MULTI-MODAL AMYL THERAPEUTICS INHIBIT AGGREGATION AND PROMOTE CLEARANCE OF AMYLOID AGGREGATES FROM NEURODEGENERATIVE DISEASES

Aditya Iyer, Julie Goemaere, Karine Goraj, Damien Toulorge
Boulevard Patience et Beaujonc 3, Boîte 12, 4000 Liège, Belgium
www.amyltx.com

With the support of Wallonia

Aims:

Preliminary results from in vitro and ex vivo studies with our pan-amyloid therapeutic (Amyl-2) demonstrate the ability to inhibit aggregation, bind and destabilize amyloid fibrils as well as promote clearance by phagocytosis of $A\beta_{1-42}$, Tau and α-synuclein aggregates.

Methods:

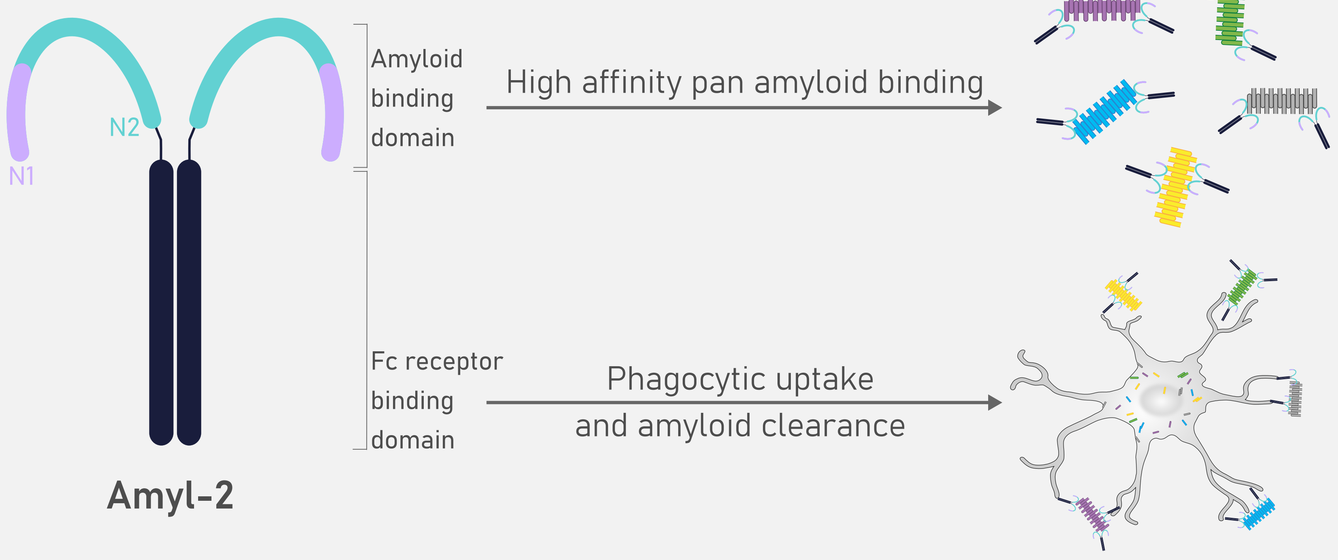
We have used fluorescence spectroscopy to assess the inhibitory effect of our therapeutics on the aggregation of $A\beta_{1-42}$, Tau, and alpha-synuclein. We have applied a combinatorial strategy where surface plasmon resonance (SPR), dot-blot, and immunogold labeling have been used to confirm in vitro binding to multiple forms of $A\beta_{1-42}$, Tau, and alpha-synuclein entities. Therapeutic-dependent phagocytosis of amyloid aggregates was evaluated in both THP-1 monocytes and human iPSC microglia, and ex vivo target engagement was assessed in mouse tissues.

Key Takeaways:

- Amyl-2 is a novel, multi-modal, non-antibody therapeutic designed to inhibit amyloid aggregation and enhance phagocytic clearance.
- It shows **robust binding to multiple amyloid species** and effectively reduces aggregation and seeding.
- It is able to enhance the phagocytic clearance of both amyloid fibrils and oligomers of three-disease related molecules by monocytes and human iPSC microglia.
- It demonstrates brain penetration and a favorable safety profile comparable to current monoclonal antibodies.
- Our approach has the potential to provide a much-needed alternative to existing therapies for neurodegenerative diseases.

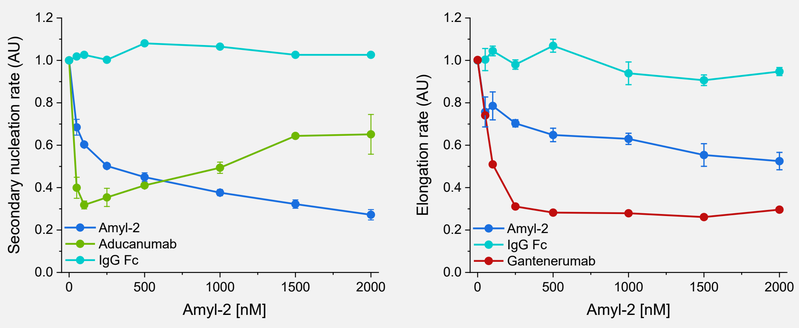
General structure and mode of action of Amyl-2

Dimer of our pan-amyloid binding protein fused to a human IgG1 Fc region

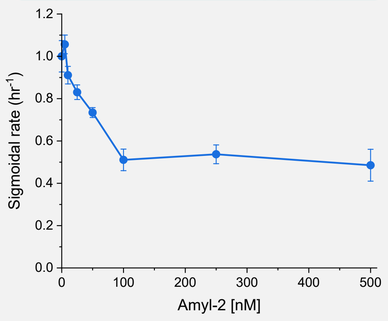


Aggregation inhibition and amyloid binding potency

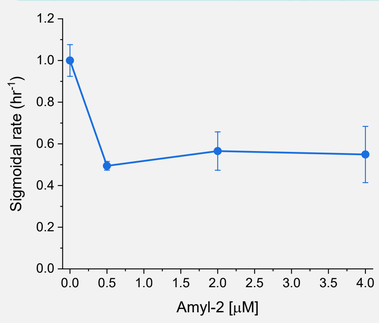
Amyl-2 inhibits 2⁰ nucleation & elongation step in $A\beta_{1-42}$ aggregation



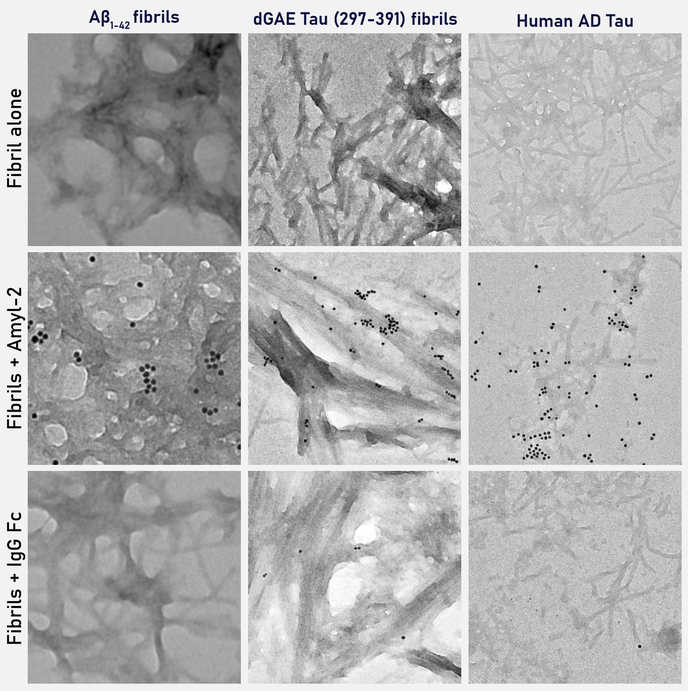
Amyl-2 inhibits Tau aggregation



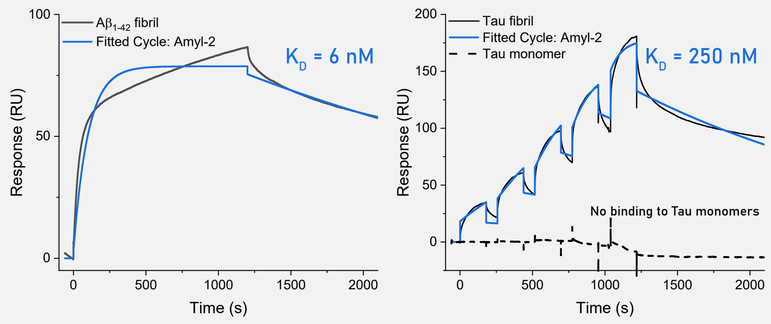
Amyl-2 inhibits α-syn aggregation



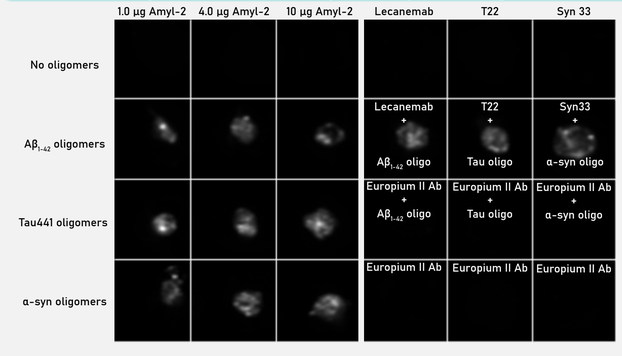
Amyl-2 binds multiple amyloid fibrils



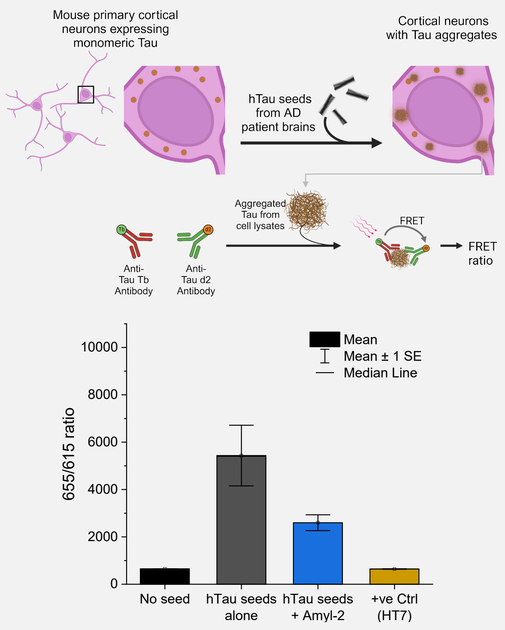
Amyl-2 binds amyloid fibrils with nM affinity



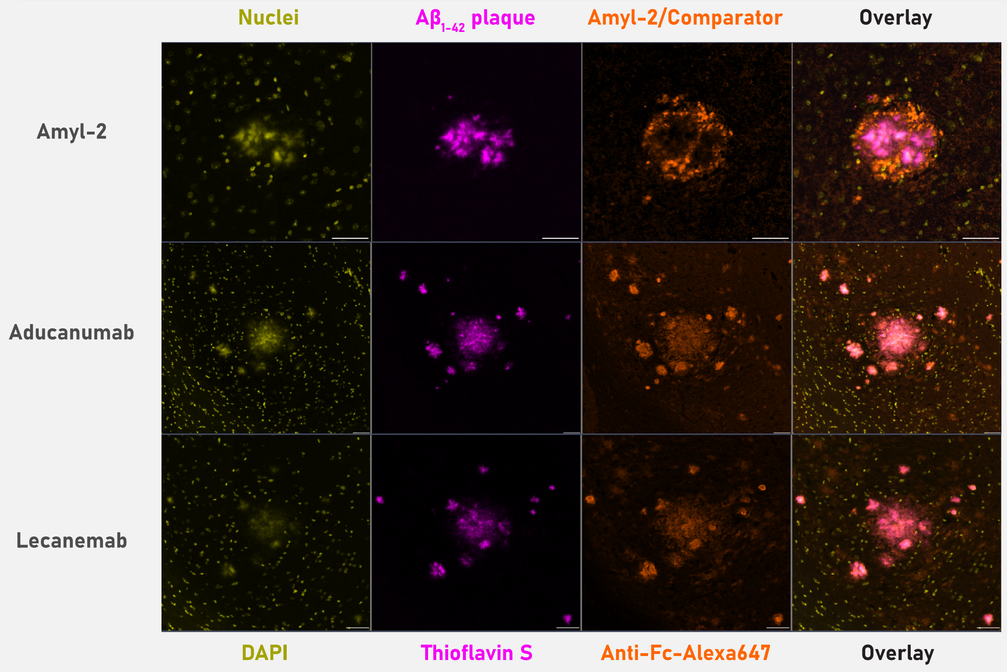
Amyl-2 binds multiple amyloid oligomers



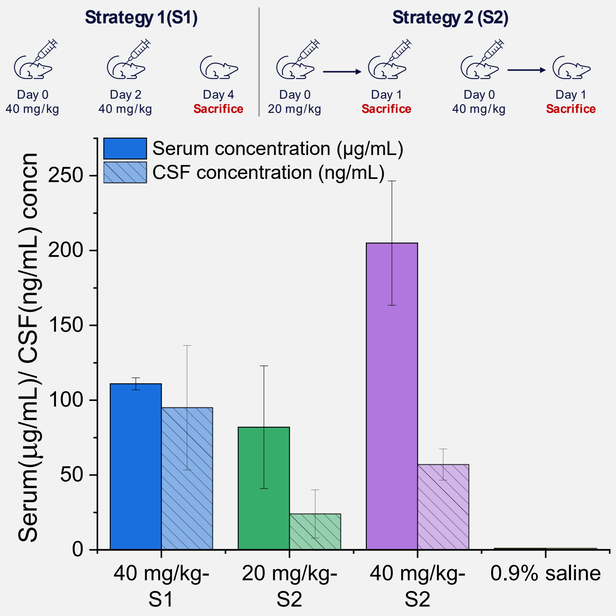
Amyl-2 inhibits seeding of human AD Tau



Amyl-2 binds $A\beta_{1-42}$ aggregates in AD mouse (tg2576) brain

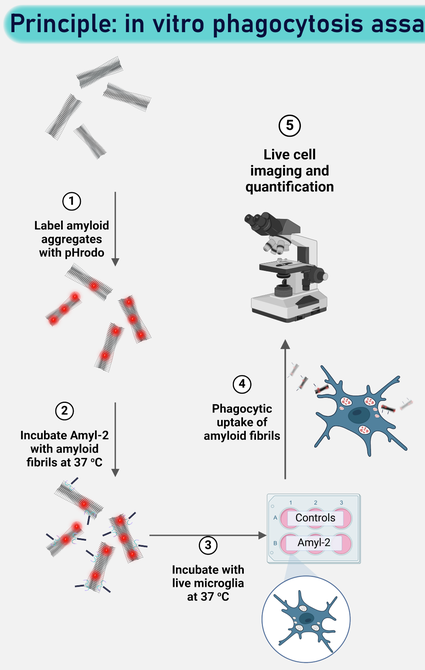


Amyl-2 penetrates the brain in the AD mouse (tg2576) model

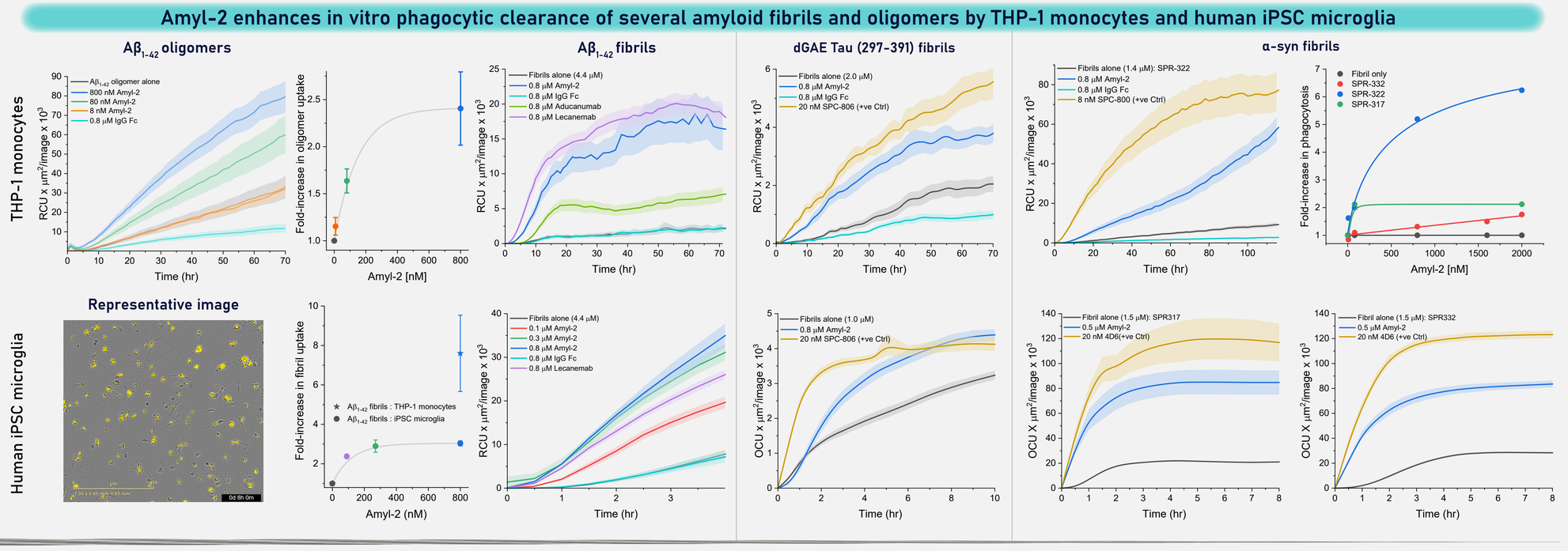


Amyloid clearance

Principle: in vitro phagocytosis assay



Amyl-2 enhances in vitro phagocytic clearance of several amyloid fibrils and oligomers by THP-1 monocytes and human iPSC microglia



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.

OUR PARTNERS

CER Groupe · C.RIS Pharma Your non-clinical CRO · University of Twente. · scantox · University of Cambridge · ETAP-Lab etap-lab.com · ULB Université Libre de Bruxelles · Liège université CIP · ExcellGene · Kimialys · cmmi excellence in preclinical imaging