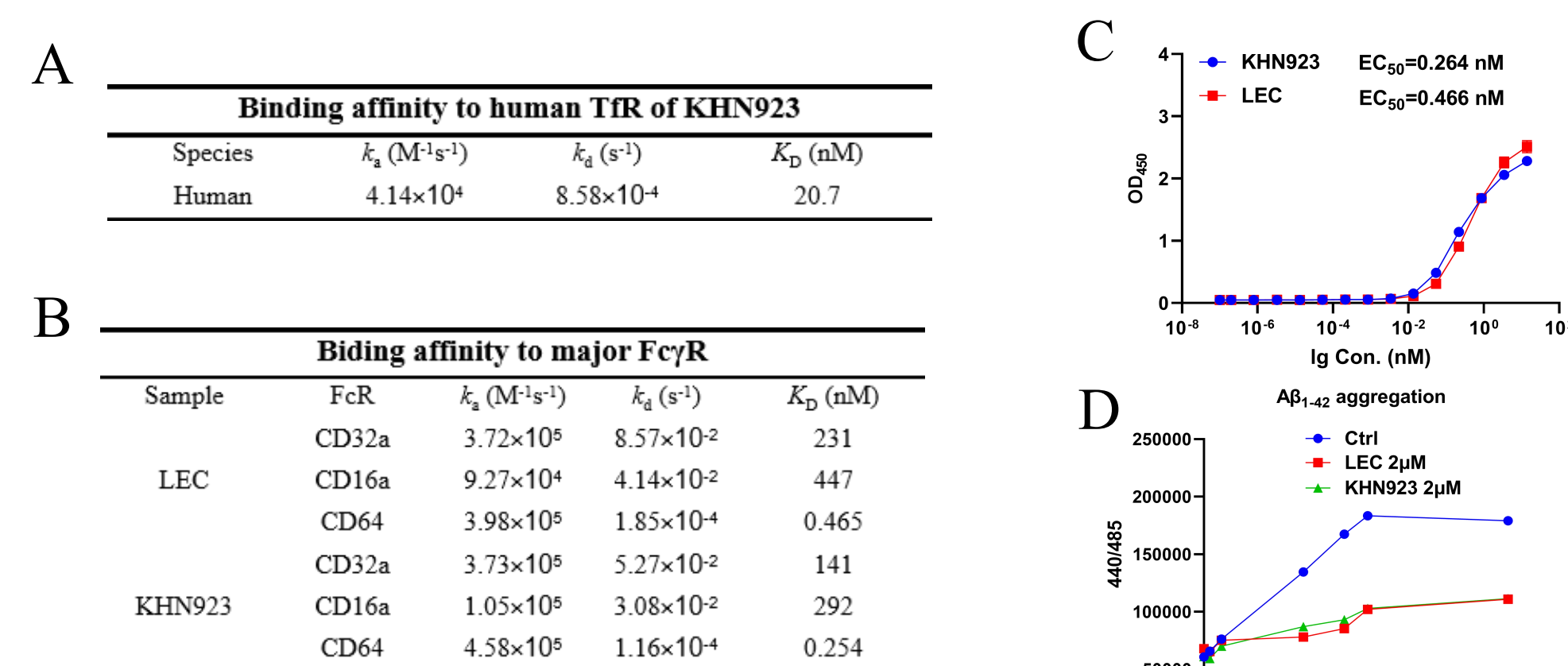


Background: The blood-brain barrier (BBB) presents a major challenge for the development of monoclonal antibody based therapies for brain disorders. KHN923 is a monoclonal bispecific antibody that has been developed for the purpose of crossing the blood-brain barrier, with the intention of delivering targeted amyloid therapy for the treatment of Alzheimer's disease. The drug was engineered using Kanghong Pharmaceutical's "TfR Nanobody-Based Blood-Brain Barrier Penetration Platform" technology, which enhances its ability to traverse the blood-brain barrier.

Methods: We identified a nanobody capable of crossing the BBB by hTfR transgenic mice. The process of fusing this humanized nanobody to the Fc segment of Lecanemab resulted in the formation of the symmetrical KHN923. We investigated the mechanism of BBB crossing of KHN923 in vitro, and compared its ability to phagocytose Aβ₄₂ protofibrils via Fc and TfR with that of competitors. Utilising an Alzheimer's disease mouse model that expresses hTfR, a comparative analysis was conducted on the BBB penetration and Aβ₄₂ protofibrils clearance capabilities of KHN923 and competitors.

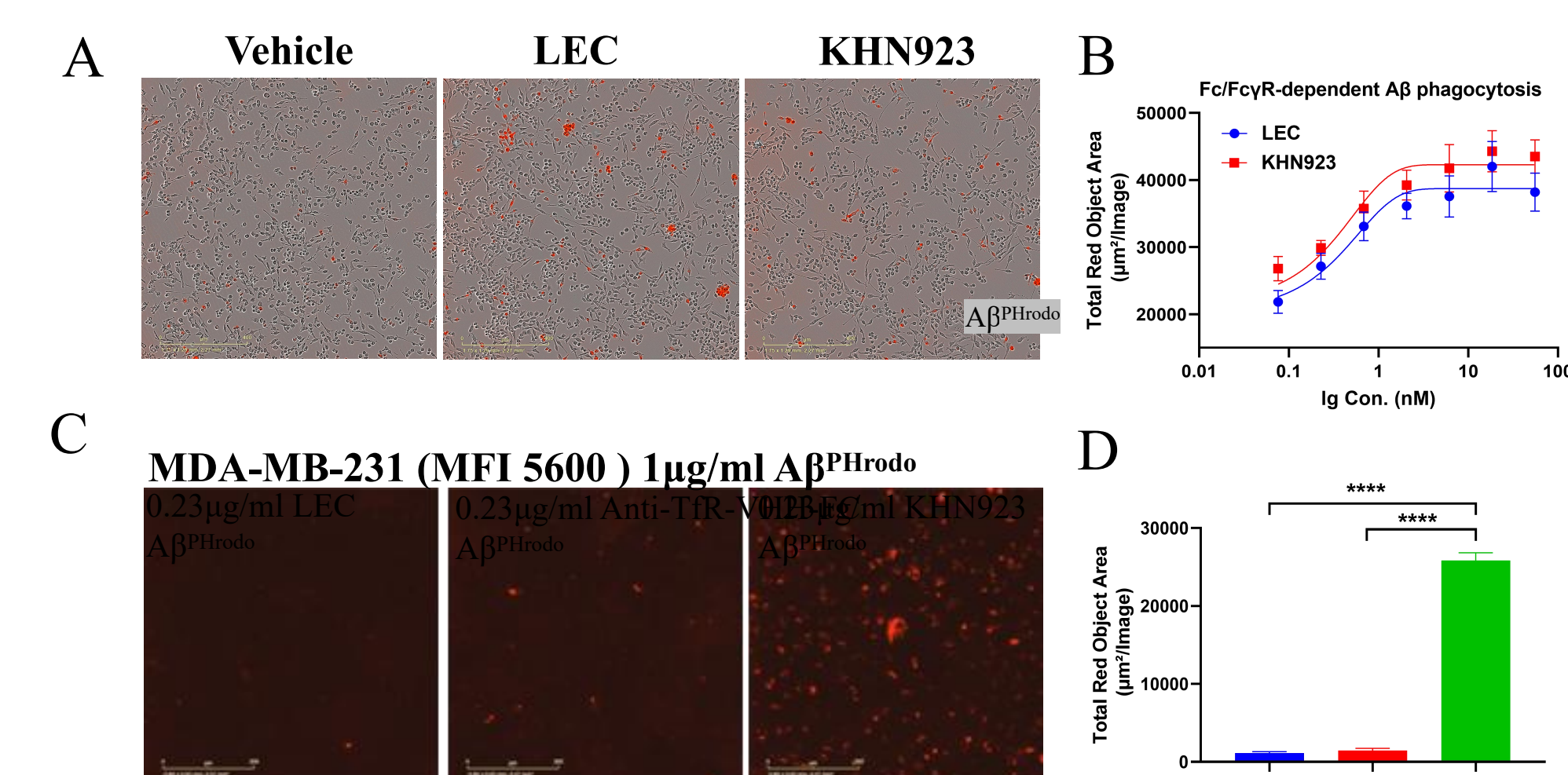
Results

The KHN923 exhibits activity equivalent to Lecanemab analog (LEC).



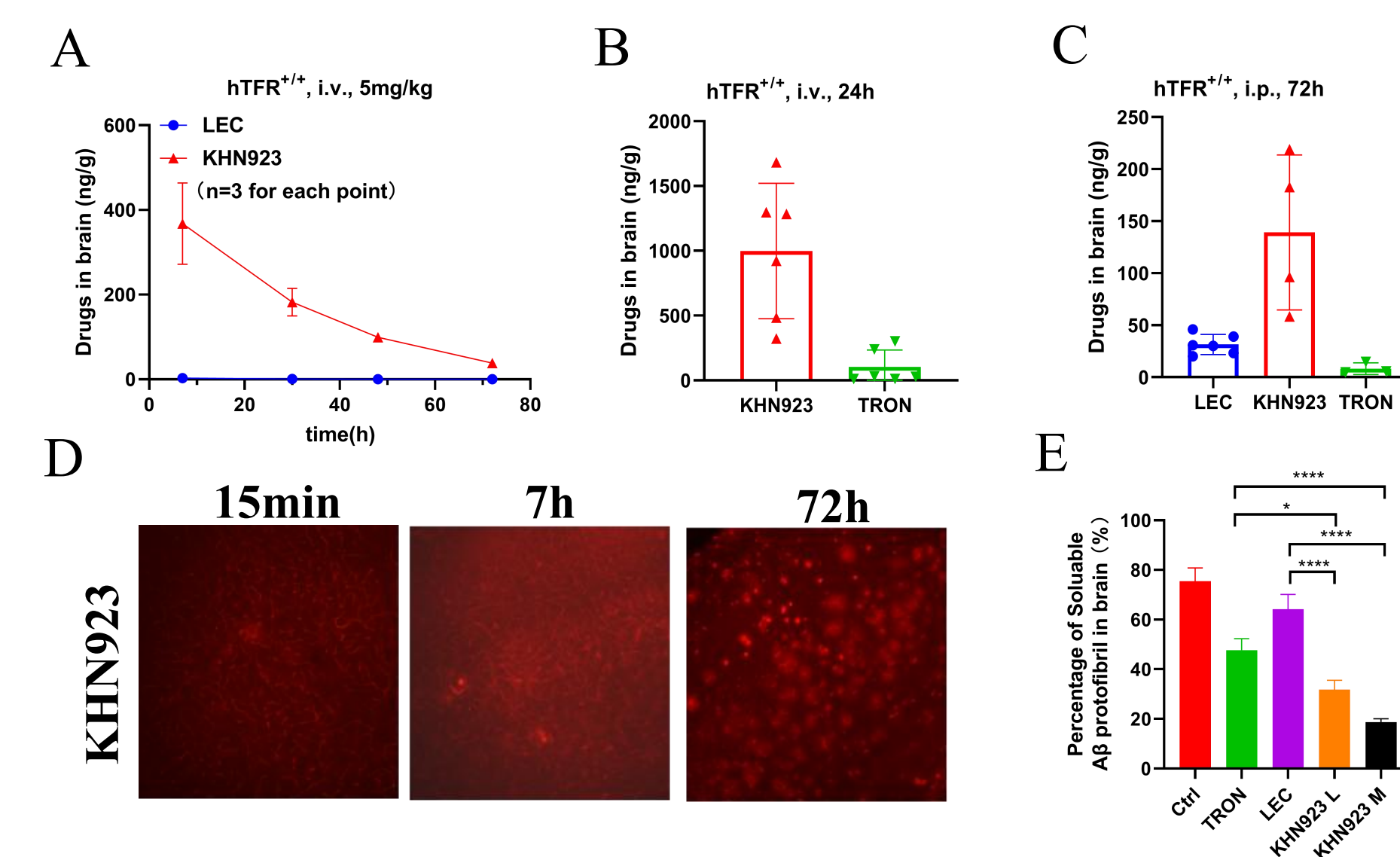
A,B. Binding affinity of KHN923 to human TfR and major FcγRs by ForteBio. **C.** KHN923 exhibits comparable binding affinity to LEC. for Aβ₄₂ protofibrils By ELISA. **D.** LEC. and KHN923 inhibit Aβ₄₂ aggregation by the thioflavin T (ThT) assay.

KHN923 maintains Lecanemab-equivalent activity and achieves efficient TfR-mediated internalization in vitro



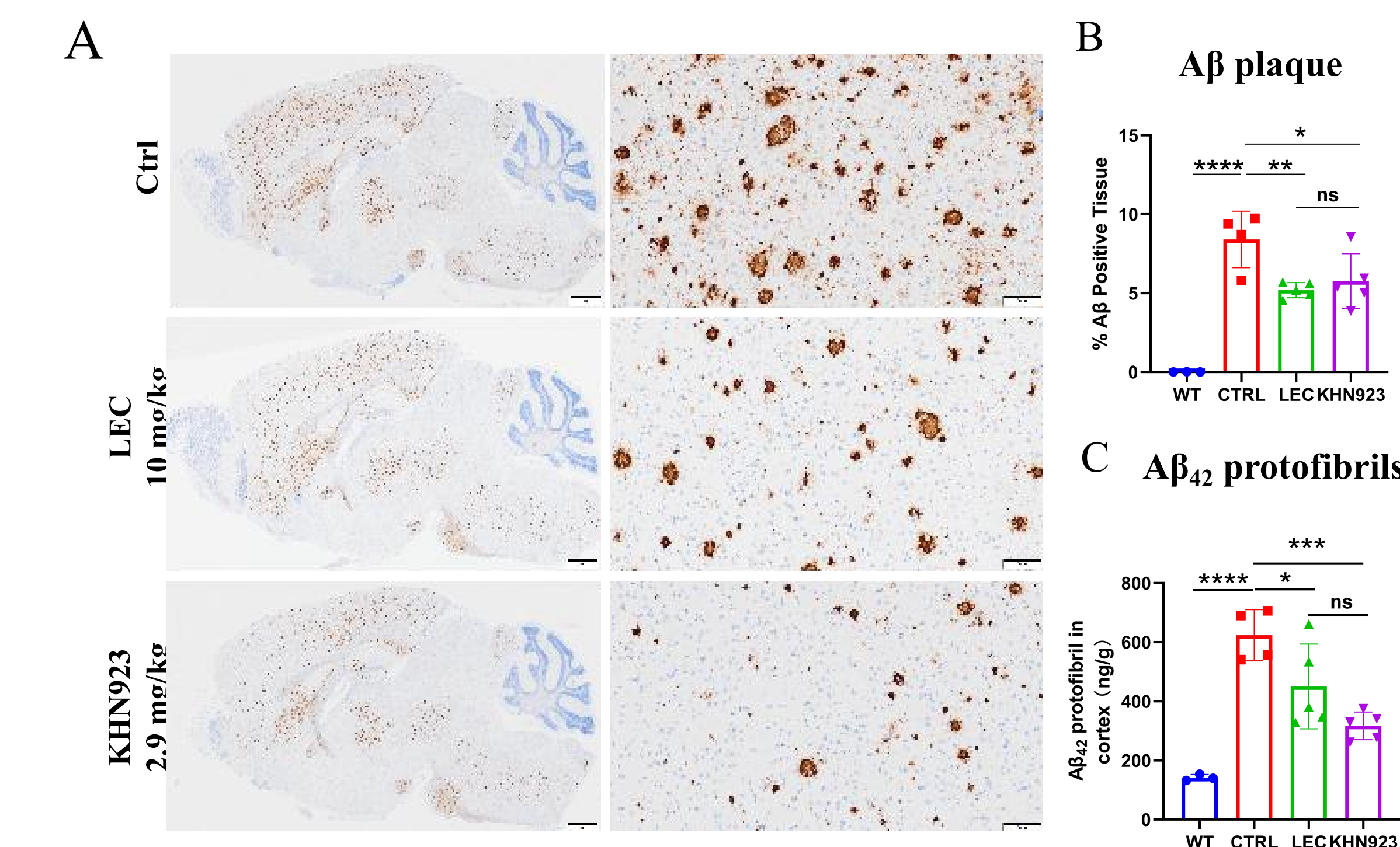
A,B. KHN923 possesses comparable capacity to LEC. for Fc/FcγR-mediated phagocytosis of Aβ₄₂ protofibrils. The red fluorescence of PHrodo-labelled Aβ₄₂ protofibrils were observed upon lysosomal internalisation following an eight-hour co-incubation with varying concentrations of LEC. or KHN923 in BV2 cells. **C,D.** KHN923 mediates phagocytic clearance of Aβ₄₂ protofibrils via TfR, Aβ₄₂ protofibrils were labelled with PHrodo and then mixed with 0.23 μg/ml antibodies in MDA-MB-231 cells to detect TfR-mediated endocytosis.

KHN923 demonstrates superior BBB permeability and clears soluble Aβ₄₂ protofibrils in brain more effectively than Lecanemab analog and Trontinemab analog



A. KHN923-S11 successfully crosses the blood-brain barrier, with brain uptake surpassing LEC more than 100-fold at 7, 30, 48 and 72 h after dosing. **B.** KHN923 exhibits 5-10 times higher brain parenchyma drug concentrations than Trontinemab. **C.** At 72 hours post-administration, KHN923 brain parenchyma drug levels were 5–10 times higher than equivalent Trontinemab doses and over 5 times higher than 35 mg/kg LEC. **D.** In hTfR^{+/+}/5×FAD mice, KHN923 rapidly binds to blood vessels post-administration, crosses the blood-brain barrier, and interact with Aβ plaque in the brain. **E.** In hTfR^{+/+}/5×FAD mice, KHN923 (M 2.9 mg/kg, 16.6 nmol/kg) cleared Aβ₄₂ protofibrils 2-fold more efficiently than equimolar trontinemab analog (TRON) and 5-fold more than LEC at a 4-fold molar dose (10 mg/kg, 66.6 nmol/kg). Even at a low dose (L 0.73 mg/kg, 4.2 nmol/kg), KHN923 still shows superior clearance efficacy over the trontinemab (16.6 nmol/kg) and LEC (66.6 nmol/kg).

KHN923 effectively removes soluble Aβ₄₂ protofibrils in hTfR^{+/+}/FAD4T mice.



Five-month-old hTfR^{+/+}/FAD4T mice received weekly dosing for 12 consecutive weeks, with soluble Aβ₄₂ protofibrils measured in the cerebral cortex. **A,B.** 2.9mg/kg KHN923 exhibits a comparable capacity to reduce brain Aβ plaques to 10mg/kg lecanemab. The burden of Aβ plaque in mouse brain tissue sections was studied using the 6E10 antibody. **C.** KHN923 demonstrates superior clearance of Aβ₄₂ protofibrils at doses of 2.9 mg/kg to Lecanemab at 10 mg/kg.

KHN923 is well tolerated in monkeys

The no-observed-adverse-effect level (NOAEL) was 100 mg/kg in cynomolgus monkeys treated with KHN923 intravenously once weekly for 5 doses, confirming a >100-fold therapeutic window.

Summary

KHN923 maintains LEC-equivalent activity and achieves efficient TfR-mediated phagocytosis and demonstrates exceptional BBB permeability, with brain uptake surpassing LEC by 100-fold and TRON by 5~10-fold. In hTfR/5x FAD mice, KHN923 reduces Aβ₄₂ protofibrils 2-fold more efficiently than equimolar TRON and 5-fold more than LEC at a 4-fold molar dose. Even at a low dose, KHN923 still shows superior clearance efficacy over competitors. In hTfR/FAD4T mice, 2.9 mg/kg of KHN923 demonstrated superior clearance of Aβ₄₂ protofibrils to 10 mg/kg of LEC. By significantly increasing brain drug delivery and accelerating plaque clearance, KHN923 represents a highly promising, next-generation disease-modifying therapy for Alzheimer's disease.

