

CLAIMS

1. An isolated monoclonal antibody that competes for binding to human tau with antibody 9F5.
2. The antibody of claim 1 that binds to the same epitope on human tau as 9F5.
3. The antibody of claim 1, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 9F5, wherein 9F5 is a mouse antibody characterized by 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.
4. The antibody of claim 1, wherein the three heavy chain CDRs CDR-H1, CDR-H2, and CDR-H3 are as defined by Kabat/Chothia Composite (SEQ ID NOs:8, 9, and 10, respectively), except that position H28 can be occupied by N or T, position H51 can be occupied by I or V, position H54 can be occupied by N or D, and position H56 can be occupied by D or E, and the three light chain CDRs CDR-L1, CDR-L2, and CDR-L3 are as defined by Kabat/Chothia Composite (SEQ ID NOs:12, 13, and 14, respectively), except that position L27b is occupied by L, D, T, or Q, position L27c is occupied by L, D, G, S, E, T, N, A, P, or I, position L30 can be occupied by I, Y, E, K, G, or Q, position L31 can be occupied by T, N, or G, position L33 is occupied by L, N, T, S, R, or G, position L51 can be occupied by M, G, E, D, K, or I, position L54 can be occupied by L, R, G, or T, position L89 is occupied by A or G, position L92 is occupied by L, D, E, G, Q, T, or I, and position L93 is occupied by E or G.
5. The antibody of claim 4, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO:50, wherein CDR-H2 has an amino acid sequence comprising SEQ ID NO:51 or SEQ ID NO:52, wherein CDR-L1 has an amino acid sequence comprising any of SEQ ID NO:53, SEQ ID NO:54, and SEQ ID NOs:172-193, wherein CDR-L2 has an amino acid sequence comprising any of SEQ ID NO:55 and SEQ ID NOs:194-205, and wherein CDR-L3 has an amino acid sequence comprising any of SEQ ID NOs:206-213.

6. The antibody of any one of the preceding claims, wherein the antibody is a humanized antibody.

7. The humanized antibody of claim 6 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 9F5 (SEQ ID NO:40, 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 9F5 (SEQ ID NOs:12-14).

8. The humanized antibody of any one of claims 1-7 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 Q or V, H11 is occupied by L or V, H12 is occupied by V or K, H17 is occupied by S or T, H20 is occupied by L or I, H23 is occupied by T or K, H28 is occupied by N or T, H38 is occupied by K, R, or Q, H40 is occupied by R or A, H42 is occupied by E or G, H43 is occupied by Q or K, H48 is occupied by I or M, H51 is occupied by I or V, H54 is occupied by N or D, H56 is occupied by D or E, H66 is occupied by K or R, H69 is occupied by I or M, H75 is occupied by S or T, H76 is occupied by N or D, H79 is occupied by Y, Q, D, N, or G, H80 is occupied by L, M, P, D, G, or E, H81 is occupied by Q or E, H82 is occupied by L, P, K, R, E, or N, H82a is occupied by S or G, H82c is occupied by L, G, D, or S, H83 is occupied by T or R, H93 is occupied by A or T, H94 is occupied by S or T, H108 is occupied by T or L, H109 is occupied by L or V, L3 is V or Q, L7 is A or S, L8 is A or P, L9 is F or L, L11 is N or L, L15 is L or P, L17 is T or E, L18 is S or P, L27b is L, D, T, or Q, L27c is L, D, G, S, E, T, N, A, P, or I, L30 is I, Y, E, K, G, L31 is T, N, or G, L33 is L, N, T, S, R, or G, L37 is L, Q, G, or I, L39 is R or K, L51 is M, G, E, D, K, or I, L54 is R, G, or T, L60 is N or D, L64 is G or S, L66 is E or G, L73 is L, P, or G, L74 is R or K, L75 is I, D, P, Q, or G, L76 is S, P, or G, L77 is R or D, L78 is V, R, D, E, P, K, G, or Q, L85 is V or G, L86 is Y or T, L89 is A or G, L92 is L, D, E, G, Q, T, or I, L93 is E or G, L100 is G or Q.

9. The humanized antibody of claim 8, wherein the heavy chain variable region comprises the amino acid sequence of SEQ ID NO:127 or SEQ ID NO:128.

10. The humanized antibody of any one of claims 1-7 wherein the mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOs:15-22 and

SEQ ID NOs:109-129, and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NO:23-29, SEQ ID NOs:61-108, and SEQ ID NOs:130-171.

11. The humanized antibody of claim 10, wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:149; or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:142, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:159, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:148, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:137, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:145, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:136, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:138, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:158, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:143, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:144, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:133, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:160, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:161, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:127 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:139, or

wherein the mature heavy chain variable region has an amino acid sequence of SEQ ID NO:128 and the mature light chain variable region has an amino acid sequence of SEQ ID NO:168.

12. The antibody of claim 1, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 10C12, wherein 10C12 is a mouse antibody characterized by 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.

13. The antibody of claim 12, wherein the antibody is a humanized antibody.

14. The humanized antibody of claim 13 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 10C12 (SEQ ID NO:40, 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 10C12 (SEQ ID NOs:12-14).

15. The humanized antibody of any one of claims 12-14 wherein at least one of the following positions is occupied by the amino acid as specified: H1 is occupied by Q or E, H24 is occupied by A, H48 is occupied by I, H67 is occupied by A, H69 is occupied by M, H93 is occupied by T, H94 is occupied by T, L64 is S, L104 is V or L.

16. The humanized antibody of any one of claims 12-14 wherein the mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOs:214-215 and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NO:216-217.

17. The antibody of claim 1, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 12C4, wherein 12C4 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:219 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:11.

18. The antibody of claim 17, wherein the antibody is a humanized antibody.

19. The humanized antibody of claim 18 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 12C4 (SEQ ID NO:40, SEQ ID NO:220, and SEQ ID NO:10) and the humanized mature light chain variable region comprises the three Kabat light chain CDRs of 12C4 (SEQ ID NOs:12-14).

20. The humanized antibody of any one of claims 17-19 wherein at least one of the following positions is occupied by the amino acid as specified: H1 is occupied by Q or E,

H48 is occupied by M or I, H93 is occupied by A or T, H94 is occupied by R or T, L64 is G or S, L104 is V or L.

21. The humanized antibody of any one of claims 17-19 wherein the mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOs:221-222 and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NO:223-224.

22. The antibody of claim 1, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 17C12, wherein 17C12 is a mouse antibody characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:225 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:228.

23. The antibody of claim 22, wherein the antibody is a humanized antibody.

24. The humanized antibody of claim 23 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 17C12 (SEQ ID NO:40, SEQ ID NO:227, and SEQ ID NO:10) and the humanized mature light chain variable region comprises the three Kabat light chain CDRs of 17C12 (SEQ ID NOs:229-231).

25. The humanized antibody of any one of claims 22-24 wherein at least one of the following positions is occupied by the amino acid as specified: H1 is occupied by Q or E, H2 is occupied by I, H24 is occupied by A, H48 is occupied by I, H67 is occupied by A, H69 is occupied by M, H93 is occupied by T, H94 is occupied by T, H108 is occupied by T or L, H113 is occupied by R or S, L2 is V, L36 is L, L43 is P or S.

26. The humanized antibody of any one of claims 22-24 wherein the mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOs:232-233 and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NO:234-235.

27. The antibody of claim 1, comprising three light chain CDRs and three heavy chain CDRs of monoclonal antibody 14H3, wherein 14H3 is a mouse antibody

characterized by a heavy chain variable region having an amino acid sequence comprising SEQ ID NO:240 and a light chain variable region having an amino acid sequence comprising SEQ ID NO:244.

28. The antibody of claim 27, wherein the three heavy chain CDRs CDR-H1, CDR-H2, and CDR-H3 are as defined by Kabat/Chothia Composite (SEQ ID NOs:241, 242, and 243, respectively), except that position H35B can be occupied by G or S, and the three light chain CDRs CDR-L1, CDR-L2, and CDR-L3 are as defined by Kabat/Chothia Composite (SEQ ID NOs:245, 246, and 247, respectively).

29. The antibody of claim 28, wherein CDR-H1 has an amino acid sequence comprising SEQ ID NO:277.

30. The antibody of any one of claims 27-29, wherein the antibody is a humanized antibody.

31. The humanized antibody of claim 30 wherein the humanized mature heavy chain variable region comprises the three Kabat heavy chain CDRs of 14H3 (SEQ ID NO:265, SEQ ID NO:242, and SEQ ID NO:243) and the humanized mature light chain variable region comprises the three Kabat light chain CDRs of 14H3 (SEQ ID NOs:245-247).

32. The humanized antibody of any one of claims 27-31 wherein at least one of the following positions is occupied by the amino acid as specified: H35B is occupied by S, H108 is occupied by M or L, H113 is occupied by L or S, L2 is V, L7 is T or S, L37 is L or Q, L87 is F, L100 is G or Q, L104 is V or L.

33. The humanized antibody of any one of claims 27-31, wherein the mature heavy chain variable region has an amino acid sequence of any one of SEQ ID NOs:248-249 and the mature light chain variable region has an amino acid sequence of any one of SEQ ID NO:250-251.

34. The antibody of any one of claims 1-33 that is an intact antibody.

35. The antibody of any one of claims 1-33 that is a binding fragment.

36. The antibody of any one of the preceding claims, wherein the isotype is human IgG1, human IgG2, or human IgG4.

37. The humanized antibody of any one of claims 6-11, 13-16, 18-21, 23-26, and 30-36 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.

38. The humanized antibody of claim 37, 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.

39. A pharmaceutical composition comprising an antibody as defined in any of claims 1-38 and a pharmaceutically-acceptable carrier.

40. A nucleic acid encoding the heavy chain and/or light chain of an antibody as described in any one of claims 1-39.

41. A method of humanizing a mouse antibody, the method comprising:

(a) selecting one or more acceptor antibody sequences;

(b) identifying 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 9F5, wherein 9F5 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,

wherein the mouse antibody is 10C12, wherein 10C12 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,

wherein the mouse antibody is 2D11, wherein 2D11 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,

wherein the mouse antibody is 12C4, wherein 12C4 is characterized by a mature heavy chain variable region of SEQ ID NO:219 and a mature light chain variable region of SEQ ID NO:11,

wherein the mouse antibody is 17C12, wherein 17C12 is characterized by a mature heavy chain variable region of SEQ ID NO:225 and a mature light chain variable region of SEQ ID NO:228,

wherein the mouse antibody is 14H3, wherein 14H3 is characterized by a mature heavy chain variable region of SEQ ID NO:240 and a mature light chain variable region of SEQ ID NO:244.

42. Use of an antibody of any one of claims 1-39 in the manufacture of a medicament for inhibiting or reducing aggregation of tau.

43. Use of an antibody as defined by any one of claims 1-39 in the manufacture of a medicament for treating or effecting prophylaxis of a tau-related disease.

44. The use of claim 43 wherein the tau-related disease is Alzheimer's disease, Down's syndrome, mild cognitive impairment, primary age-related tauopathy, postencephalitic parkinsonism, posttraumatic dementia or dementia pugilistica, Pick's disease, type C Niemann-Pick disease, supranuclear palsy, frontotemporal dementia, frontotemporal lobar degeneration, argyrophilic grain disease, globular glial tauopathy, amyotrophic lateral sclerosis/parkinsonism dementia complex of Guam, corticobasal degeneration (CBD), dementia with Lewy bodies, Lewy body variant of Alzheimer disease (LBVAD), chronic traumatic encephalopathy (CTE), globular glial tauopathy (GGT), Parkinson's disease, or progressive supranuclear palsy (PSP).

45. An isolated monoclonal antibody that specifically binds to a peptide consisting of residues (Q/E)IVYK(S/P) (SEQ ID NO:56), or QIVYKP (SEQ ID NO:57), or EIVYKSP (SEQ ID NO:58), or EIVYKS (SEQ ID NO:277).

46. Use of an immunogen comprising a tau peptide of up to 20 contiguous amino acids of SEQ ID NO:1 to which antibody 9F5, 10C12, 2D11, 12C4, 17C12, or 14H3 specifically binds, wherein the peptide induces formation of antibodies specifically binding to tau in the manufacture of a medicament for treating or effecting prophylaxis of a tau-related disease.