

Claims

1. An isolated monoclonal antibody or a binding fragment thereof that binds to human tau, ~~comprising wherein the three Kabat/Chothia Composite~~ heavy chain CDRs as defined by Kabat/Chothia Composite are SEQ ID NOs: 8, 9, and 10, and the three light chain CDRs as defined by Kabat/Chothia Composite are SEQ ID NOs: 12, 13, and 14,~~CDR-H1 of SEQ ID NO:8, CDR-H2 of SEQ ID NO:9, and CDR-H3 of amino acid sequence LDF, and three Kabat/Chothia Composite light chain CDRs, CDR-L1 of SEQ ID NO:12, CDR-L2 of SEQ ID NO:13, and CDR-L3 of SEQ ID NO:14, except that position H27 is occupied by F or Y, H28 is occupied by N or T, H29 is occupied by I or F, H30 is occupied by K or T, position H51 is occupied by I or V, position H54 is occupied by N or D, position H60 is occupied by D or A, H61 is occupied by P or E, and H102 is occupied by F or Y.~~

~~2. The antibody of claim 1, comprising three Kabat/Chothia Composite heavy chain CDRs, CDR-H1 of SEQ ID NO:8, CDR-H2 of SEQ ID NO:9, and CDR-H3 of amino acid sequence LDF, and three Kabat/Chothia Composite light chain CDRs, CDR-L1 of SEQ ID NO:12, CDR-L2 of SEQ ID NO:13, and CDR-L3 of SEQ ID NO:14.~~

~~2.3.~~ The antibody or binding fragment of claim 1 comprising a mature heavy chain variable region comprising ~~of~~ SEQ ID NO: 7 and a mature light chain variable region comprising ~~of~~ SEQ ID NO:11,~~or a chimeric, veneered, or humanized form thereof.~~

3. The antibody or binding fragment of claim 1 that is a chimeric, veneered, or humanized antibody.

~~4. The antibody of claim 1, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 42, 58, 59 or 60.~~

~~5. The antibody of claim 1, wherein CDR-H2 has an amino acid sequence comprising SEQ ID NO: 43, 61, 62, 63 or 64.~~

~~6. The antibody of claim 1, wherein CDR-H3 has amino acid sequence LDY.~~

~~4.7.~~ The antibody or binding fragment of claim 1, wherein the antibody is a humanized antibody.

~~8. The humanized antibody of claim 7, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 42 and CDR-H2 has an amino acid sequence comprising SEQ ID NO: 43.~~

~~9. The humanized antibody of claim 7, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 42 and CDR-H2 has an amino acid sequence comprising SEQ ID NO:61.~~

~~10. The humanized antibody of claim 7, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 42 and CDR-H2 has an amino acid sequence comprising SEQ ID NO:64.~~

~~11. The humanized antibody of claim 7, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 42, CDR-H2 has an amino acid sequence comprising SEQ ID NO:63, and CDR-H3 has amino acid sequence LDY.~~

~~12. The humanized antibody of claim 7, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 58 and CDR-H2 has an amino acid sequence comprising SEQ ID NO:62.~~

~~13. The humanized antibody of claim 7, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 59 and CDR-H2 has an amino acid sequence comprising SEQ ID NO:63.~~

~~14. The humanized antibody of claim 7, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO: 60 and CDR-H2 has an amino acid sequence comprising SEQ ID NO:62.~~

~~15. The antibody of claim 3, that is humanized or chimeric.~~

~~16. The humanized antibody of claim 15 comprising a humanized mature heavy chain variable region comprising CDR-H1 of SEQ ID NO:8, CDR-H2 of SEQ ID NO:9, and CDR-H3 of amino acid sequence LDF, and a humanized mature light chain variable region comprising CDR-L1 of SEQ ID NO:12, CDR-L2 of SEQ ID NO:13, and CDR-L3 of SEQ ID NO:14.~~

~~17. A humanized antibody that binds human tau comprising a mature heavy chain variable region comprising three heavy chain CDRs of SEQ ID NO:7 and a mature light chain variable region comprising three light chain CDRs of SEQ ID NO:11, wherein the CDRs are of a definition selected from the group consisting of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact.~~

~~18. The humanized antibody of claim 17 wherein the humanized mature heavy chain variable region comprises the three Kabat/Chothia Composite heavy chain CDRs, CDR-H1 of SEQ ID NO:8, CDR-H2 of SEQ ID NO:9, and CDR-H3 of amino acid sequence LDF, and the humanized mature light chain variable region comprises the three Kabat/Chothia Composite light chain CDRs, CDR-L1 of SEQ ID NO:12, CDR-L2 of SEQ ID NO:13, and CDR-L3 of SEQ ID NO:14.~~

~~19. The humanized antibody of claim 17 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs, CDR-H1 of SEQ ID NO:32, CDR-H2 of SEQ ID NO:9, and CDR-H3 of amino acid sequence LDF, and the humanized mature light chain variable region comprises the three Kabat light chain CDRs, CDR-L1 of SEQ ID NO:12, CDR-L2 of SEQ ID NO:13, and CDR-L3 of SEQ ID NO:14.~~

~~20. The humanized antibody of claim 17 wherein the humanized mature heavy chain variable region comprises the three Chothia heavy chain CDRs, CDR-H1 of SEQ ID NO:33, CDR-H2 of SEQ ID NO:34, and CDR-H3 of amino acid sequence LDF, and the humanized~~

mature light chain variable region comprises the three Chothia light chain CDRs, CDR L1 of SEQ ID NO:12, CDR L2 of SEQ ID NO:13, and CDR L3 of SEQ ID NO:14.

21. The humanized antibody of claim 17 wherein the humanized mature heavy chain variable region comprises the three AbM heavy chain CDRs, CDR H1 of SEQ ID NO:8, CDR H2 of SEQ ID NO:35, and CDR H3 of amino acid sequence LDF, and the humanized mature light chain variable region comprises the three AbM light chain CDRs, CDR L1 of SEQ ID NO:12, CDR L2 of SEQ ID NO:13, and CDR L3 of SEQ ID NO:14.

22. The humanized antibody of claim 17 wherein the humanized mature heavy chain variable region comprises the three Contact heavy chain CDRs, CDR H1 of SEQ ID NO:39, CDR H2 of SEQ ID NO:40, and CDR H3 of SEQ ID NO:41, and the humanized mature light chain variable region comprises the three Contact light chain CDRs, CDR L1 of SEQ ID NO:36, CDR L2 of SEQ ID NO:37, and CDR L3 of SEQ ID NO:38.

5.23. The humanized antibody of claim 415, comprising a humanized mature heavy chain variable region comprising ~~having~~ an amino acid sequence at least 90% identical to SEQ ID NO: 18~~any one of SEQ ID NOs:15-19 and SEQ ID NOs:46-57~~ and a humanized mature light chain variable region comprising ~~having~~ an amino acid sequence at least 90% identical to SEQ ID NO: 21~~any one of SEQ ID NOs: 20-23, except that position H17 can be T or S, and position H20 can be I or V.~~

24. The humanized antibody of claim 23, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H38 is occupied by R and H93 is occupied by S.

25. The humanized antibody of claim 23, provided positions H38 and H93 in the VH region are occupied by R and S, respectively.

26. The humanized antibody of claim 23 wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H38 is occupied by R, H43 is occupied by Q, H83 is occupied by T, and H93 is occupied by S.

~~27. The humanized antibody of claim 26, provided positions H38, H43, H83, and H93 in the VH region are occupied by R, Q, T, and S, respectively.~~

~~28. The humanized antibody of claim 26, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H12 is occupied by V, H24 is occupied by A, H48 is occupied by I, H67 is occupied by A, H80 is occupied by L, H81 is occupied by Q, and H91 is occupied by F.~~

~~29. The humanized antibody of claim 28, provided positions H12, H24, H48, H67, H80, H81, and H91 in the VH region are occupied by V, A, I, A, L, Q, and F, respectively.~~

~~30. The humanized antibody of claim 28, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H13 is occupied by R and H66 is occupied by K.~~

~~31. The humanized antibody of claim 30, provided positions H13 and H66 in the VH region are occupied by R and K, respectively.~~

~~32. The humanized antibody of claim 28, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H40 is occupied by R and H82a is occupied by G.~~

~~33. The humanized antibody of claim 32, provided positions H40 and H82a in the VH region are occupied by R and G, respectively.~~

~~34. The humanized antibody of claim 26, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H42 is occupied by E and H76 is occupied by N.~~

~~35. The humanized antibody of claim 34, provided positions H42 and H76 in the VH region are occupied by E and N, respectively.~~

~~36. The humanized antibody of claim 24, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H40 is occupied by R, H82a is occupied by G, and H83 is occupied by T.~~

~~37. The humanized antibody of claim 36, provided positions H40, H82a, and H83 in the VH region are occupied by R, G, and T, respectively.~~

~~38. The humanized antibody of claim 36, wherein H12 in the VH region is occupied by V.~~

~~39. The humanized antibody of claim 38, wherein H80 in the VH region is occupied by L.~~

~~40. The humanized antibody of claim 39, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H24 is occupied by A, H48 is occupied by I, H67 is occupied by A, H80 is occupied by L, and H91 is occupied by F.~~

~~41. The humanized antibody of claim 40, provided positions H24, H48, H67, H80, and H91 in the VH region are occupied by A, I, A, L, and F, respectively.~~

~~42. The humanized antibody of claim 39, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H43 is occupied by Q, and H81 is occupied by Q.~~

~~43. The humanized antibody of claim 42, provided positions H43 and H81 in the VH region are occupied by Q, and Q, respectively.~~

~~44. The humanized antibody of claim 36, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H24 is occupied by A, and H91 is occupied by F.~~

~~45. The humanized antibody of claim 44, provided positions H24 and H91 in the VH region are occupied by A and F, respectively.~~

~~46. The humanized antibody of claim 44, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H13 is occupied by R, H17 is occupied by L, H29 is occupied by F, H42 is occupied by E, H43 is occupied by Q, H61 is occupied by E, H76 is occupied by N, H80 is occupied by L, H81 is occupied by Q.~~

~~47. The humanized antibody of claim 46, provided positions H13, H17, H29, H42, H43, H61, H76, H80, and H81 in the VH region are occupied by R, L, F, E, Q, E, N, L, and Q, respectively.~~

~~48. The humanized antibody of claim 38, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H24 is occupied by A, H28 is occupied by T, H48 is occupied by I, H54 is occupied by D, H60 is occupied by A, H67 is occupied by A, H80 is occupied by L, and H91 is occupied by F.~~

~~49. The humanized antibody of claim 48, provided positions H24, H28, H48, H54, H60, H67, H80, and H91 in the VH region are occupied by A, T, I, D, A, A, L, and F, respectively.~~

~~50. The humanized antibody of claim 38, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H10 is occupied by D, H17 is occupied by L, H24 is occupied by A, H28 is occupied by T, H43 is occupied by Q, H48 is occupied by I, H60 is occupied by A, H61 is occupied by E, H91 is occupied by F, H108 is occupied by T, and H109 is occupied by L.~~

~~51. The humanized antibody of claim 50, provided positions H10, H17, H24, H28, H43, H48, H60, H61, H91, H108, and H109 in the VH region are occupied by D, L, A, T, Q, I, A, E, F, T, and L, respectively.~~

~~52. The humanized antibody of claim 39, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H17 is occupied by L, H27 is occupied by Y, H29 is occupied by F, and H61 is occupied by E.~~

~~53. The humanized antibody of claim 52, provided positions H17, H27, H29, and H61 in the VH region are occupied by L, Y, F, and E, respectively.~~

~~54. The humanized antibody of claim 24, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H17 is occupied by L, H27 is occupied by Y, H29 is occupied by F, H61 is occupied by E, H76 is occupied by N, and H82a is occupied by G.~~

~~55. The humanized antibody of claim 54, provided positions H17, H27, H29, H61, H76, and H82a in the VH region are occupied by L, Y, F, E, N, and G, respectively.~~

~~56. The humanized antibody of claim 24, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H12 is occupied by V, H17 is occupied by L, H24 is occupied by A, H43 is occupied by Q, H48 is occupied by I, H83 is occupied by T, and H91 is occupied by F.~~

~~57. The humanized antibody of claim 56, provided positions H12, H17, H24, H43, H48, H83, and H91 in the VH region are occupied by V, L, A, Q, I, T, F, respectively.~~

~~58. The humanized antibody of claim 24, wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H12 is occupied by V, H24 is occupied by A, H48 is occupied by I, H67 is occupied by A, H80 is occupied by L, H83 is occupied by T, and H91 is occupied by F.~~

~~59. The humanized antibody of claim 58, provided positions H12, H24, H48, H67, H80, H83, and H91 in the VH region are occupied by V, A, I, A, L, T, and F, respectively.~~

~~60. The humanized antibody of claim 23 wherein at least one of the following positions in the VH region is occupied by the amino acid as specified: H10 is occupied by E or D, H12 is occupied by K or V, H13 is occupied by K or R, H17 is occupied by T, L or S, H24 is occupied by V or A, H27 is occupied by F or Y, H28 is occupied by N or T, H29 is occupied by I or F, H30 is occupied by K or T, H38 is occupied by Q or R, H40 is occupied by A or R, H42 is occupied by G or E, H43 is occupied by K or Q, H48 is occupied by M or I, H51 is occupied by V or I, H54 is occupied by N or D, H60 is occupied by D or A, H61 is occupied by P or E, H66 is occupied by R or K, H67 is occupied by V or A, H76 is occupied by D or N, H80 is occupied by M or L, H81 is occupied by E or Q, H82a is occupied by S or G, H83 is occupied by T or R, H91 is occupied by Y or F, H93 is occupied by A or S, H102 is occupied by F or Y, H108 is occupied by T or L, H109 is occupied by L or V.~~

~~61. The humanized antibody of claim 60, provided positions H12, H13, H17, H24, H38, H42, H43, H48, H66, H67, H76, H80, H81, H83, H91, and H93 in the VH region are occupied by V, R, L, A, R, E, Q, I, K, A, N, L, Q, T, F, and S, respectively.~~

~~62. The humanized antibody of claim 60, provided positions H38, H42, H43, H76, H83, and H93 in the VH region are occupied by R, E, Q, N, T, and S, respectively.~~

~~63. The humanized antibody of claim 60, provided positions H12, H13, H17, H24, H38, H40, H42, H43, H48, H66, H67, H76, H80, H81, H82A, H83, H91, and H93 in the VH region are occupied by V, R, L, A, R, R, E, Q, I, K, A, N, L, Q, G, T, F, and S, respectively.~~

~~64. The humanized antibody of claim 60, provided positions H12, H24, H38, H40, H43, H48, H67, H80, H81, H82A, H83, H91, and H93 in the VH region are occupied by V, A, R, R, Q, I, A, L, Q, G, T, F, and S, respectively.~~

65. The humanized antibody of claim 60 provided positions H12, H24, H28, H38, H40, H43, H48, H54, H60, H67, H80, H81, H82A, H83, H91, and H93 in the VH region are occupied by V, A, T, R, R, Q, I, D, A, A, L, Q, G, T, F, and S, respectively.

66. The humanized antibody of claim 60 provided positions H12, H24, H28, H38, H40, H48, H51, H54, H60, H67, H80, H82A, H83, H91, and H93 in the VH region are occupied by V, A, T, R, R, I, V, D, A, A, L, G, T, F, and S, respectively.

67. The humanized antibody of claim 60 provided positions H12, H24, H28, H38, H40, H48, H54, H60, H67, H80, H82A, H83, H91, and H93 in the VH region are occupied by V, A, T, R, R, I, D, A, A, L, G, T, F, and S, respectively.

68. The humanized antibody of claim 60 provided positions H13, H17, H24, H29, H38, H40, H42, H43, H54, H61, H76, H80, H81, H82A, H83, H91, and H93 in the VH region are occupied by R, L, A, F, R, R, E, Q, N, E, N, L, Q, G, T, F, and S, respectively.

69. The humanized antibody of claim 60 provided positions H13, H17, H24, H27, H28, H29, H30, H38, H40, H42, H43, H51, H54, H60, H61, H76, H80, H81, H82A, H83, H91, and H93 in the VH region are occupied by R, L, A, Y, T, F, T, R, R, E, Q, V, D, A, E, N, L, Q, G, T, F, and S, respectively.

70. The humanized antibody of claim 60 provided positions H10, H12, H17, H24, H28, H38, H40, H42, H43, H48, H54, H60, H61, H76, H80, H82A, H83, H91, H93, H108, and H109 in the VH region are occupied by D, V, L, A, T, R, R, E, Q, I, N, A, E, N, L, G, T, F, S, T, and L, respectively.

71. The humanized antibody of claim 60 provided positions H10, H12, H17, H24, H28, H38, H40, H43, H48, H51, H54, H60, H61, H82A, H83, H91, H93, H102, H108, and H109 in the VH region are occupied by D, V, L, A, T, R, R, Q, I, V, D, A, E, G, T, F, S, Y, T, and L, respectively.

~~72. The humanized antibody of claim 60 provided positions H38 and H93 in the VH region are occupied by R and S, respectively.~~

~~73. The humanized antibody of claim 60 provided positions H17, H27, H29, H38, H61, H76, H82A, and H93 in the VH region are occupied by L, Y, F, R, E, N, G, and S, respectively.~~

~~74. The humanized antibody of claim 60 provided positions H17, H27, H28, H29, H30, H38, H51, H54, H60, H61, H76, H82A, and H93 in the VH region are occupied by L, Y, T, F, T, R, V, D, A, E, N, G, and S, respectively.~~

~~75. The humanized antibody of claim 60 provided positions H12, H38, H40, H48, H66, H67, H76, H80, H82A, H83, and H93 in the VH region are occupied by V, R, R, I, K, A, N, L, G, T, and S, respectively.~~

~~76. The humanized antibody of claim 60 provided positions H12, H17, H27, H29, H38, H40, H61, H80, H82A, H83, and H93 in the VH region are occupied by V, L, Y, F, R, R, E, L, G, T, and S, respectively.~~

~~77. The humanized antibody of claim 60 provided positions H12, H17, H27, H28, H29, H30, H38, H40, H51, H54, H60, H61, H80, H82A, H83, and H93 in the VH region are occupied by V, L, Y, T, F, T, R, R, V, D, A, E, L, G, T, and S, respectively.~~

~~78. The humanized antibody of claim 23, wherein at least one of the following positions in the VL region is occupied by the amino acid as specified: L36 is occupied by L, L37 is occupied by L, and L100 is occupied by G.~~

~~79. The humanized antibody of claim 78, provided positions L36, L37, and L100 in the VL region are occupied by L, L, and G, respectively.~~

~~80. The humanized antibody of claim 78, wherein at least one of the following positions in the VL region is occupied by the amino acid as specified: L12 is occupied by S and L45 is occupied by K.~~

~~81. The humanized antibody of claim 80, provided positions L12 and L45 in the VL region are occupied by S and K, respectively.~~

~~82. The humanized antibody of claim 23, wherein at least one of the following positions in the VL region is occupied by the amino acid as specified: L2 is V or I, L7 is S or T, L12 is P or S, L15 is L or I, L36 is L, L37 is L, L45 is R or K, L60 is D or S, L100 is G.~~

~~83. The humanized antibody of claim 82, provided positions L12, L36, L37, L45, and L100 in the VL region are occupied by S, L, L, K, and G, respectively.~~

~~84. The humanized antibody of claim 82, provided positions L36, L37, and L100 in the VL region are occupied by L, L and G, respectively.~~

~~85. The humanized antibody of claim 82, provided positions L36, L37, L60, and L100 in the VL region are occupied by L, L, S, and G, respectively.~~

~~86. The humanized antibody of claim 82, provided positions L2, L7, L12, L15, L36, L37, L45, and L100 in the VL region are occupied by I, T, S, I, L, L, K, and G, respectively.~~

~~87. The humanized antibody of claim 82, provided positions L2, L7, L12, L15, L36, L37, L45, and L100 in the VL region are occupied by V, S, P, L, L, L, R, and G, respectively.~~

~~6.88. The humanized antibody of claim 423, comprising a mature heavy chain variable region comprising **having** an amino acid sequence at least 95% identical to SEQ ID NO: 18 **any one of** SEQ ID NOs:15-19 and SEQ ID NOs:46-57 and a mature light chain variable region comprising **having** an amino acid sequence at least 95% identical to SEQ ID NO: 21 **any one of** SEQ ID NOs: 20-23, except that position H17 can be T or S, and position H20 can be I or V.~~

~~7.89. The humanized antibody of claim 488, comprising a mature heavy chain variable region comprising **having** an amino acid sequence at least 98% identical to SEQ ID NO: 18 **any**~~

~~one of SEQ ID NOs:15-19 and SEQ ID NOs:46-57 and a mature light chain variable region comprising having an amino acid sequence at least 98% identical to SEQ ID NO: 21 ~~any one of SEQ ID NOs: 20-23, except that position H17 can be T or S, and position H20 can be I or V.~~~~

~~8.90. The humanized antibody of claim 489, wherein the mature heavy chain variable region comprises ~~has~~ an amino acid sequence of SEQ ID NO: 18 ~~any of SEQ ID NOs:15-19 and SEQ ID NOs:46-57~~ and the mature light chain variable region comprises ~~has~~ an amino acid sequence of SEQ ID NO: 21 ~~any one of SEQ ID NOs:20-23.~~~~

~~91. The humanized antibody of claim 90 wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:15 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~92. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:15 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~93. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:15 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~94. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:15 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~95. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:16 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~96. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:16 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~97. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:16 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~98. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:16 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~99. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:17 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~100. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:17 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~101. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:17 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~102. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:17 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~103. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:18 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~104. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:18 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~105. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:18 the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~106. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:18 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~107. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:19 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~108. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:19 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~109. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:19 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~110. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:19 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~111. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:46 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~112. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:46 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~113. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:46 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~114. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:46 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~115. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:47 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~116. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:47 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~117. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:47 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~118. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:47 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~119. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:48 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~120. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:48 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~121. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:48 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~122. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:48 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~123. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:49 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~124. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:49 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~125. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:49 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~126. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:49 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~127. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:50 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~128. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:50 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~129. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:50 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~130. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:50 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~131. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:51 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~132. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:51 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~133. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:51 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~134. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:51 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~135. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:52 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~136. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:52 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~137. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:52 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~138. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:52 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~139. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:53 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~140. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:53 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~141. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:53 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~142. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:53 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~143. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:54 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~144. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:54 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~145. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:54 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~146. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:54 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~147. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:55 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~148. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:55 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~149. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:55 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~150. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:55 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~151. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:56 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~152. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:56 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~153. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:56 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~154. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:56 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~155. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:57 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:20.~~

~~156. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:57 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:21.~~

~~157. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:57 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:22.~~

~~158. The humanized antibody of claim 90, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:57 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:23.~~

~~159. The antibody of claim 1, wherein the antibody is a chimeric antibody.~~

~~160. The antibody of claim 1, wherein the antibody is a veneered antibody.~~

~~9.161.~~ The antibody or binding fragment of any one of claims 1-8~~claim 1,~~ that is an intact antibody.

~~10.162.~~ The antibody or binding fragment of any one of claims 1-8 ~~claim 1,~~ that is a binding fragment.

~~11.163.~~ The antibody or binding fragment of claim ~~10~~~~162~~, wherein the binding fragment is a single-chain antibody, Fab, or Fab'₂ fragment.

~~12.164.~~ The antibody or binding fragment of claim 1, wherein the antibody has an isotype of ~~is~~ human IgG1.

~~13.165.~~ The humanized antibody of claim ~~4~~~~15~~, 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.

~~14.166.~~ The humanized antibody of claim ~~13~~~~165~~, wherein the heavy chain constant region is a mutant form of a natural human heavy chain constant region which has reduced binding to a Fcγ receptor relative to the natural human heavy chain constant region.

~~15.167.~~ The humanized antibody of claim ~~13~~ or ~~14~~~~166~~, wherein the heavy chain constant region is of IgG1 isotype.

~~16.168.~~ The antibody or binding fragment of claim 1, wherein the antibody comprises ~~having~~ at least one mutation in the constant region.

~~17.169.~~ The antibody or binding fragment of claim ~~16~~~~168~~, wherein the at least one mutation reduces complement fixation or activation by the constant region.

~~18.170.~~ The antibody or binding fragment of claim ~~17~~~~169~~, wherein the at least one mutation is ~~having~~ a mutation at one or more of positions 241, 264, 265, 270, 296, 297, 318, 320, 322, 329 and 331 by EU numbering.

~~19.171.~~ The antibody or binding fragment of claim ~~18~~¹⁷⁰ having an alanine at positions 318, 320 and 322.

~~20.172.~~ The antibody or binding fragment of claim 1, wherein the antibody is of ~~the isotype is of~~ human IgG2 or IgG4 isotype.

~~173. The antibody of claim 1, wherein the antibody is at least 95% w/w pure.~~

~~21.174.~~ The antibody or binding fragment of claim 1, wherein the antibody or binding fragment is conjugated to a therapeutic, cytotoxic, cytostatic, neurotrophic, or neuroprotective agent.

~~22.175.~~ A pharmaceutical composition comprising the antibody or binding fragment of any one of claims 1-21~~claim 1~~ and a pharmaceutically-acceptable carrier.

~~23.176.~~ A nucleic acid encoding the heavy chain and ~~and/or~~ light chain of the antibody of any one of claims 1-9 and 12-21~~claim 1~~.

~~24.177.~~ A recombinant expression vector comprising a nucleic acid of claim ~~23~~¹⁷⁶.

~~25.178.~~ A host cell transformed with the recombinant expression vector of claim ~~24~~¹⁷⁷.

~~26.179.~~ 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.

~~27.180.~~ A method of producing a 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,
wherein the antibody is the antibody of claim 3.

~~28.181.~~ A method of producing a cell line producing a 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,
wherein the antibody is the antibody of claim 3.

~~182. The method of claim 181 further comprising propagating the cells under selective conditions and screening for cell lines naturally expressing and secreting at least 100 mg/L/10⁶ cells/24 h.~~

~~29.183.~~ The antibody or binding fragment of any one of claims 1-21 ~~claim 1~~ for use in inhibiting or reducing aggregation of tau in a subject having or at risk of developing a tau-mediated amyloidosis.

~~30.184.~~ The antibody or binding fragment of any one of claims 1-21 ~~claim 1~~ for use in treating or effecting prophylaxis of a tau-related disease in a subject.

~~31.185.~~ The antibody or binding fragment of any one of claims 1-21 ~~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.

~~32.186.~~ The antibody or binding fragment of any one of claims 1-21~~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.

~~33.187.~~ 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 or binding fragment of any one of claims 1-21~~claim 1~~, and detecting a first amount of the antibody or binding fragment 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 or binding fragment, and detecting the antibody or binding fragment bound to tau in the subject,

wherein a decrease in the level of tau protein deposits indicates a positive response to treatment.

~~34.188.~~ 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 or binding fragment of any one of claims 1-21~~claim 1~~, and detecting a first amount of antibody or binding fragment 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 or binding fragment, and detecting a second amount of antibody or binding fragment bound to tau in the subject,

wherein no change in the level of tau protein deposits indicates a positive response to treatment.

~~189. The antibody of claim 1, wherein CDR-L1 has the amino acid sequence comprising SEQ ID NO:12 or 36.~~

~~190. The antibody of claim 1, wherein CDR-L2 has the amino acid sequence comprising SEQ ID NO:13 or 37.~~

~~191. The antibody of claim 1, wherein CDR-L3 has the amino acid sequence comprising SEQ ID NO:14 or 38.~~

~~192. The antibody of claim 5, wherein CDR-H3 has the amino acid sequence LDY.~~

~~193. The antibody of claim 192, wherein CDR-L1 has the amino acid sequence comprising SEQ ID NO:12 or 36.~~

~~194. The antibody of claim 192, wherein CDR-L2 has the amino acid sequence comprising SEQ ID NO: 13 or 37.~~

~~195. The antibody of claim 192, wherein CDR-L3 has the amino acid sequence comprising SEQ ID NO: 14 or 38.~~

35.~~196.~~ A method of generating an antibody that competes with a reference antibody for binding to human tau comprising immunizing an animal or B cells with an immunogen comprising human tau or a fragment thereof including residues 257-271 or 320-334 of SEQ ID NO:1 to produce antibodies, and performing a competition assay with the produced antibodies, the reference antibody, and human tau to identify a subset of produced antibodies that inhibit binding of the reference antibody to the human tau; wherein the reference antibody comprises a heavy chain variable region having an amino acid sequence comprising SEQ ID NO: 7 and a light chain variable region having an amino acid sequence comprising SEQ ID NO: 11.