

Small Molecule GAL-201 under development for oral AD treatment: Modulation of A β aggregation directly influences synaptic plasticity and also affects neuroinflammation

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OBJECTIVES

GAL-201, a small molecule currently under development as an oral therapy for Alzheimer's Disease (AD) binds to misfolded, aggregation-prone A β monomers with high selectivity and affinity thereby preventing the formation of toxic oligomers. Here, we further investigate its biological activity.

METHODS

LTP experiments are extended to investigate whether the protective effect of GAL-201 on synaptic plasticity is also observed in regard to a toxicity induced by other A β isoforms besides A β ₁₋₄₂. Furthermore, a potential antiinflammatory effect of GAL-201 is examined by using fluorescence activated cell sorting. In addition, after a positive outcome in behavioral tests with Tg-ArcSwe mice, plaques are visualized using a methoxy-X04 staining.

Figure 1: A β oligomers and protofibrils have been validated as targets for AD treatment

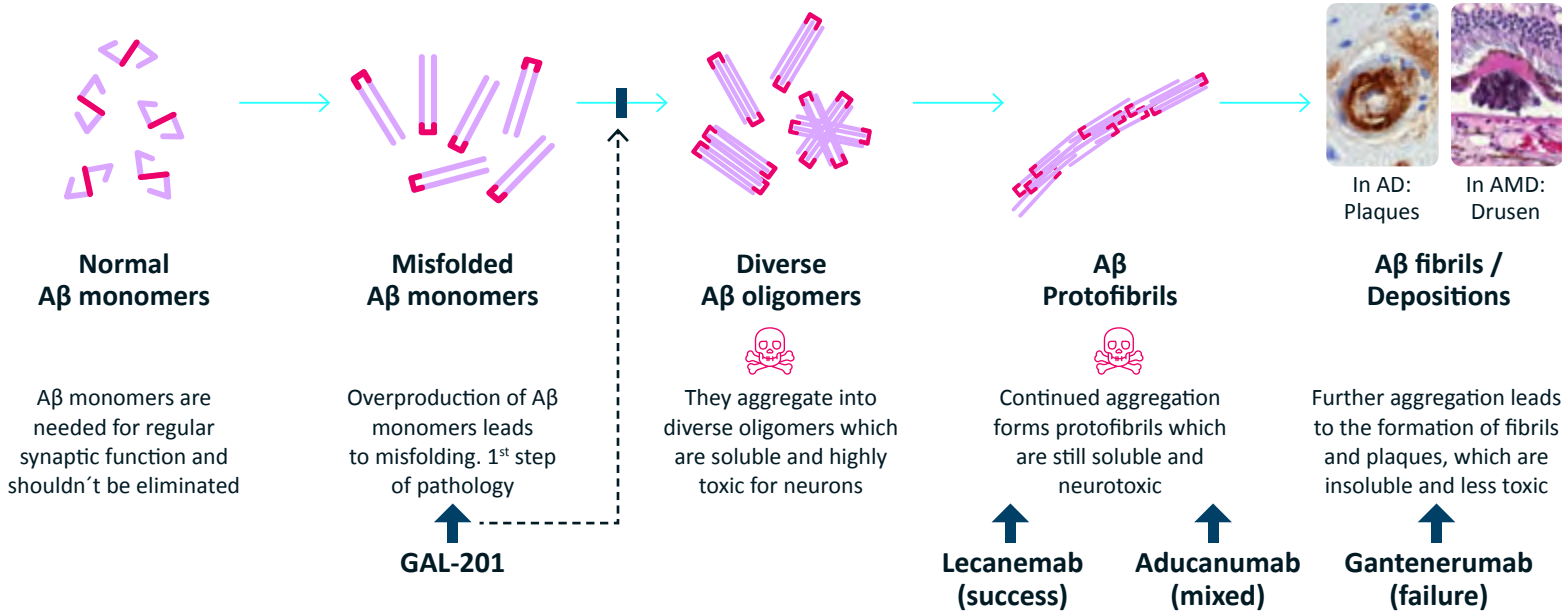


Figure 2: GAL-201 prevented detrimental effects of different A β subspecies on CA1-LTP – even after serial dilution

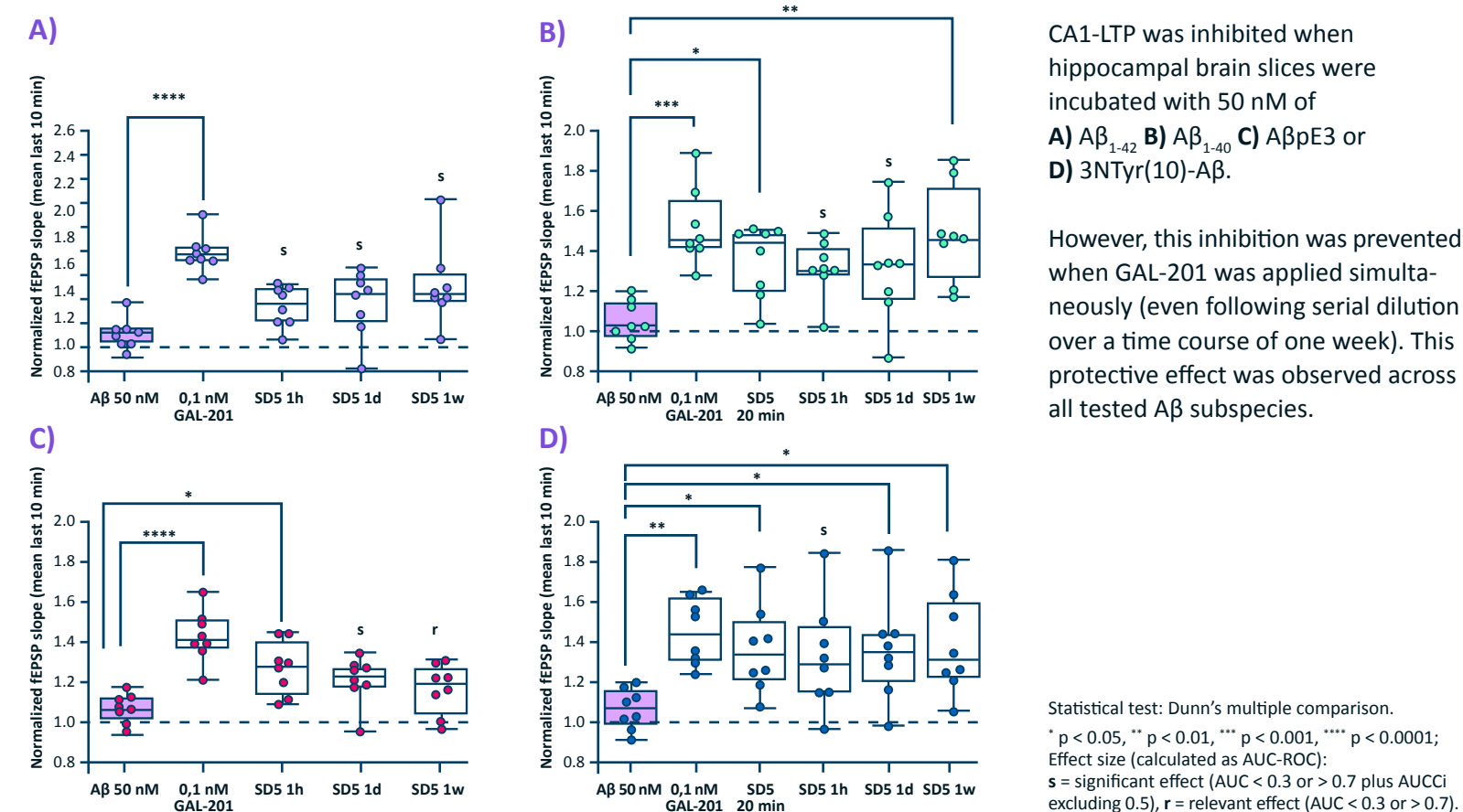


Figure 3: GAL-201 prevented an A β ₁₋₄₂-induced microglia activation

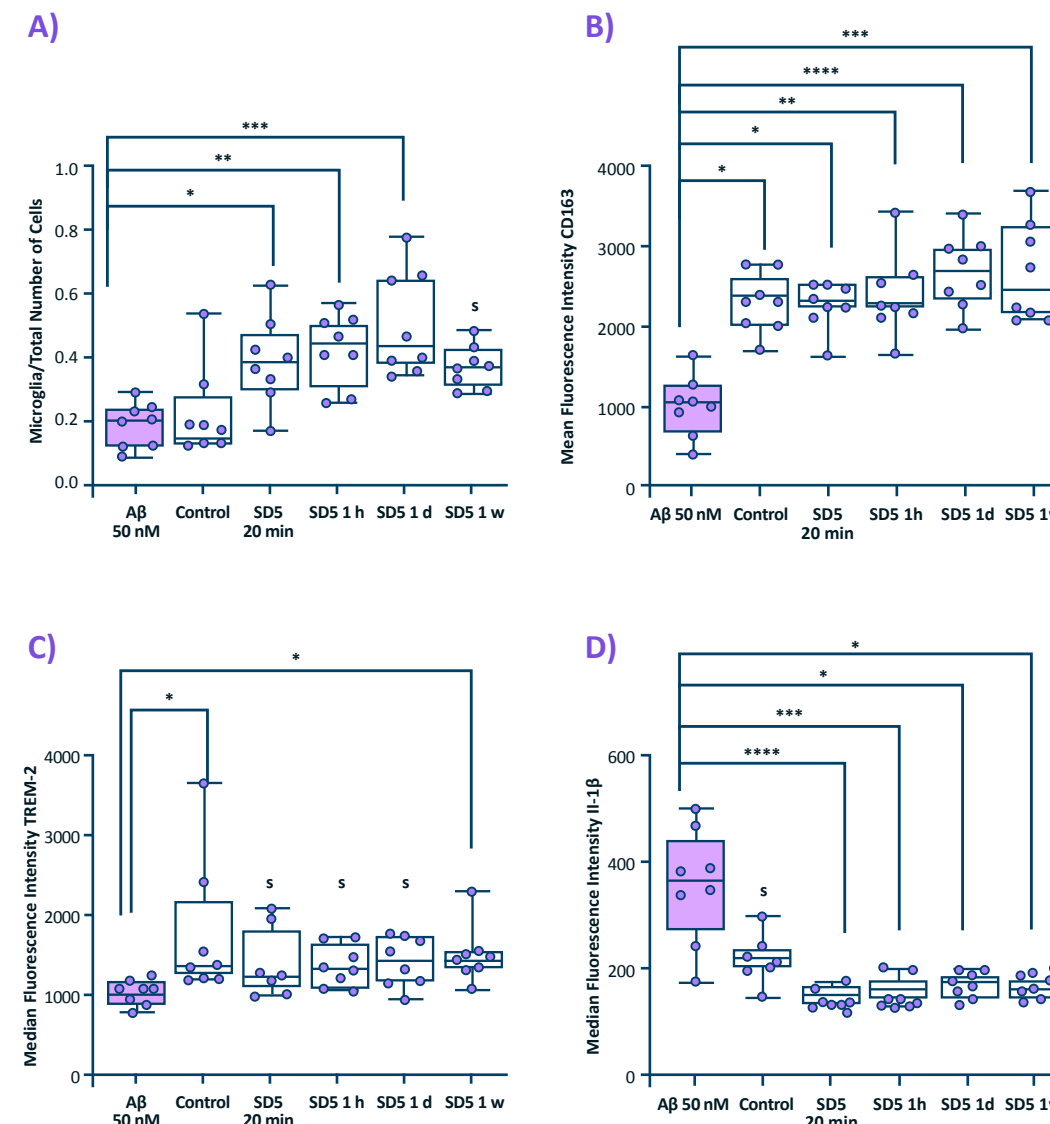


Figure 4: GAL-201 also prevented an A β ₁₋₄₂-induced astrocyte activation

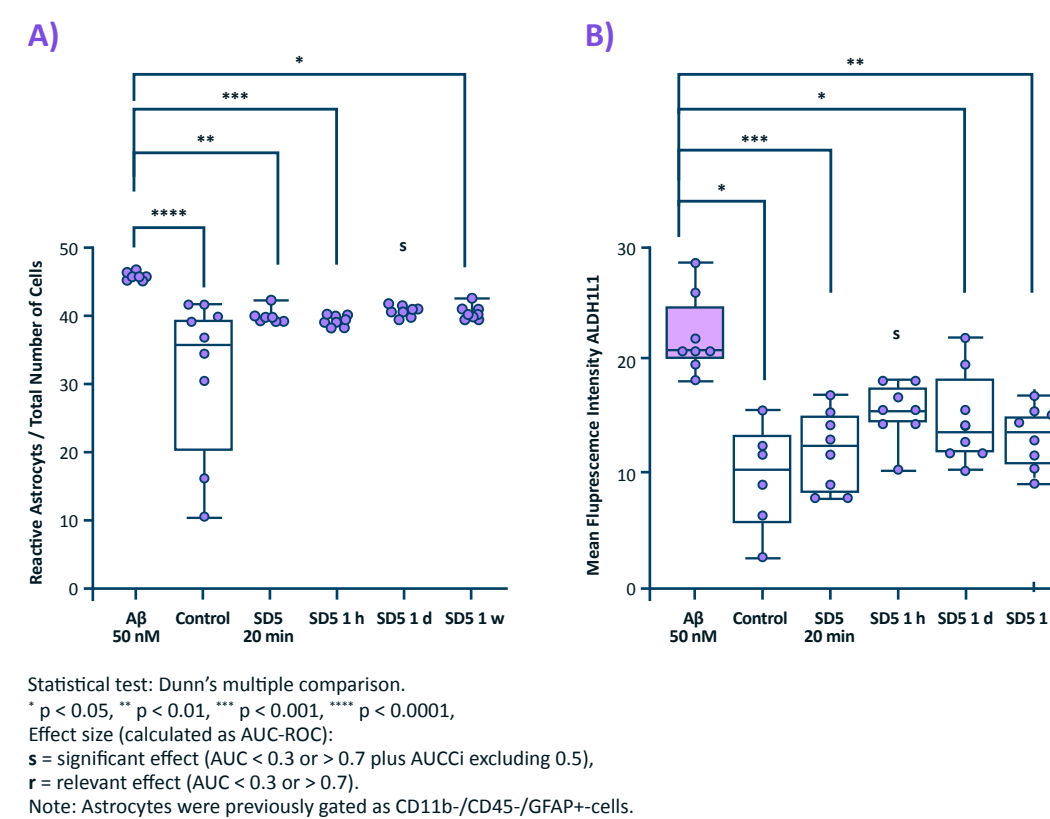
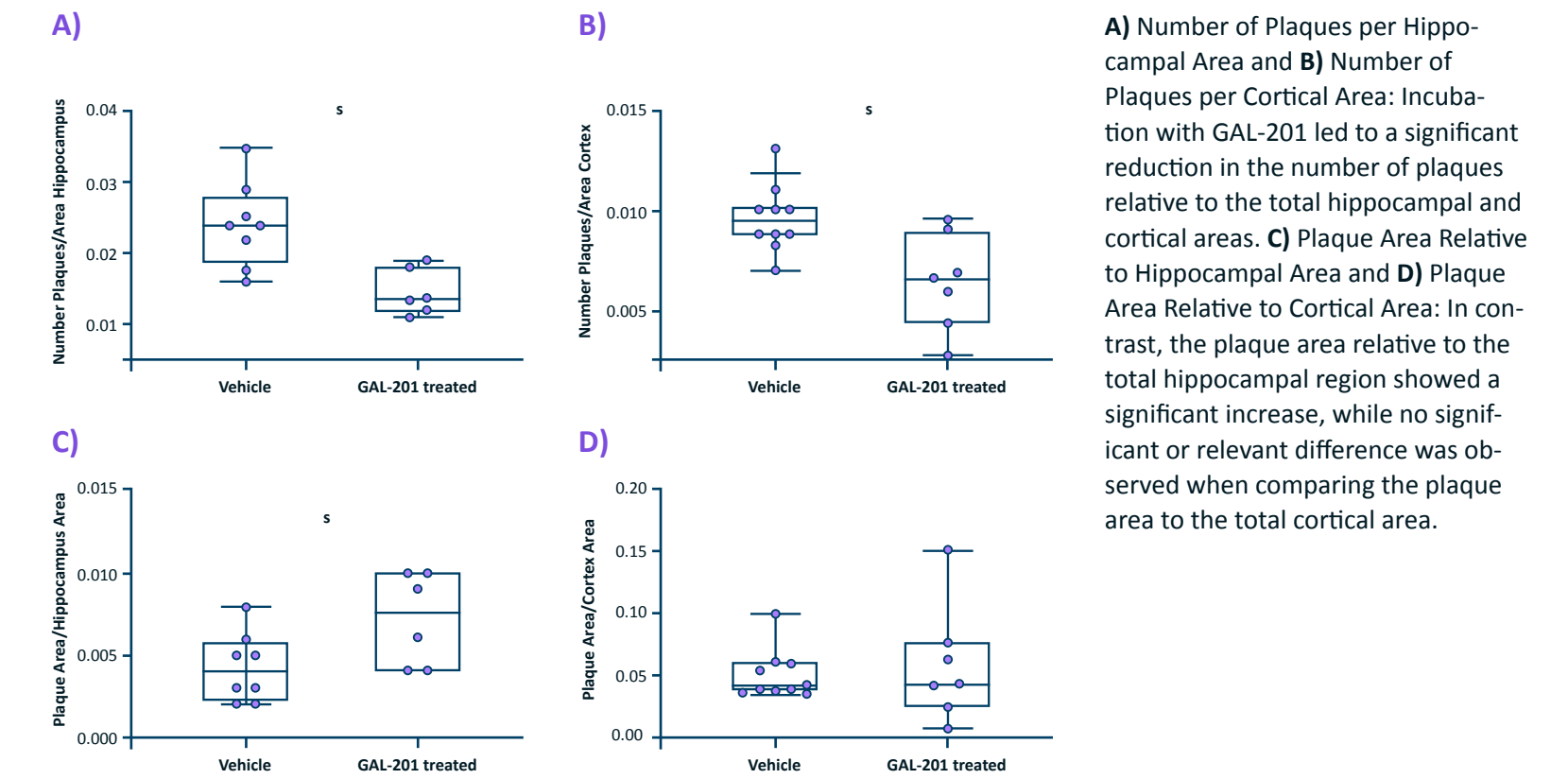


Figure 5: GAL-201 reduced the number of plaques while increasing the plaque area



RESULTS

We show that GAL-201 prevents an A β ₁₋₄₂-induced increase of proinflammatory microglia and reactive astrocytes. Furthermore, we demonstrate that the effect of GAL-201 is irrespective of A β cleavages and posttranslational modifications, present in A β ₁₋₄₀^{3NTyr(10)}-A β and A β pE3. In addition, we observe changes in plaque morphology, supporting the prion-like effect of GAL-201.

CONCLUSIONS

As GAL-201 binds to A β at the key hydrophobic sequence (amino acids 16-24/KLVFF-region), different A β isoforms are targeted in the same way and their aggregation to toxic forms is blocked, which is confirmed by LTP experiments. Furthermore, as A β toxicity is closely related to neuroinflammation, GAL-201 also shows a beneficial effect on A β ₁₋₄₂-induced microglia and astrocyte activation. In addition, the deposition pattern of A β in brain tissue is affected by GAL-201. These findings are in line with a non- β -sheet agglomeration towards removable A β deposits in the presence of GAL-201 in contrast to persistent β -sheet aggregate build up from toxic oligomers/protofibrils (plaque type) in the absence of GAL-201. These and the other data with GAL-201 generated so far, position the molecule consistently as a promising candidate for clinical development in AD.

References:
 Russ H, Mazzanti M, Parsons C, Riemann K, Gebauer A, Rammes G. The Small Molecule GAL-201 Efficiently Detoxifies Soluble Amyloid β Oligomers: New Approach towards Oral Disease-Modifying Treatment of Alzheimer's Disease. *Int J Mol Sci*. 2022 May 21;23(10):5794. doi: 10.3390/ijms23105794. PMID: 35628602 Riemann K, von Ahsen J, Böhm T, Russ H, Parsons C, Rammes G. GAL-201 is a Novel A β -Targeting Small Molecule for Alzheimer's Disease Treatment: Consistent Effects on Synaptic Plasticity, Behavior and Neuroinflammation (under review).

