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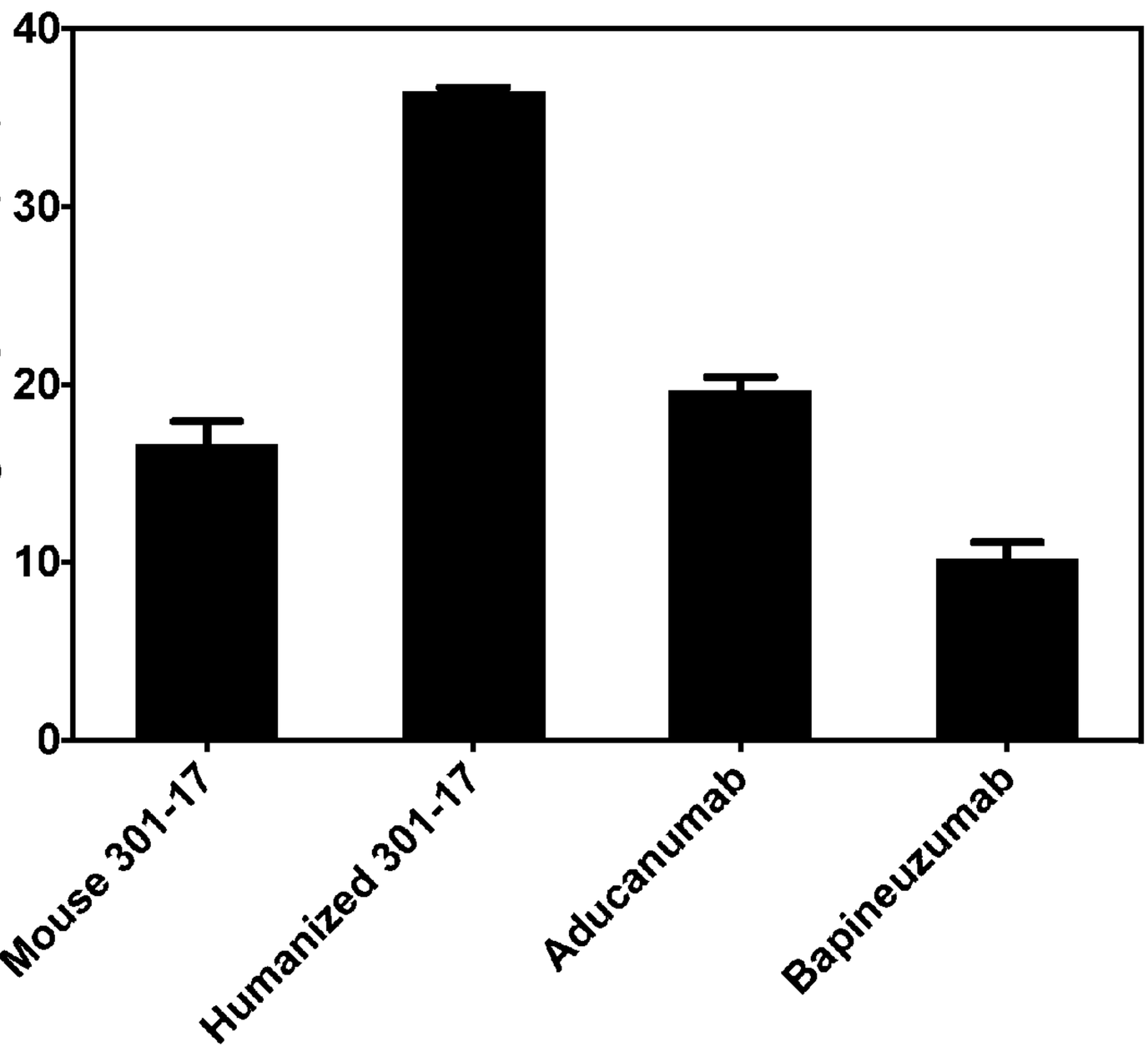
(54) Titre : ANTICORPS ANTI-BETA-AMYLOIDE
(54) Title: ANTIBODIES TO AMYLOID BETA

Fig. 2




(57) Abrégé/Abstract:
The disclosure pertains to antibodies that bind A-beta oligomers and methods of making and using said antibodies. Also provided are chimeric or humanized antibodies, including antibodies having CDRs in Table 2 and/or having a sequence as set forth in Table 4B or a sequence with at least 50% sequence identity thereto optionally wherein the CDR amino acid sequences are as set for forth in SEQ ID Nos: 74-79. Also provided are methods and uses thereof as well as kits comprising said antibodies.

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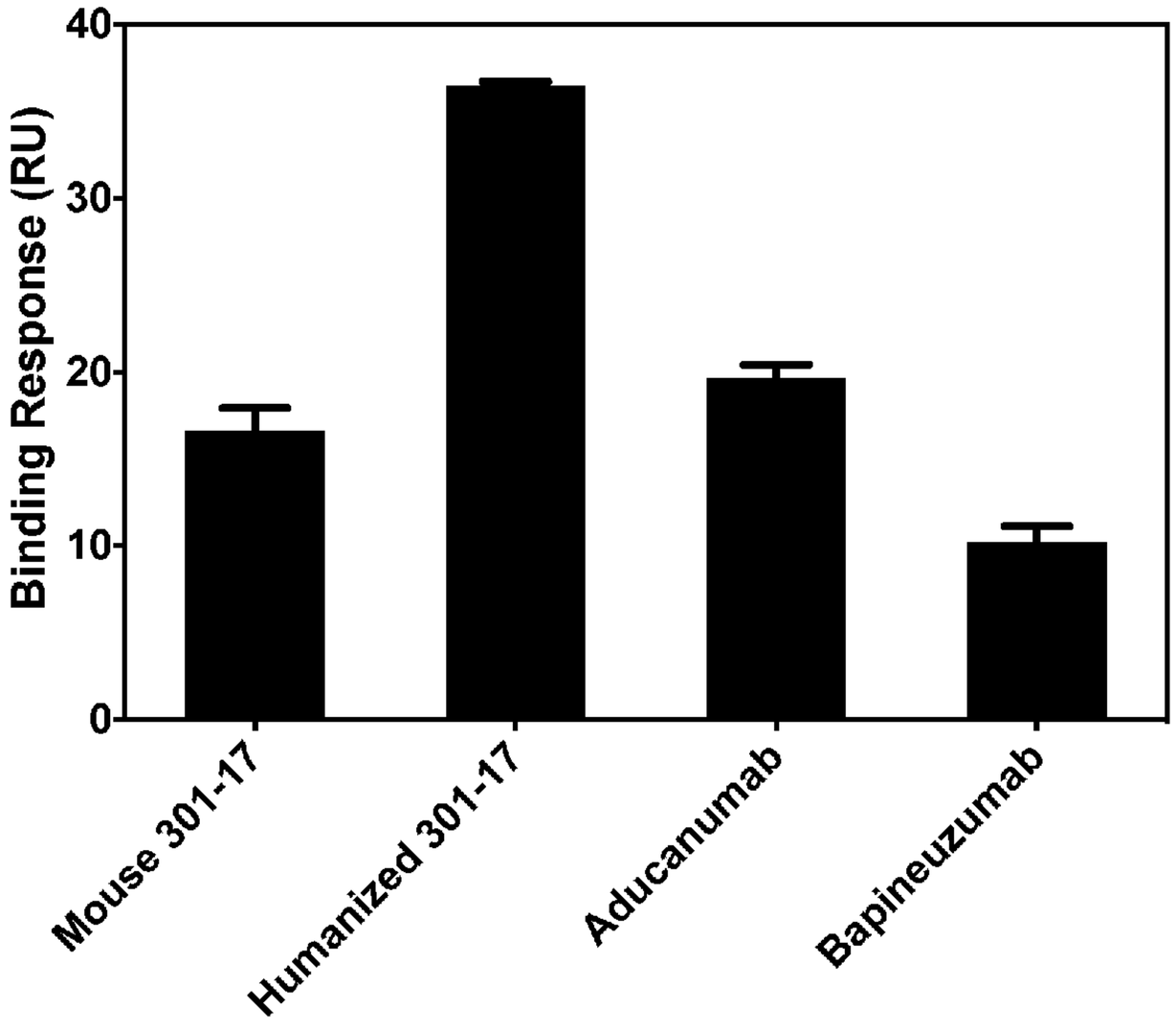
Fig. 2




(57) Abstract: The disclosure pertains to antibodies that bind A-beta oligomers and methods of making and using said antibodies. Also provided are chimeric or humanized antibodies, including antibodies having CDRs in Table 2 and/or having a sequence as set forth in Table 4B or a sequence with at least 50% sequence identity thereto optionally wherein the CDR amino acid sequences are as set for forth in SEQ ID Nos: 74-79. Also provided are methods and uses thereof as well as kits comprising said antibodies.

*[Continued on next page]*

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**Claims:**

1. A chimeric or humanized antibody comprising a sequence as set forth in Table 4B or a sequence with at least 50% sequence identity thereto wherein the CDR amino acid sequences are as set for forth in SEQ ID Nos: 74-79.

2. The chimeric or humanized antibody of claim 1, wherein the chimeric or humanized antibody comprises a heavy chain variable region comprising: i) an amino acid sequence as set forth in any one of SEQ ID NO: 42 44, 46, 48, 50, 52 and 54; ii) an amino acid sequence with at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% sequence identity to any one of SEQ ID NO: 42, 44, 46, 48, 50, 52 and 54, wherein the CDR sequences are the sequences shown underlined therein (also in SEQ ID NO: 74-76), or iii) a conservatively substituted amino acid sequence of i) wherein the CDR sequences are the sequences shown underlined therein (e.g. SEQ ID NO: 74-76).

3. The chimeric or humanized antibody of claim 1 or 2, wherein the antibody comprises a light chain variable region comprising i) an amino acid sequence as set forth any one of SEQ ID NO: 56, 58, 60, 62, 64, 66 and 68, ii) an amino acid sequence with at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% sequence identity to any one of SEQ ID NO: 56 58, 60, 62, 64, 66 and 68, wherein the CDR sequences are the sequences shown underlined therein (also in SEQ ID NOs:77-79), or iii) a conservatively substituted amino acid sequence of i) wherein the CDR sequences are the sequences shown underlined therein (also in SEQ ID NOs:77-79).

4. The chimeric or humanized antibody of any one of claims 1 to 3, wherein the heavy chain variable region amino acid sequence is encoded by a nucleotide sequence as set forth in any one of SEQ ID NO: 41, 43, 45, 47, 49, 51 and 53; or a codon degenerate or optimized version thereof; and/or the antibody comprises a light chain variable region amino acid sequence encoded by a nucleotide sequence as set out in any one of SEQ ID NO: 55, 57, 59, 61, 63, 65 and 67 or a codon degenerate or optimized version thereof.

5. The chimeric or humanized antibody of any one of claims 1 to 4, wherein the antibody comprises SEQ ID NO: 42 and 56; SEQ ID NO: 44 and 58; SEQ ID NO: 46 and 60; SEQ ID NO: 48 and 62; SEQ ID NO: 50 and 64; SEQ ID NO: 52 and 66; or SEQ ID NO: 54 and 68, or sequences with sequence with at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% sequence identity thereto wherein the CDRs are maintained as shown underlined therein (also in in SEQ ID Nos:74-79).

6 The chimeric or humanized antibody of claim 5, wherein the humanized antibody has a heavy chain variable sequence and a light chain variable sequence as shown in Table 4B.

7. The chimeric or humanized antibody of any one of claism 1 to 6, wherein the antibody has a KD of at least or about 1x $10^{-10}$, at least or about 8 x$10^{-11}$, at least or about 6x $10^{-11}$, at least or about 4 x $10^{-11}$ or at least or about 2 x $10^{-11}$ for a cyclic peptide with sequence of SEQ ID NO: 12.

8. The humanized antibody of any one of claims 1 to 6, wherein the antibody comprises the sequences of VH2 Vk5.

9. The antibody of any one of claims 1 to 8, wherein the antibody is an antibody binding fragment selected from Fab, Fab', F(ab')2, scFv, dsFv, ds-scFv, dimers, nanobodies, minibodies, diabodies, and multimers thereof.

10. The chimeric or humanized antibody claim 9, wherein the antibody binding fragment is a Fab fragment, optionally comprising any of the variable regions in Table 4B.

11. The humanized antibody of claim 10, wherein the Fab fragment comprises VH2 Vk5.

12. The chimeric or humanized antibody of any one of claims 1 to 11, comprising the CH1 and/or CL sequence or a part thereof of lgG4, preferably wherein the I CH1 and/or CL sequence comprises SEQ ID NO: 70 or 72 or a part thereof, or a conservative variant thereof or a sequence with at least 50%, 60%, 70%, 89%, 90% or 95% sequence identity to SEQ ID NO: 70 and/or 72.

13 The chimeric or humanized antibody of any one of claims 1 to 8, wherein the antibody comprises SEQ ID NO: 70 and/or 72, and/or CH1 and CH2 of SEQ ID NO: 70 or a conservative variant of any of the foregoing or a sequence with at least 50%, 60%, 70%, 89%, 90% or 95% sequence identity to any of the foregoing.

14. The chimeric or humanized antibody of any one of claims 1 to 13 for inhibiting A-beta oligomer propagation in a subject.

15. The humanized antibody of any one of claims 1 to 13 for treating AD and/or other A-beta amyloid related diseases.

16. The antibody of any one of claims 1 to 15, wherein the antibody is a single chain antibody.

17. An immunoconjugate comprising the antibody of any one of claims 1 to 16 and a detectable label or cytotoxic agent.

18. The immunoconjugate of claim 17, wherein the detectable label comprises a positron emitting radionuclide, optionally for use in subject imaging such as PET imaging.

19. A composition comprising the antibody of any one of claims 1 to 16, or the immunoconjugate of claim 17 or 18, optionally with a diluent.

20. A nucleic acid molecule encoding the antibody of any one of claims 1 to 16.

21. A vector comprising the nucleic acid of claim 20.

22. A cell expressing an antibody of any one of claims 1 to 16, optionally wherein the cell is a hybridoma comprising the vector of claim 21.

23. A kit comprising the antibody of any one of claims 1 to 16 , the nucleic acid molecule of claim 20, the vector of claim 21 or the cell of claim 22.

24. A method of making an antibody of claim 1 t comprising administering a cyclopeptide having an A-beta sequence of SEQ ID NO: 12 or a composition comprising said cyclopeptide to a subject, such as a non-human mammal, and isolating antibody and/or cells expressing antibody which has CDRs or competes with an antibody comprising or consisting of the CDRs selected from SEQ ID Nos in Table 2 and producing the chimeric antibody or humanized antibody optionally in a human IgG4 framework.

25 A method of determining if a biological sample comprises A-beta, the method comprising:

a. contacting the biological sample with an antibody of any one of claims 1 to 16 or the immunoconjugate of claim 17 or 18; and

b. detecting the presence of any antibody complex.

26. The method of claim 25 for determining if the biological sample contains A-beta oligomer the method comprising:

a. contacting the sample with the antibody of any one of claims 1 to 16 or the immunoconjugate of claim 17 or 18 that is specific and/or selective for A-beta oligomers under conditions permissive for forming an antibody: A-beta oligomer complex; and

b. detecting the presence of any complex;

wherein the presence of detectable complex is indicative that the sample may contain A-beta oligomer.

27. The method of claim 26, wherein the amount of complex is measured.

28. The method of any one of claims 25 to 27, wherein the sample comprises brain tissue or an extract thereof, whole blood, plasma, serum and/or CSF.

29. The method of any one of claims 25 to 28, wherein the sample is compared to a control, optionally a previous sample.

30. A method of measuring a level of A-beta in a subject, the method comprising administering to a subject at risk or suspected of having or having AD, an immunoconjugate comprising an antibody of

claims 17 or 18 wherein the antibody is conjugated to a detectable label; and detecting the label, optionally quantitatively detecting the label.

31. The method of claim 30, wherein the label is a positron emitting radionuclide.

32. A method of inhibiting A-beta oligomer propagation, the method comprising contacting a cell or tissue expressing A-beta with or administering to a subject in need thereof an effective amount of an A-beta oligomer specific or selective antibody or immunoconjugate of any one of claims 1 to 18, to inhibit A-beta aggregation and/or oligomer propagation.

33. A method of treating AD and/or other A-beta amyloid related diseases, the method comprising administering to a subject in need thereof i) an effective amount of an antibody or immunoconjugate of any one of claims 1-18, or a pharmaceutical composition comprising said antibody; or 2) a nucleic acid or vector comprising a nucleic acid encoding said antibody, to a subject in need thereof.

34. The method of claim 33, wherein a biological sample from the subject to be treated is assessed for the presence or levels of A-beta using an antibody described herein.

35. The method of claim any one of claims 32 to 34, wherein the antibody, immunoconjugate, composition or nucleic acid or vector is administered directly to the brain or other portion of the CNS.

36. The method of any one of claims 32 to 35, wherein the composition is a pharmaceutical composition comprising the antibody or immunoconjugate in admixture with a pharmaceutically acceptable, diluent or carrier.