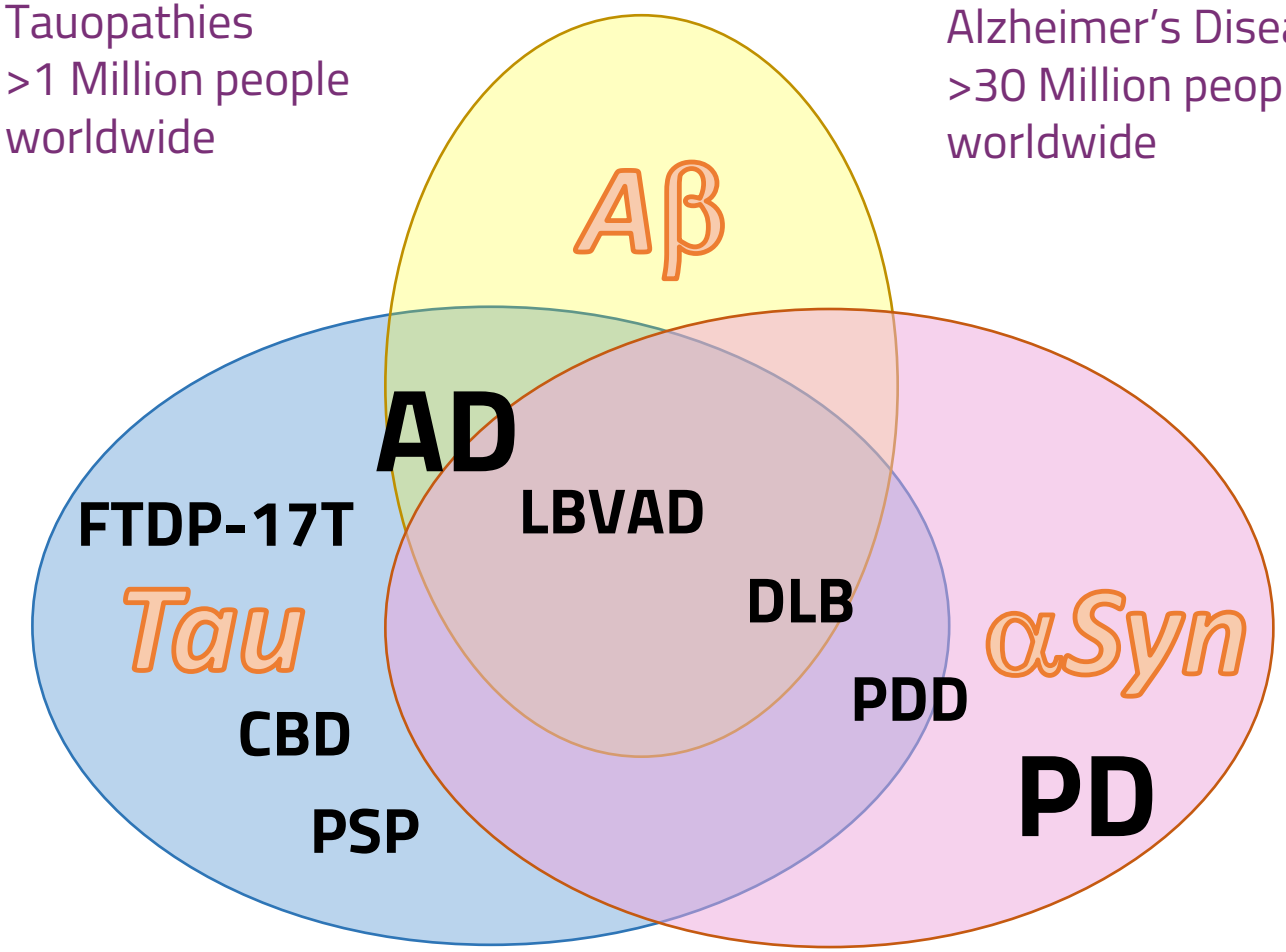
Disclosures

- S. Selvarajah, A. Vick, M. Klein, N. Angell- Employees at Attralus Inc, San Francisco, California, USA
- P. Stocki[2], A. Gauhar[2], S. Coker[2], L.J. Rutkowski - Employees at Ossianix Inc, Stevenage, UK
- J. Wall-Founder and stock-holder at Attralus Inc
- J. S. Foster, S. Macy, A. Williams, M. Balachandran- No Disclosures

Overlap of CNS (Abeta, Tau and alpha-Synuclein) Proteinopathies

Tauopathies
>1 Million people
worldwide

Alzheimer's Diseases (AD)
>30 Million people
worldwide



Parkinson's Disease (PD)
>10 Million people worldwide

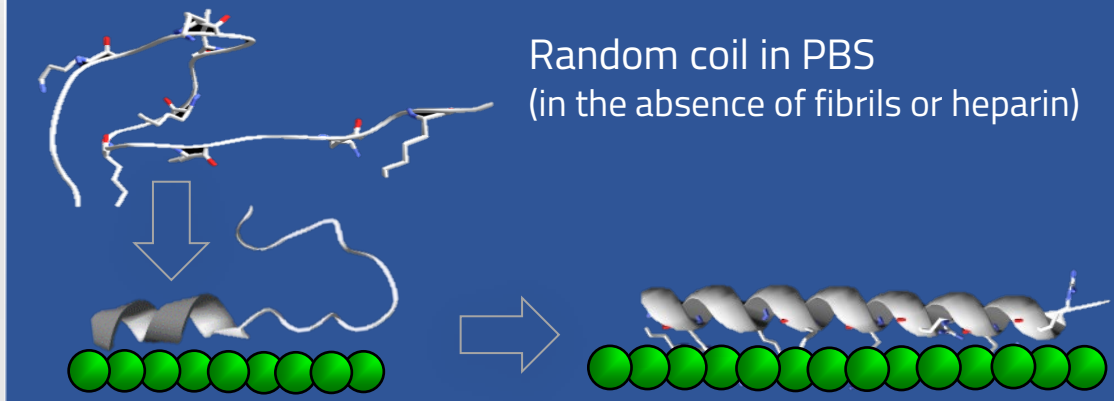
AD- Alzheimers Disease; **PSP**- progressive supranuclear palsy; **CBD**-corticobasal degeneration; **FTDP-17T** Frontotemporal dementia and parkinsonism linked to chromosome 17; **DLB**- Dementia with Lewy bodies; **LBVAD**- Lewy body variant AD; **PD**-Parkinson's Disease ; **PDD**-Parkinson's Disease Dementia;

Pan-Amyloid Targeting Peptide – A Synthetic Polybasic Amyloidophilic Peptide

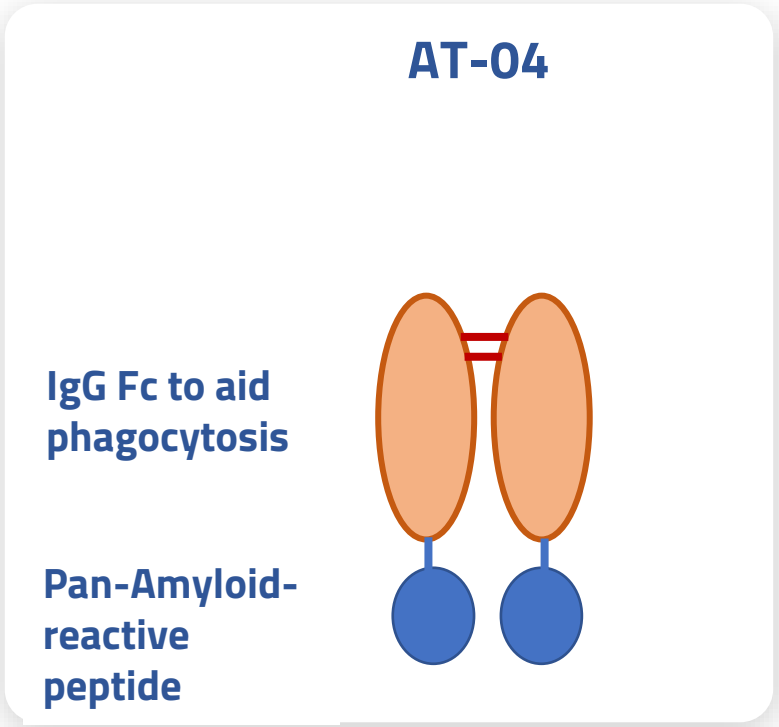
Targeting Mechanism

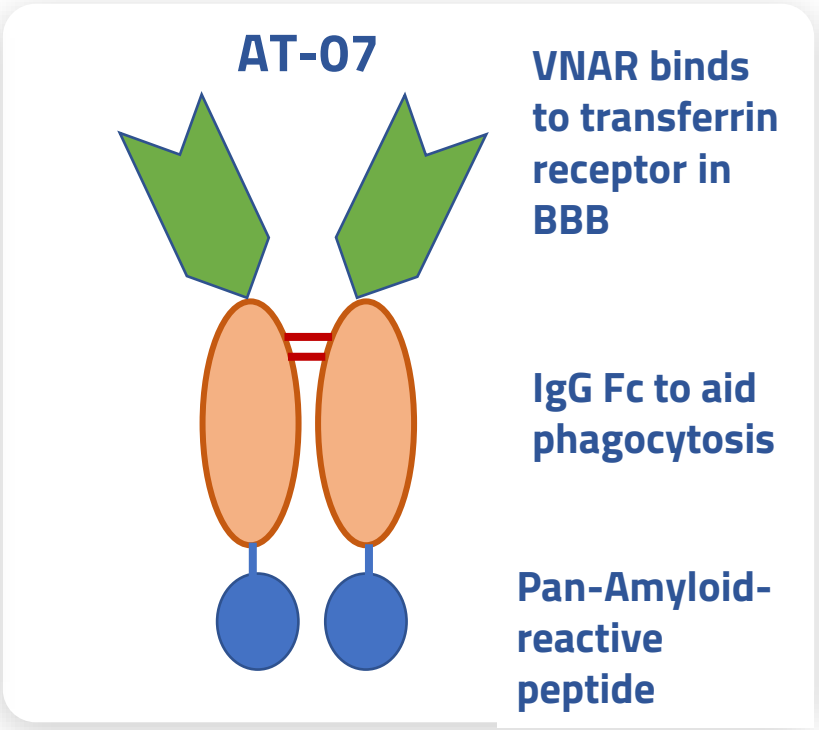
- All amyloid deposits and tau tangles contain heparan sulfate proteoglycans (HSPG) and protein fibrils
- Heparin binding peptides selectively bind amyloid through the HSPG and fibrils
- Peptide specifically binds amyloid fibrils

Mode of Action



Overview of AT-04 Peptibody and AT-07 VNAR Modalities

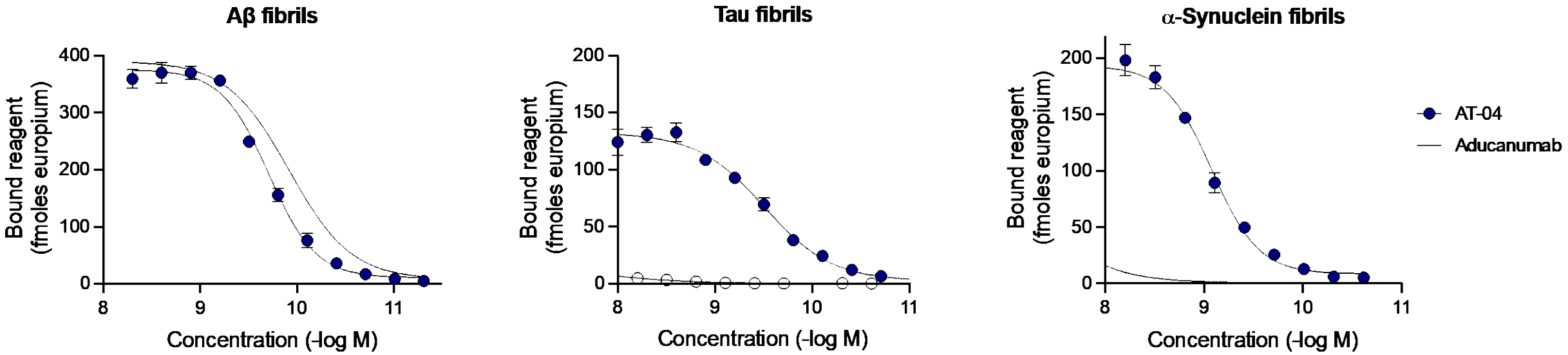




	AT-04	AT-07
Construct	PAR-Peptide Fc Fusion	PAR-Peptide Fc Fusion + VNAR
Binding	Abeta, Tau, Alpha-Synuclein	Similar
Size	59 kDa (vs. 150 kDa for mAb)	80 kDa
Brain Shuttle	No	α-TfR1 single domain antibody

AT-04 Demonstrates Sub-nanomolar Binding to Abeta, Tau, and α-Synuclein Fibrils

Ability to bind multiple types of fibrils (Abeta, Tau and alpha-Synuclein) provides a novel approach to addressing neurodegenerative diseases that exhibit several different extracellular protein fibrils



EC50:

AT-04 = 0.2 nM
*Aducanumab = 0.12 nM

AT-04 = 0.19 nM
*Aducanumab= No binding

AT-04 = 0.8 nM
*Aducanumab = No binding

*Aducanumab homolog manufactured from published sequence

AT-04 Demonstrates Target Engagement in 5xFAD Model

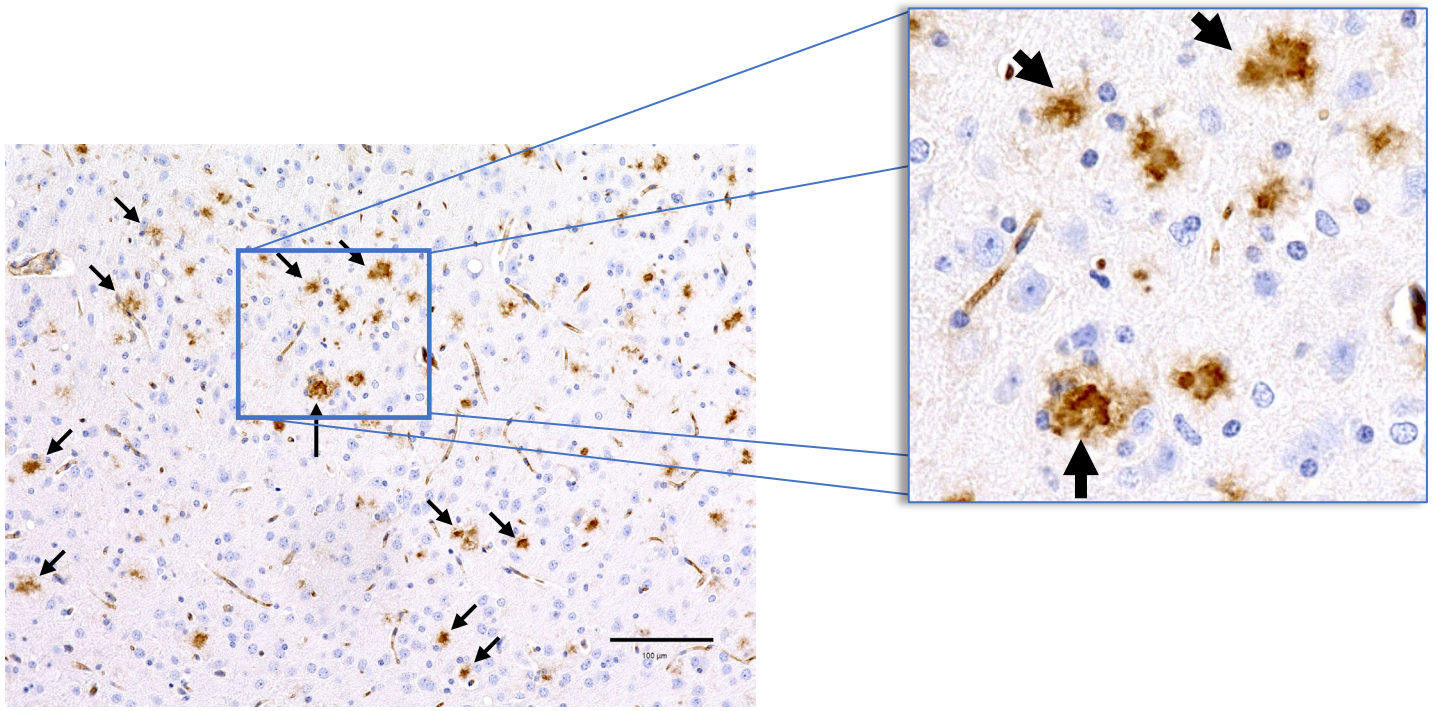
5xFAD mice
n=5

Day 1– IV
(^{125}I) AT-04 mAb
50 mg/kg
(1 mg; 100 µCi)

Day 4 – IV
(^{125}I) AT-04 mAb
50 mg/kg
(1 mg; 100 µCi)

Day 8– IV
(^{125}I) AT-04 mAb
50 mg/kg
(1 mg; 100 µCi)

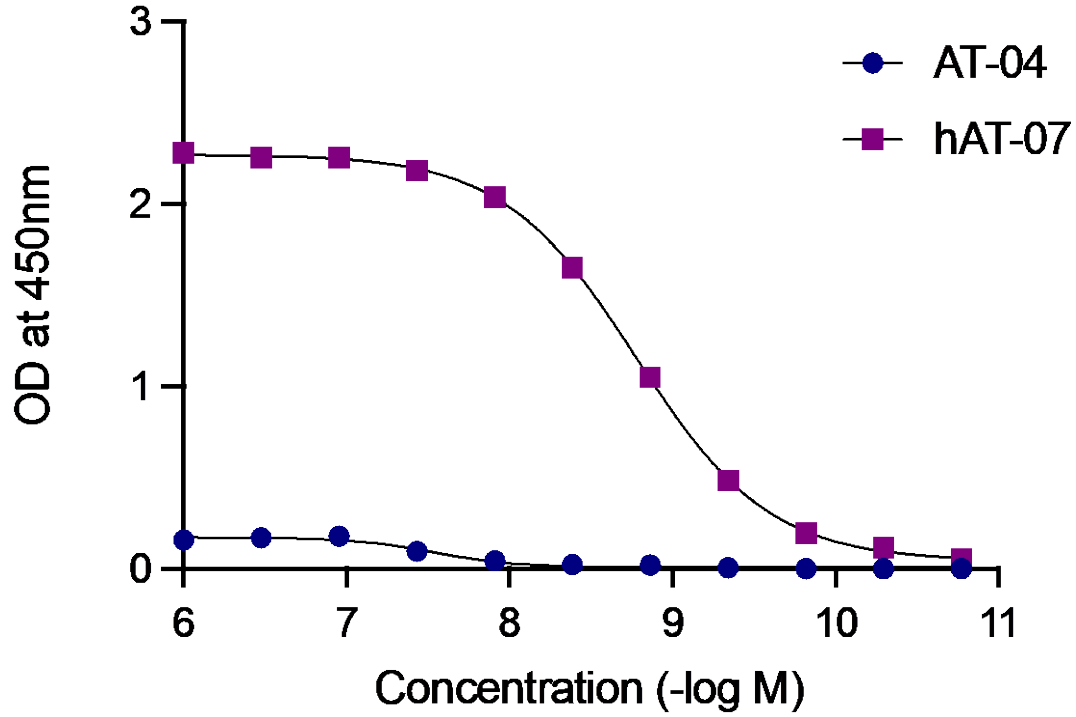
Day 10-Brain tissue harvest

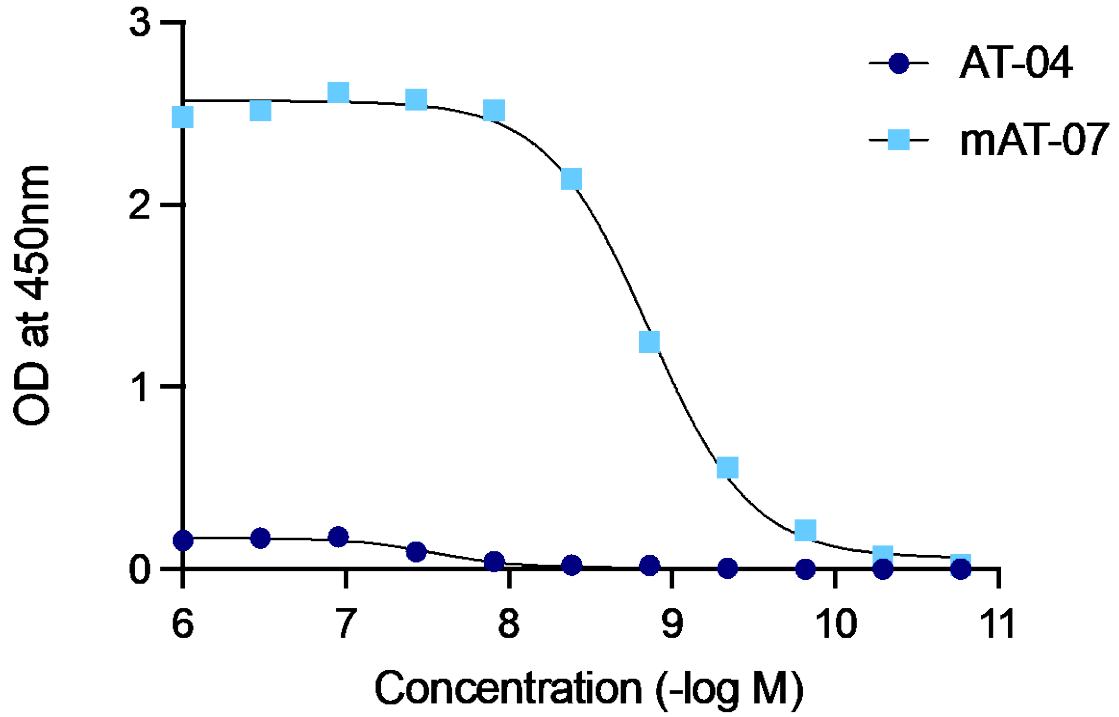


Bar is 100 µm

AT-04 binds to abeta plaques in 5xFAD mouse brain following IV route of administration

AT-07 VNAR Shuttle Binds to the Transferrin Receptor

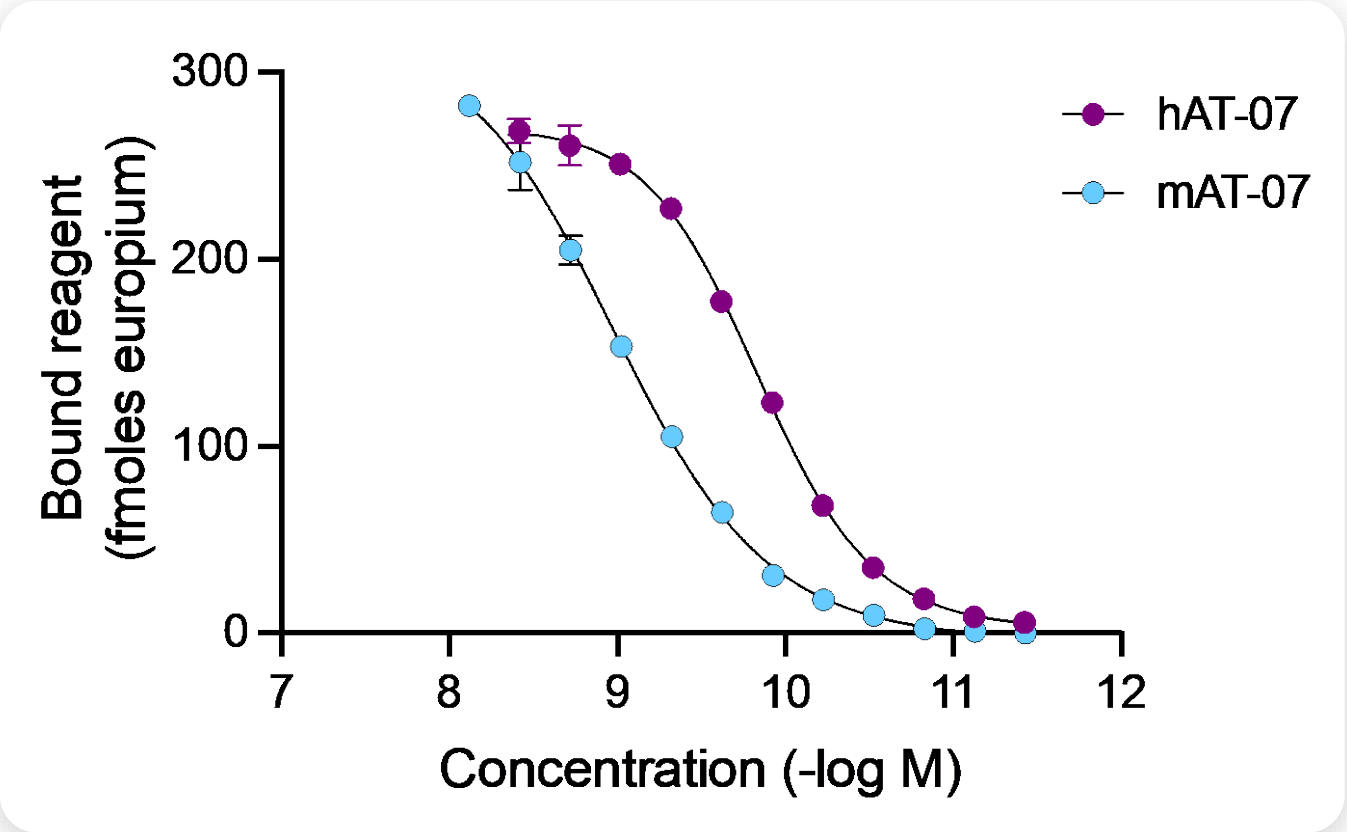




EC50 hAT-07 (human) = 1.7 nM to human TfR1

mAT-07 (mouse) = 1.4 nM to mouse TfR1

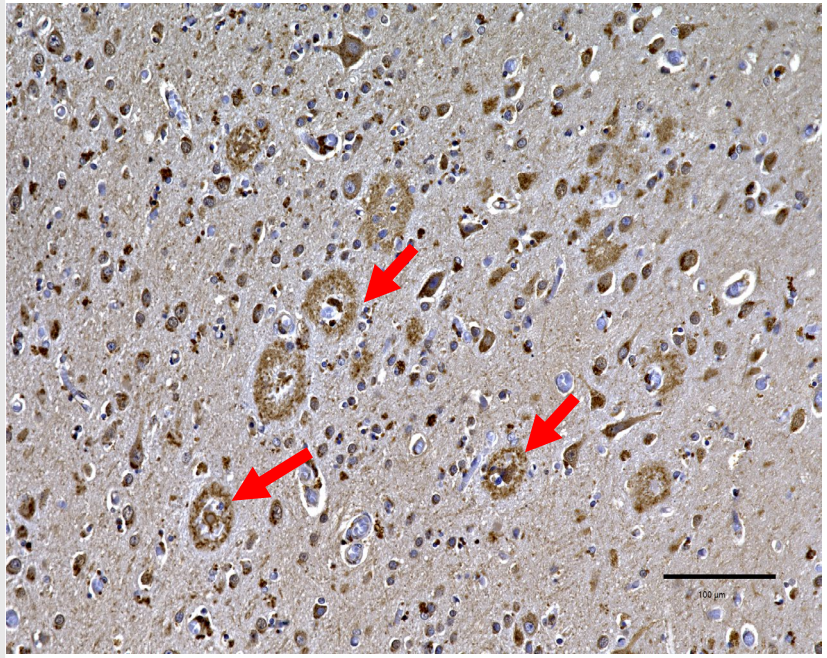
AT-07 Constructs Bind to Abeta Fibrils



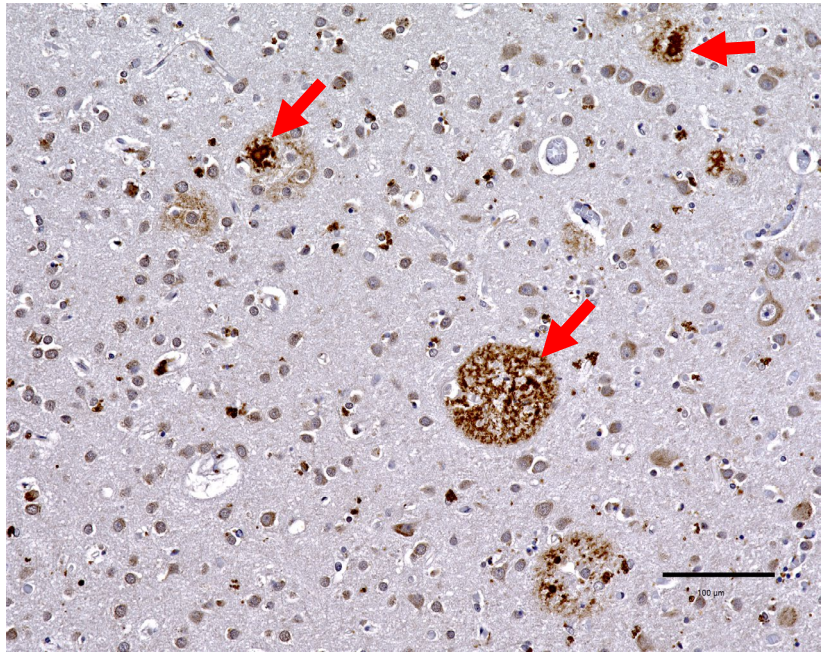
EC50: hAT-07 = 0.16 nM
mAT-07= 0.9 nM

AT-04 and AT-07 bind to Abeta Plaques in Human Alzheimer's brain tissue

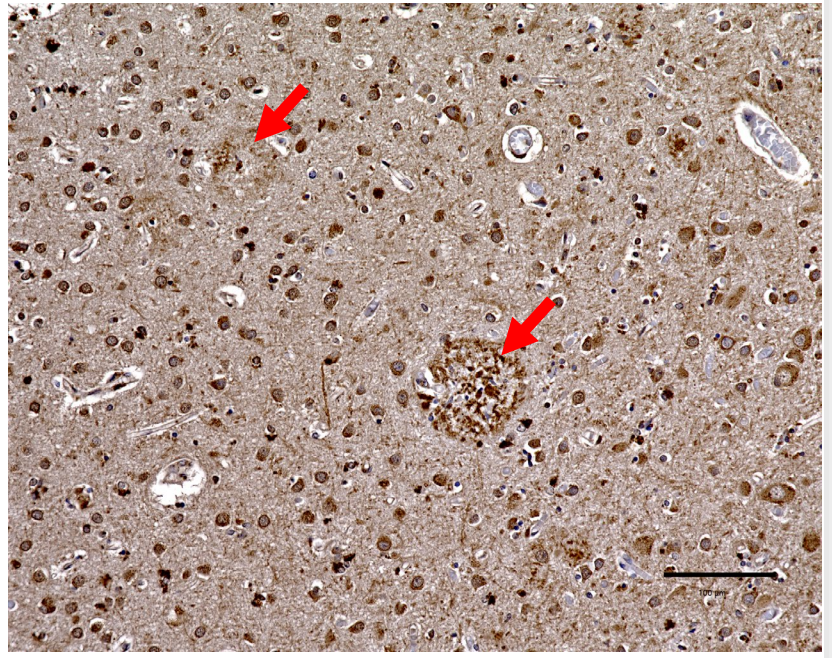
AT-04



mAT-07



hAT-07

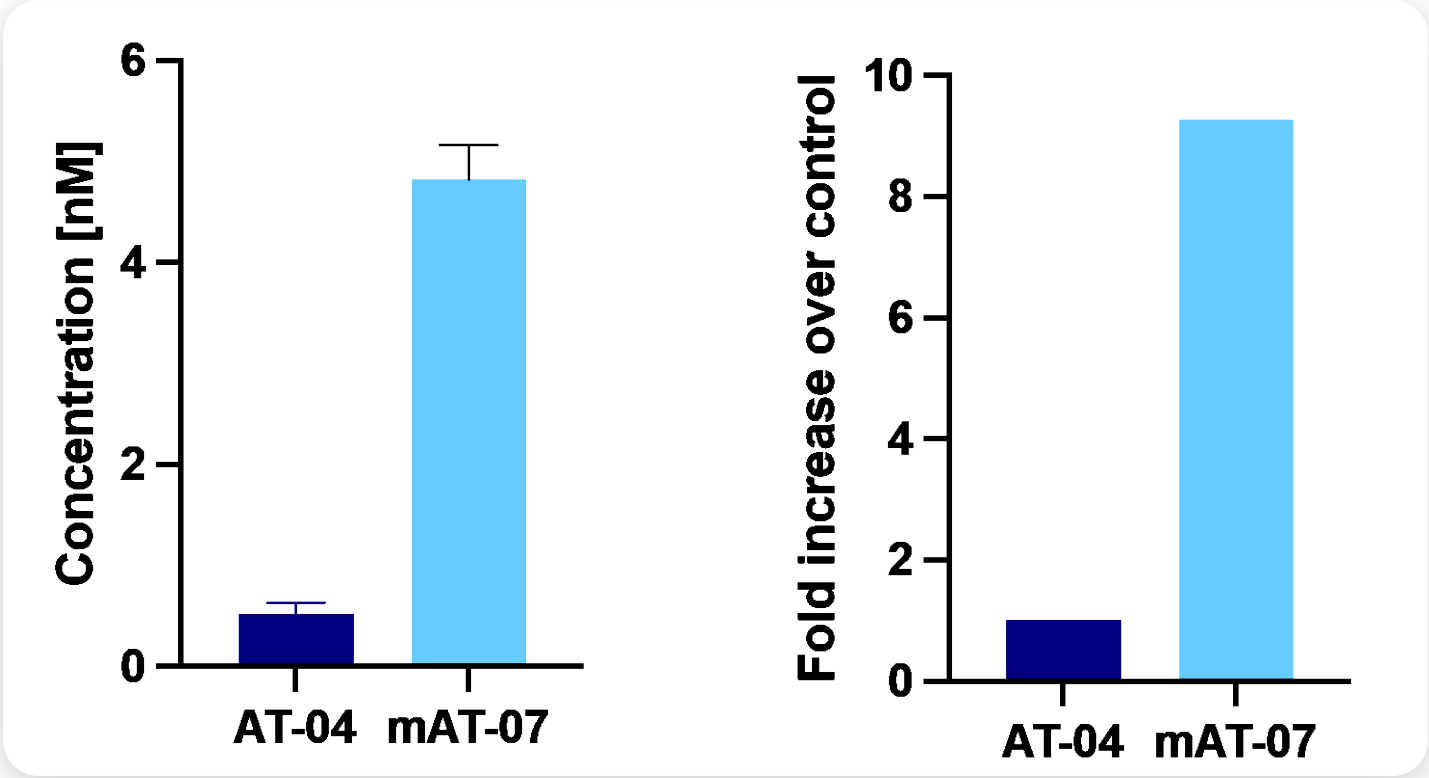


Bar is 100 µm

AT-07 demonstrated a Ten-fold Higher Brain Exposure vs AT-04

12.5nmol/kg (~2mg/kg), 18h, IV

(mean, ±SD, n=3)



AT-04 achieves 1.4% of plasma level in the mouse brain. The range of 0.1-1.5% is like other human AD mAbs.

AT-07 achieves ~15% of plasma level in the mouse brain

Summary

- Patients with neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, and Lewy Body Disease exhibit multiple proteinopathies (Abeta, Tau and alpha-Synuclein)
  - All three of the pathologies are commonly exhibited in the brain of these patients

- AT-04 is a novel pan-amyloid immunotherapeutic that has the potential to target multiple pathologies (e.g. Abeta, tau, alpha-synuclein) in neurodegenerative diseases
  - Sub-nanomolar binding demonstrated to Abeta, Tau, alpha-Synuclein fibrils

- AT-07, an engineered AT-04 containing a VNAR-derived brain shuttle, enhanced brain penetration in mice and has the potential to increase effectiveness in clearing neuropathic fibrillar deposits.
  - AT-07 demonstrated a 10-fold increase in brain penetration versus AT-04 in a PK study in wild-type mice