Whole brain 3D imaging of Aβ plaque architecture following treatment with a BBB shuttle-enhanced Aducanumab biosimilar in a mouse model of AD

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Background & Aim

Accumulation of amyloid β (Aβ) in the brain is the neuropathological hallmark of Alzheimer's disease (AD). Recently approved Aβ-directed antibodies such as Aducanumab have demonstrated modest efficacy in AD, which may potentially be explained by poor blood-brain barrier (BBB) penetration. Transferrin receptor (TfR) mediated enhanced brain delivery of monoclonal antibodies across the BBB is a promising concept in drug development for CNS disorders. The present study aimed to visualize, map and quantify amyloid plaque load following long-term therapy with a BBB shuttle-enhanced Aβ-directed antibody in a mouse model of AD.

Methods

7-10 month-old APP/PS1 transgenic mice (Arte10) were treated (IP) with Aducanumab biosimilar (AduBS, 10 or 50 nmol/kg), Aducanumab biosimilar fused with a mTfR binder as BBB-shuttle (AduBS-BBB, 10 nmol/kg), or control human IgG (50 nmol/kg) once weekly for 12 weeks (n=8-10 per group). Whole hemispheres were stained with antibodies against Aβ and human IgG, cleared and scanned on a LSFM.
A deep-learning image analysis algorithm was developed and validated for automated whole-brain visualization, segmentation, anatomical mapping and quantification of Aβ plaques in 840 brain regions using a custom mouse brain atlas.

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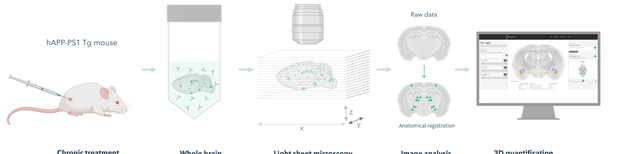
1 Quantitative whole brain imaging pipeline



Group	Name	Treatment	Number of animals	Age (weeks)
1	Control	Control IgG 50 nmol/kg	8	44.8 +/- 2.14
2	AduBS 50	Aducanumab BS 50 nmol/kg	10	43.6 +/- 2.06
3	AduBS 10	Aducanumab BS 10 nmol/kg	8	43.8 +/- 2.53
4	AduBS-BBB 10	Aducanumab BS-BBB 10 nmol/kg	9	41 +/- 3.52

2 Combined 3D imaging of amyloid plaque and therapeutic antibody distribution

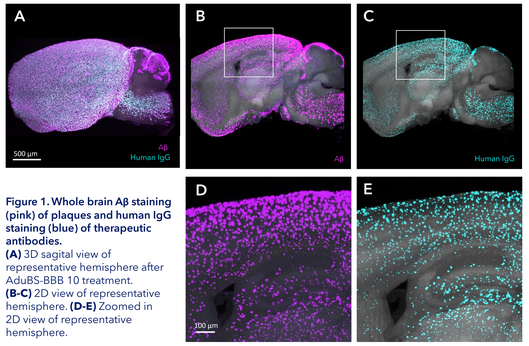


Figure 1. Whole brain Aβ staining (pink) of plaques and human IgG staining (blue) of therapeutic antibodies.
(A) 3D sagital view of representative hemisphere after AduBS-BBB 10 treatment. **(B-C)** 2D view of representative hemisphere. **(D-E)** Zoomed in 2D view of representative hemisphere.

3 Treatment with BBB-shuttle enhanced Aducanumab BS lowers Aβ plaque burden in AD mice

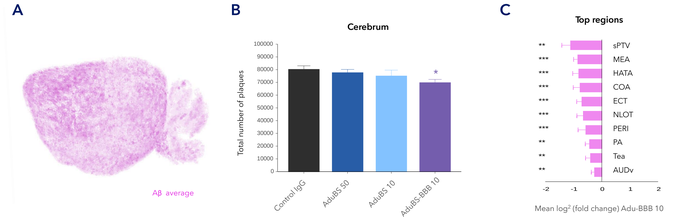


Figure 2. Whole brain analysis of the number of Aβ plaques in the brain after treatment with Aducanumab BS.
(A) 3D sagittal view of group-averaged Aβ signal in AduBS-BBB 10 nmol/kg treated AD mice. **(B)** Total number of plaques in the cerebrum. **(C)** Top-10 regions with most reduced plaque load after AduBS-BBB 10 nmol/kg treatment compared to Control IgG (log2-fold change). *p<0.05, **p<0.01, ***p<0.001 vs. Control IgG (Dunnett's test negative binomial generalized linear model). Abbreviations: sPTV (subparafascicular thalamic nucleus, ventral part); MEA (medial amygdala); HATA (hypothalamic attack area); COA (cortical amygdala); ECT (entorhinal cortex); NLOT (nucleus of the lateral olfactory tract); PERI (perirhinal cortex); PA (posterior amygdala); Tea (anterior temporal area); AUDv (ventral auditory area).

4 Comparison of Aβ plaque-lowering efficacy of AduBS with and without BBB-shuttle

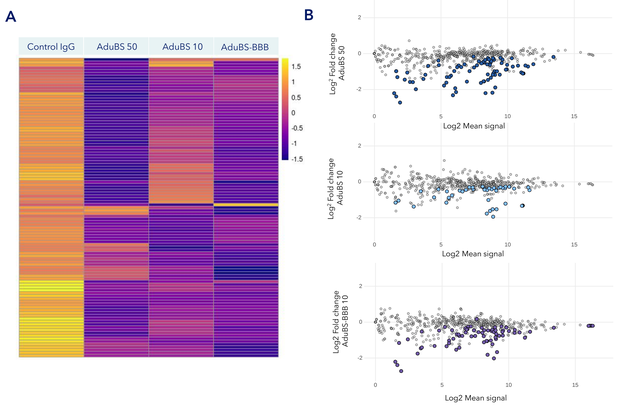


Figure 3. Global comparative analysis of plaque load following AduBS and AduBS-BBB treatment. (A) Heatmap of the 105 regions with significantly reduced plaque number in AduBS or AduBS-BBB treated groups relative to control IgG. **(B)** MA-plots depicting Log2 fold-change in plaque numbers for all regions analyzed as compared to Control IgG group. Colored dots indicate brain regions with significant change (p<0.05, Dunnett's test negative binomial generalized linear model).

5 Plaque lowering efficacy of AduBS and AduBS-BBB in a discrete subset of brain regions

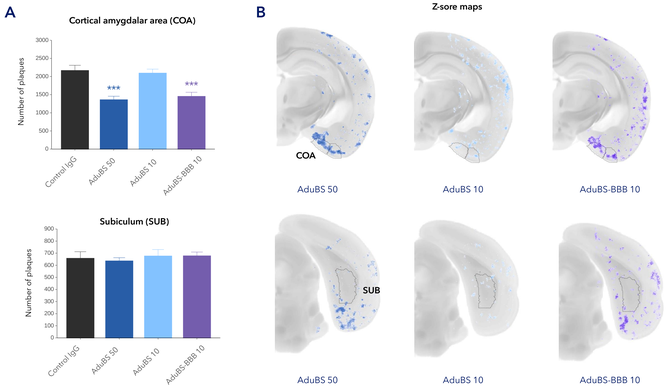


Figure 4. Example of brain regions with and without treatment response. (A) Total number of plaques in cortical amygdalar area (COA) and subiculum (SUB), respectively. **p<0.01, ***p<0.001 vs. Control IgG (Dunnett's test negative binomial generalized linear model). **(B)** Voxel-wise Z-score maps reflecting statistically significant differences in number of plaques between the treatment groups (AduBS 50 and 10, and AduBS-BBB 10) and Control IgG.

Conclusion

- Quantitative whole brain imaging enables the visualization of Aβ plaque distribution and the quantification of treatment effects in models of AD.
- AduBS and AduBS-BBB elicited plaque-lowering effects in a discrete number of brain regions in AD mice.
- Plaque lowering efficacy of AduBS-BBB shuttle was achieved using a five times lower dose compared to AduBS

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