

The amyloid beta aggregation modulator GAL-201 is under development for oral AD treatment: Cognitive improvement in a transgenic AD model

Hermann Russ¹, Katrin Riemann², Jeldrik von Ahnen², Gerhard Rammes²

¹ Galimedix Therapeutics Inc., 3704 Calvend Lane, Kensington, MD 20895, USA
² Clinic for Anesthesiology and Intensive Care Medicine from the Technical University of Munich, Klinikum rechts der Isar, Ismaningerstr. 22, 81675 Munich, Germany



AD/PD™ 2024
 ADVANCES IN SCIENCE & THERAPY

International Conference on
 Alzheimer's and Parkinson's Diseases
 and related neurological disorders
 March 5 - 9, 2024 | Lisbon, Portugal **Hybrid**



BACKGROUND
 The small molecule GAL-201 has recently been characterized as a promising development candidate for oral treatment of AD. It binds with high affinity ($K_i=2.9$ nM) to the misfolded form of monomeric amyloid beta and prevents aggregation to the neurotoxic amyloid beta oligomers and protofibrils. These amyloid species have been validated by recent positive Phase 3 studies with antibody drugs, such as lecanemab, as an AD drug target.

OBJECTIVES
 Prior to beginning clinical development, GAL-201 should be investigated in an established transgenic (tg) model of AD for its neuroprotective and symptomatic potential.

METHODS
 The tgArcSwe mouse model of AD was chosen since it carries, besides the Swedish mutation (APP^{Swe}), the amyloid beta-associated Arctic mutation (ArcAb). Tg and wild-type mice (12 months) were tested for their cognitive performance in the water-cross maze after administration of 80 mg/kg GAL-201 subcutaneously on the day before the experiment. Long-term-potential(LTP) was electrophysiologically monitored in the CA1 region of hippocampal brain slices.

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

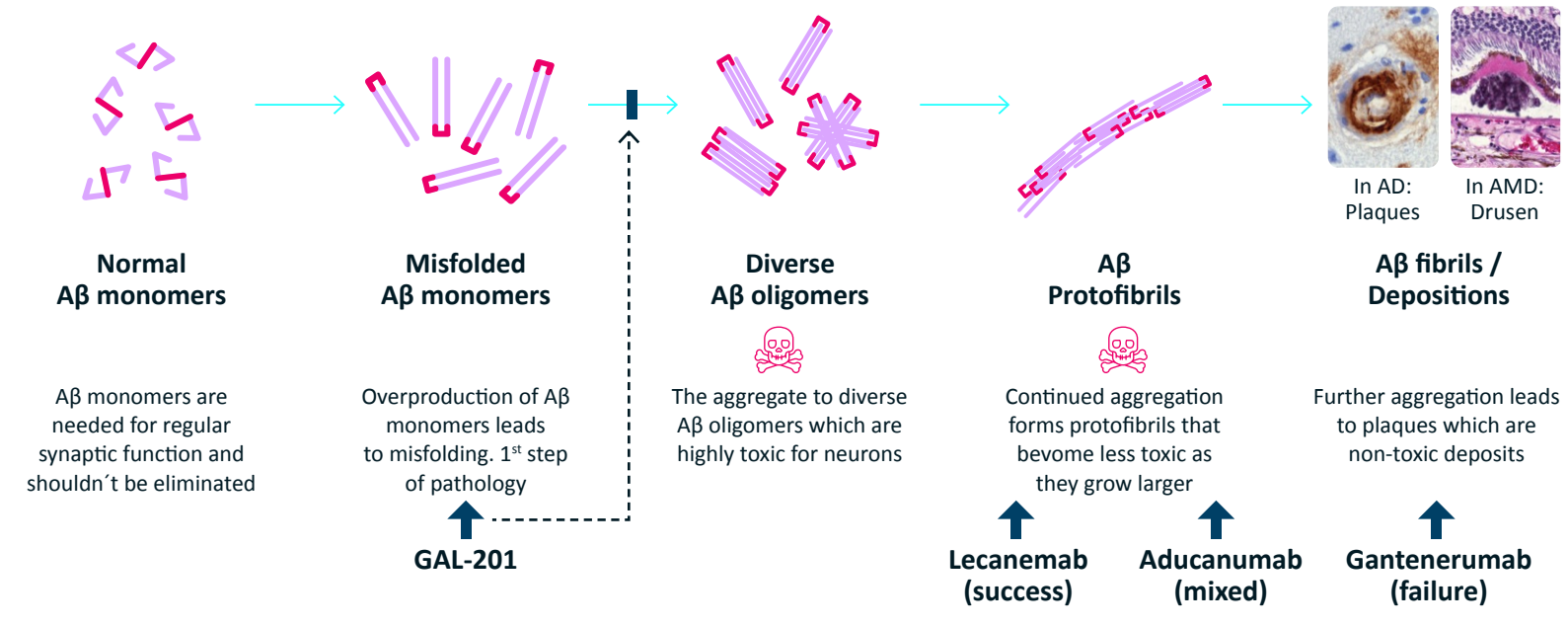


Figure 2: GAL-201 targets misfolded Aβ₁₋₄₂ with high affinity and prevents the formation of oligomers and protofibrils

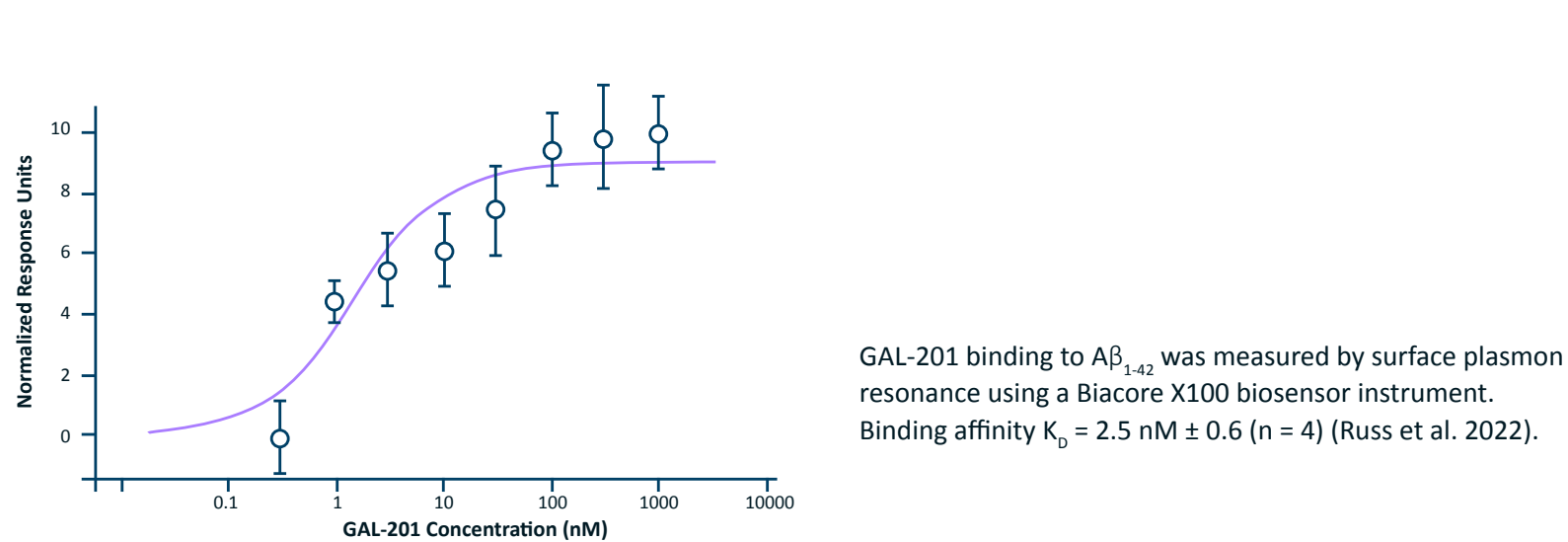


Figure 3: GAL-201 prevents Aβ₁₋₄₂-induced suppression of long-term potentiation

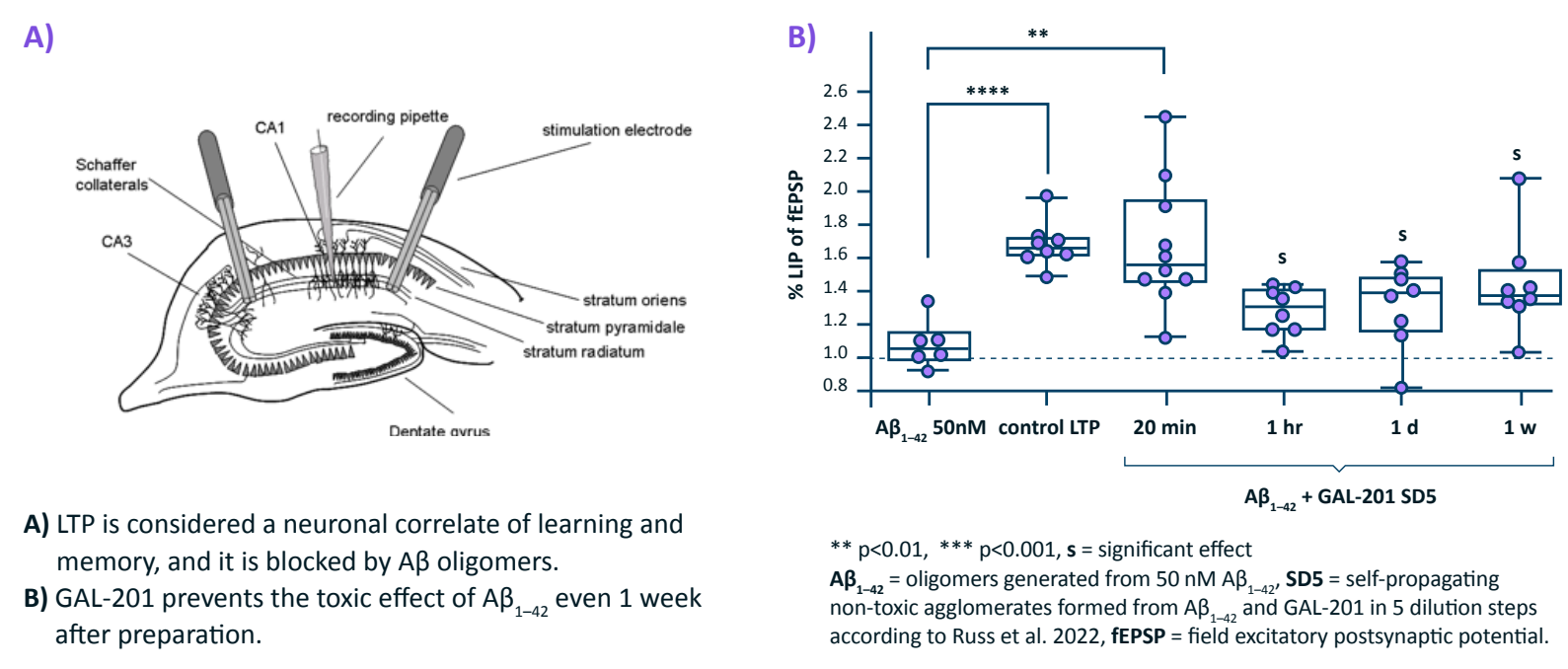


Figure 4: The protective effect on LTP directly correlates with spine protection or prevention of spine loss

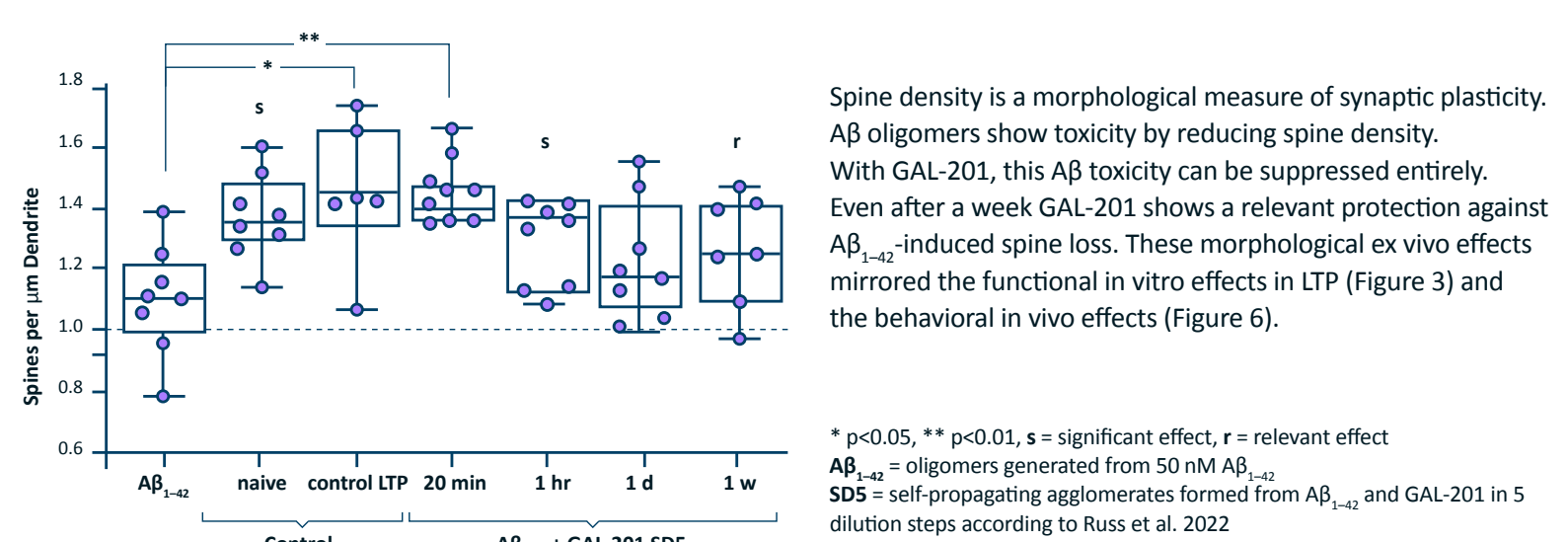


Figure 5: Aβ₁₋₄₂-induced spine loss is visually prevented by GAL-201

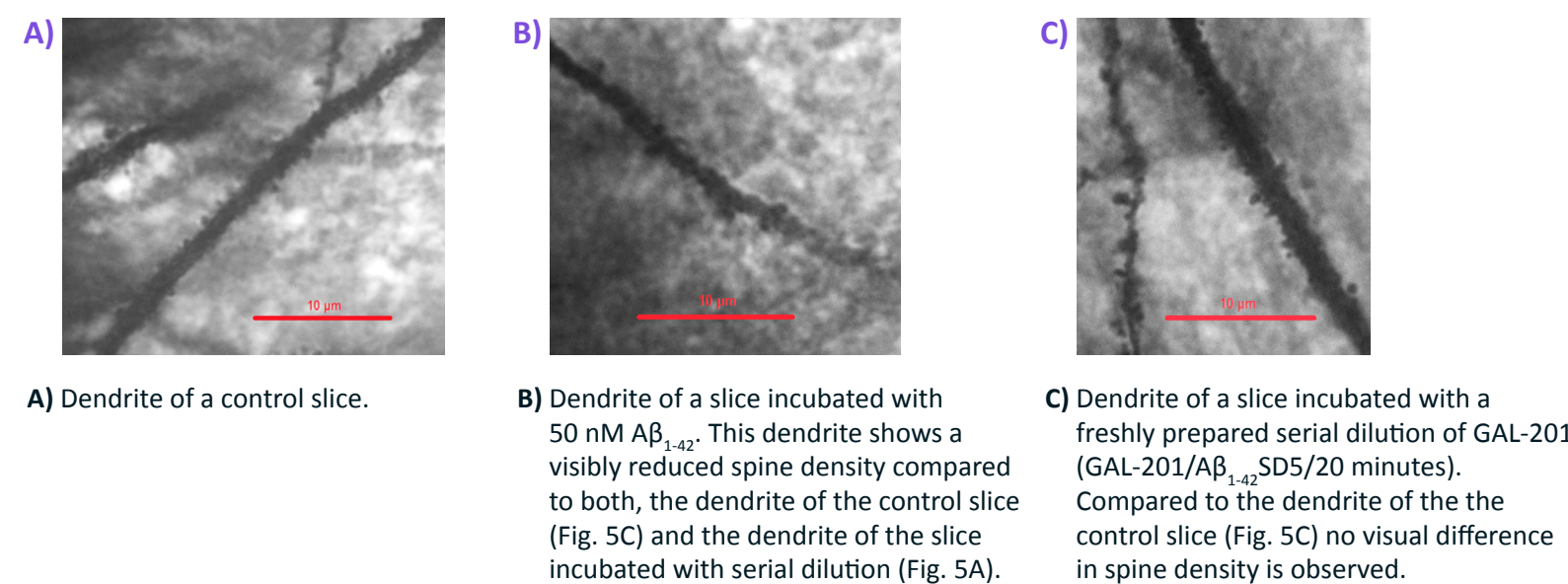
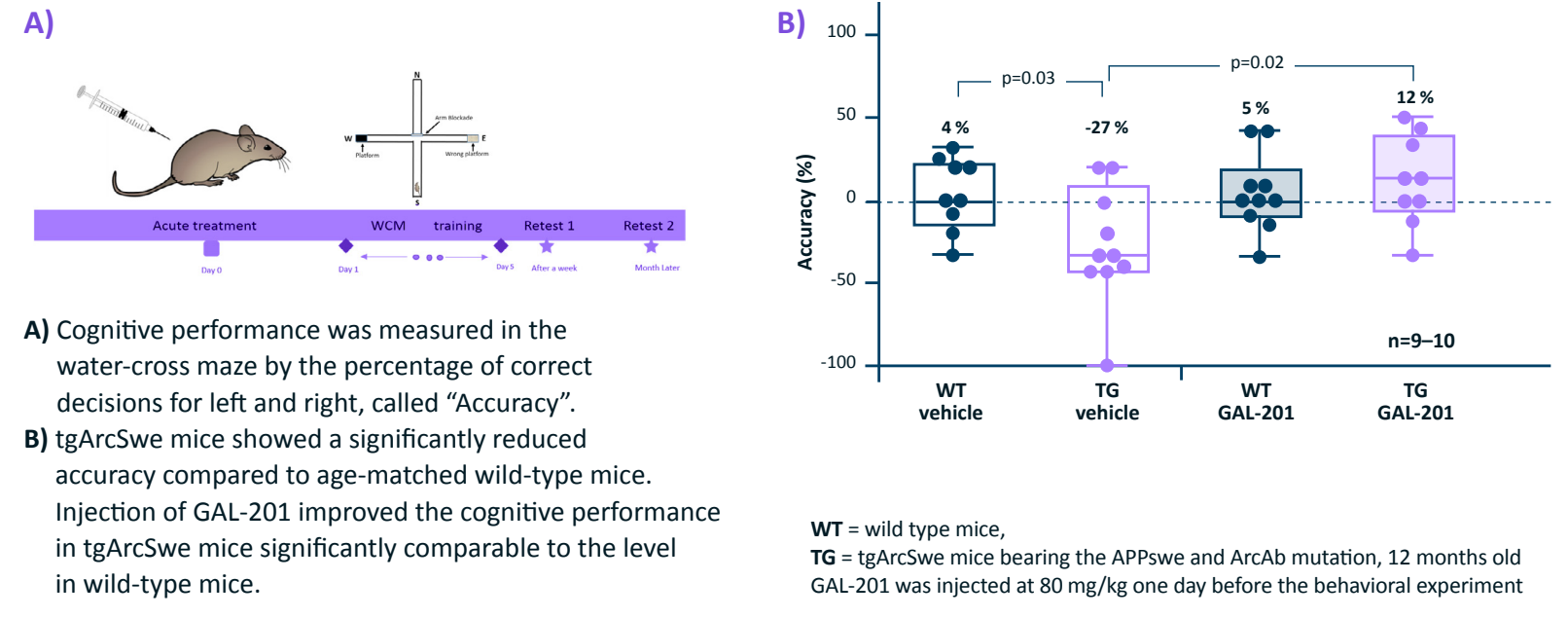


Figure 6: In behavioral experiments with transgenic AD mice, a single injection of GAL-201 improved cognition significantly.



RESULTS
 GAL-201 significantly improved the cognition in the mutants compared to placebo. The escape latency, which is the duration the animals need to perform the test, was clearly shorter since the transgenic mice showed a cognitive improvement when treated with GAL-201 (n=9-10 per group, p=0.06). In the accuracy experiment, the improvement of the GAL-201-treated transgenic mice was even more pronounced (n=9-10 per group, p=0.02). In addition, new in vitro data about the duration of the biological activity of GAL-201 will be presented.

CONCLUSIONS
 The available results of the animal study in the Arctic mutation AD model further strengthen the profile of GAL-201 as a promising development candidate for oral AD therapy. The next step will be the initiation of an IND-enabling program before starting a classic Ph 1 SAD/MAD study.

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

