CROSSING MOLECULAR BOUNDARIES

AN IMMUNOTHERAPEUTIC SIMULTANEOUSLY TARGETING AMYLOID β, TAU, AND α-SYNUCLEIN AMYLOID AGGREGATES

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SCAN ME

KEY TAKEAWAYS

Problem: Neurodegenerative diseases often present mixed pathologies—multiple proteins misfold into amyloid aggregates, believed to drive the progression of Alzheimer's and Parkinson's diseases. Current therapeutic strategies primarily focus on the selective removal of single amyloid species using monoclonal antibodies. Given that amyloid-β (Aβ), microtubule associated protein Tau, and α-synuclein aggregates share a conserved cross-β sheet fold, targeting this common structural conformation could enable simultaneous neutralization of multiple aggregates.

Approach: We developed Amyl-2, a pan-amyloid immunotherapeutic combining a human IgG Fc region with a conformational binder targeting the shared amyloid fold found in many neurodegenerative diseases. A single structure-guided therapeutic could neutralize multiple amyloid species, simplifying treatment compared to multiple monoclonal antibodies.

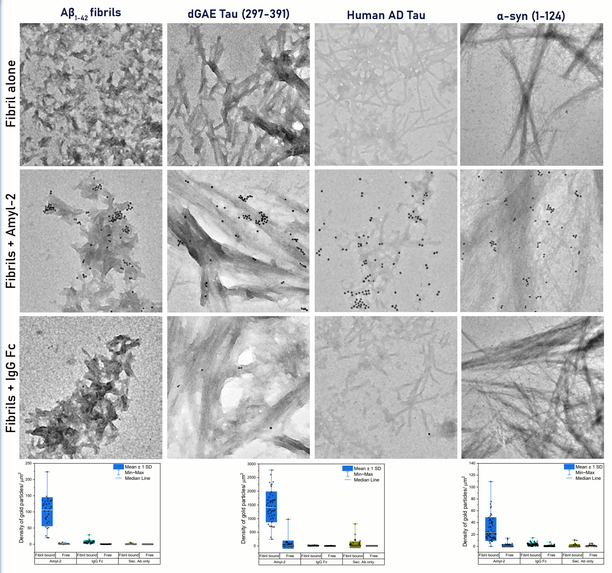
Selectivity: Amyl-2 binds strongly to amyloid fibrils/oligomers, but not to monomers. Amyl-2 shows minimal cross-reactivity to healthy human tissues and membrane proteins.

Results:

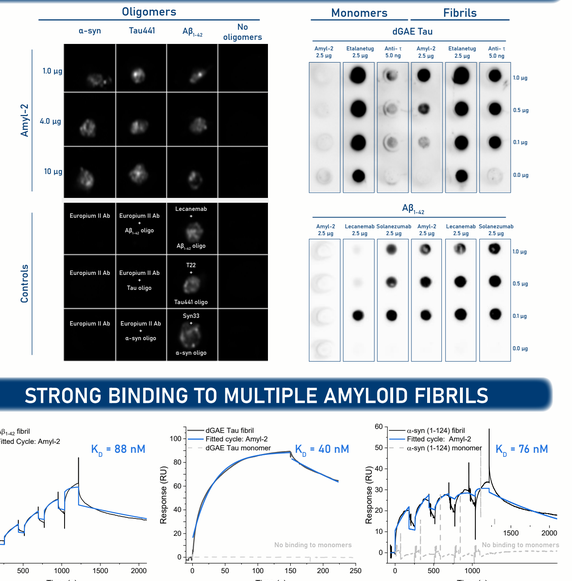
- Amyl-2 specifically binds amyloid aggregates of Aβ, Tau, and α-synuclein in vitro and amyloid deposits in AD mice and AD human brains ex vivo.
- Amyl-2 effectively inhibits aggregation of Aβ, Tau, and α-synuclein in vitro.
- Amyl-2 promotes clearance of fibrils/oligomers by monocytes and iPSC-derived microglia.
- Amyl-2 has an IgG-comparable brain permeability.
- Blocks Tau seeding in primary neurons from AD patient material.

Outlook: Amyl-2 provides a foundation for a multi-target therapy strategy in amyloid-mediated diseases. Ongoing work is focused on improving binding affinity and brain penetration.

BINDING TO MULTIPLE AMYLOID FIBRILS

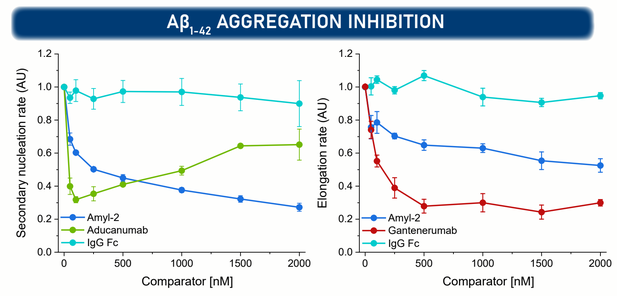


BINDING TO MULTIPLE AMYLOID FORMS

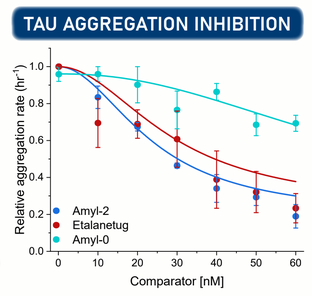


STRONG BINDING TO MULTIPLE AMYLOID FIBRILS

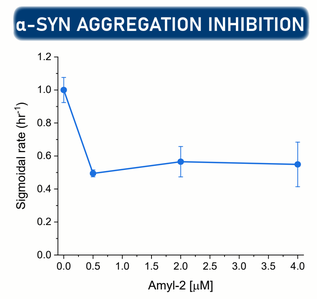
Aβ1-42 AGGREGATION INHIBITION



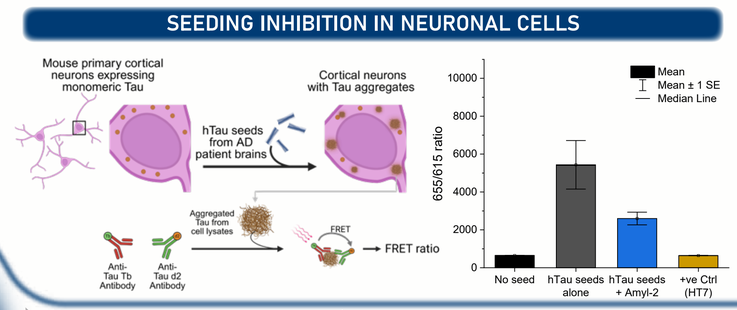
TAU AGGREGATION INHIBITION

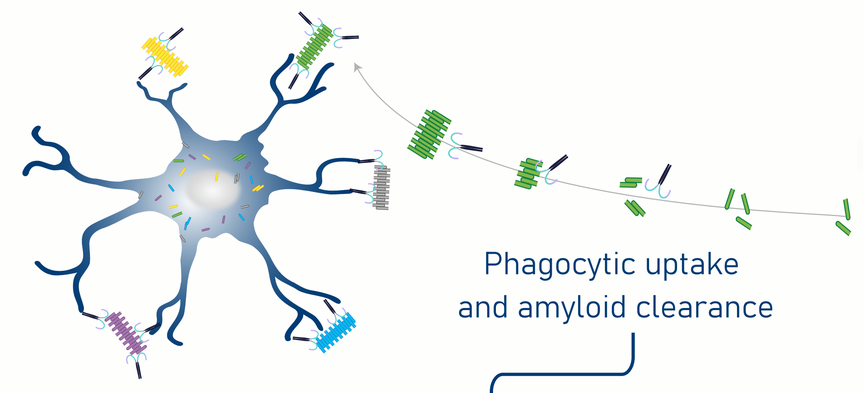


α-SYN AGGREGATION INHIBITION

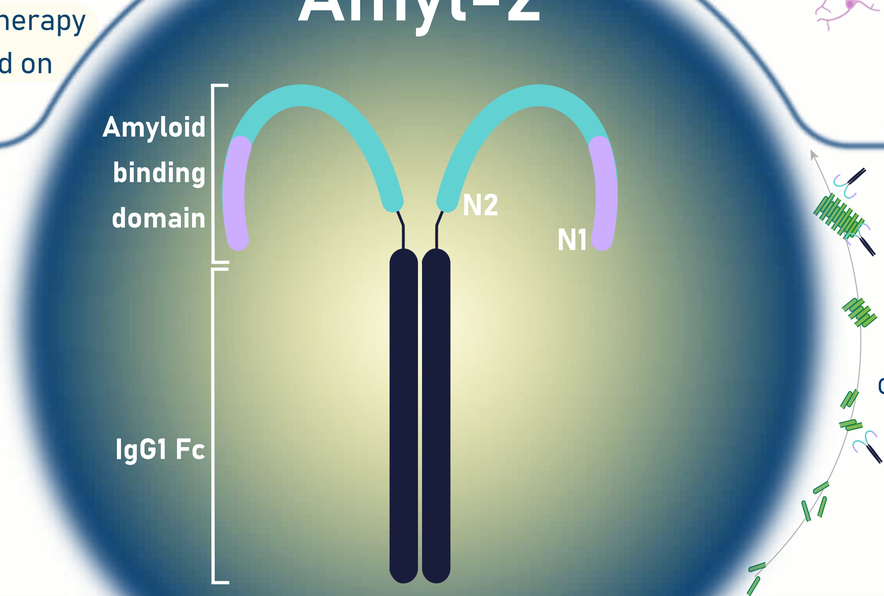


SEEDING INHIBITION IN NEURONAL CELLS



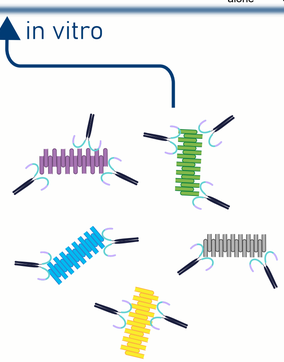


Phagocytic uptake and amyloid clearance



Inhibition of aggregation

in vitro

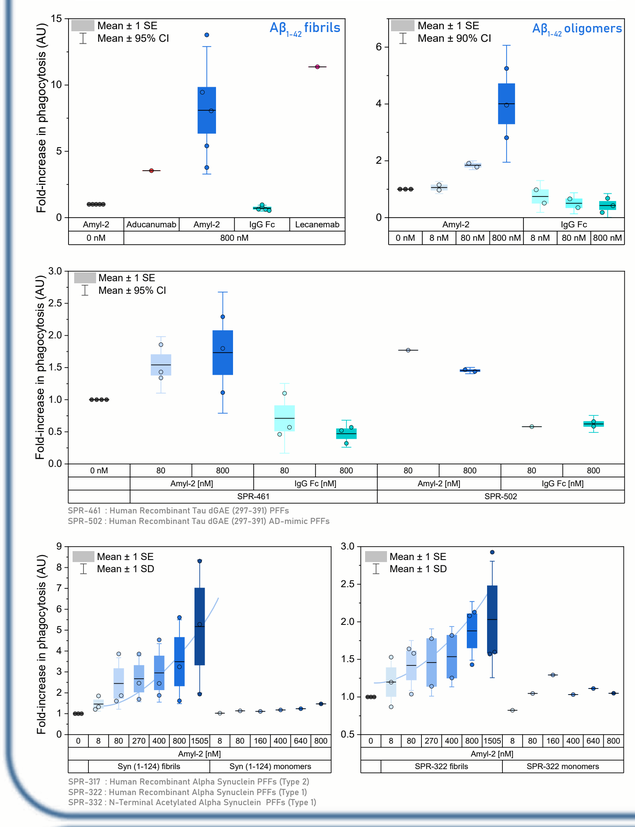


Strong and specific pan amyloid binding

ex vivo

SPECIFIC CLEARANCE OF AMYLOID AGGREGATES BY PHAGOCYTOSIS

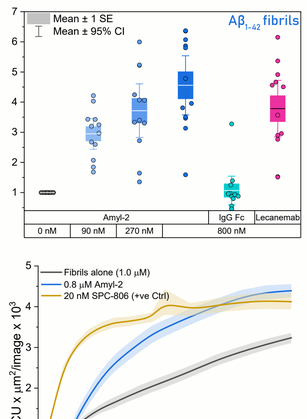
Human THP-1 monocytes



SPR-461 : Human Recombinant Tau dGAE (297-391) PFFs
SPR-502 : Human Recombinant Tau dGAE (297-391) AD-mimic PFFs

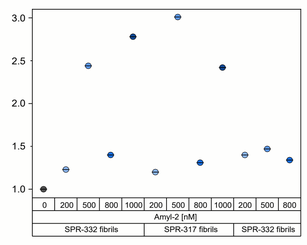
SPR-317 : Human Recombinant Alpha Synuclein PFFs (Type 2)
SPR-322 : Human Recombinant Alpha Synuclein PFFs (Type 1)
SPR-332 : N-Terminal Acetylated Alpha Synuclein PFFs (Type 1)

Human iPSC microglia

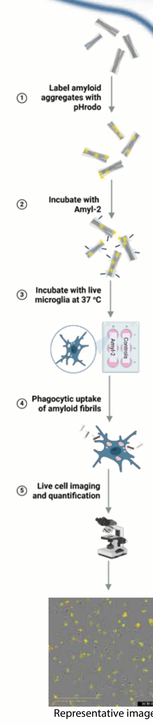


Aβ1-42 aggregates

dGAE Tau fibrils

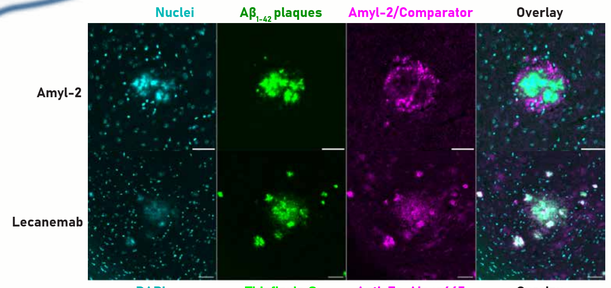


α-synuclein fibrils

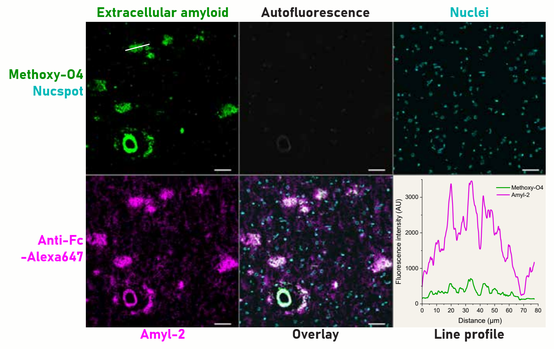


SPECIFIC EX VIVO BINDING IN HUMAN AND MICE BRAIN TISSUES

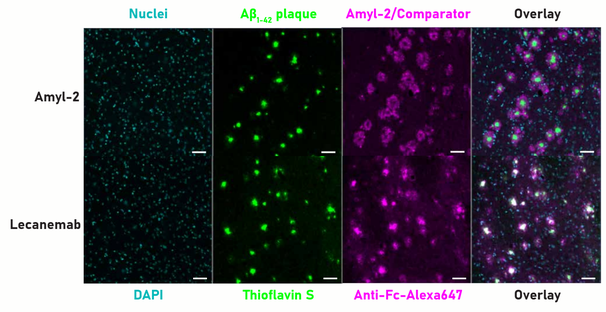
Tg2576 (Amyloid β aggregates)



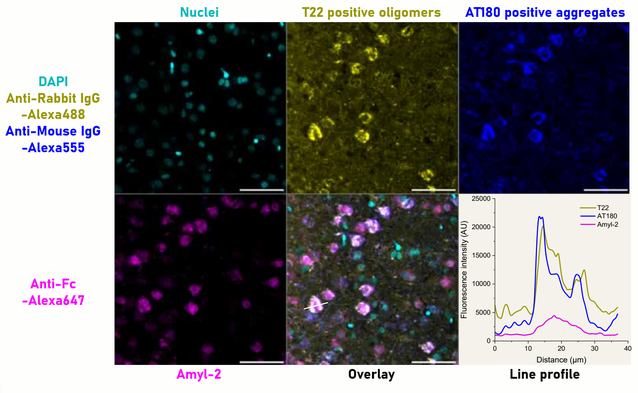
Human AD patient (amyloid aggregates)



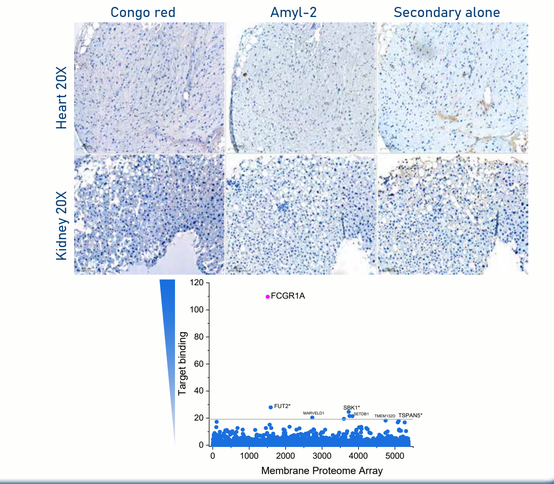
5XFAD (Amyloid β aggregates)



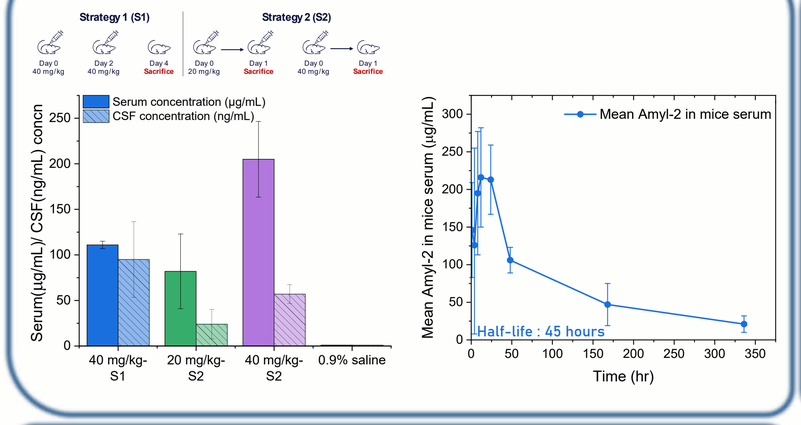
rTG4510 mice (P301L Tau aggregates)



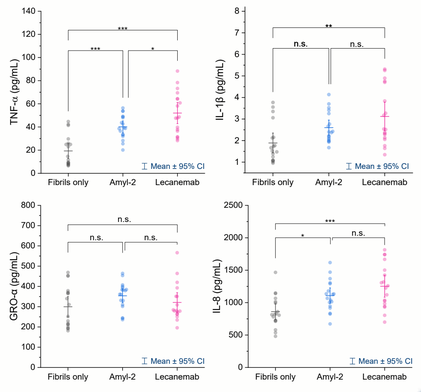
Low cross-reactivity to healthy human tissues & > 6000 proteins



BRAIN PERMEABILITY AND HALF-LIFE



SIMILAR CYTOKINE RESPONSE



* p<=0.05 ** p<=0.01 *** p<=0.001

ACKNOWLEDGEMENTS

1. Amylofit software used with permission from G. Meisl et al, Nat. Protoc., 11, 252–2 al. 2019
2. Human AD Tau PHFs obtained kindly from Prof. Karelle Leroy from ULB, Belgium
3. Artwork created in https://BioRender.com and Adobe Illustrator

OUR PARTNERS

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