

Claims

1. An isolated monoclonal antibody, comprising three heavy chain CDRs of SEQ ID NO:7 and three light chain CDRs of SEQ ID NO:11.
2. The antibody of claim 1, wherein the three heavy chain CDRs are as defined by Kabat/Chothia Composite (SEQ ID NOs: 8, 9, and 10) and the three light chain CDRs are as defined by Kabat/Chothia Composite (SEQ ID NOs: 12, 13, and 14).
3. The antibody of claim 1 that is chimeric, veneered, or humanized.
4. An isolated monoclonal antibody, wherein the three heavy chain CDRs are as defined by Kabat/Chothia Composite (SEQ ID NOs: 8, 9, and 10) and the three light chain CDRs are as defined by Kabat/Chothia Composite (SEQ ID NOs: 12, 13, and 14); provided that position H31 is occupied by S or G, position H60 is occupied by N or A and position H64 is occupied by K or Q.
5. The antibody of claim 4, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 49.
6. The antibody of claim 1, wherein the antibody is a humanized antibody.
7. The humanized antibody of claim 1, wherein the CDRs are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact.
8. The humanized antibody of claim 7 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of SEQ ID NO:39, SEQ ID NO:9, and SEQ ID NO:10 and the humanized mature light chain variable region comprises the three Kabat light chain CDRs of SEQ ID NOs: 12-14.
9. The humanized antibody of claim 7, comprising a humanized mature heavy chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NO:15-17, 19, and 21-27 and a humanized mature light chain variable region having an amino acid sequence at least 90% identical to any one of SEQ ID NO: 28-30.

10. The humanized antibody of claim 9, wherein at least one of the following positions is occupied by the amino acid as specified: H1 is occupied by E, H5 is occupied by Q, H7 is occupied by P, H9 is occupied by S, H10 is occupied by V, H11 is occupied L, H12 is occupied by V, H13 is occupied by R, H20 is occupied by L, H40 is occupied by R, H48 is occupied by I, H66 is occupied by K, H67 is occupied by A, H69 is occupied by L, H71 is occupied by V, H73 is occupied by I, H75 is occupied by S, H80 is occupied by V, H82a is occupied by T, H82b is occupied by S, H83 is occupied by T, and H85 is occupied by E.

11. The humanized antibody of claim 10, provided positions H1, H5, H7, H9, H10, H11, H12, H13, H20, H40, H48, H66, H67, H69, H71, H73, H75, H80, H82a, H82b, H83, and H85 in the VH region are occupied by, E, Q, P, S, V, L, V, R, L, R, I, K, A, L, V, I, S, V, T, S, T, and E, respectively.

12. The humanized antibody of claim 10, provided positions H1, H5, H7, H9, H10, H11, H12, H13, H20, H48, H69, H71, H82a, H82b, H83, and H85 in the VH region are occupied by E, Q, P, S, V, L, V, R, L, I, L, V, T, S, T, and E, respectively.

13. The humanized antibody of claim 10, provided positions H1, H5, H11, H12, H20, H48, H69, H71, H82a, H82b, H83, and H85 in the VH region are occupied by E, Q, L, V, L, I, L, V, T, S, T, and E, respectively.

14. The humanized antibody of claim 10, provided positions H1, H12, H40, H48, H60, H69, H73, and H83 in the VH region are occupied by are occupied by E, V, R, I, A, L, I, and T, respectively.

15. The humanized antibody of claim 10, provided positions H1, H12, H40, H48, H69, H73, and H83 in the VH region are occupied by are occupied by E, V, R, I, L, I, and T, respectively.

16. The humanized antibody of claim 10, provided positions H1, H12, H40, H48, H66, H67, H69, H71, H73, and H83 in the VH region are occupied by are occupied by E, V, R, I, K, A, L, V, I, and T, respectively.

17. The humanized antibody of claim 10, provided positions H1, H12, H40, H48, H69, H73, and H83 in the VH region are occupied by E, V, R, I, L, I, and T, respectively.

18. The humanized antibody of claim 10, provided positions H7, H71, and H73 in the VH region are occupied by P, V, and I, respectively.

19. The humanized antibody of claim 10, provided position H60 in the VH region is occupied by A.

20. The humanized antibody of claim 9 wherein at least one of the following positions is occupied by the amino acid as specified: H1 is occupied by Q or E, H5 is occupied by V or Q, H7 is occupied by S or P, H9 is occupied by A or S, H10 is occupied by E or V, H11 is occupied V or L, H12 is occupied by K or V, H13 is occupied by K or R, H20 is occupied by V or L, H37 is occupied by V or A, H 38 is occupied by R or K, H40 is occupied by A or R, H48 is occupied by M or I, H60 is occupied by A or N, H64 is occupied by Q or K, H66 is occupied by R or K, H67 is occupied by V or A, H69 is occupied by M or L, H71 is occupied by R or V, H73 is occupied by T or I, H75 is occupied by I, S, or A, H80 is occupied by M or V, H82a is occupied by S or T, H82b is occupied by R or S, H83 is occupied by R or T, and H85 is occupied by D or E.

21. The humanized antibody of claim 20, provided positions H1, H5, H7, H9, H10, H11, H12, H13, H20, H37, H38, H40, H48, H66, H67, H69, H71, H73, H75, H80, H82a, H82b, H83, and H85 in the VH region are occupied by E, Q, P, S, V, L, V, R, L, A, K, R, I, K, A, L, V, I, S, V, T, S, T, and E, respectively.

22. The humanized antibody of claim 20, provided positions H1, H5, H11, H12, H20, H48, H69, H71, H75, H82a, H82b, H83, and H85 in the VH region are occupied by E, Q, L, V, L, I, L, V, A, T, S, T, and E, respectively.

23. The humanized antibody of claim 20, provided positions H1, H12, H40, H48, H66, H67, H69, H71, H73, and H83 in the VH region are occupied by E, V, R, I, K, A, L, V, I, and T, respectively.

24. The humanized antibody of claim 20, provided positions H1, H12, H40, H48, H60, H66, H67, H69, H71, H73, and H83 in the VH region are occupied by E, V, R, I, A, K, A, L, V, I, and T, respectively.

25. The humanized antibody of claim 20, provided positions H1, H12, H40, H48, H69, H73, and H83 in the VH region are occupied by E, V, R, I, L, I, and T, respectively.

26. The humanized antibody of claim 20, provided positions H1, H12, H40, H48, H60, H66, H67, H69, H71, H73, and H83 in the VH region are occupied by Q, V, R, I, A, K, A, L, V, I, and T, respectively.

27. The humanized antibody of claim 20, provided positions H1, H7, H71, and H73 in the VH region are occupied by Q, P, V and I, respectively.

28. The humanized antibody of claim 20, provided positions H1, H12, H40, H48, H60, H64, H69, H73, and H83 in the VH region are occupied by, E, V, R, I, A, Q, L, I, and T, respectively.

29. The humanized antibody of claim 20, provided positions H1, H5, H7, H9, H10, H11, H12, H13, H20, H48, H69, H71, H75, H82a, H82b, H83, and H85 in the VH region are occupied by E, Q, P, S, V, L, V, R, L, I, L, V, A, T, S, T, and E.

30. The humanized antibody of claim 20, provided positions H1, H5, H11, H12, H20, H48, H66, H67, H69, H71, H73, H75, H82a, H82b, H83, and H85 in the VH region are occupied by , E, Q, L, V, L, I, K, A, L, V, I, S, T, S, T, and E.

31. The humanized antibody of claim 20, provided positions H1, H5, H7, H9, H10, H11, H12, H13, H20, H38, H40, H48, H66, H67, H69, H71, H73I, H75, H80, H82a, H82b, H83, and H85 in the VH region are occupied by E, Q, P, S, V, L, V, R, L, K, R, I, K, A, L, V, I, S, V, T, S, T, and E, respectively.

32. The humanized antibody of claim 20, provided positions H1, H5, H7, H9, H10, H11, H12, H13, H20, H40, H48, H66, H67, H69, H71, H73, H75, H80, H82a, H82b, H83, and H85 in the VH region are occupied by Q, P, S, V, L, V, R, L, R, I, K, A, L, V, I, S, V, T, S, T, and E, respectively.

33. The humanized antibody of claim 20, provided positions H7, H71, and H73 in the VH region are occupied by P, V, and I, respectively.
34. The humanized antibody of claim 20, provided position H71 in the VH region is occupied by V.
35. The humanized antibody of claim 20, provided positions H1, H7, H71, and H73 in the VH region are occupied by E, P, V, and I.
36. The humanized antibody of claim 9, provided positions L4, L9, L15, L22, and L43 in the VL region are occupied by L, S, V, S, and S, respectively.
37. The humanized antibody of claim 9, wherein at least one of the following positions is occupied by the amino acid as specified: L4 is occupied by L, L9 is occupied by S, L15 is occupied by V, L18 is occupied by K, L19 is occupied by V, L21 is occupied by M, L22 is occupied by S, and L43 is occupied by S.
38. The humanized antibody of claim 37, provided positions L4, L9, L15, L18, L19, L21, L22, and L43 in the VL region are occupied by L, S, V, K, V, M, S, and S, respectively.
39. The humanized antibody of claim 9, comprising a mature heavy chain variable region having an amino acid sequence at least 98% identical to any one of SEQ ID NO: 15-17, 19, and 21-27 and a mature light chain variable region having an amino acid sequence at least 98% identical to any one of SEQ ID NO: 28-30.
40. The humanized antibody of claim 39 wherein the mature heavy chain variable region has an amino acid sequence of any of SEQ ID NO: 15-17, 19, and 21-27 and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NO:28-30.
41. The humanized antibody of claim 40, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:27 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:29.
42. The antibody of claim 1 that is an intact antibody.

43. The antibody of claim 1 that is a binding fragment.
44. The antibody of claim 43, wherein the binding fragment is a single-chain antibody, Fab, or Fab'2 fragment.
45. The antibody of claim 1, wherein the isotype is human IgG1.
46. The humanized antibody of claim 7, wherein the mature light chain variable region is fused to a light chain constant region and the mature heavy chain variable region is fused to a heavy chain constant region.
47. The antibody of claim 46 having at least one mutation in the constant region.
48. The antibody of claim 47, wherein the mutation reduces complement fixation or activation by the constant region or binding to an Fcγ receptor relative to the natural human heavy chain constant region .
49. The antibody of claim 48 having a mutation at one or more of positions 241, 264, 265, 270, 296, 297, 318, 320, 322, 329 and 331 by EU numbering or having an alanine at positions 318, 320 and 322.
50. The antibody of claim 1, wherein the isotype is of human IgG2 or IgG4 isotype.
51. The antibody of claim 1, wherein the antibody is conjugated to a therapeutic, cytotoxic, cytostatic, neurotrophic, or neuroprotective agent.
52. A pharmaceutical composition comprising the antibody of claim 1 and a pharmaceutically-acceptable carrier.
53. A nucleic acid encoding the heavy chain and/or light chain of the antibody of claim 1, or a recombinant expression vector comprising the nucleic acid or a host cell transformed with the expression vector.
54. A method of humanizing a mouse antibody, the method comprising:

(a) selecting one or more acceptor antibodies;

(b) identifying the amino acid residues of the mouse antibody to be retained;

(c) synthesizing a nucleic acid encoding a humanized heavy chain comprising CDRs of the mouse antibody heavy chain and a nucleic acid encoding a humanized light chain comprising CDRs of the mouse antibody light chain; and

(d) expressing the nucleic acids in a host cell to produce a humanized antibody;

wherein the mouse antibody is characterized by a mature heavy chain variable region of SEQ ID NO: 7 and a mature light chain variable region of SEQ ID NO:11.

55. A method of producing the humanized, chimeric, or veneered antibody of claim 3, the method comprising:

(a) culturing cells transformed with nucleic acids encoding the heavy and light chains of the antibody, so that the cells secrete the antibody; and

(b) purifying the antibody from cell culture media.

56. A method of producing a cell line producing the humanized, chimeric, or veneered antibody of claim 3, the method comprising:

(a) introducing a vector encoding heavy and light chains of the antibody and a selectable marker into cells;

(b) propagating the cells under conditions to select for cells having increased copy number of the vector;

(c) isolating single cells from the selected cells; and

(d) banking cells cloned from a single cell selected based on yield of antibody.

57. The antibody of claim 1 for use in inhibiting or reducing aggregation of tau in a subject having or at risk of developing a tau-mediated amyloidosis.

58. The antibody of claim 1 for use in treating or effecting prophylaxis of a tau-related disease in a subject.

59. The antibody of claim 1 for use in reducing aberrant transmission of tau, inducing phagocytosis of tau, inhibiting tau aggregation or deposition, or inhibiting formation of tau tangles.

60. The antibody of claim 1 for use in detecting tau protein deposits in a subject having or at risk of a disease associated with tau aggregation or deposition.

61. A method of measuring efficacy of treatment in a subject being treated for a disease associated with tau aggregation or deposition, comprising

(a) measuring a first level of tau protein deposits in a first sample obtained from the subject prior to treatment by the antibody of claim 1, and detecting a first amount of the antibody bound to tau in the subject,

(b) measuring a second level of tau protein deposits in a second sample obtained from the subject after treatment by the antibody, and detecting the antibody bound to tau in the subject,

wherein a decrease between the first level and the second level of tau protein deposits is detected indicating a positive response to treatment.

62. A method of measuring efficacy of treatment in a subject being treated for a disease associated with tau aggregation or deposition, comprising

(a) measuring a first level of tau protein deposits in a first sample obtained from the subject prior to treatment by the antibody of claim 1, and detecting a first amount of antibody bound to tau in the subject,

(b) measuring a second level of tau protein deposits in a second sample obtained from the subject after treatment by the antibody, and detecting a second amount of antibody bound to tau in the subject,

wherein no change between the first and second level of tau protein deposits is detected indicating a positive response to treatment.

63. The antibody of claim 4, wherein CDR-H2 has an amino acid sequence comprising SEQ ID NO: 50.

64. The antibody of claim 4, wherein CDR-H2 has an amino acid sequence comprising SEQ ID NO: 51.

65. The antibody of claim 4, having a mature heavy chain variable region comprising an amino sequence SEQ ID NO: 18 or SEQ ID NO: 20.