CROSSING MOLECULAR BOUNDARIES

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

Aditya Iyer, Chiara Vollaro, Sandra Parys, Dafni Birmpili, Elodie Hendrick, Julie Goemaere, Karine Goraj, Damien Toulorge
Boulevard Patience et Beaujonc 3, Boîte 12, 4000 Liège, Belgium
www.amyltx.com

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.

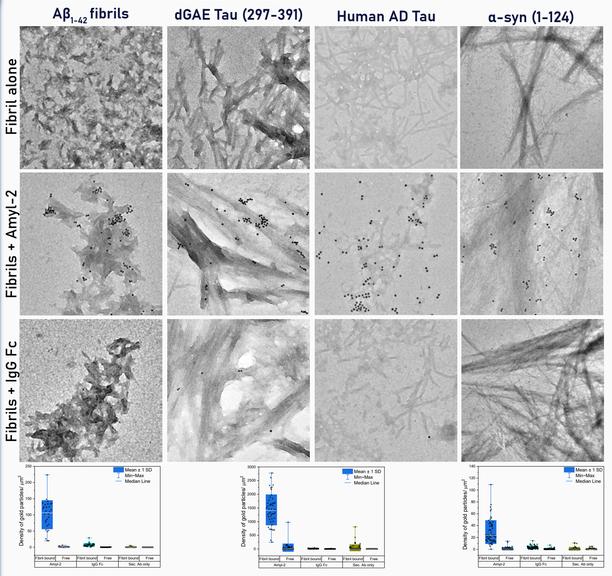
Selectivity: Amyl-2 binds strongly to amyloid fibrils/oligomers, but not to monomers. Amyl-2 shows minimal cross-reactivity to healthy human tissues and membrane proteins.

Results:

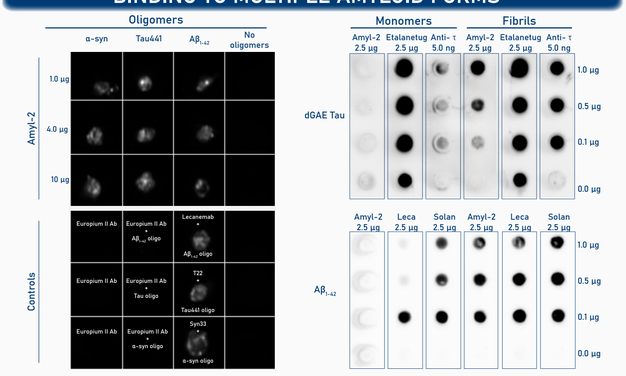
- Amyl-2 specifically binds amyloid aggregates of Aβ, Tau, and α-synuclein in vitro and amyloid deposits in AD mice and AD human brains ex vivo.
- Amyl-2 effectively inhibits aggregation of Aβ, Tau, and α-synuclein in vitro.
- Amyl-2 promotes clearance of fibrils/oligomers by monocytes and iPSC-derived microglia.
- Amyl-2 blocks Tau seeding from AD patient material in mouse primary neurons .
- A new improved candidate p02-im-01 outperforms Amyl-2.

Outlook: Amyl-2 provides a foundation for a multi-target therapy strategy in amyloid-mediated diseases. Improved candidates are poised for optimized performance.

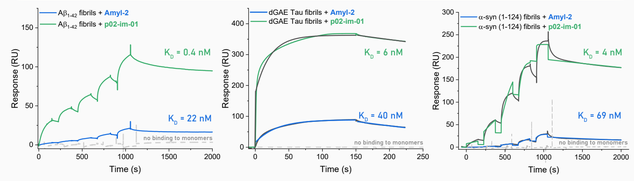
BINDING TO MULTIPLE AMYLOID FIBRILS



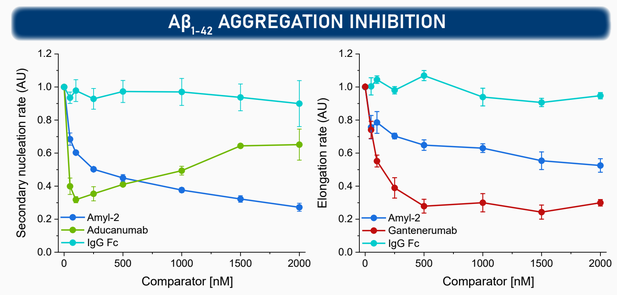
BINDING TO MULTIPLE AMYLOID FORMS



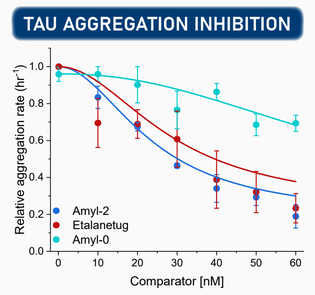
STRONG BINDING TO MULTIPLE AMYLOID FIBRILS



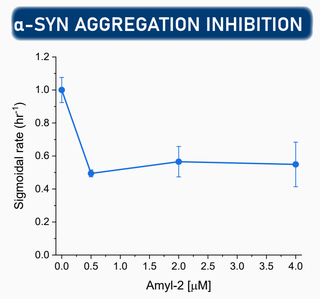
Aβ1-42 AGGREGATION INHIBITION



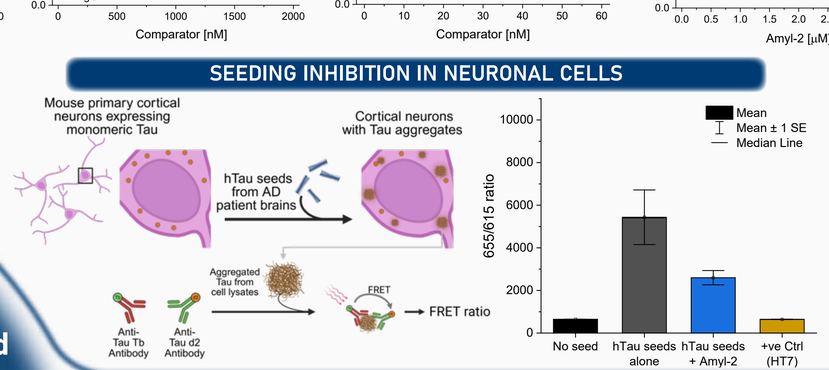
TAU AGGREGATION INHIBITION

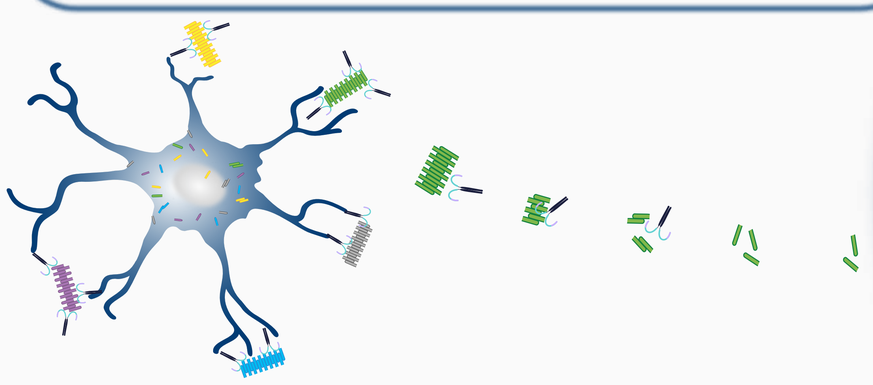


α-SYN AGGREGATION INHIBITION

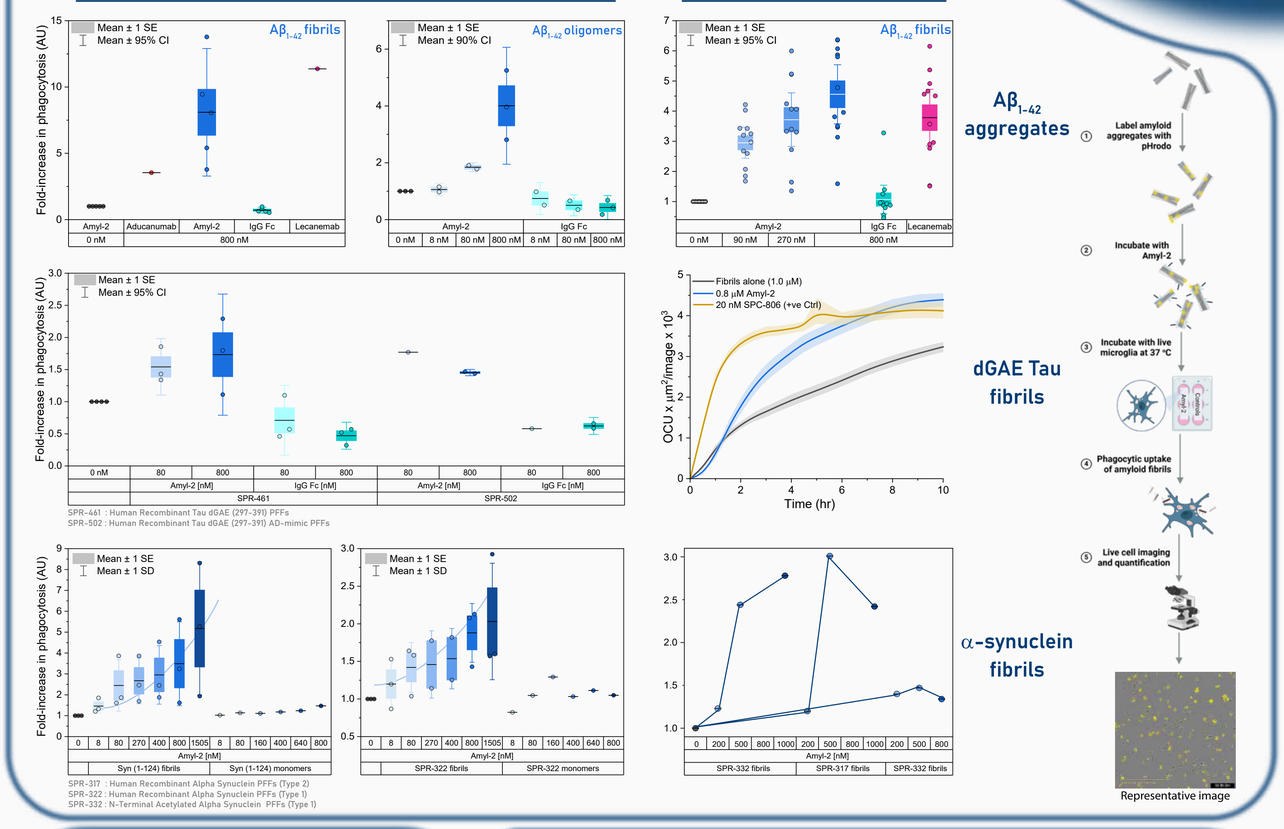


SEEDING INHIBITION IN NEURONAL CELLS



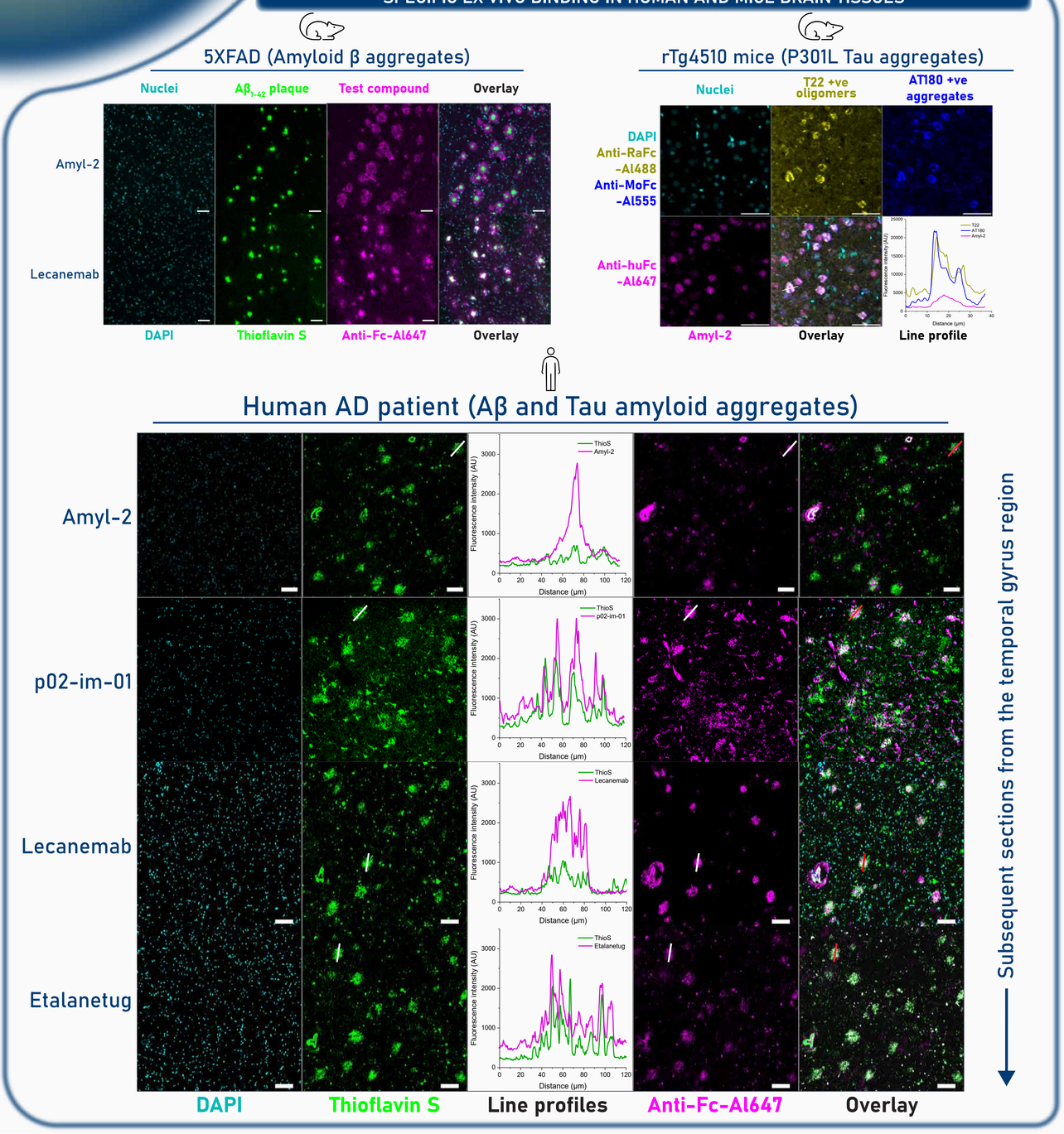


SPECIFIC CLEARANCE OF AMYLOID AGGREGATES BY PHAGOCYTOSIS

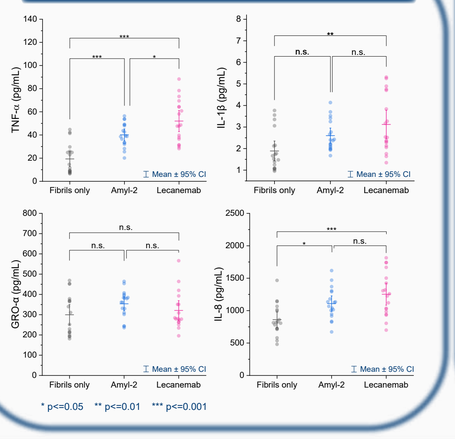


SPR-461 : Human Recombinant Tau dGAE (297-391) PFFs
SPR-502 : Human Recombinant Tau dGAE (297-391) AD-mimic PFFs
SPR-317 : Human Recombinant Alpha Synuclein PFFs (Type 2)
SPR-322 : Human Recombinant Alpha Synuclein PFFs (Type 1)
SPR-332 : N-Terminal Acetylated Alpha Synuclein PFFs (Type 1)

SPECIFIC EX VIVO BINDING IN HUMAN AND MICE BRAIN TISSUES

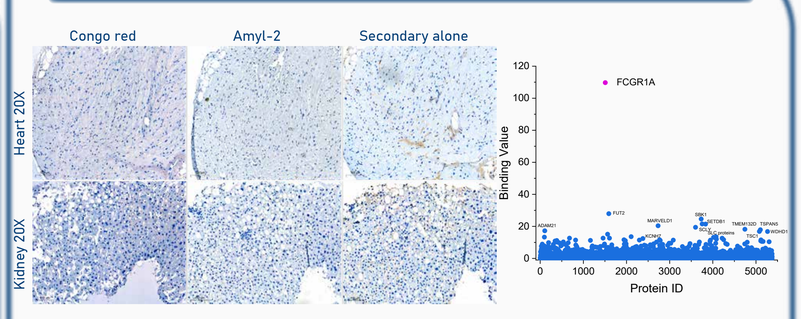


SIMILAR CYTOKINE RESPONSE



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

NO OFF-TARGET BINDING



No significant binding to healthy human tissues (left) and more than 6000 membrane proteins (right)

ACKNOWLEDGEMENTS

Amylofit software used with permission from G. Meisl et al, Nat. Protoc., 11, 252–2 al. 2019. The human AD Tau PHFs were provided by Prof. Karelle Leroy from ULB, Belgium. The artwork was created in https://BioRender.com and Adobe Illustrator.

OUR PARTNERS

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