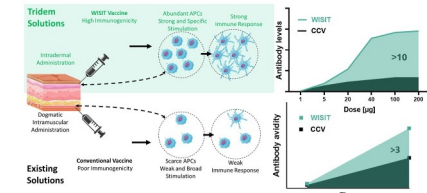


AMYLOID BETA-BASED WISIT VACCINES: SUPERIOR IMMUNOGENICITY AND IN VIVO PROOF OF CONCEPT

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1) BACKGROUND Advances in the development of vaccines for Alzheimer's disease (AD) are progressing, however, most vaccines in development are limited in their immunogenicity and require substantial quantities of adjuvant to achieve efficacy. Tridem has developed the WISIT vaccine platform, that harnesses innate immune cells to develop long-term, functional antibody (Ab) responses, thereby boosting potency and specificity of AD vaccination and inducing exceptional Ab levels with high specificity and avidity towards pathologic forms of Aβ (Aβ).

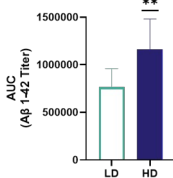
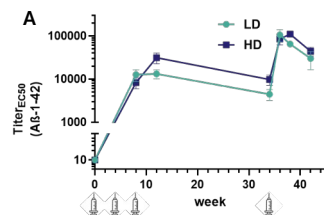


Schematic illustration describing the Mode of Action of WISIT (Win the Skin Immune System Trick) and CCV (conventional vaccine).

METHODS

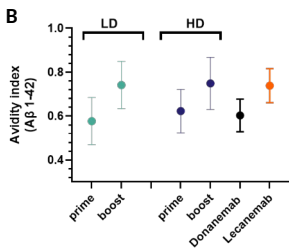
AD WISIT candidates have been tested in mice for their immunological and therapeutic potential. Abs induced by WISIT vaccines were also benchmarked to lecanemab and donanemab for binding characteristics towards different Aβ species.

2) High, dose-dependent and boostable Ab response

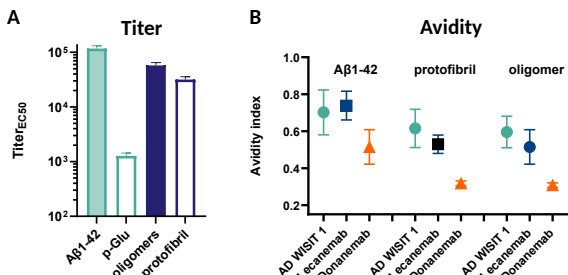


(A) Vaccination of AD WISIT 1 induces high, dose-dependent and boostable Ab responses.

(B) WISIT vaccine induced Ab responses display avidity maturation and similar avidity and specificity towards full length Aβ1-42 as Lecanemab or Donanemab. mean +/-SEM; **p<0,01 LD... low dose; HD... high dose

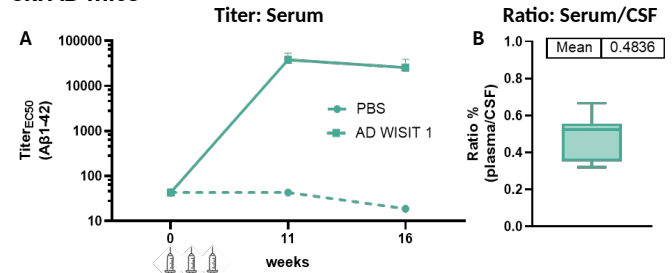


3) AD WISIT 1 - induced Abs recognize highly toxic Aβ species with high specificity and avidity



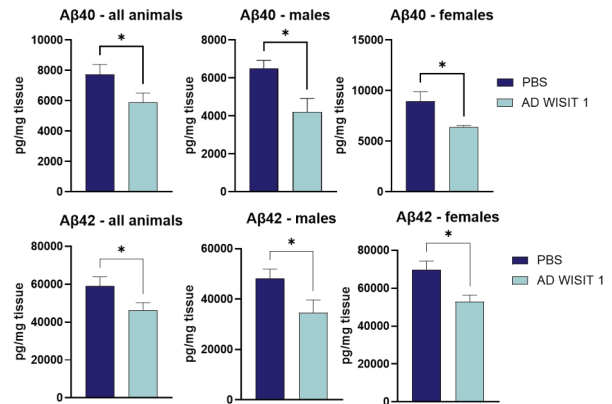
(A) Vaccination of AD WISIT 1 induces a strong anti-Aβ 1-42 Ab response and generation of Abs that bind Aβ oligomers and protofibrils, as well as truncated pyroglutamate modified Aβp(E)3-40/42 (p-Glu). (B) AD WISIT 1 induced Abs display similar avidity and specificity towards full length, oligomeric and proto-fibrillar Aβ as Lecanemab or Donanemab. mean +/-SEM

4) Low Dose AD WISIT 1 induces strong Ab responses in 5xFAD mice



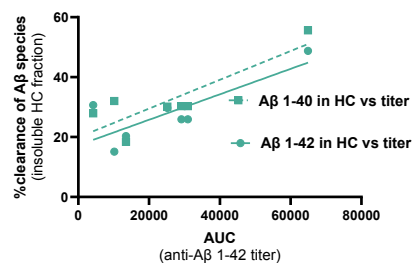
(A) Vaccination of low doses of AD WISIT 1 (5μg peptide per animal) induces strong anti-Aβ 1-42 responses in individual mice (n = 8 male and 8 female) (serum and CSF). (B) Ratio of Ab levels in the cerebrospinal fluid (CSF) compared to plasma levels (%). mean +/-SEM

5) AD WISIT 1 reduces insoluble amyloid in 5xFAD mice



Low dose- AD WISIT 1 (5μg peptide per animal) induced anti-Aβ 1-42 Abs reduce insoluble Aβ in 5xFAD mice. Quantification of Aβ 1-40/1-42 in the hippocampus of male and female 5xFAD mice immunized with AD WISIT 1 compared to brain fractions from animals vaccinated with PBS. mean +/-SEM; *p<0,05.

6) Reduction of insoluble amyloid strongly correlates with AD WISIT 1 induced anti-Aβ 1-42 responses.



Correlation between the clearance of amyloid (Aβ 1-40/1-42) in the HC of male and female 5xFAD mice immunized with AD WISIT 1 (in %) and AD WISIT 1 induced anti-Aβ 1-40/42 Ab levels over time (AUC).

(r = 0.8541; CI (95%), p* = 0.0144, and R^2 = 0.7294) and for reduction of Aβ 1-42 (r = 0.8059; CI (95%), p* = 0.0286 and R^2 = 0.6954. p<0.05.

7) CONCLUSION Our studies provide proof-of-concept for the efficacy of Aβ targeting WISIT AD vaccines and support further preclinical and clinical development.

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