Crossing therapeutic boundaries:

An immunotherapeutic simultaneously targeting amyloid-β, Tau, and α-synuclein amyloid aggregates

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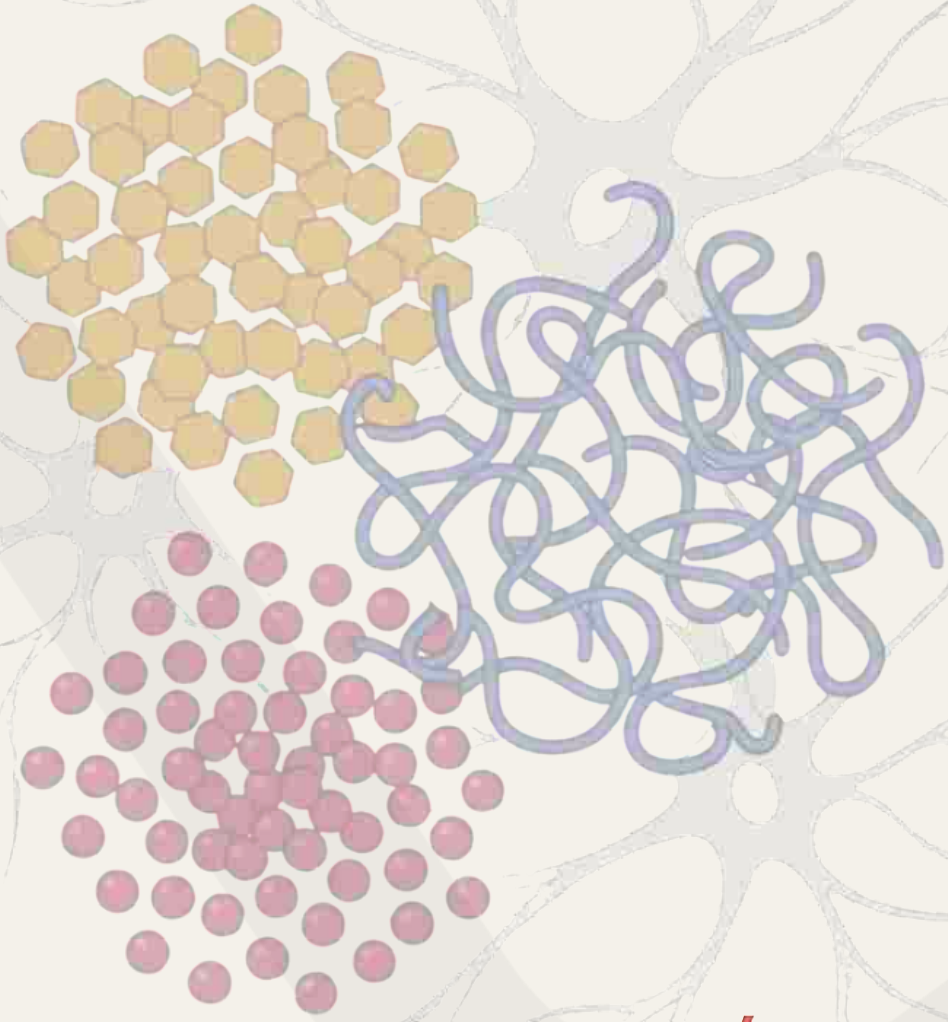

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	No, Nothing to disclose
X	Yes, please specify

Company / Name	Honoraria / Expense	Consulting / Advisory Board	Funded Research	Royalties / Patent	Stock Options	Ownership / Equity Position	Employee	Other (Please specify)
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Acknowledgements

With support from Wallonia

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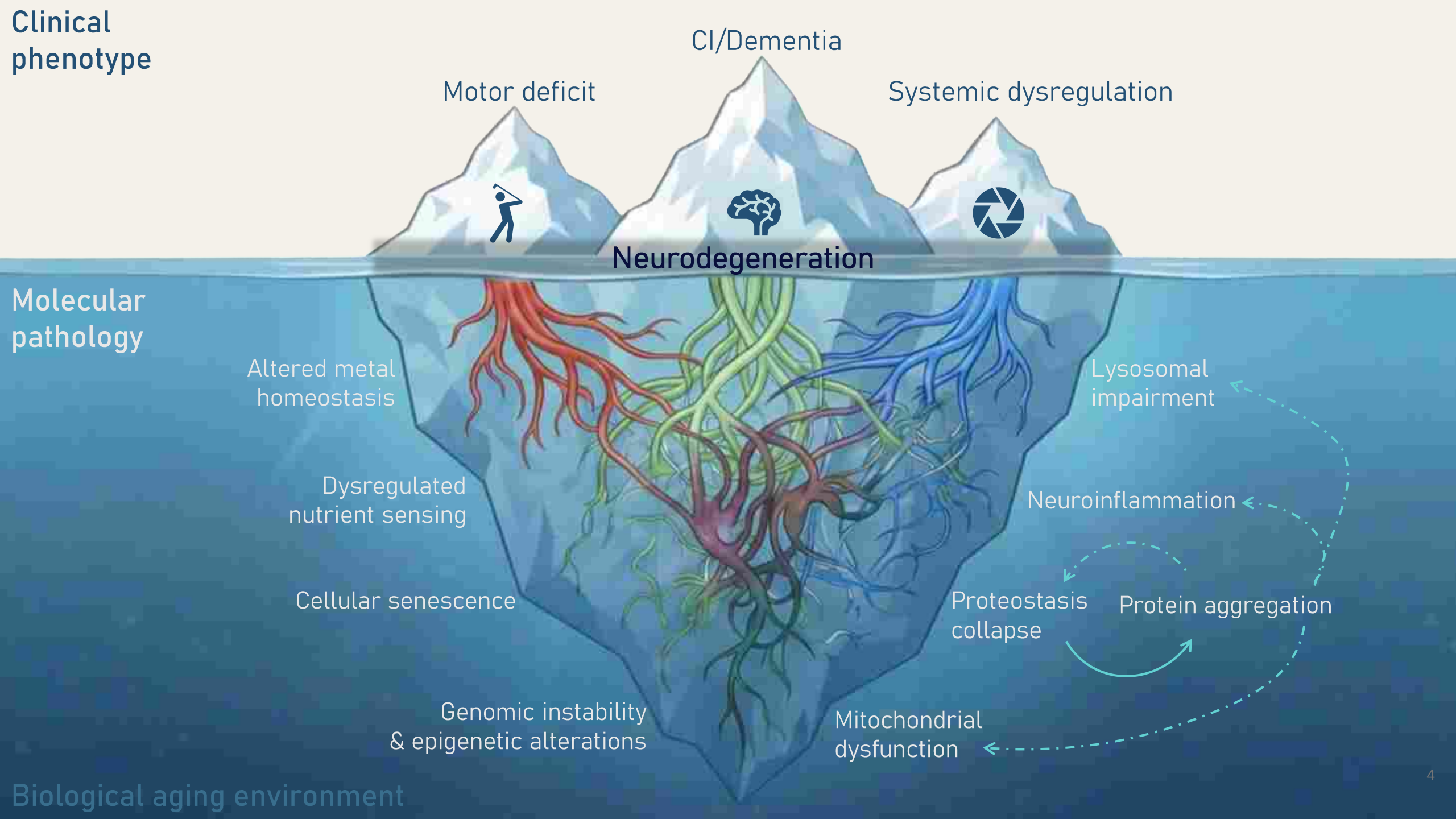
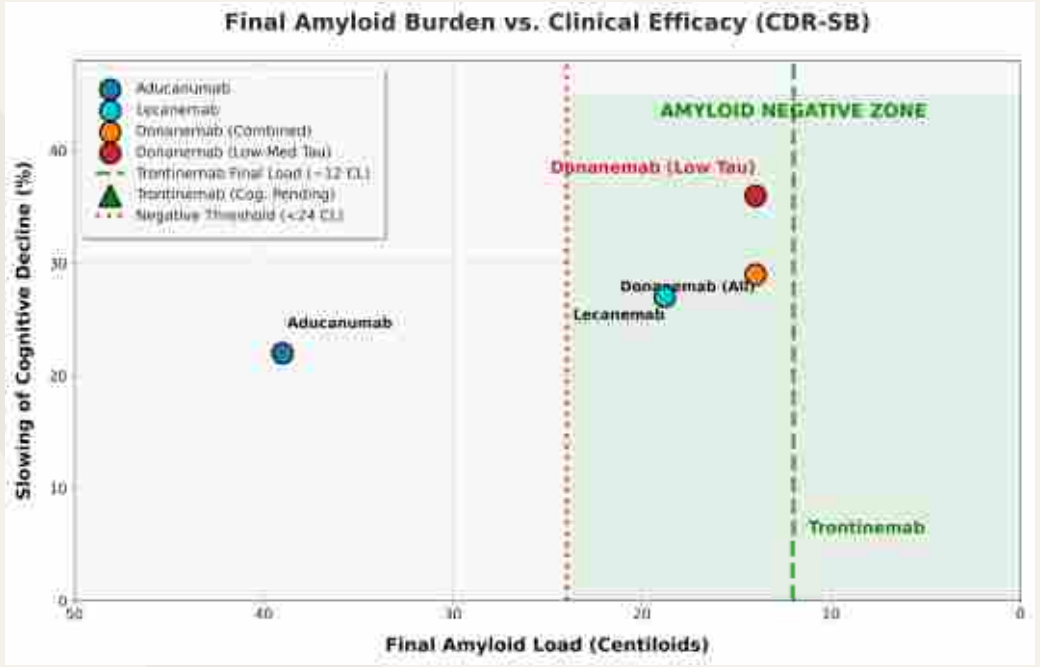

Clinical phenotype
CI/Dementia
Motor deficit
Systemic dysregulation
Neurodegeneration
Molecular pathology
Altered metal homeostasis
Lysosomal impairment
Dysregulated nutrient sensing
Neuroinflammation
Cellular senescence
Proteostasis collapse
Protein aggregation
Genomic instability & epigenetic alterations
Mitochondrial dysfunction
Biological aging environment

The therapeutic ceiling for passive immunotherapeutics?

Recent approvals validate amyloid clearance in passive immunotherapies but highlight the limitations of single-target strategies for age-associated neurodegenerative diseases (AANDs)



(mono-therapies)
Aβ: Lecanemab, Donanemab
Tau: Etalanetug (E-2814)*
α-syn: Prasinezumab*

(mono-therapies)
Aβ: Trontinemab*

What's next ?

Passive immunotherapy

ARIA risks
Low brain permeation

Improved brain permeation
Reduced ARIA

Combo-therapies*
Lecanemab +
Etalanetug

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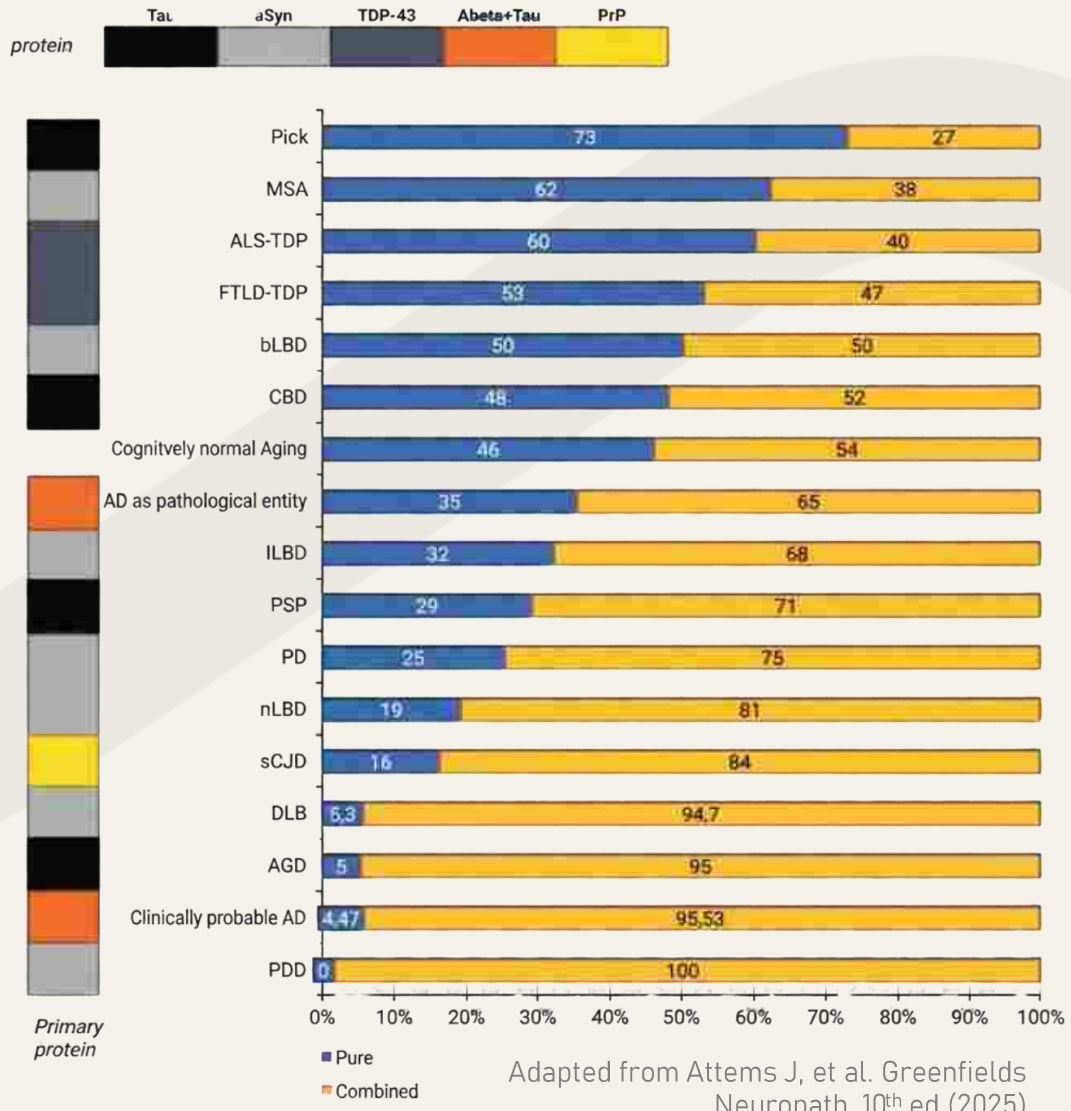
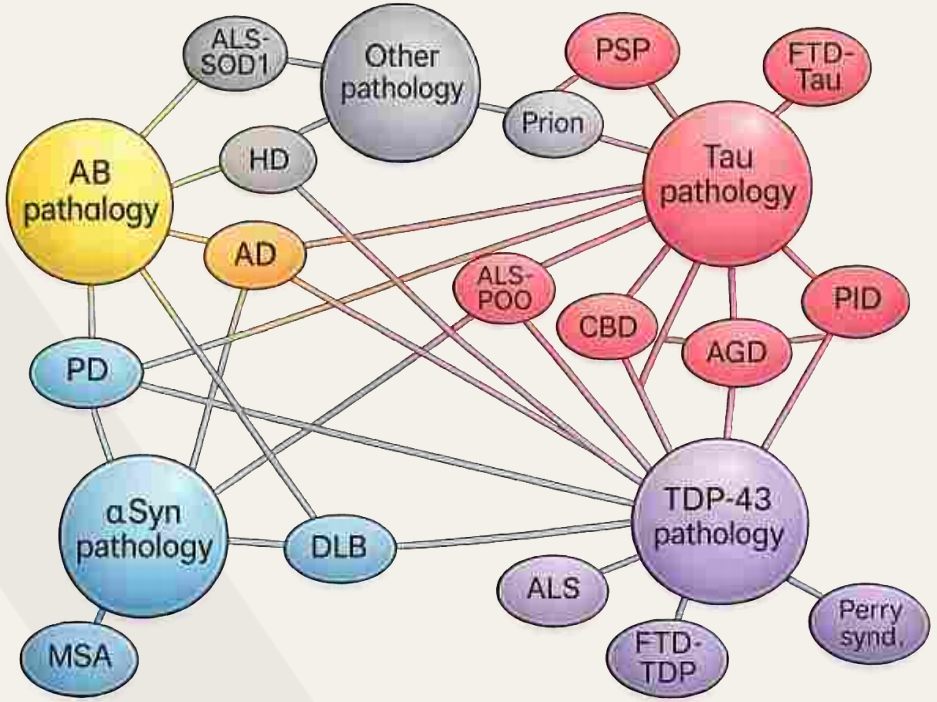
* Ongoing trials. Aducanumab (ENGAGE), Lecanemab (Clarity AD), Donanemab (TRAILBLAZER-ALZ 2) and Trontinemab (Roche press)

Pure amyloid pathology is an exception, not the rule



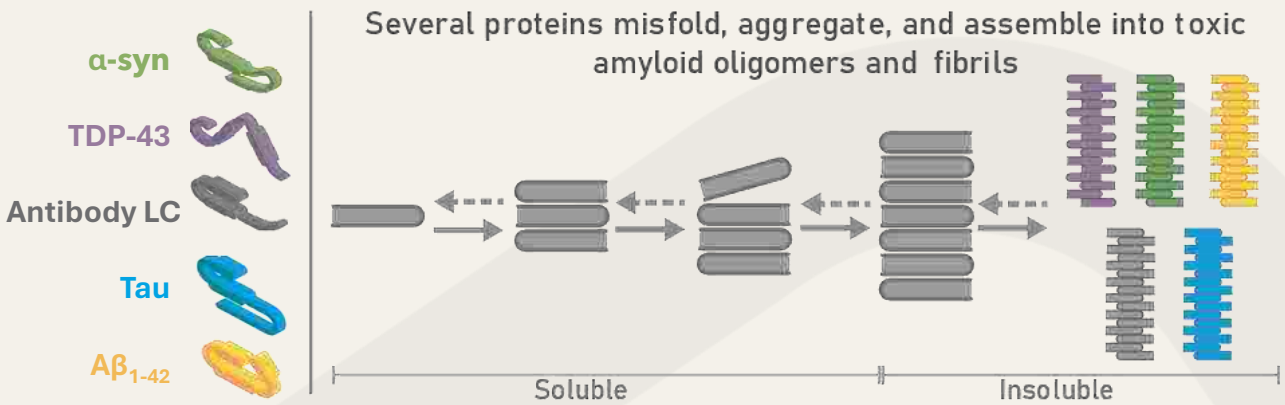
Adapted from Attems J, et al. Greenfields Neuropath, 10th ed (2025) pp 1216-25

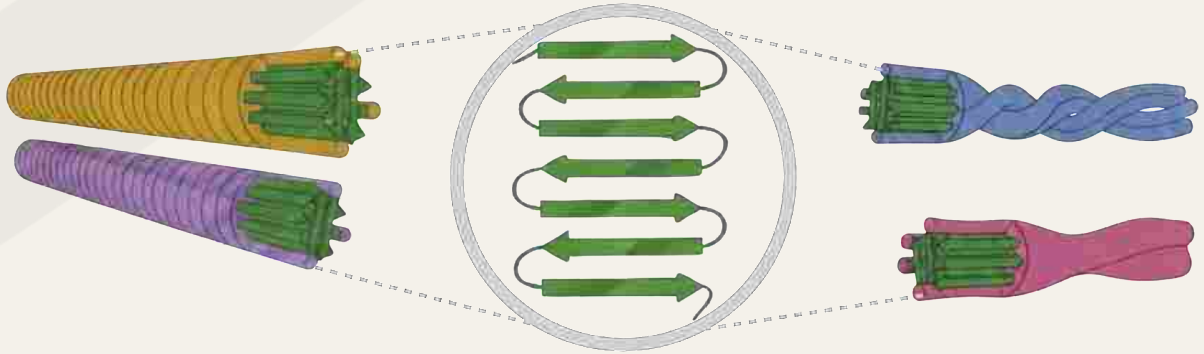
Mixed pathology is the norm in several age-associated neurodegenerative diseases



Adapted from Golde. et. al. 2013

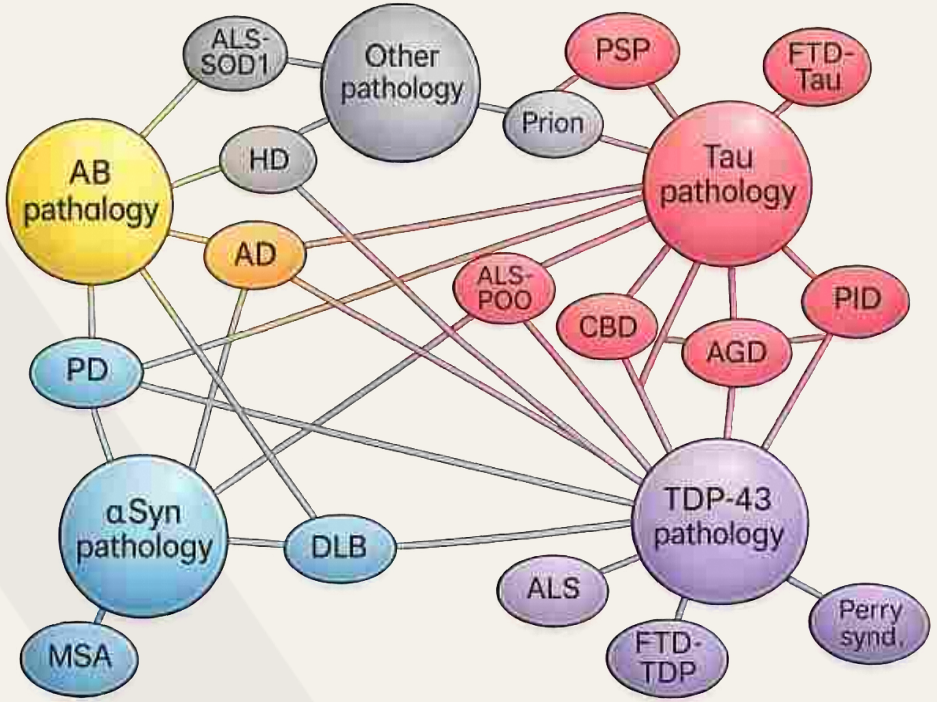
Mixed pathologies are united by a common structural architecture





Cross β-sheet architecture

Mixed pathology is the norm in several age-associated neurodegenerative diseases



Adapted from Golde. et. al. 2013

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A mixed-amyloid disease perhaps requires a therapeutic acting on multiple amyloids simultaneously

“a pan-amyloid therapeutic”

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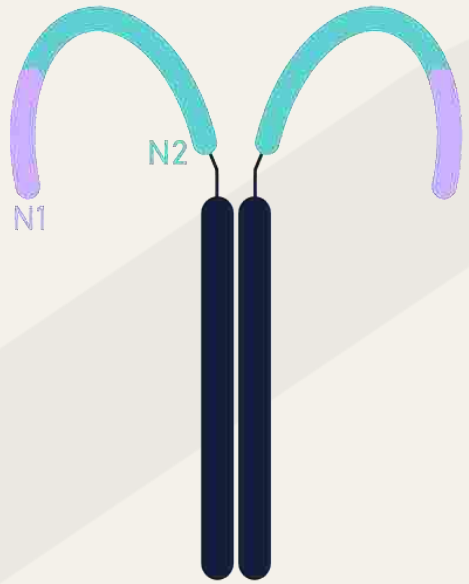
* Ongoing clinical trials

At Amyl Therapeutics, we are building such a therapeutic



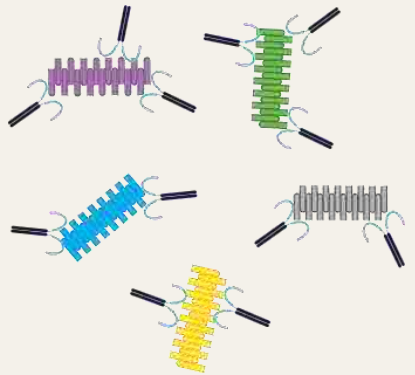
Amyloid binding domain

Fc receptor binding domain

Amyl-2

Fusion of a bacteriophage protein with a human antibody backbone

High affinity pan amyloid binding



Phagocytic uptake

Amyloid clearance

Targeting the universal cross-β sheet allows Amyl-2 to bind amyloid aggregates and facilitate phagocytic uptake.

As a bonus it inhibits aggregation too!

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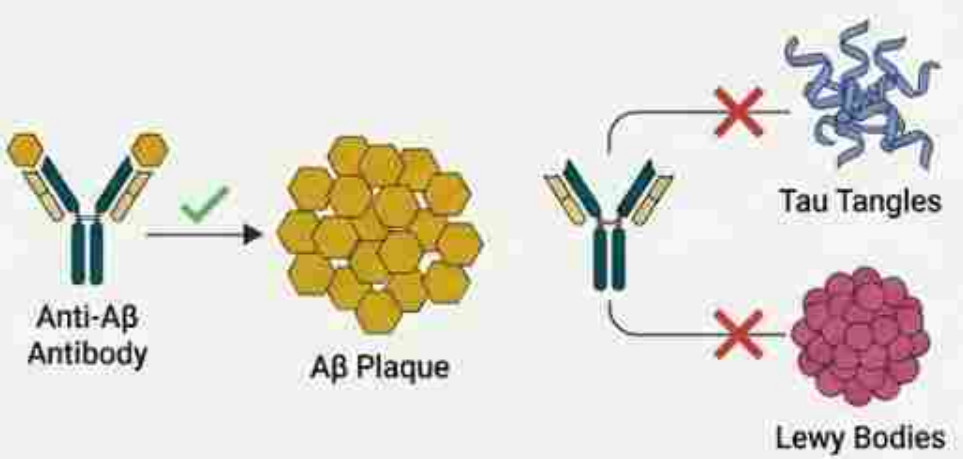
From sequence-specific to conformation-specific targeting

Protein specific (Monotherapy)

Target: Amino acid sequence (linear epitope) e.g. Aβ.

Mechanism: Recognition of a specific protein followed by phagocytic clearance of the protein. Narrow spectrum

Limitation: Ineffective against other co-existing pathological proteins (Tau, α-syn), clearance of functional monomer(?) etc.

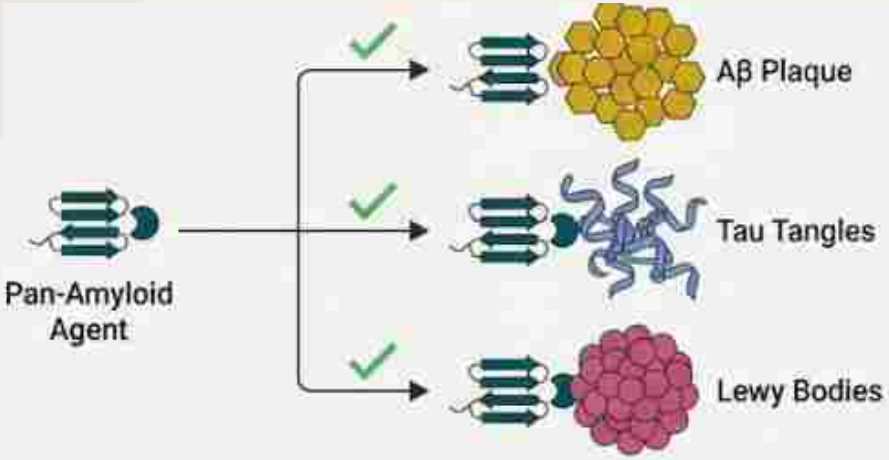


Conformation-specific (Pan-Amyloid therapy)

Target: Generic cross-β sheet structure.

Mechanism: Recognition of cross-β sheets followed by specific phagocytic clearance of amyloid aggregates. Broad spectrum

Limitation: Possible off-target binding to functional amyloids



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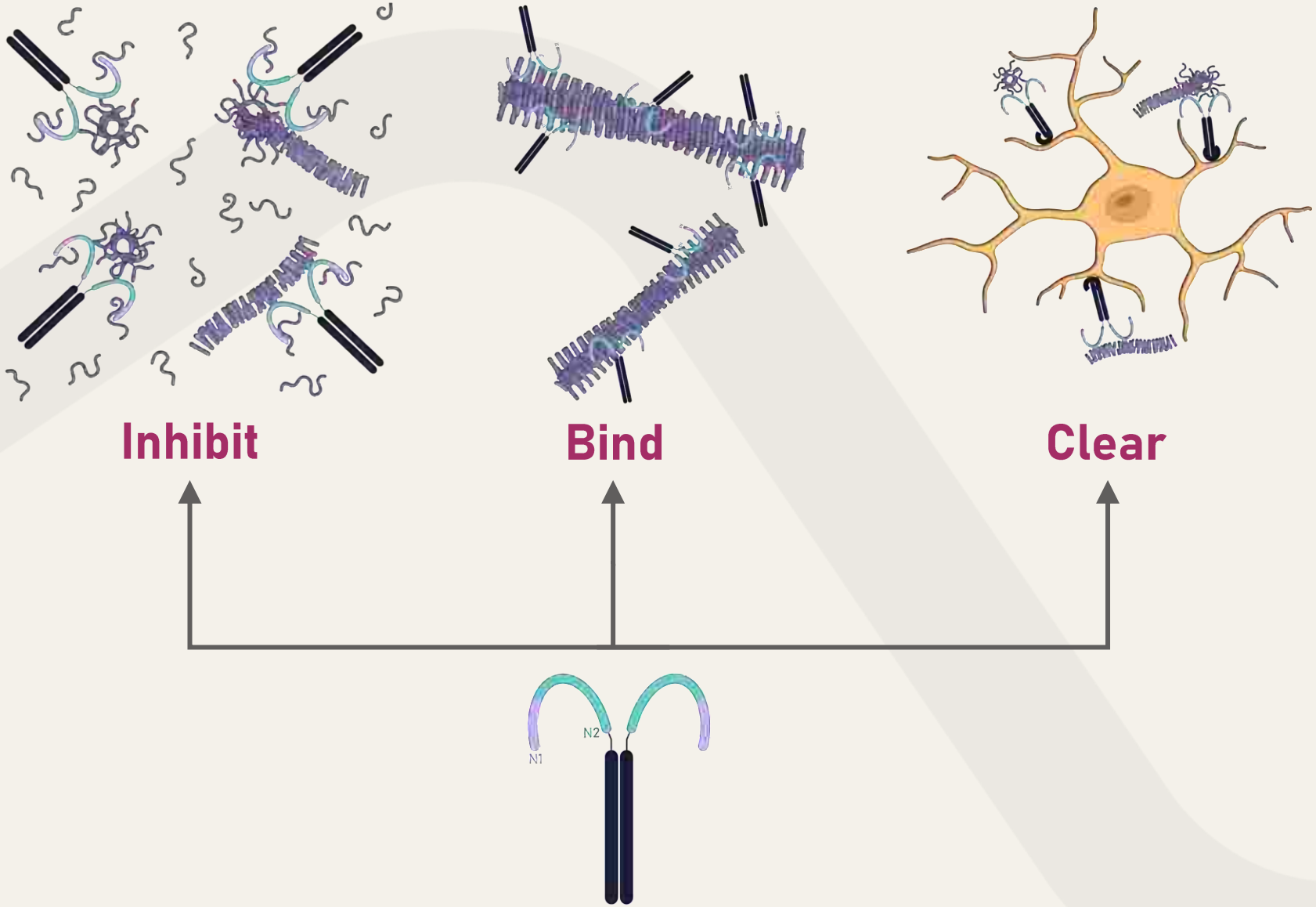
The central mechanism of Amyl-2



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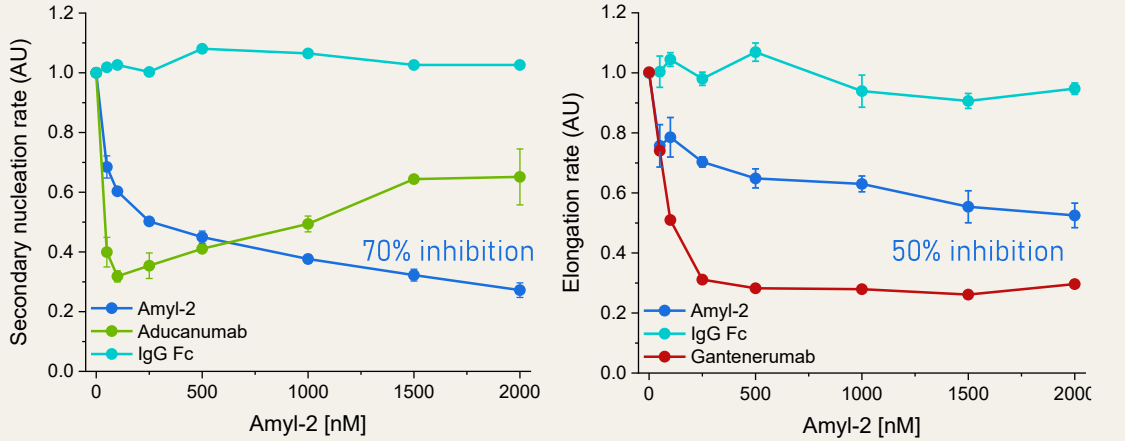
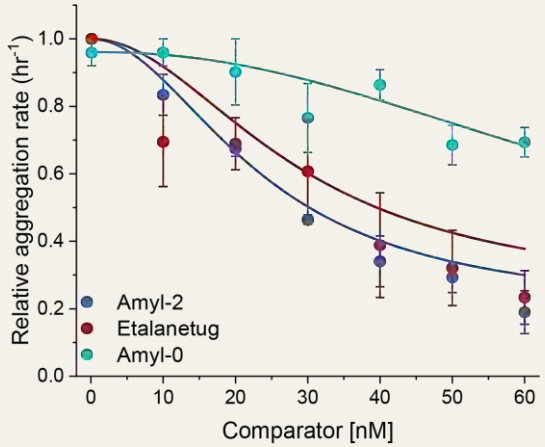
Amyl-2 inhibits aggregation of multiple amyloid proteins in vitro

$A\beta_{1-42}$



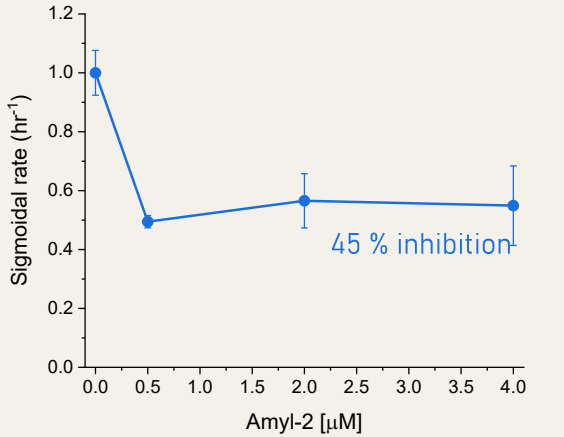
3.2 µM $A\beta_{1-42}$ aggregated in PBS buffer at pH 7.4 without shaking at 37 °C. Data shown are mean values from at least 5 independent measurements. Error bars represent s.e.m. (n=6)

dGAE Tau

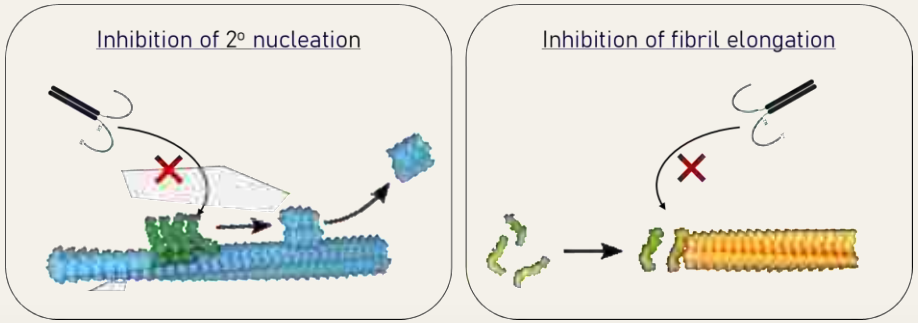


40 µM dGAE Tau aggregated in PBS buffer at pH 7.4, shaking at 600 rpm with 1 glass bead at 37 °C. Data shown are mean values from a single experiment. Error bars represent s.e.m. (n=6)

1-124 α-syn



30 µM 1-124 α-syn aggregated in PBS buffer at pH 7.4, shaking at 200 rpm at 37 °C. Data shown are mean values from a single experiment. Error bars represent s.e.m.(n=3)

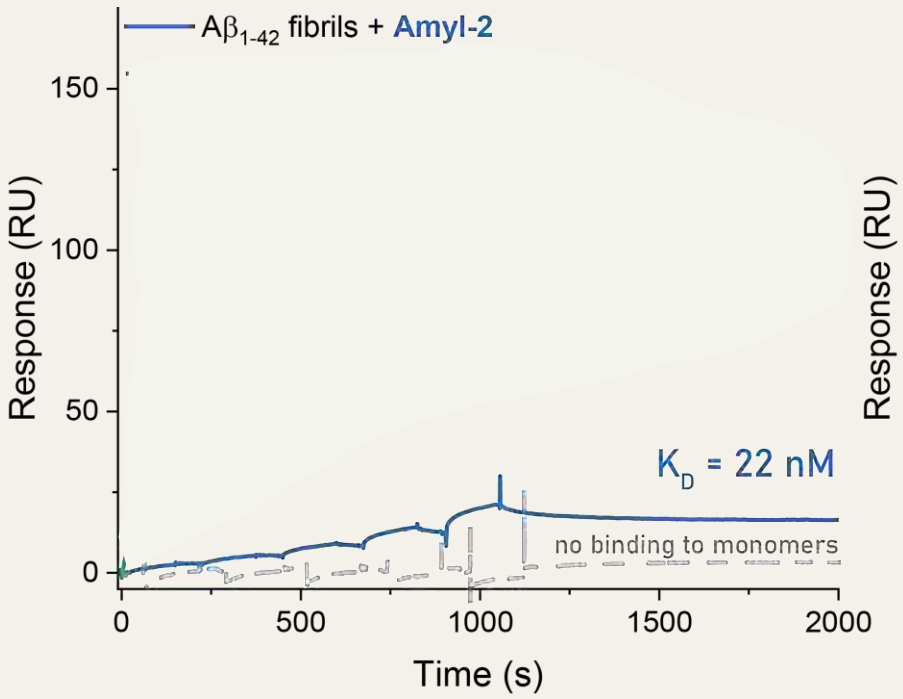


Amyl-2 inhibits the secondary nucleation and elongation step of $A\beta_{1-42}$ aggregation

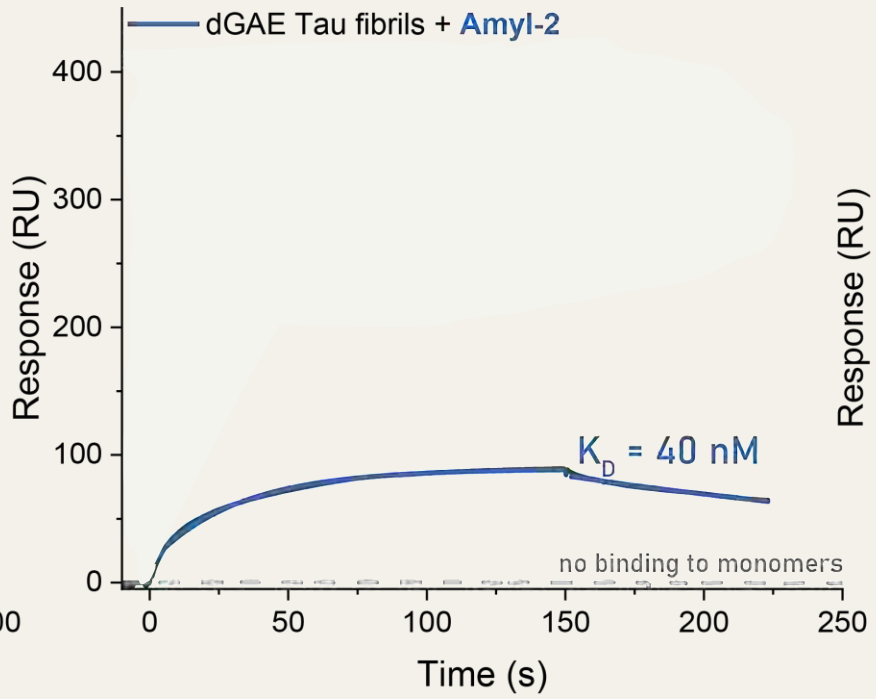
Preliminary data showing inhibitory effect of Amyl-2 on dGAE Tau and 1-124 α-syn aggregation

Amyl-2 binds multiple amyloid fibrils in vitro: SPR

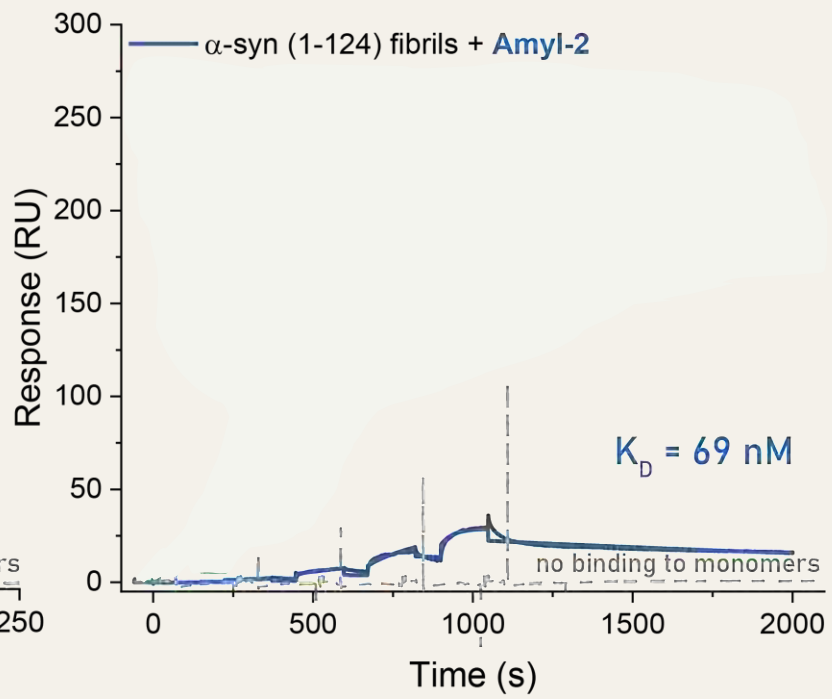
$A\beta_{1-42}$ fibrils



dGAE Tau fibrils

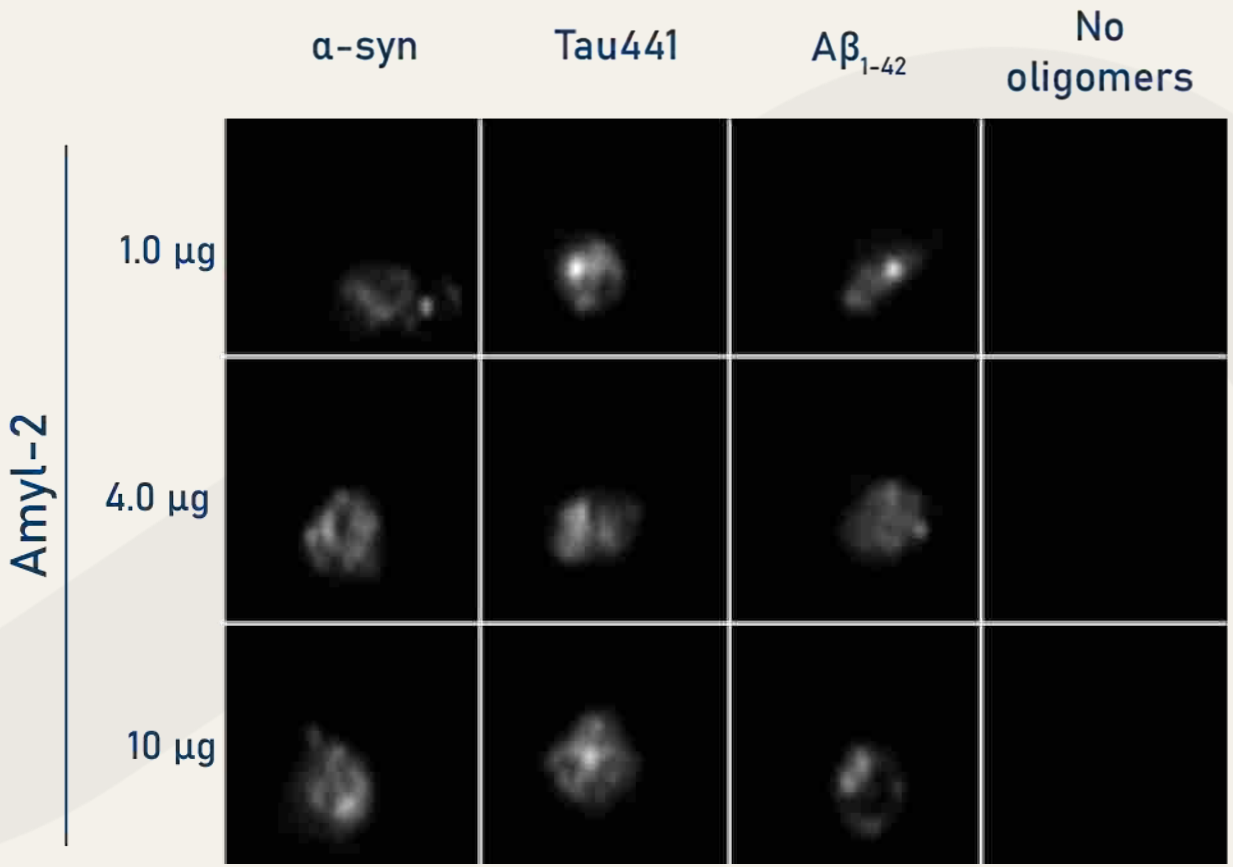


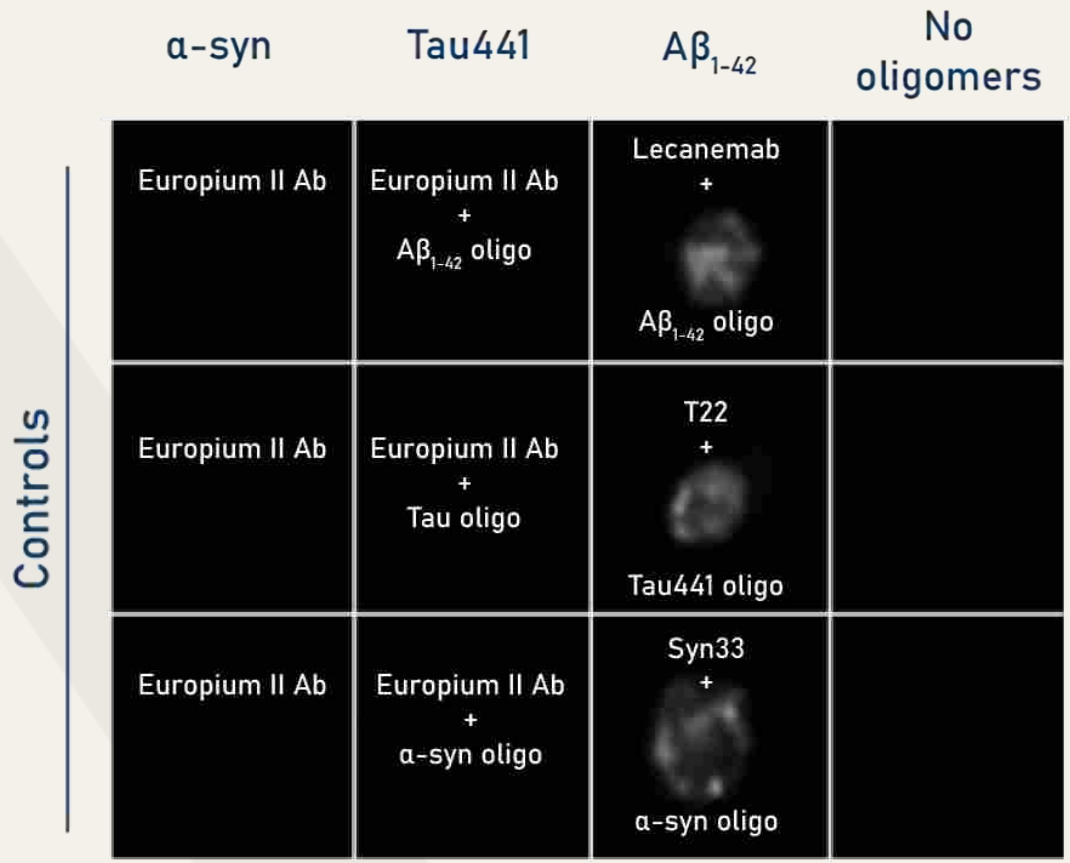
α-syn fibrils



Next-generation candidates already developed with K_D ~ 0.5-5 nM

Amyl-2 binds multiple amyloid oligomers in vitro: Dot-blot assays





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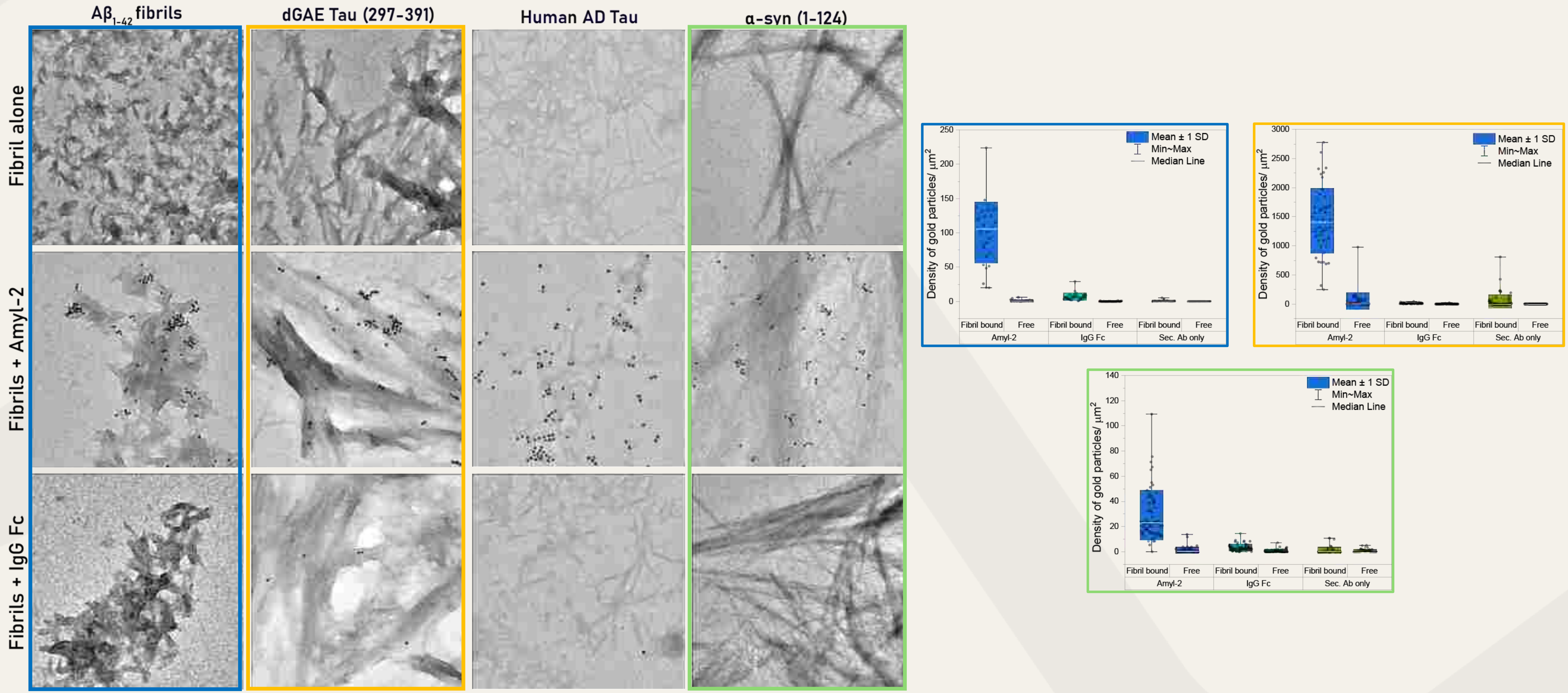
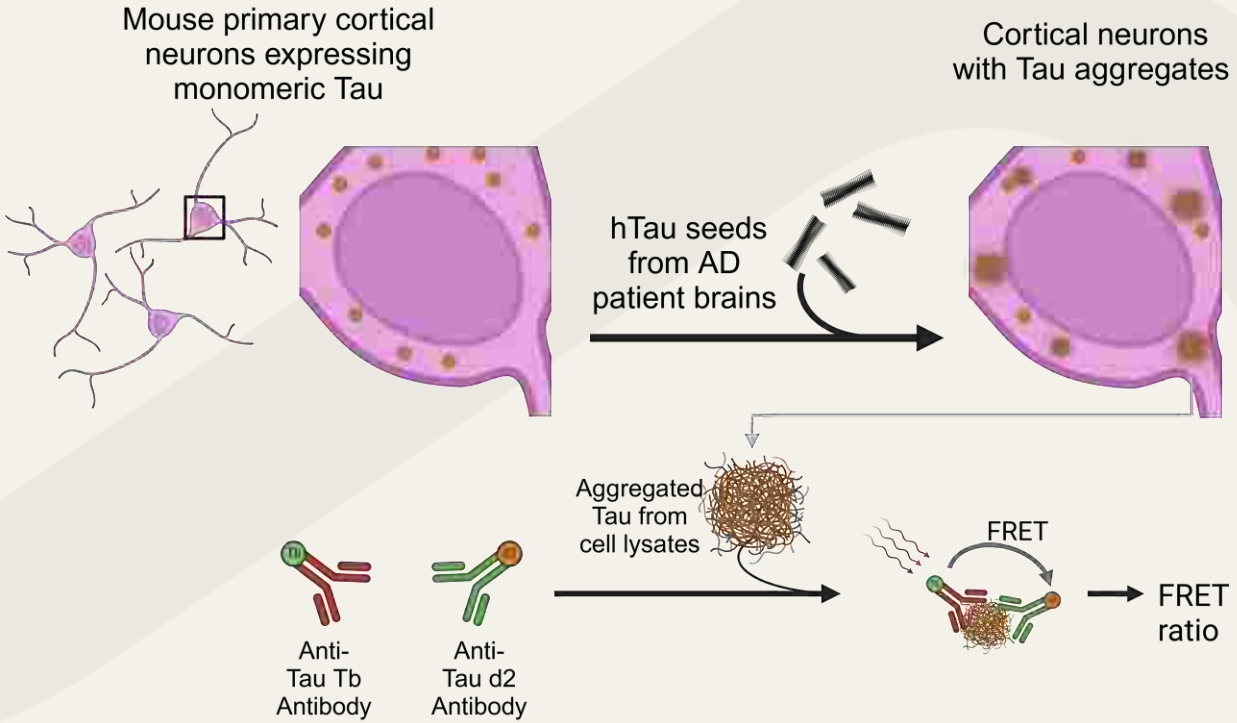
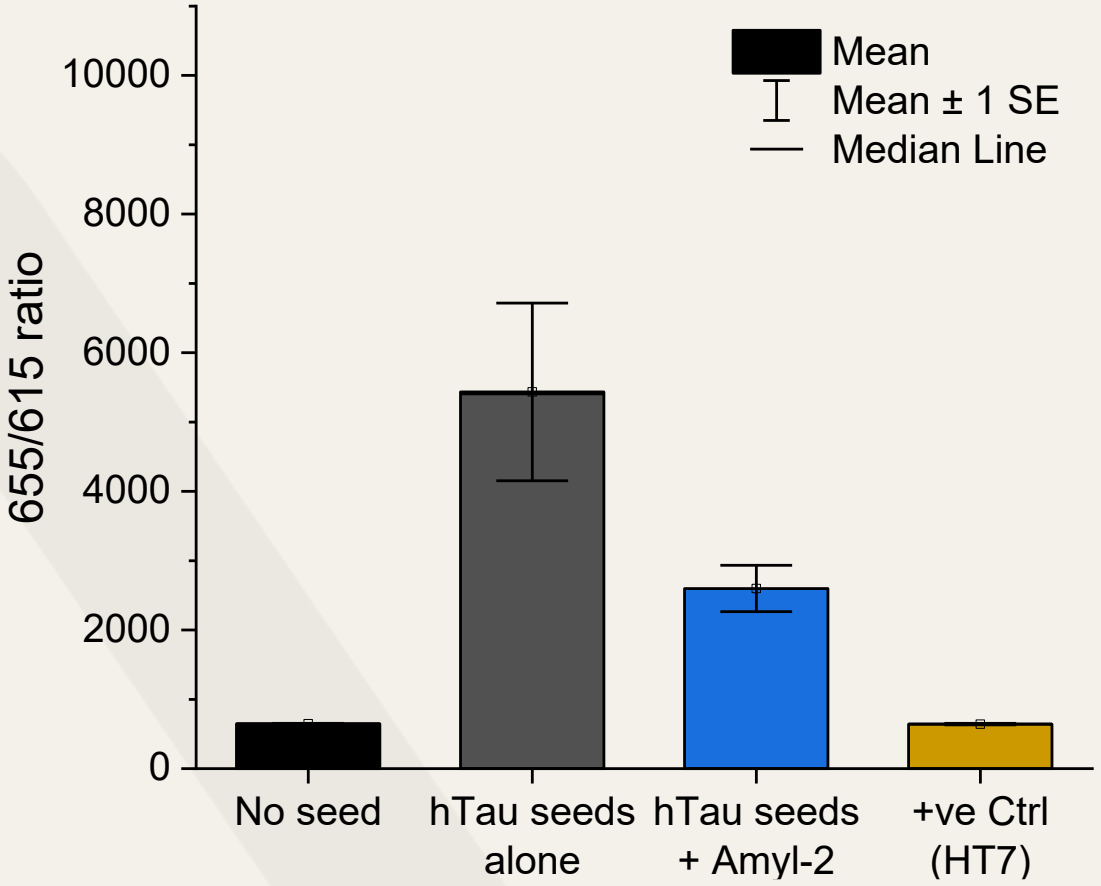
Amyl-2 binds multiple amyloid species in vitro: TEM gold



Amyl-2 inhibits seeding of Tau in mouse primary cortical neurons





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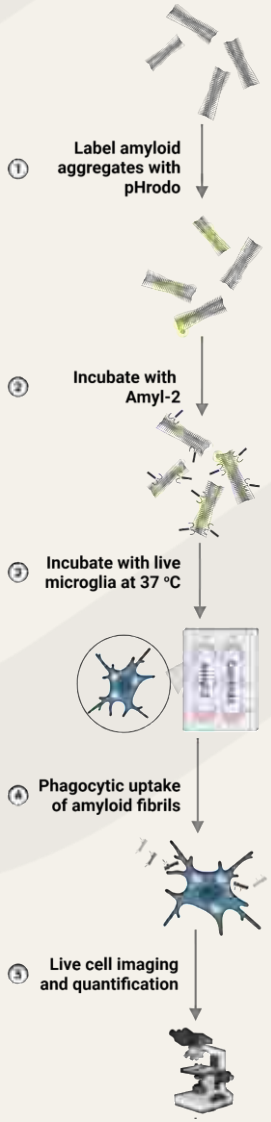
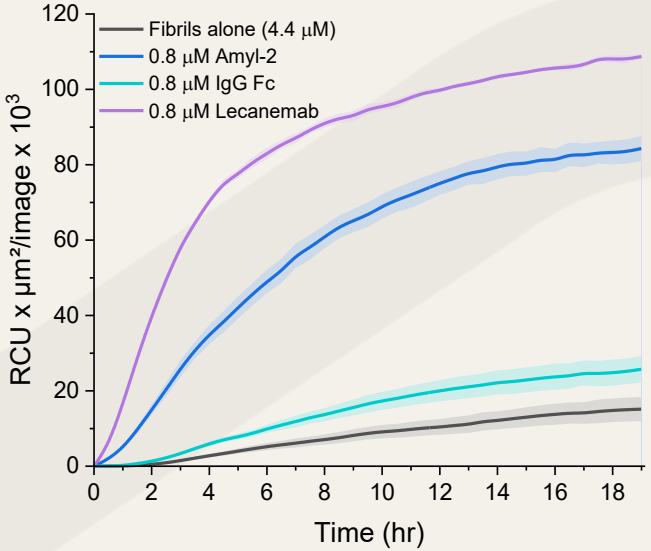
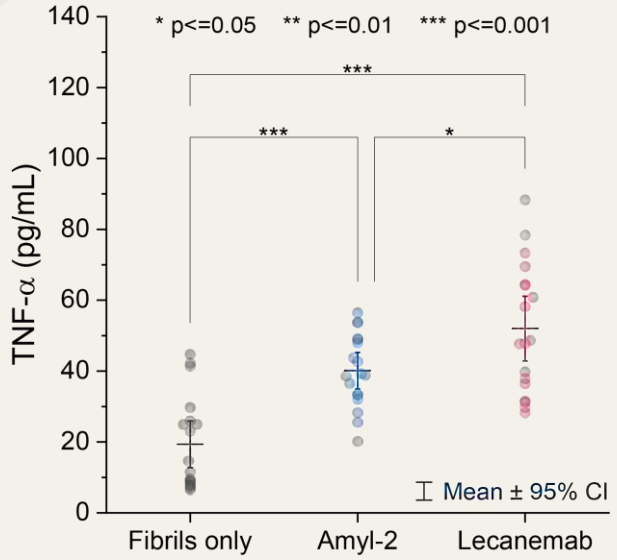
Amyl-2 enhances clearance of multiple amyloid species

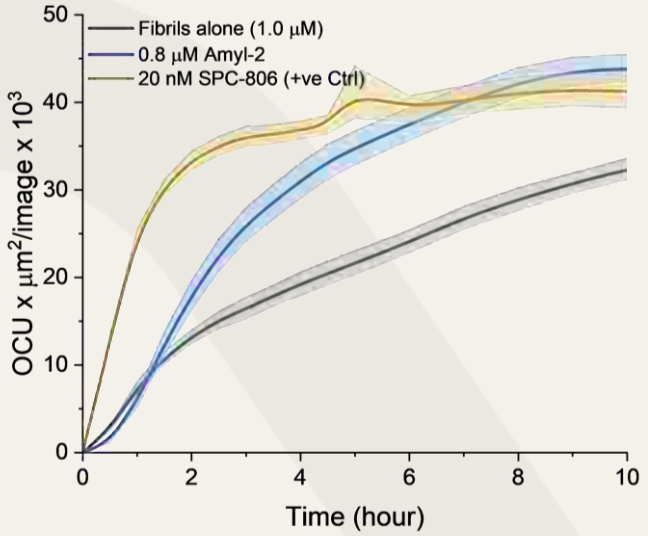


$A\beta_{1-42}$ fibrils

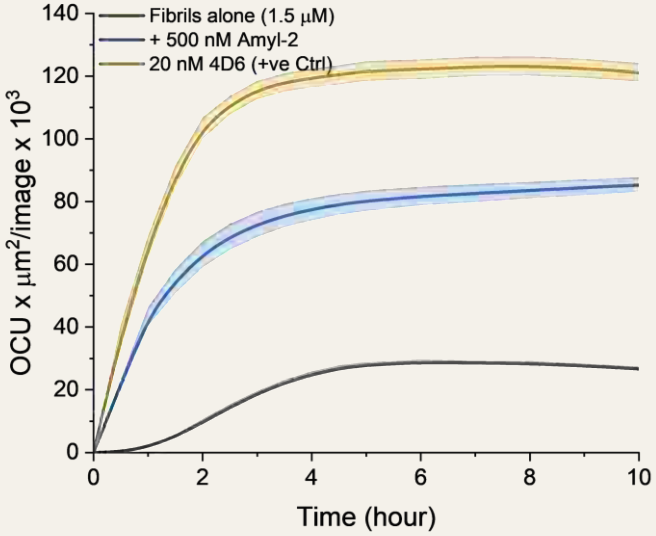




dGAE Tau fibrils



α-syn fibrils



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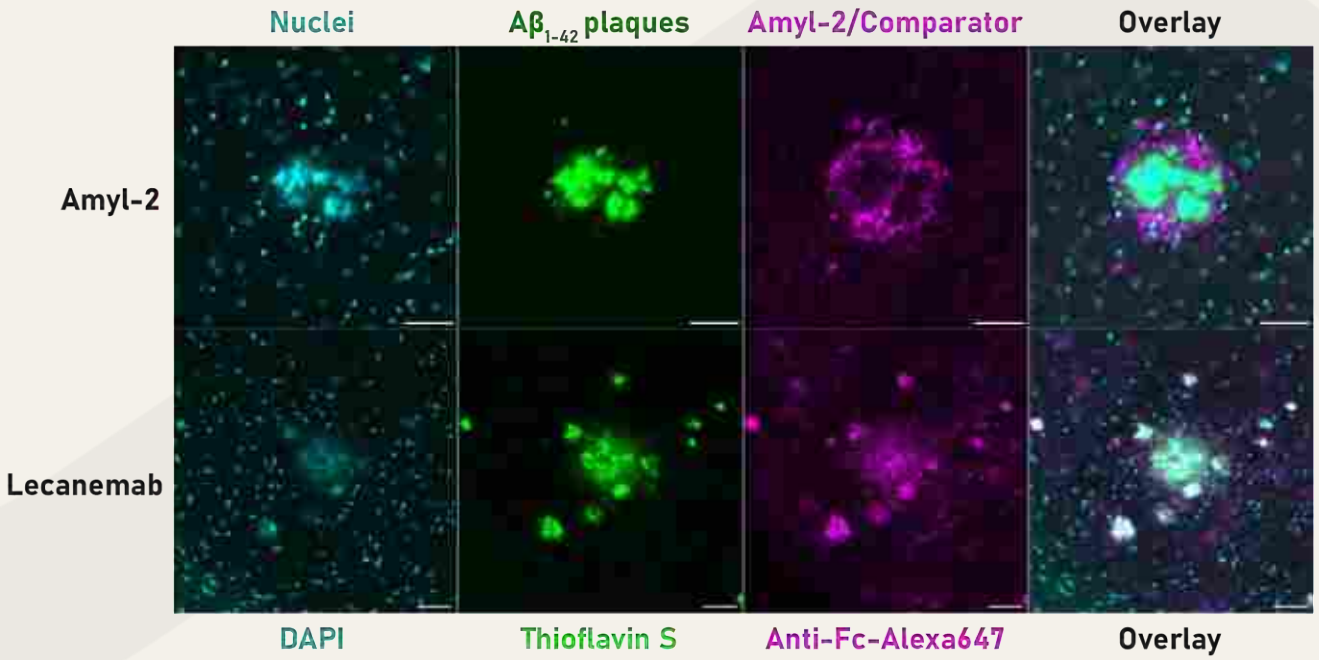
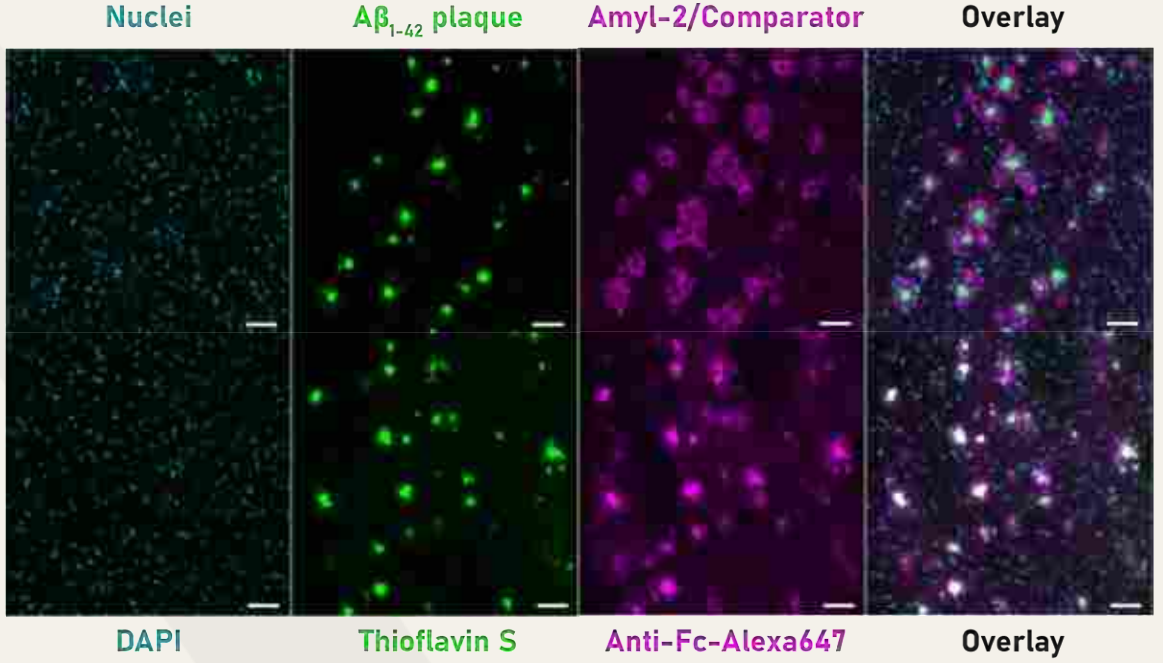
Amyl-2 binds Aβ aggregates in AD mice models ex vivo

Tg2576 (APP_Swe)



The mice overexpress a mutant form of APP (isoform 695) with the Swedish mutation (KM670/671NL)

5XFAD



The mice express human APP and PSEN1 transgenes with a total of five AD-linked mutations: the Swedish (K670N/M671L), Florida (I716V), and London (V717I) mutations in APP, and the M146L and L286V mutations in PSEN1.

Amyl-2 exhibits a preference for amyloid plaque periphery

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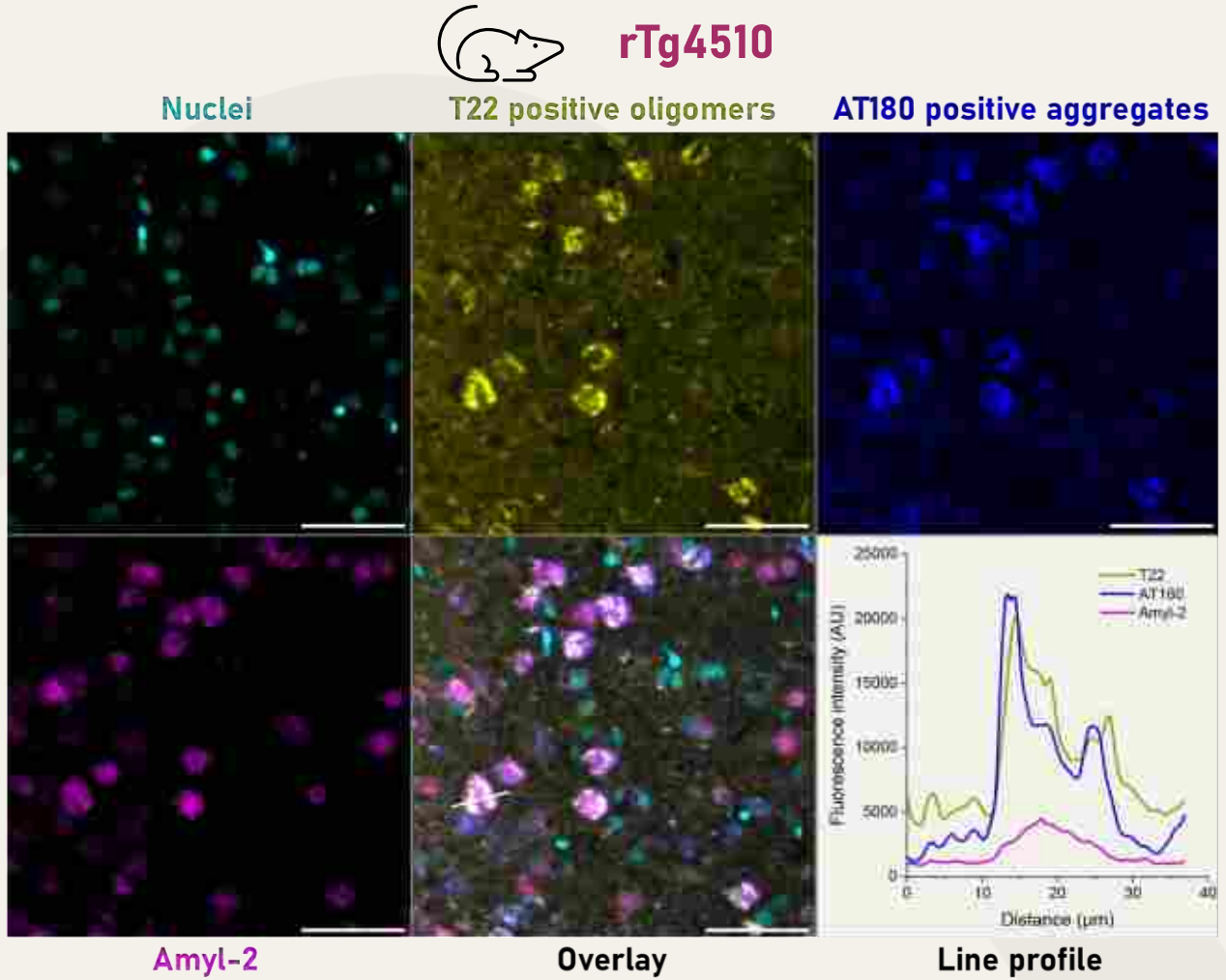
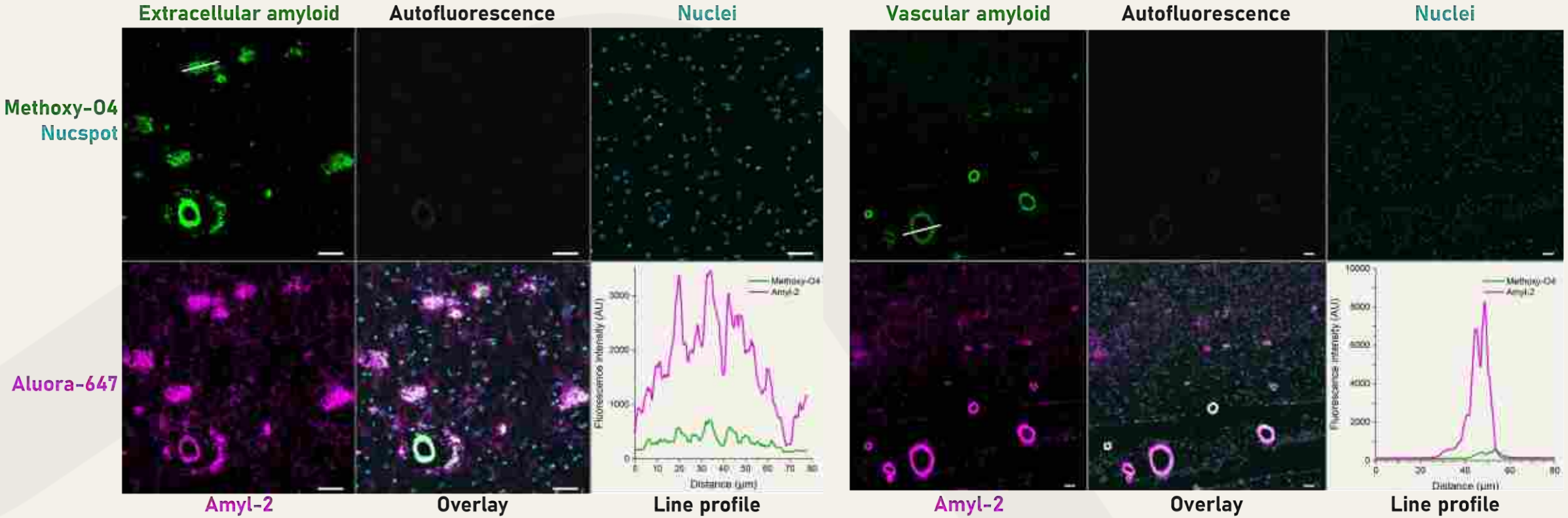
Amyl-2 binds Tau aggregates in AD mouse model ex vivo



The mice overexpress a repressible form of human tau containing the P301L mutation

Amyl-2 shows binding to both oligomeric and fibrillar Tau

Amyl-2 binds amyloid aggregates in human AD brain tissues



AD patient samples from the temporal gyrus region. No binding observed in age-matched controls from the same region

Amyl-2 exhibits a uniform binding behavior and non-discriminant between parenchymal or vascular amyloid aggregates.

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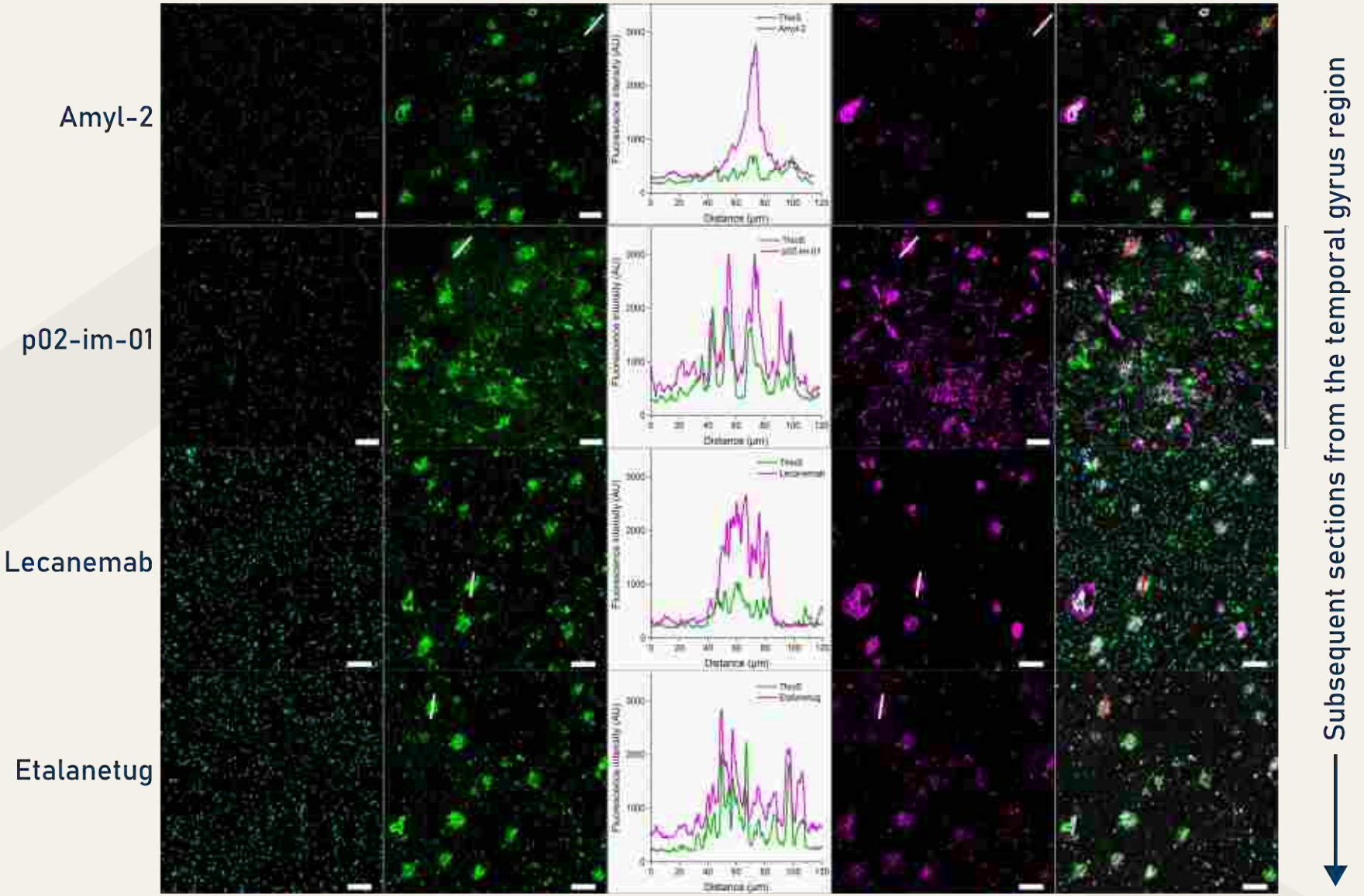
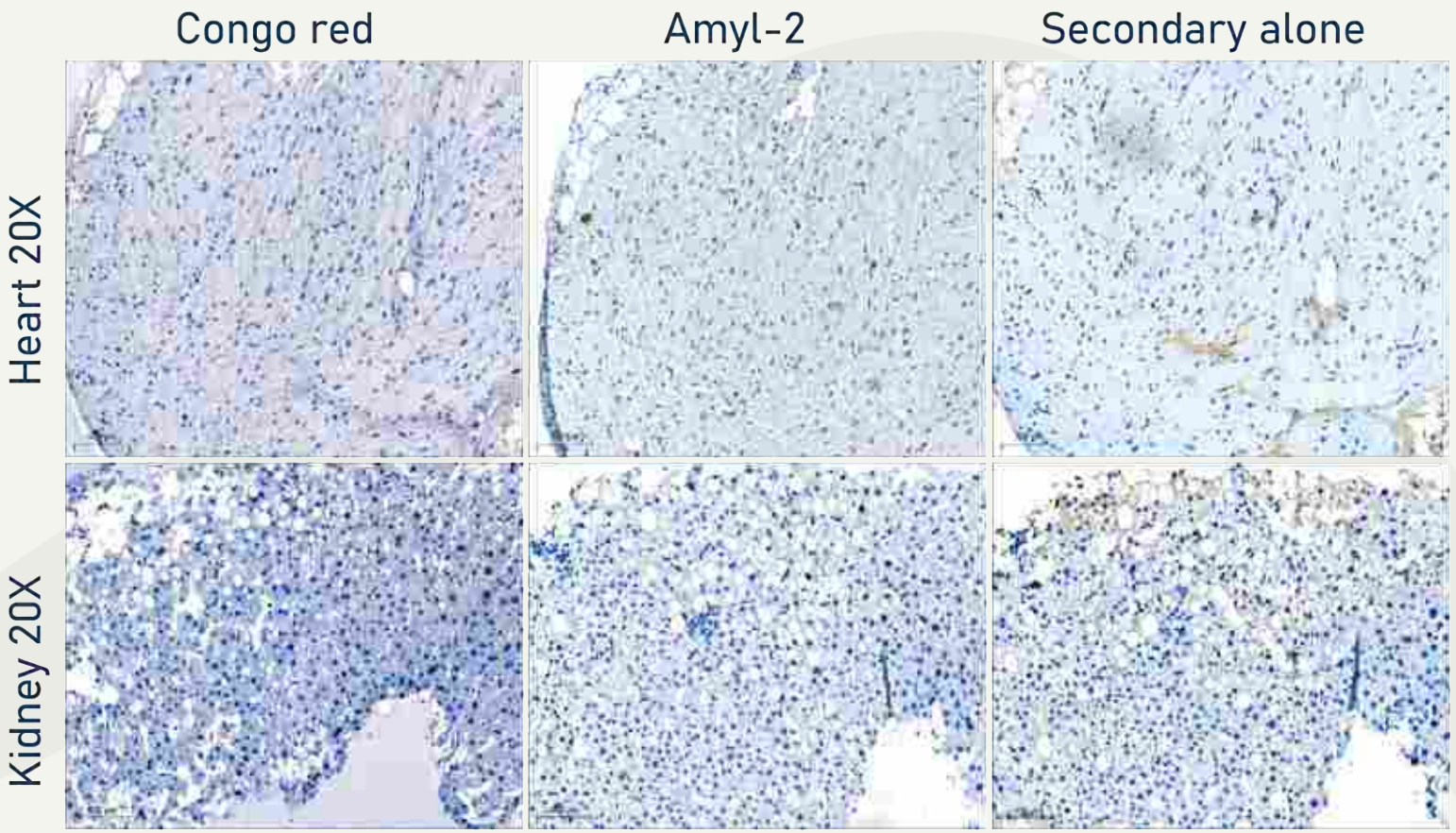
AD tissues obtained from Netherlands Brain Bank

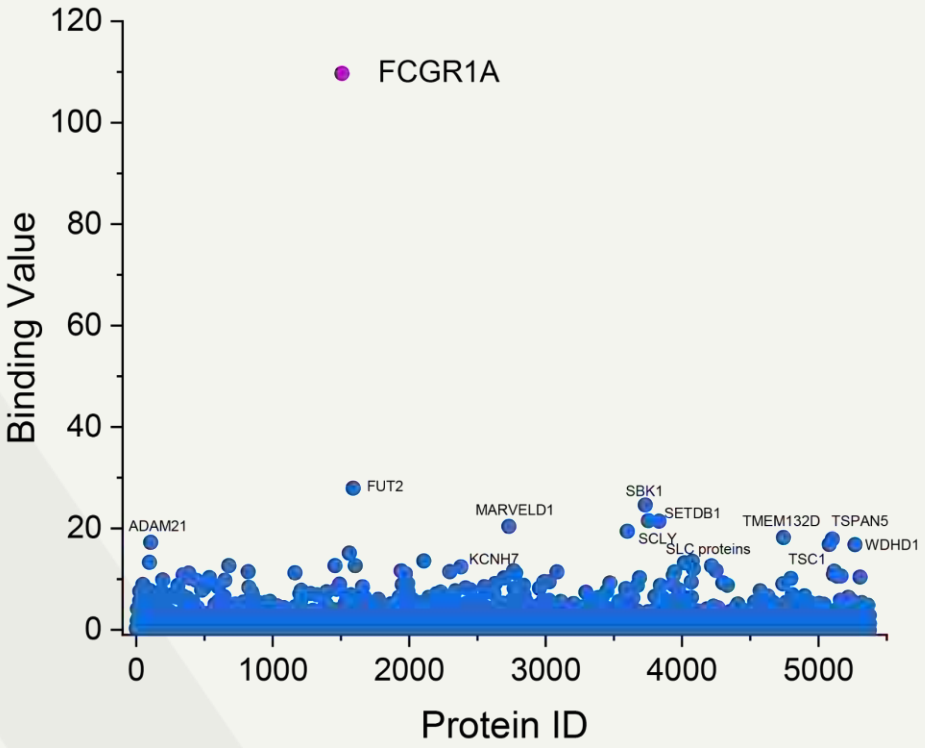
Amyl-2 binds amyloid aggregates in human AD brain tissues



AD tissues obtained from Netherlands Brain Bank

Amyl-2 has no off-target binding





No binding to healthy human tissues and >6000 membrane proteins

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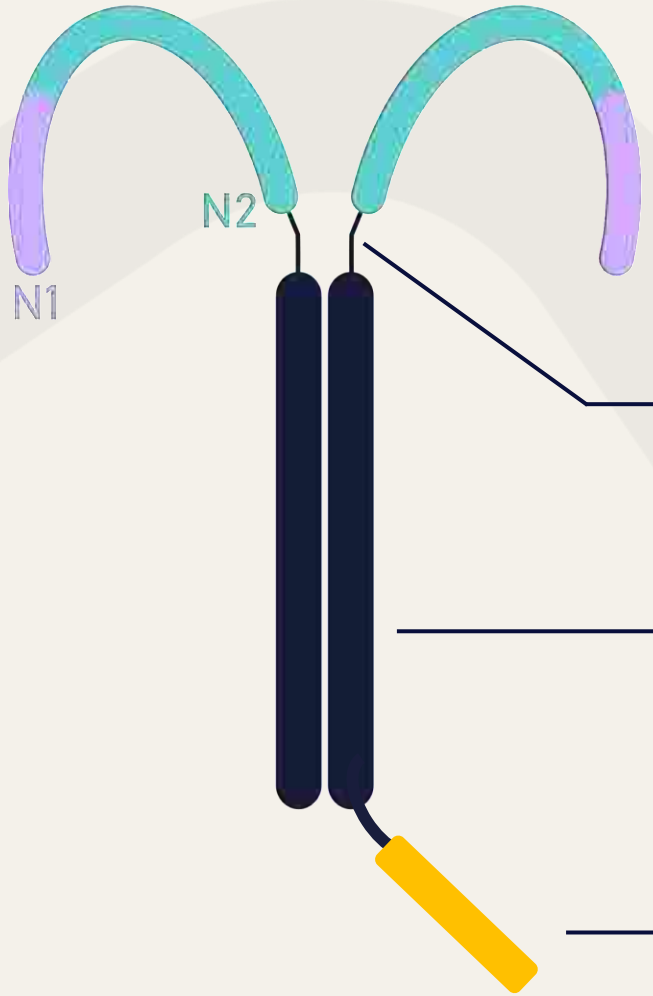
Lead optimization to improve Amyl-2 is complete



N1-N2 domain
To improve binding affinity and reduce immunogenicity

Linker
To improve production yield

Fc domain
To reduce risk of ARIA-related adverse events

Transport vehicle
To improve brain penetration

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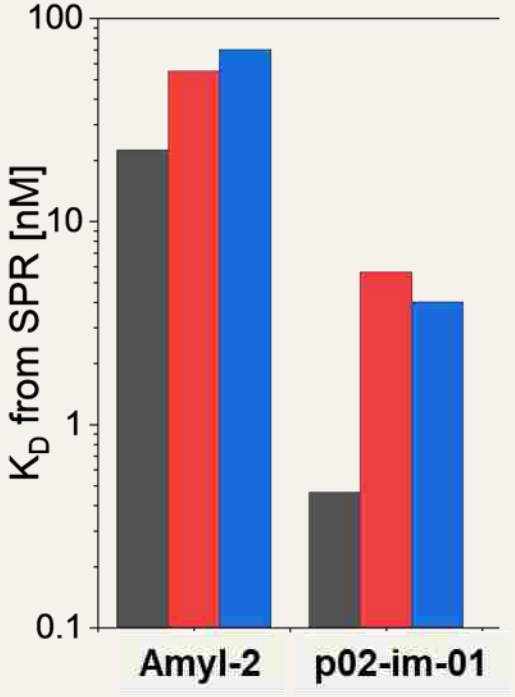
Lead optimization to improve Amyl-2 is complete

Binding affinity

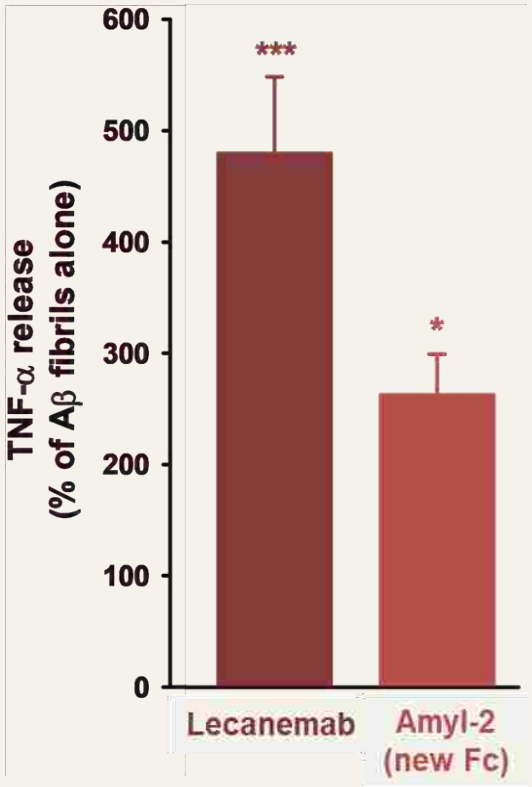


Aβ, Tau, and α-syn fibril binding like commercial mAbs

K_D <10nM

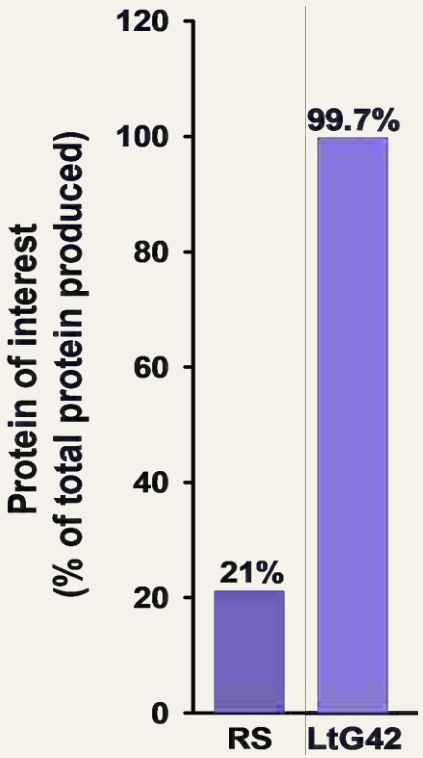
IC_{50} < 10 nM

Inflammation



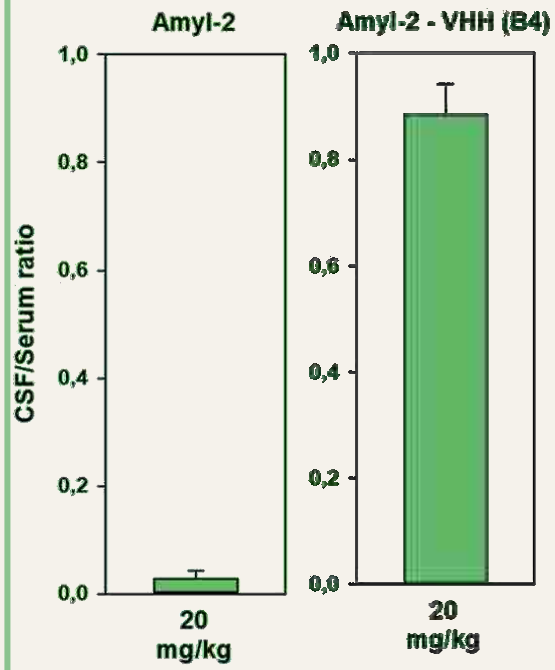
TNF-α release: - 50% compared to Lecanemab

Productivity



From 21% to 99,7% of production of protein of interest

Brain penetration



30-fold CSF/serum ratio improvement

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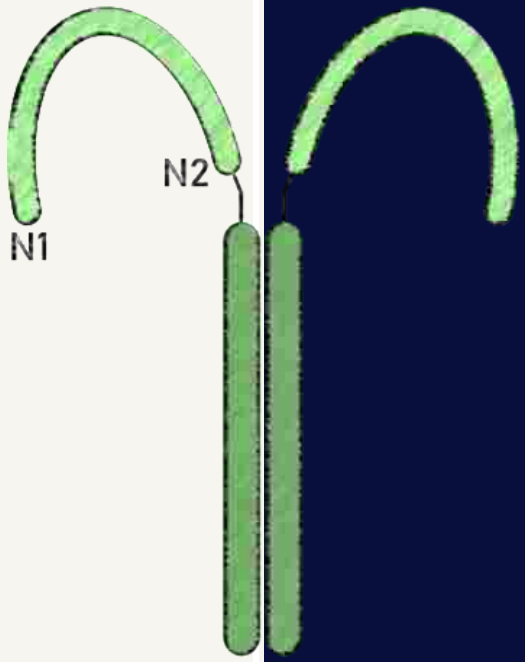
We are not there yet..

- Target engagement shown in vitro and ex vivo studies. In vivo mouse studies ongoing
- Benchmarking studies for BBB passage ongoing
- ARIA-E/H events remain a concern
- The impact on functional amyloids remains to be ascertained.



Amyl Tx is developing THE treatment needed by AD patients

With high binding potency for $A\beta_{1-42}$, Tau, and α-synuclein aggregates but NOT monomers.

With reduced neuroinflammatory potential without impacting microglial clearance

With improved passage through the blood-brain barrier

4 Lead candidates selected

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