Brain delivery and efficacy of a BBB shuttle-enhanced aducanumab biosimilar in a mouse model of Alzheimer's disease

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Background & Aim

Improved CNS access of amyloid β (Aβ)-directed antibodies may increase therapeutic benefits while reducing dose-dependent adverse effects of this drug class. Using light sheet fluorescence microscopy, we aimed to 3D visualize and quantify whole-brain distribution of a blood-brain barrier (BBB) shuttle-enhanced aducanumab biosimilar in a mouse model of Alzheimer's disease (AD).

Methods

7-11 months old transgenic APP/PS1 [APP(KM670/671NL(swe)/PS1(L166P)], n=8-10) mice were administered (i.p.) Aducanumab (10 or 50 nmol/kg) or Aducanumab fused with a mTfR1 binder as BBB-shuttle (TfR1-Aducanumab, 10 nmol/kg) or control human IgG (50 nmol/kg) once weekly for 12 weeks. Mice were terminated 72h after last dosing. Whole hemispheres were stained with antibodies against human IgG and Aβ, optically cleared and scanned on a light sheet fluorescence microscope (LSFM) for AI-assisted automated anatomical mapping and quantification of compound distribution and plaque load using a custom mouse brain atlas.

Conclusion

+ **TfR1 BBB-shuttle enhances brain delivery of Aducanumab**
+ **TfR1-Aducanumab lowers plaque load in more brain regions compared to Aducanumab**

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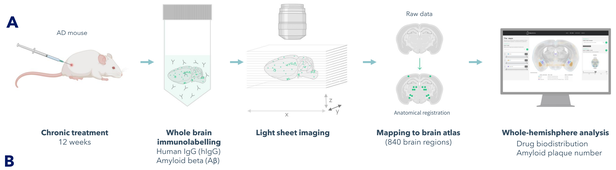
1 Quantitative 3D whole-brain LSFM imaging pipeline



B

Study design	Group	Treatment	Number of animals	Age (weeks)
Chronic treatment (i.p., once weekly for 12 weeks)	1	Control hIgG 50 nmol/kg	8	44 ± 2
	2	Aducanumab 10 nmol/kg	8	43 ± 3
	3	Aducanumab 50 nmol/kg	10	43 ± 2
	4	TfR1-Aducanumab 10 nmol/kg	9	41 ± 4

Figure 1. Study outline and automated quantitative 3D light sheet fluorescence microscopy imaging workflow. **(A)** AI-based automated whole-brain imaging pipeline applied for comparative evaluation of whole-hemisphere distribution and therapeutic efficacy of Aducanumab vs. Aducanumab fused with a mTfR1 binder as BBB-shuttle (TfR-Aducanumab) following chronic treatment (12 weeks) in a transgenic APP/PS1 (ARTE10) mouse model of Alzheimer's disease. **(B)** Treatment groups and average age at start of treatment.

2 TfR1 BBB-shuttle enhances CNS delivery of Aducanumab

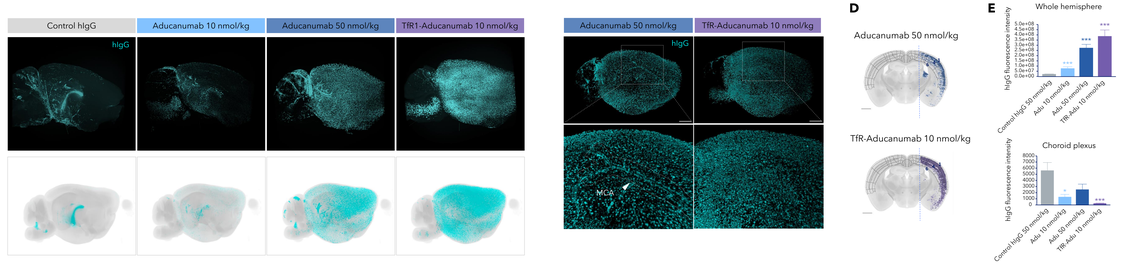


Figure 2. TfR BBB-shuttle enhances brain delivery of Aducanumab in AD mice. **(A)** Representative images of human IgG (hIgG) staining in 3D LSFM-imaged whole-hemispheres. **(B)** Average intensity brain maps (n=8-10) of the different groups registered to our brain atlas. **(C)** Whole-hemisphere distribution of hIgG after Aducanumab treatment (50 nmol/kg) , demonstrating notable drug accumulation in superficial arteries including the the middle cerebral artery (MCA). Compared to Aducanumab, TfR1-Aducanumab (10 nmol/kg) showed a more homogeneous brain distribution. **(D)** Coronal view of average intensity brain map of Aducanumab 50 nmol/kg and TfR-Aducanumab 10 nmol/kg, indicating cortical layers I-VI. TfR1-Aducanumab consistently distributed to deep cortical layers. **(E)** Accumulated hIgG fluorescence intensity in the whole hemisphere and in the choroid plexus. *p<0.05, ***p<0.001 vs. Control hIgG (Dunnett's test negative binomial generalized linear model).

3 3D maps of therapeutic Aβ antibody distribution

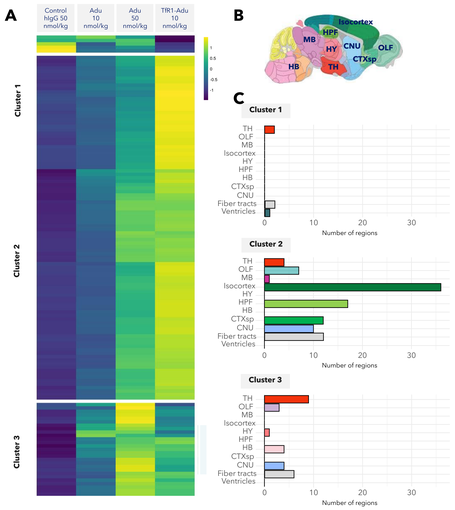


Figure 3. TfR1 BBB-shuttle enhanced brain delivery of Aducanumab in AD mice. **(A)** Heatmap on all brain regions (divided into 3 main clusters) with significantly increased compound fluorescence signal in treatment groups relative to the Control hIgG group. **(B)** Upper panel: Map of main brain areas, including the thalamus (TH), olfactory areas (OLF), midbrain (MB), isocortex, hypothalamus (HY), hippocampal formation (HPF), hindbrain (HB), cortical subplate (CTXsp), cerebral nuclei (CNU), fiber tracts and ventricles. **(C)** Number of anatomical regions of each main brain area with compound accumulation.

4 3D maps of the plaque-clearing effects of TfR1-Aducanumab and Aducanumab

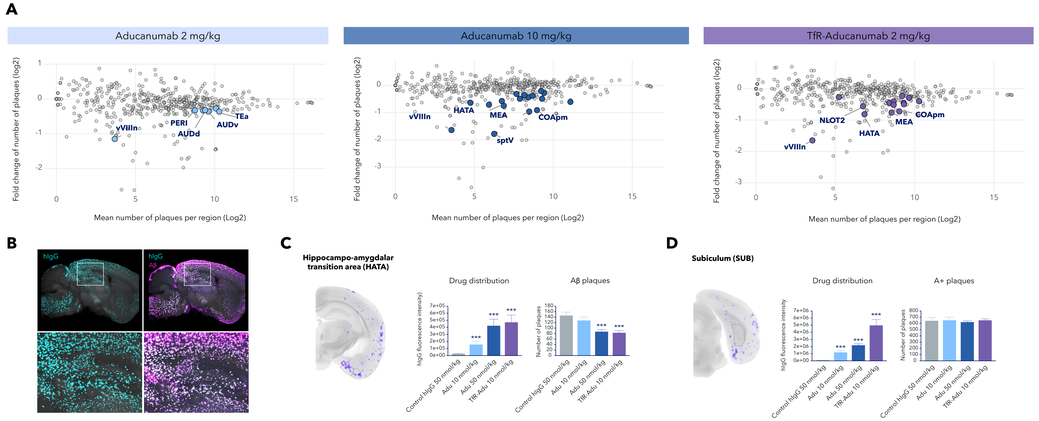


Figure 4. TfR-Aducanumab and Aducanumab reduces Aβ plaque load in a discrete set of brain regions. **(A)** MA-plots depicting log2 fold-change in the number of plaques for all 840 brain regions analyzed. Coloured dots indicate brain regions with significant change compared to the Control IgG group (p<0.05, Dunnett's test negative binomial generalized linear model). **(B)** Upper panels: Sagittal 2D view of a representative brain from TfR-Aducanumab group (10 nmol/kg). Lower panels: Increased magnification of imaged cortico-hippocampal area. **(C-D)** Quantitative plaque load in two selected brain regions including the hippocampo-amygdalar transition area (HATA) and subiculum (SUB). Coronal images: Z-score map depicting regional statistically significant differences in the number of plaques in the TfR-Aducanumab group (10 nmol/kg) vs. the Control IgG group. Bar graphs: Accumulated hIgG fluorescence intensity (drug distribution) and total number of amyloid plaques. ***p<0.001 vs. Control IgG (Dunnett's test negative binomial generalized linear model). *Abbreviations*: AUDv (Auditory area ventral), AUDd (Auditory area dorsal), TEa (Temporal association area), PERI (Perirhinal Area), vVIIIn (Vestibular nerve), (HATA (Hippocampo-amygdalar transition area), MEA (Medial amydala), COApm (Cortical amygdala posteromedial), sptV (spinal tract of trigeminal nerve), NLOT2 (nucleus of the lateral olfactory tract, pyramidal).