Morphomer® small molecules targeting Tau for the treatment of Alzheimer’s disease

Nicolas Preitner, PhD | ADPD 2025 | April 2025

AC Immune

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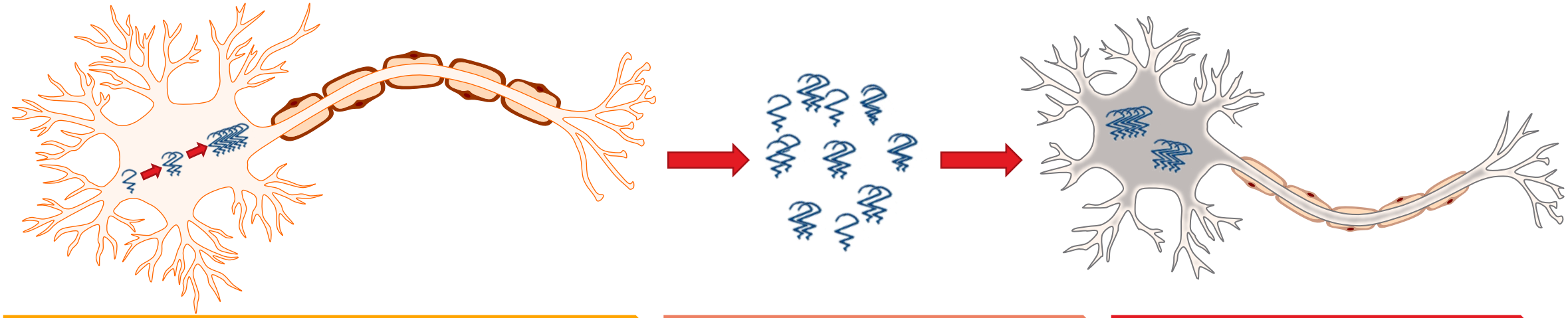
Conflict of interest disclosure

Nicolas Preitner is an employee of AC Immune SA entitled to stock options.

Intra- and extracellular Tau species drive pathology progression in AD[1]

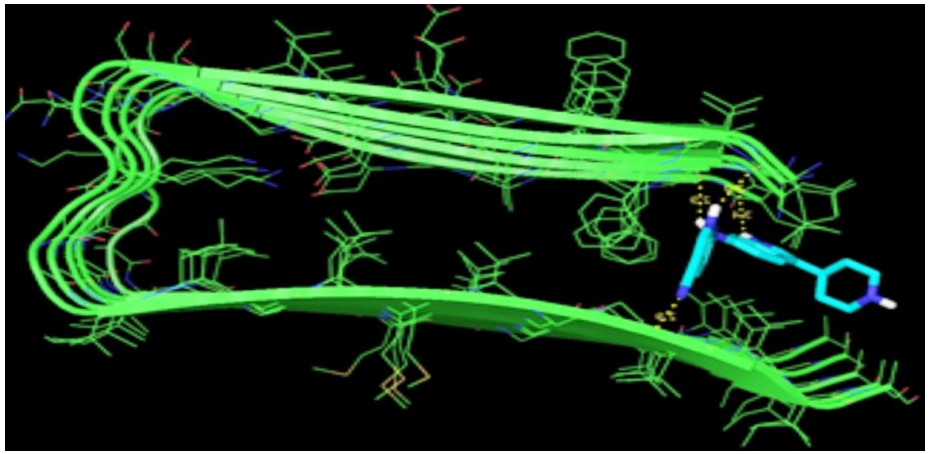


- In AD and other Tauopathies, **Tau undergoes conformational changes leading to** intracellular Tau aggregation, with the accumulation of both **soluble and insoluble aggregates**
- **Uptake of aggregated soluble Tau species** into healthy neurons enables the spread of pathology
- **Intra- and extracellular aggregates** confer **Tau-mediated neurotoxicity**

(1) Alzheimer's disease

Targeting Tau aggregation with small molecules

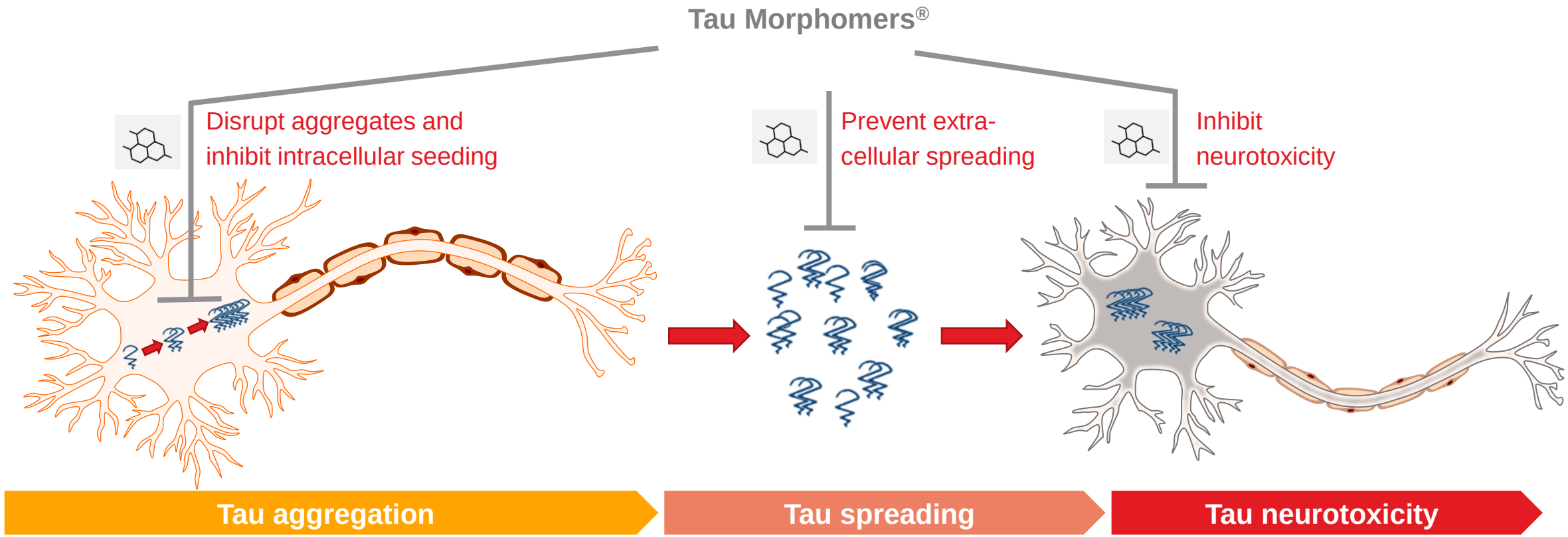
Proprietary Morphomer® platform



- Robust library of conformation-specific, non-peptidic small molecules with desirable CNS[1] properties constructed and continuously expanded via rational design over many years
- Used with comprehensive screening assays of high translational value to rapidly generate highly specific hits
- Clinically validated platform with two diagnostic PET tracers showing excellent target engagement

(1) Central nervous system

Multimodal targeting of Tau pathology with Morphomers®



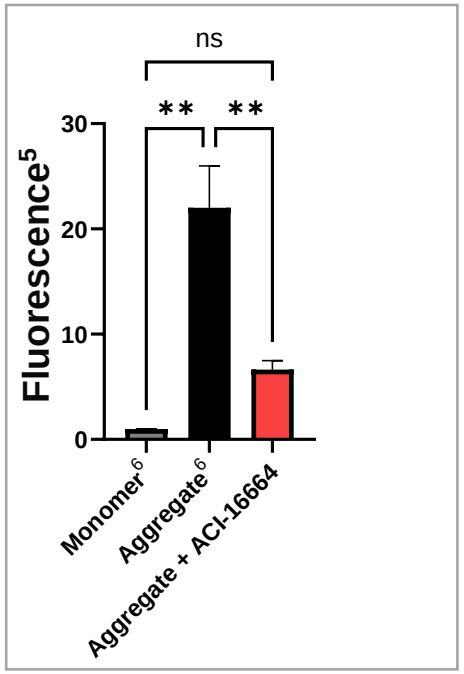
- Morphomers® are:
  - designed to interfere directly with soluble and insoluble Tau species intra- and extracellularly
  - aimed to reduce Tau pathology in patients, slowing down or even halting disease progression

ACI-16664: a Morphomer® that disrupts pathological Tau aggregates

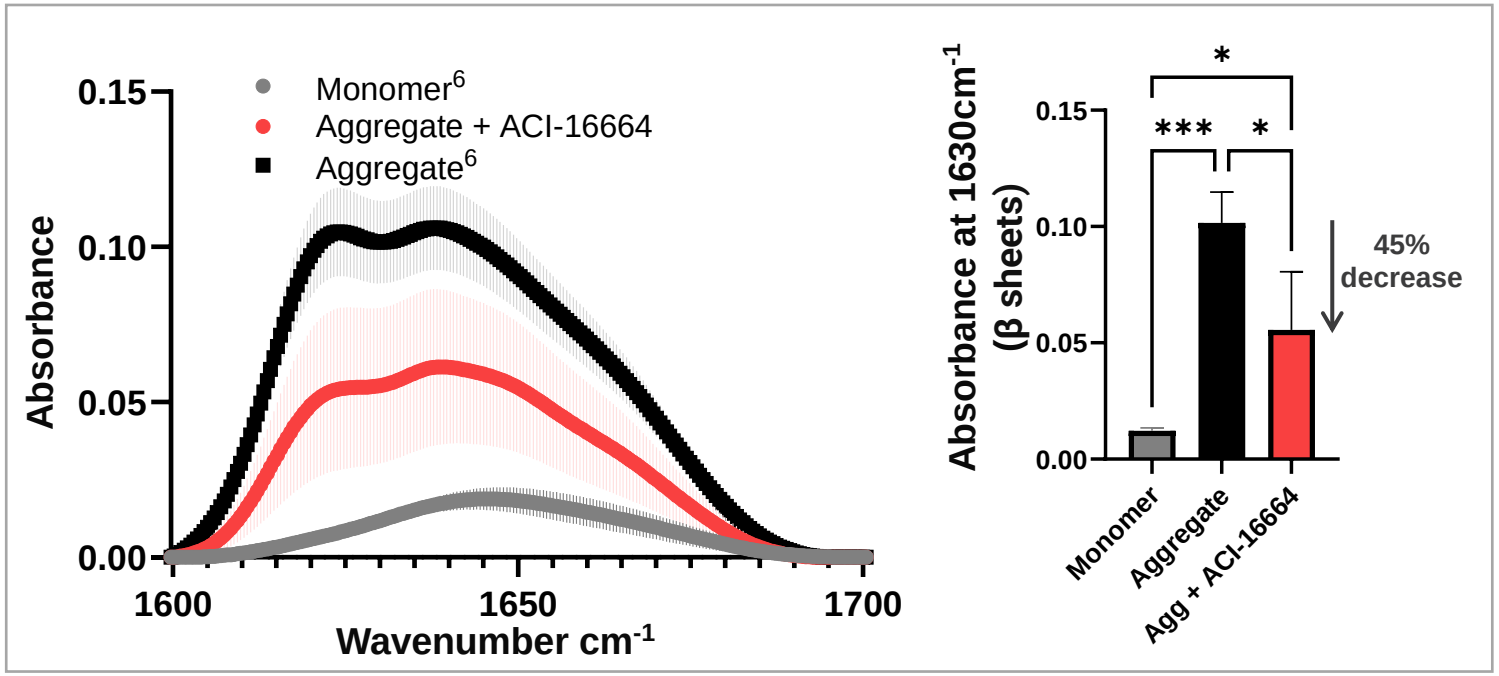
Change in Tau aggregate[1] structure assessed using ThT[2] and ATR-IR[3] assays

ThT Assay[4]

(Beta-sheet fluorescent dye)



ATR-IR Spectroscopy



Error bars = SD of 4 independent experiments; statistical significance *<0.05 **<0.01 *** <0.001 based on one-way ANOVA

- Morphomers® disrupt the pathological conformation of pre-formed Tau aggregates by removing beta-sheet structures

(1) PHF-seeded 2N4R Tau aggregates (2) Thioflavin T (3) Attenuated Total Reflection – Infrared spectroscopy; (4) ThT fluoresces when bound to beta sheets; (5) fold increase over PBS (6) vehicle (DMSO)-treated

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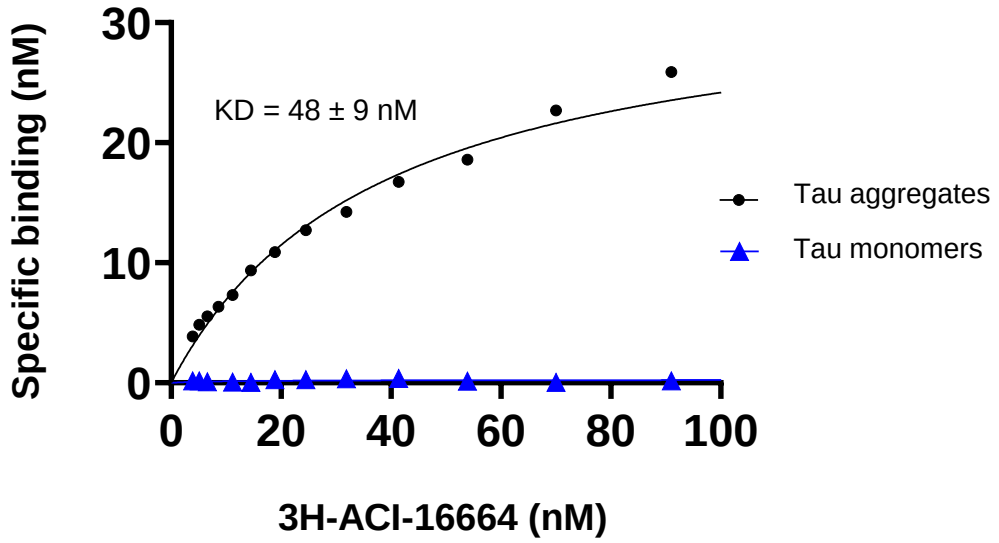
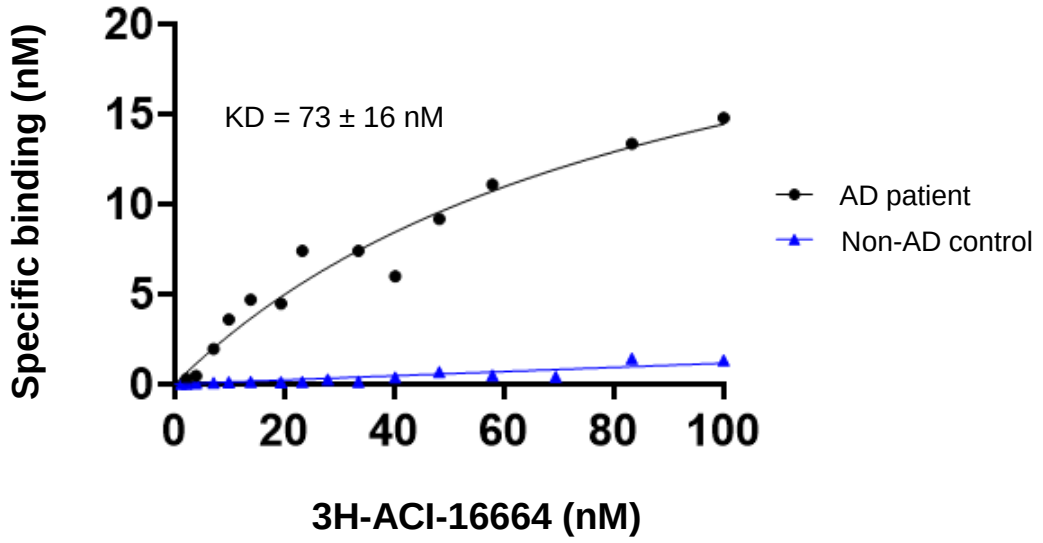
ACI-16664 binds specifically to pathological Tau

Assessed with monomeric, aggregated and brain-derived insoluble Tau species

Binding to recombinant Tau aggregates vs monomers[1]



Binding to Tau PHF[2] **from AD vs control brains**[3]



- ACI-16664 exhibits high affinity and selectivity for pathological Tau species
- Lack of binding to the physiological monomeric form of Tau reduces safety risks
- Selectivity versus other targets was also confirmed using a broad off-target panel[4]

(1) PHF-seeded 2N4R Tau aggregates vs 2N4R Tau monomers, average KD from 3 experiments is shown; (2) sarkosyl-insoluble fraction (3) ; ACI-16664 was tested on several AD patients; average KD of 6 experiments is shown; (4) Bioprint pannel with 135 safety-relevant targets

ACI-16664 inhibits intracellular Tau seeding

With primary rat cortical neurons and AD-brain derived insoluble or soluble Tau as seeds

Endogenous Tau aggregates[2]

Tau aggregate count[3]

MAP2 GFAP DAPI

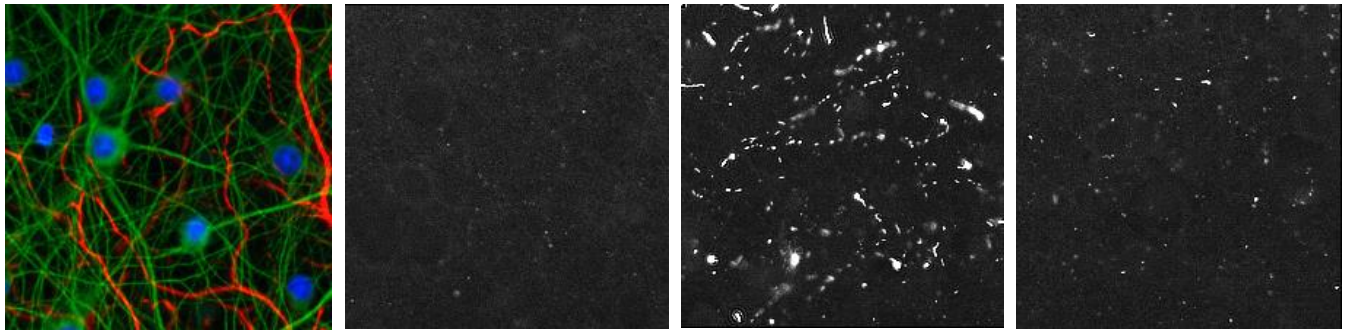
No Tau seed

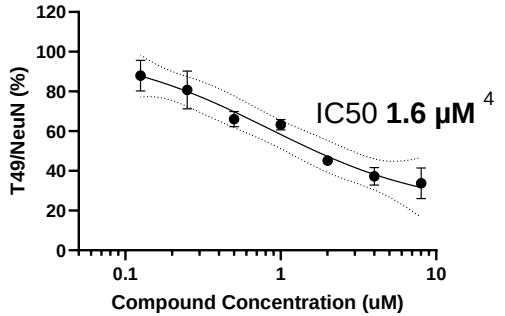
Tau seed

+ vehicle (DMSO)

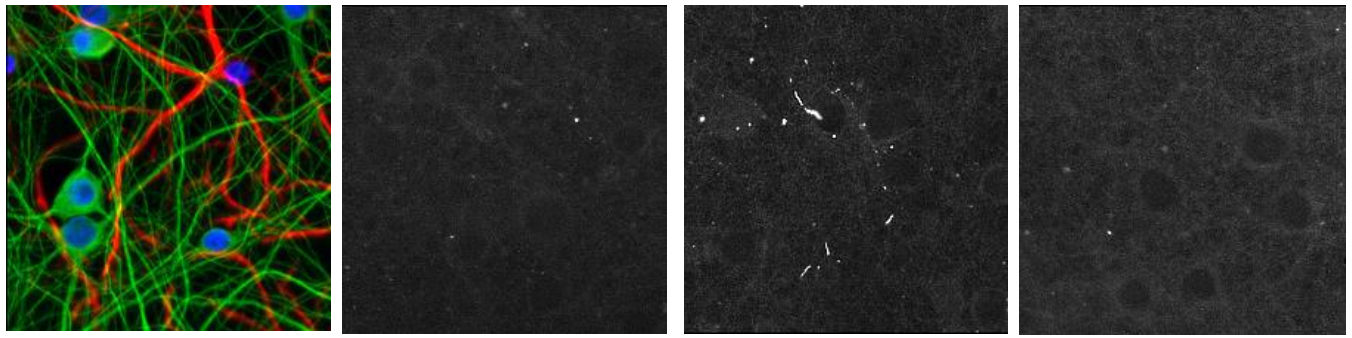
+ ACI-16664 (4 μM)

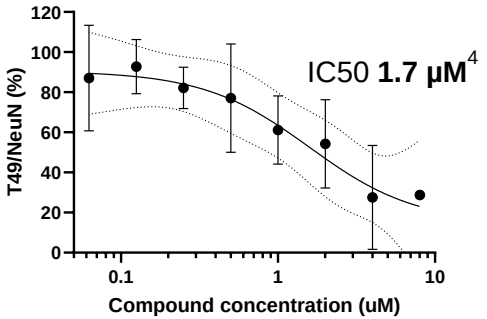
With insoluble AD Tau seeds[1]





With soluble AD Tau seeds[1]





Error bars = SD of independent experiments

- ACI-16664 inhibits intracellular Tau seeding induced with AD-brain derived soluble or insoluble Tau seeds

(1) Tau seeds isolated from AD brain used; Insoluble Tau seeds = Tau paired helical filaments (PHF); Soluble Tau seeds = soluble high molecular weight Tau aggregates isolated by size-exclusion chromatography; (2) Endogenous Tau aggregates labeled with T49, a rodent-specific Tau mAb; (3) Normalized to neuron count; (4) Mean values with SD error bars from n=5 (insoluble) or n=3 (soluble) experiments, absolute IC_{50} values are shown; (5) Imax, maximum % of inhibition = 100 – lowest value of T49/NeuN (%) from the average dose response curve

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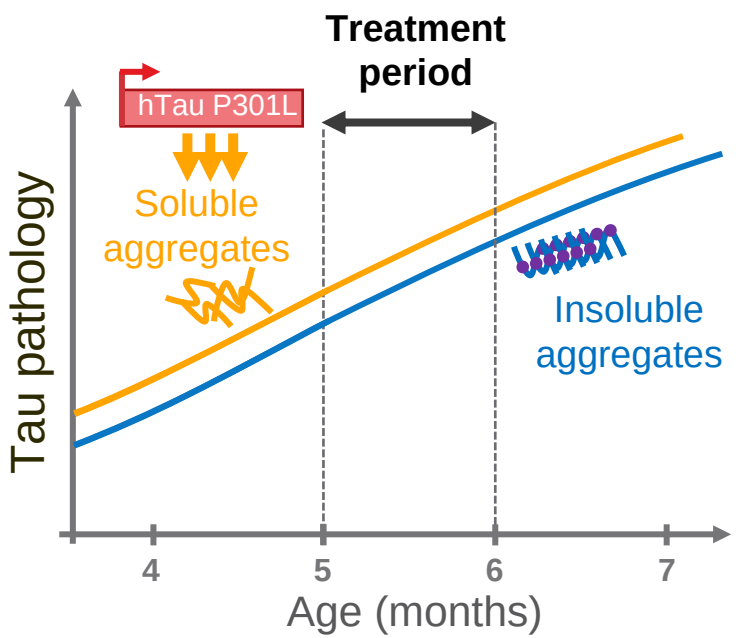
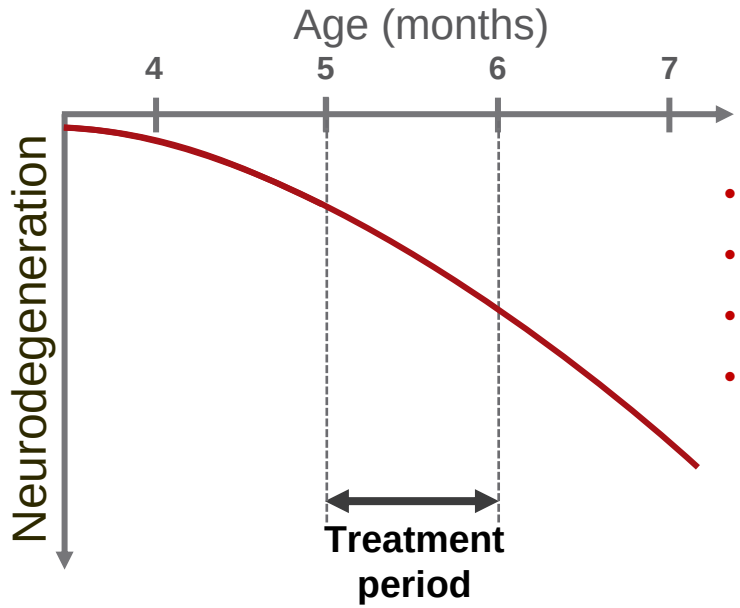
Evaluating efficacy *in vivo* using the Tg4510 mouse model





- neuronal loss
- neurite loss
- synapse loss
- cortical tissue loss

Mouse group	Nb of mice	Test article	Frequency/ Dose
tTA[1] (non-diseased controls)	11	vehicle	BID
Tg4510	20	vehicle	BID
Tg4510	21	ACI-16664	100mg/kg BID

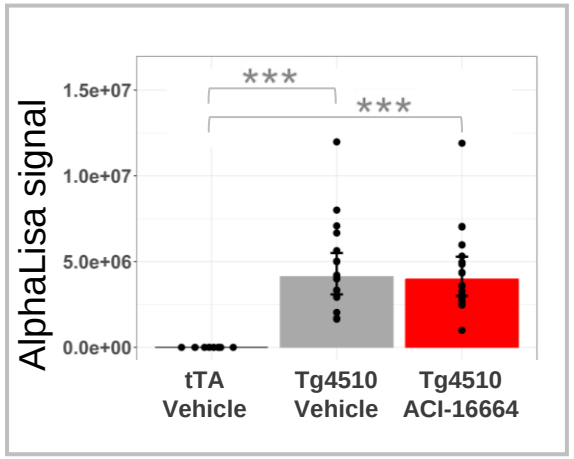
- Tg4510 transgenic mice represent an aggressive model of tauopathy displaying rapid accumulation of soluble and insoluble Tau aggregates as well as neurodegeneration
- A short 4-week treatment was initiated when the Tau pathology was already advanced

(1) Control mice that are genetically identical to the Tg4510 mice but lack the Tau transgene and hence are devoid of Tau pathology

ACI-16664 decreases pathological Tau aggregates *in vivo*

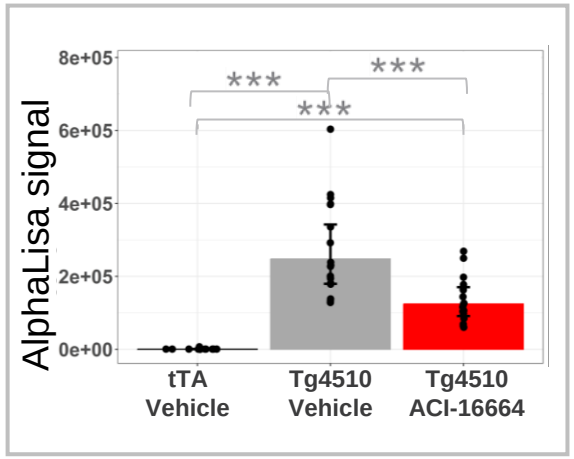
Biochemical and histological assessment of Tau levels in the cortex of Tg4510 mice

Total Tau[1]



unchanged

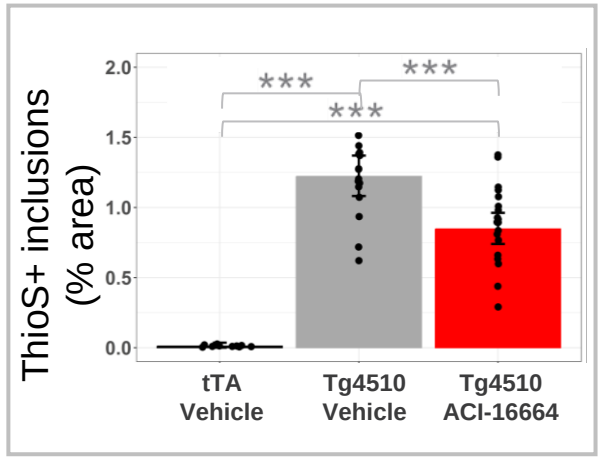
Total Tau aggregates[2]



↓ 51% decrease

p=0.001

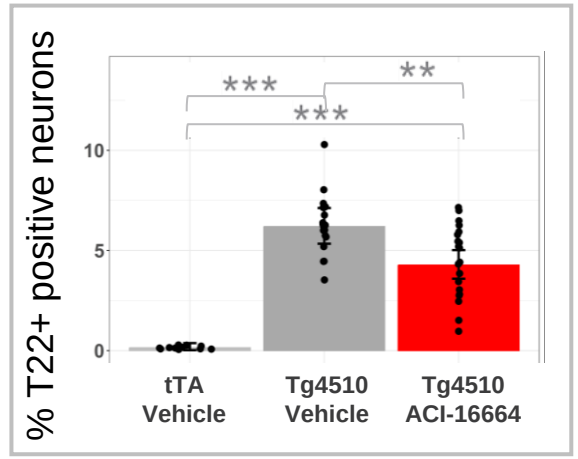
Tangles (insoluble Tau)[3]



↓ 31% decrease

p=0.001

Soluble Tau Oligomers[4]



↓ 31% decrease

p=0.006

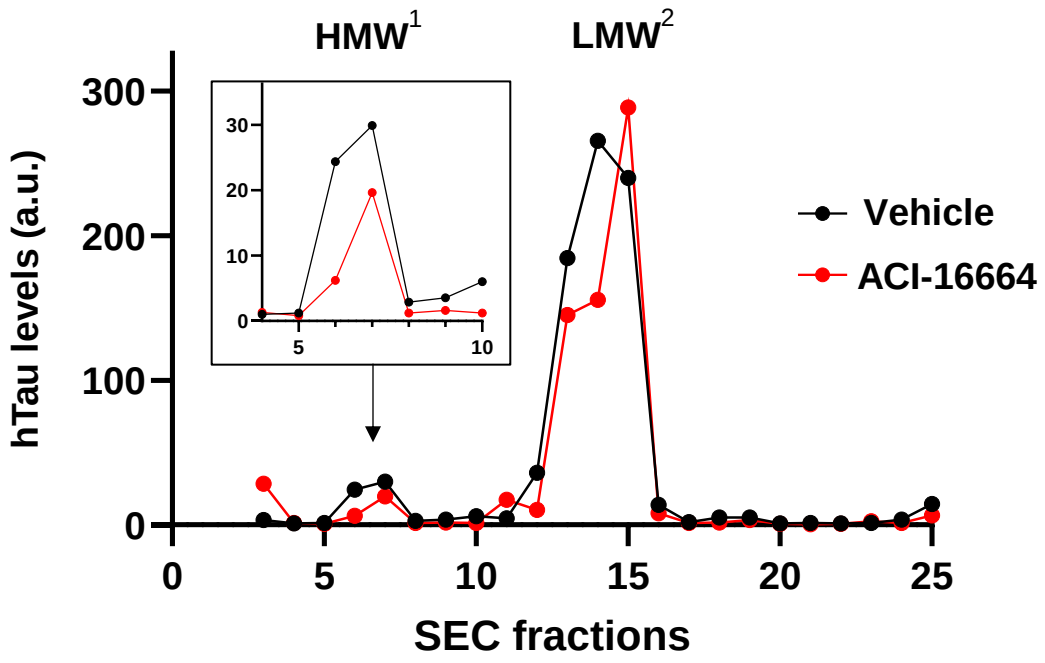
Group means, standard deviations, and uncorrected p-values based on linear mixed models are shown

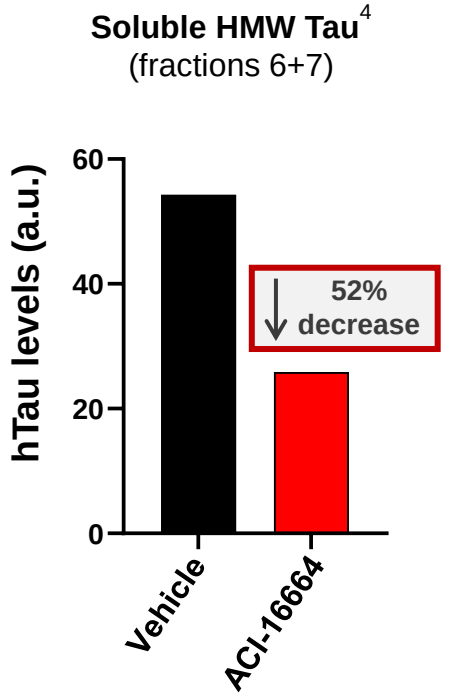
- Treatment with ACI-16664 significantly decreased Tau aggregation with reduction of both soluble and insoluble pathological species

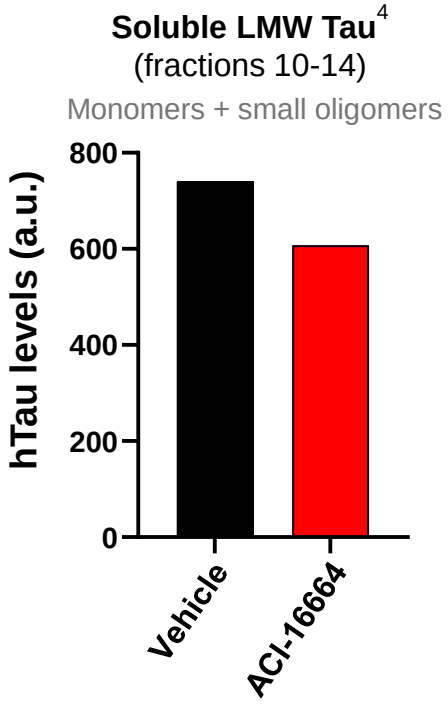
(1) AlphaLisa on total cortical homogenates with mAb pair, Tau13/HT7 specific for human Tau; (2) AlphaLisa on total cortical homogenates with mAb pair; HT//HT/ for aggregated Tau (3) ThioS-positive tangle-shaped inclusions on frontal cortex sections (4) by immunolabeling with antibodies for T22 (oligomers) and NeuN (neurons) on frontal cortex sections ; ** p ≤ 0.01; *** p ≤ 0.001

ACI-16664 decreases key soluble Tau species *in vivo*

Soluble cortical extracts obtained from Tg4510 mice and fractionated by SEC[3]





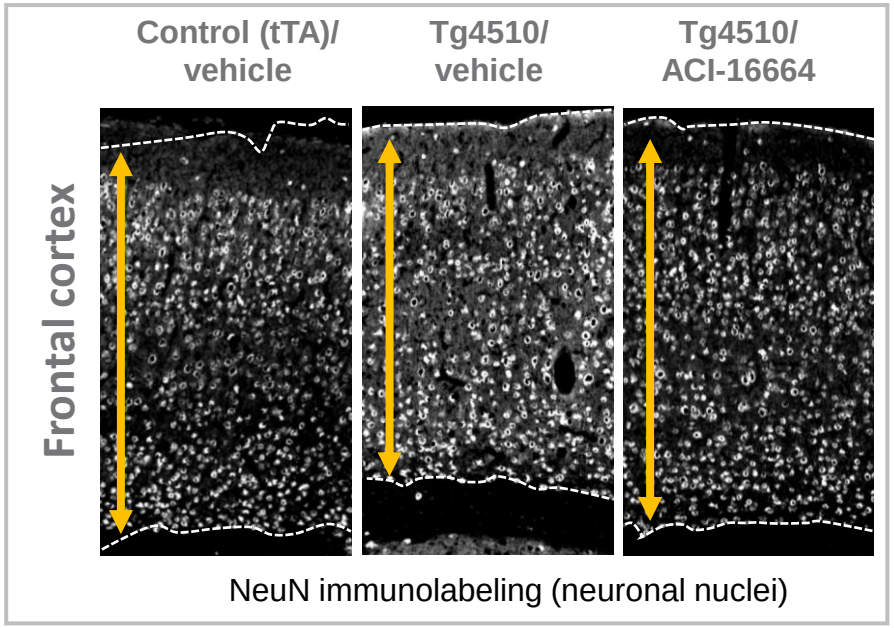


- Treatment with ACI-16664 resulted in a major reduction of soluble HMW Tau aggregates, a key species for Tau spreading and disease progression in AD

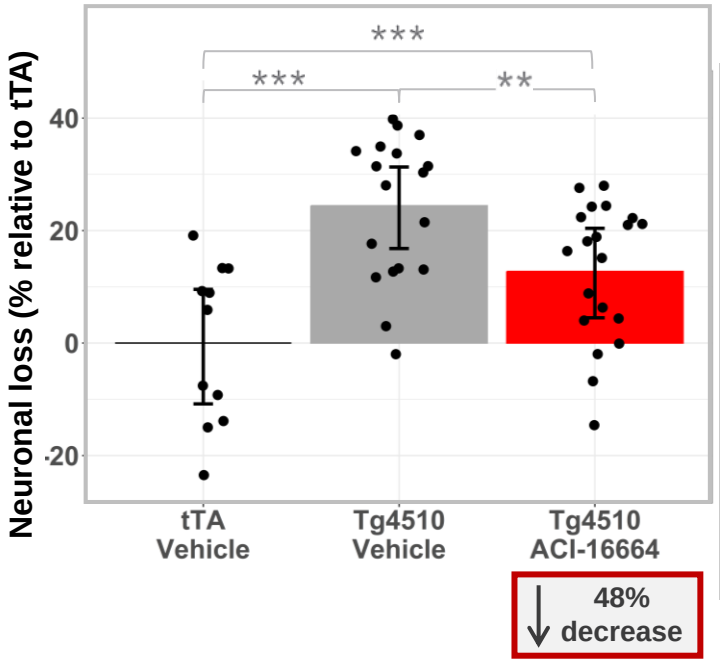
(1) high molecular weight (2) low molecular weight (3) size-exclusion chromatography (4) All mice of each group were pooled for this analysis

ACI-16664 prevents neurodegeneration *in vivo*

Neuronal count and neuritic area in frontal cortex

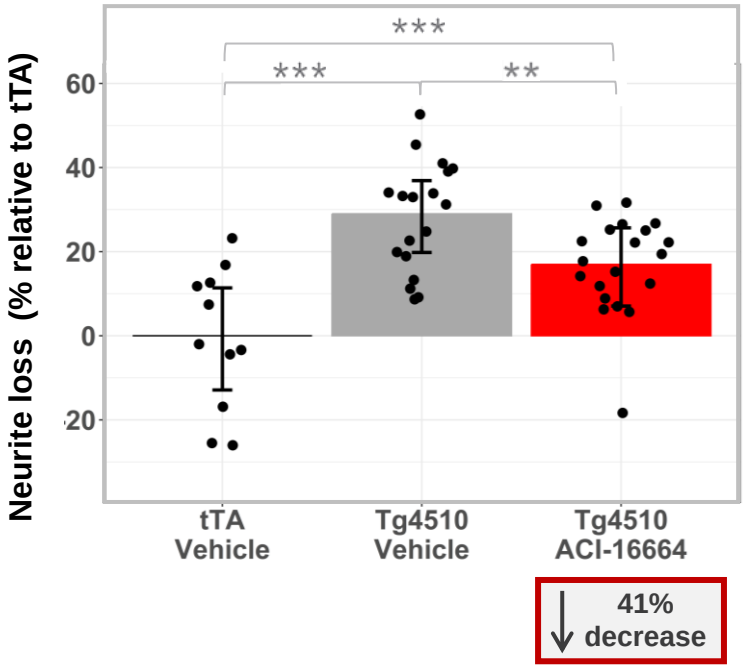


Neuronal loss[1]



p=0.002

Neurite loss[2]



p=0.005

Group means, standard deviations, and uncorrected p-values based on linear mixed models are shown

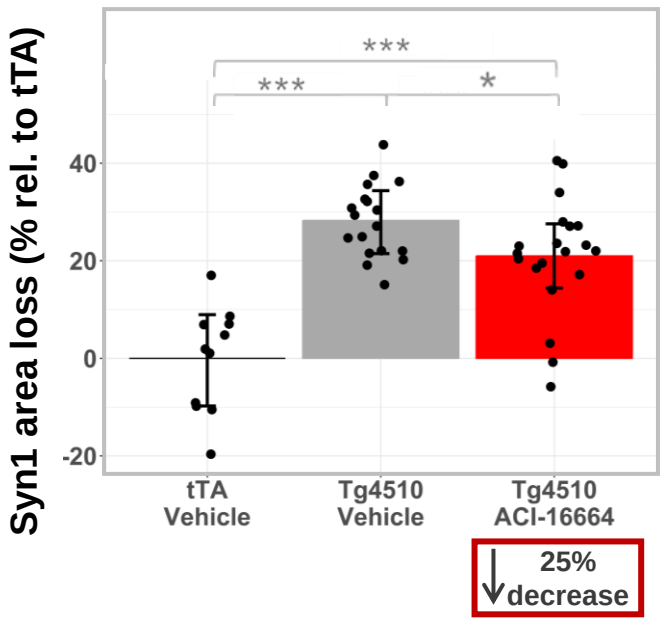
- Treatment with ACI-16664 improved multiple clinically-relevant neurodegeneration endpoints supporting its expected therapeutic benefit

(1) Based on neuron count assessed with NeuN Ab; (2) Based on delineation of neuritic area using the pan-neuronal marker PNM ; ** p ≤ 0.01; *** p ≤ 0.001

ACI-16664 prevents synapse loss *in vivo*

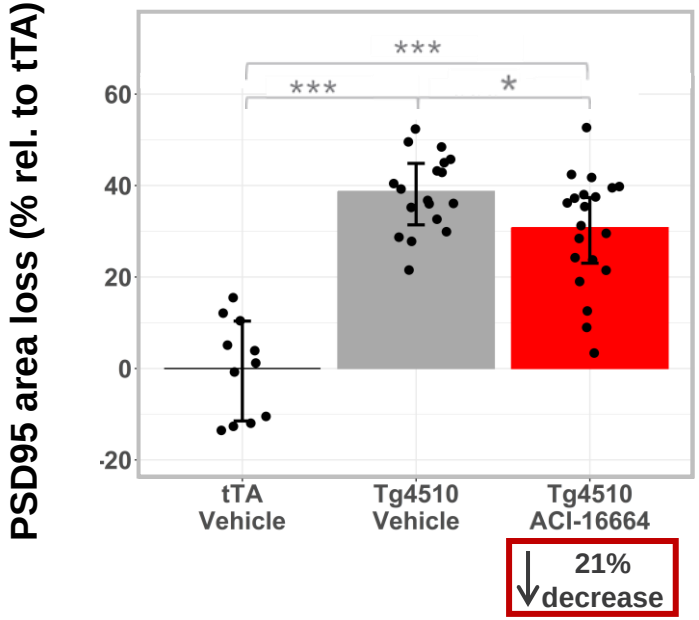
Synaptic loss and correlation with Tau pathology

Presynaptic loss[1]



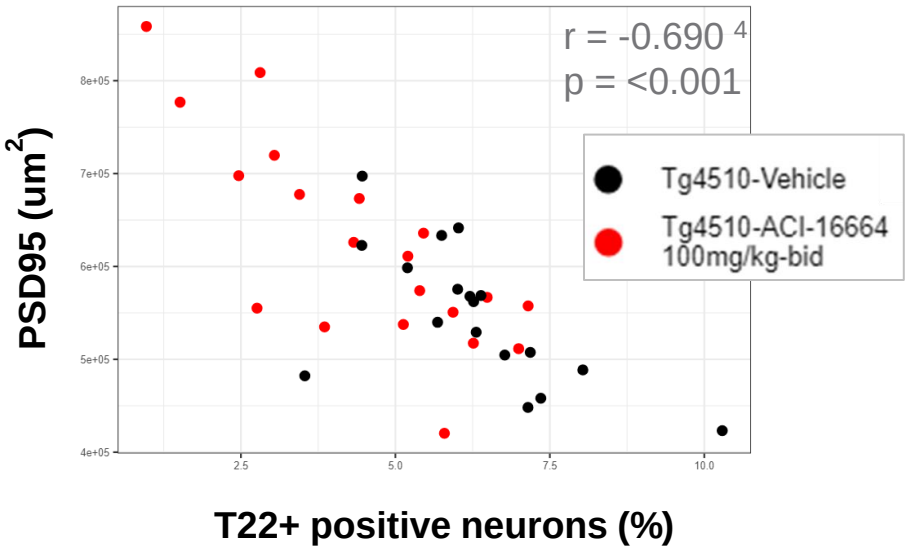
p=0.025

Postsynaptic loss[2]



p=0.047

Postsynaptic area versus soluble aggregates

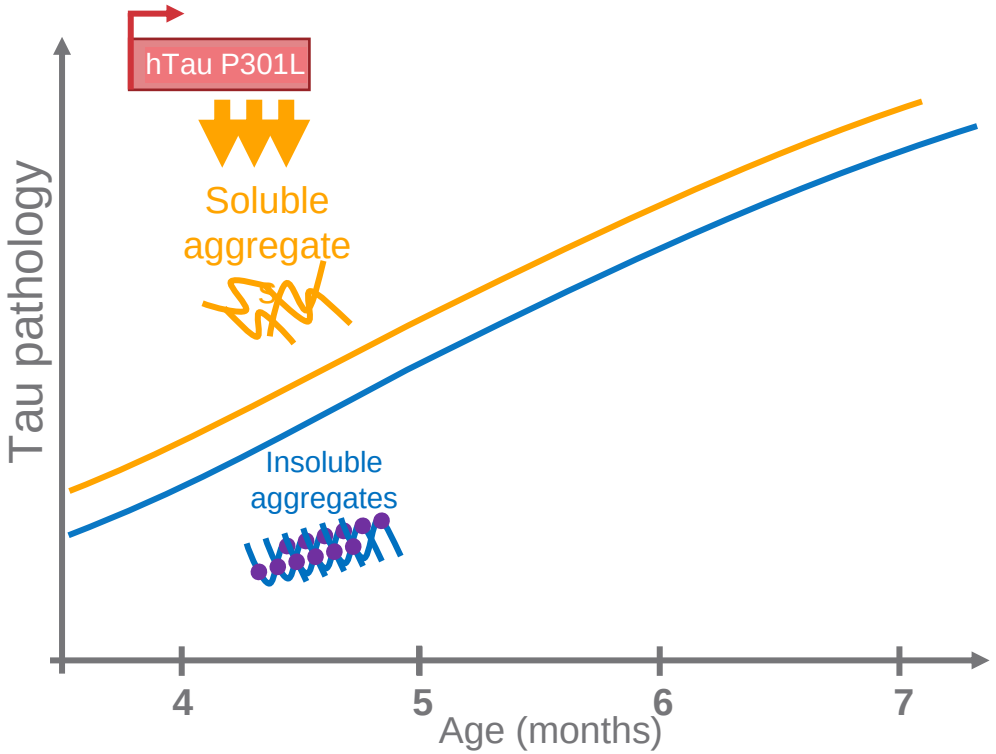


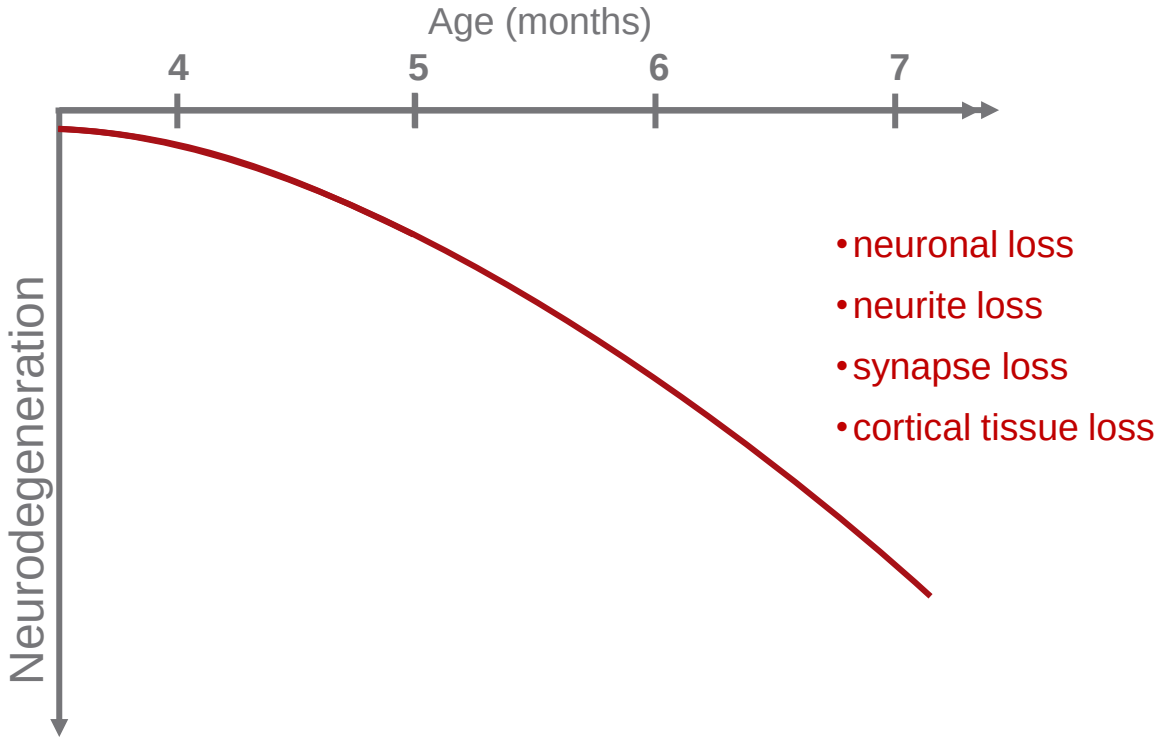
Group means, standard deviations, and uncorrected p-values based on linear mixed models are shown

- Treatment with ACI-16664 resulted in the preservation of both pre- and post-synaptic structures which strongly correlated with the decrease in soluble Tau aggregates

(1) Synaptophysin 1 immuno-positive area (2) PSD95 immuno-positive area (3) Number of neurons positive for the anti-Tau (T22) antibody labeling Tau oligomers (4) Pearson's correlation coefficient ; * ≤ 0.05 ; ** p ≤ 0.01; *** p ≤ 0.001

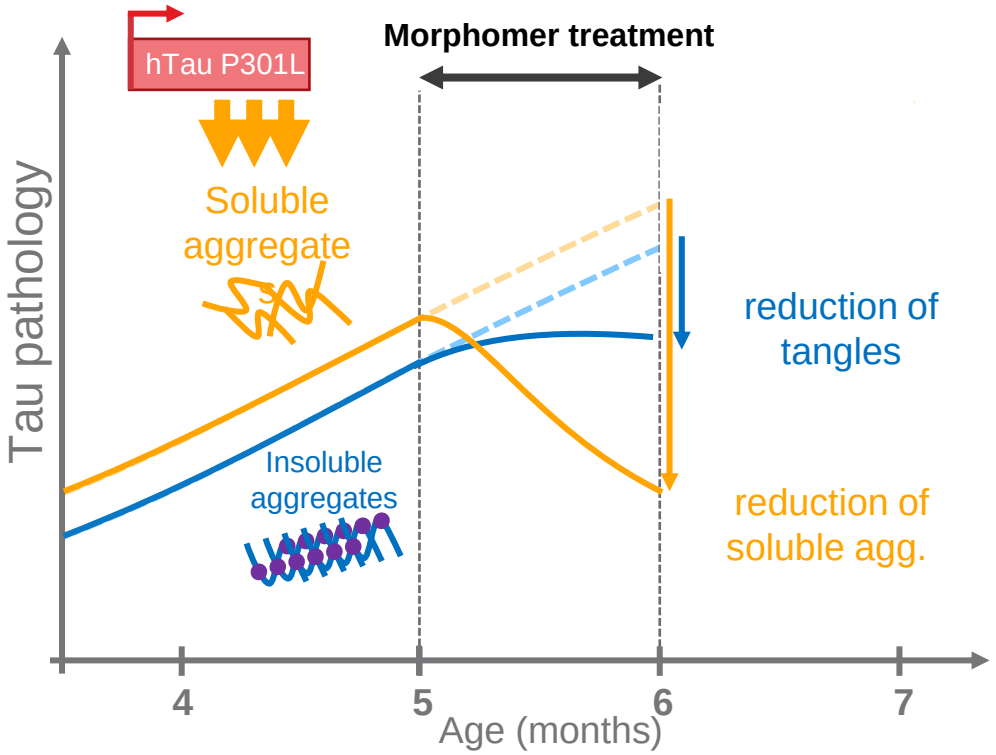
Evaluating efficacy *in vivo* using the Tg4510 mouse model

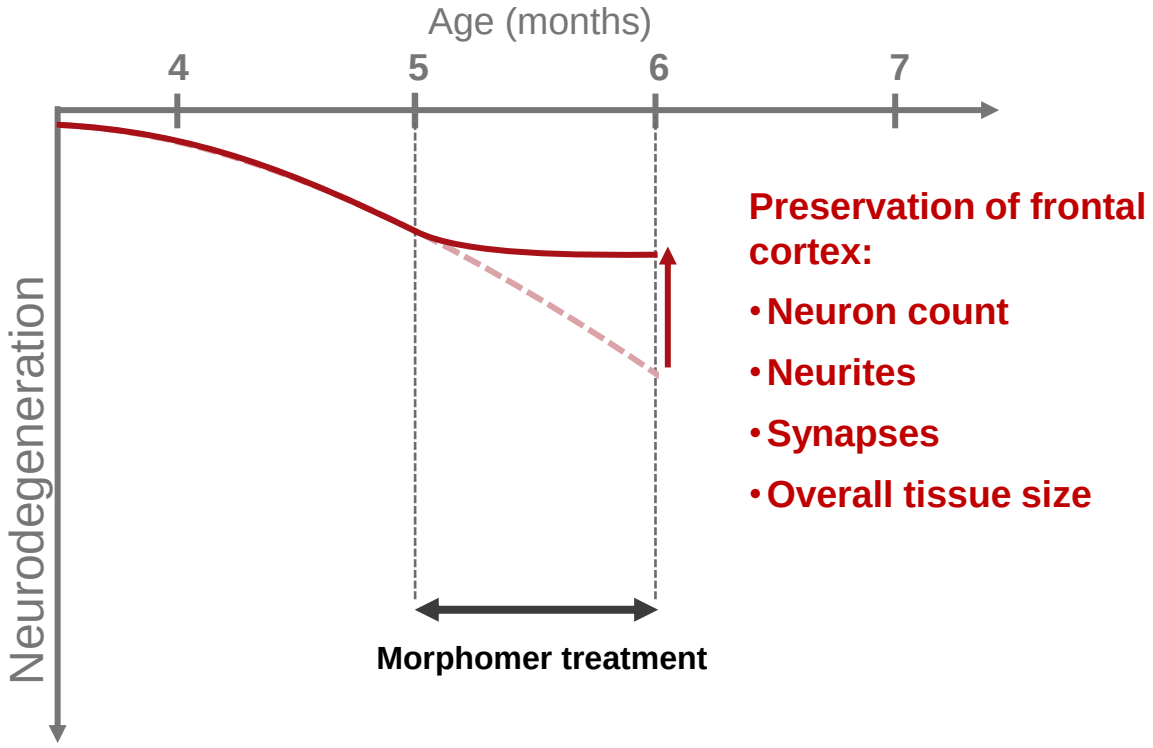




Broad action across Tau pathological species ensures neuroprotection

Unprecedented changes in multiple clinically relevant readouts in the Tg4510 model





- *In vivo,* treatment with ACI-16664 demonstrated a broad action on soluble and insoluble pathological Tau species resulting in a strong protection from neurodegeneration

Conclusions

First-in-class orally active, CNS[1]-penetrant small molecule Tau Morphomers®

First-in-class

- **Eliminate** pathological Tau beta-sheets
- **Prevent** pathological Tau aggregation

Broad acting

- Target **insoluble and soluble** pathological Tau species
- Active in both **intracellular and extracellular** compartments

Selective

- **Highly selective for aggregated Tau** over physiological Tau and other protein targets maximizing safety

Efficacious

- **Efficaciously reduce Tau pathology** and **prevent neurodegeneration *in vivo*** in an aggressive tauopathy model

Clinical impact

- Tau Morphomers® represent a novel, broad acting therapeutic approach **to halt disease progression and deliver clinical benefits in Tau-driven pathologies**

(1) Central nervous system

Acknowledgements

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