

CLAIMS

1. A humanized anti-tau antibody, or a tau-binding fragment thereof, wherein said antibody or binding fragment comprises:
 - a heavy chain variable region comprising CDR-H1, CDR-H2, and CDR-H3 of SEQ ID NOs. 1, 2, and 3, respectively, and a framework from human immunoglobulin M65092 (SEQ ID NO. 71);
 - a light chain variable region comprising CDR-L1, CDR-L2, and CDR-L3 of SEQ ID NOs. 4, 5, and 6, respectively, and a framework from human immunoglobulin X72449 (SEQ ID NO. 65); and
 - heavy chain and light chain constant regions each from a human immunoglobulin; and wherein said heavy chain framework has been substituted at one or more of positions selected from 9, 21, 27, 28, 30, 38, 48, 67, 68, 70, and 95; said light chain framework has either not been substituted or has been substituted at position 5; and wherein said positions are according to Kabat.
2. The antibody or binding fragment of claim 1, wherein heavy chain position 9 is occupied by P, position 21 is occupied by P, position 27 is occupied by Y, position 28 is occupied by I, position 30 is occupied by T, position 38 is occupied by K, position 48 is occupied by I, position 67 is occupied by K, position 68 is occupied by A, position 70 is occupied by L, and/or position 95 is occupied by F.
3. The antibody or binding fragment of any one of claims 1 and 2, wherein light chain position 5 is occupied by S.
4. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region is selected from SEQ ID NOs. 13-25 (RHA through RHM); and the sequence of the light chain variable region is SEQ ID NO. 26 (RKA).

5. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region is selected from SEQ ID NOs. 13-25 (RHA through RHM); and the sequence of the light chain variable region is SEQ ID NO. 27 (RKB).
6. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 13 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
7. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 14 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
8. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 15 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
9. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 16 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
10. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 17 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
11. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 18 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
12. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 19 and the sequence of the light chain variable region comprises SEQ ID NO. 26.

13. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 20 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
14. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 21 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
15. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 22 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
16. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 23 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
17. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 24 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
18. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 25 and the sequence of the light chain variable region comprises SEQ ID NO. 26.
19. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 13 and the sequence of the light chain variable region comprises SEQ ID NO. 27.

20. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 14 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
21. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 15 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
22. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 16 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
23. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 17 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
24. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 18 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
25. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 19 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
26. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 20 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
27. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 21 and the sequence of the light chain variable region comprises SEQ ID NO. 27.

28. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 22 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
29. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 23 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
30. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 24 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
31. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 25 and the sequence of the light chain variable region comprises SEQ ID NO. 27.
32. The antibody or binding fragment of claims 6-31 wherein the antibody is of the IgG1 isotype.
33. The antibody or binding fragment of claims 6-31 wherein the antibody is of the IgG4 isotype.
34. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 14, the sequence of the light chain variable region comprises SEQ ID NO. 26, and the antibody is of the IgG1 isotype.
35. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 16, the sequence of the light chain

variable region comprises SEQ ID NO. 26, and the antibody is of the IgG1 isotype.

36. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 17, the sequence of the light chain variable region comprises SEQ ID NO. 26, and the antibody is of the IgG1 isotype.
37. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 25, the sequence of the light chain variable region comprises SEQ ID NO. 26, and the antibody is of the IgG1 isotype.
38. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 16, the sequence of the light chain variable region comprises SEQ ID NO. 27, and the antibody is of the IgG1 isotype.
39. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 17, the sequence of the light chain variable region comprises SEQ ID NO. 27, and the antibody is of the IgG1 isotype.
40. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 16, the sequence of the light chain variable region comprises SEQ ID NO. 27, and the antibody is of the IgG4 isotype.
41. The antibody or binding fragment of claim 1, wherein the sequence of the heavy chain variable region comprises SEQ ID NO. 17, the sequence of the light chain

variable region comprises SEQ ID NO. 27, and the antibody is of the IgG4 isotype.

42. A humanized anti-tau antibody, or a tau-binding fragment thereof, wherein said antibody or binding fragment comprises:
 - a. a heavy chain variable region comprising CDR-H1, CDR-H2, and CDR-H3 of SEQ ID NOs. 1, 2, and 3, respectively, and a framework from human immunoglobulin M65092 (SEQ ID NO. 71); and
 - b. a light chain variable region comprising CDR-L1, CDR-L2, and CDR-L3 of SEQ ID NOs. 4, 5, and 6, respectively, and a framework from human immunoglobulin X72449 (SEQ ID NO. 65); and
 - c. heavy chain and light chain constant regions from a human immunoglobulin.
43. An anti-tau antibody, or a tau-binding fragment thereof, wherein said antibody or binding fragment comprises:
 - a. a heavy chain comprising the amino acid sequence of any one of SEQ ID NO. 28-40 and 43-55; and
 - b. a light chain comprising the amino acid sequence of any one of SEQ ID NO. 57 and 58.
44. An antibody, or a tau-binding fragment thereof, according to any one of claims 1-43 wherein said antibody or binding fragment binds at least one epitope chosen from HQPGGG (SEQ ID NO: 148), HVPGGG (SEQ ID NO: 149), and HKPGGG (SEQ ID NO: 150).
45. A pharmaceutical composition comprising the antibody or binding fragment according to any one of claims 1-44 and a pharmaceutically acceptable carrier, diluent, excipient, or stabilizer.

46. An immunoconjugate having the formula (A)-(L)-(C), wherein: (A) is an antibody or binding fragment thereof of any one of claims 1-44; (L) is a linker; and (C) is an agent; and wherein said linker (L) links (A) to (C).
47. A nucleic acid molecule encoding any of the antibodies or binding fragments of any one of claims 1-44.
48. A vector comprising a nucleic acid according to claim 47.
49. A host cell comprising a vector according to claim 48.
50. A method of producing an antibody or tau-binding fragment thereof that binds to human tau comprising culturing the host cell of claim 49 so that the nucleic acid is expressed and the antibody, tau-binding fragment, heavy chain, or light chain thereof produced.
51. A composition comprising an antibody or tau-binding fragment according to any one of claims 1-44, or a pharmaceutical composition according to claim 45, for use in the treatment of Alzheimer's Disease or another tauopathy in a subject having Alzheimer's Disease or another tauopathy.
52. A composition comprising an antibody or tau-binding fragment according to any one of claims 1-44, or a pharmaceutical composition according to claim 45, for use in promoting clearance of tau aggregates from the brain of a subject having, suspected of having, or being prone to have Alzheimer's Disease or another tauopathy.

53. A composition comprising an antibody or tau-binding fragment according to any one of claims 1-44, or a pharmaceutical composition according to claim 45, for use in slowing progression of AD or another tauopathy in a subject having, suspected of having, or being prone to have Alzheimer's Disease or another tauopathy.
54. A composition comprising an antibody or tau-binding fragment according to any one of claims 1-44, or a pharmaceutical composition according to claim 45, for use in ameliorating the symptoms of AD or a related in a subject having, suspected of having, or being prone to have Alzheimer's Disease or another tauopathy.
55. A composition comprising an antibody or tau-binding fragment according to any one of claims 1-44, or a pharmaceutical composition according to claim 45, for use in treating cognitive impairment in a subject having Alzheimer's Disease or another tauopathy.
56. A composition comprising an antibody or tau-binding fragment of any one of claims 1-44, for use in evaluating a subject having, suspected of having, or being prone to have Alzheimer's Disease or another tauopathy by detecting binding of the antibody or tau-binding fragment to a component of a biological sample from the subject, wherein the detection of binding to the biological sample is indicative of Alzheimer's Disease or another tauopathy in the subject.