

Claim

1. An isolated antibody specifically binding to human tau, comprising:

a ~~mature~~ heavy chain variable region comprising CDR-H1 comprising SEQ ID NO: 8, CDR-H2 comprising SEQ ID NO: 9 ~~or SEQ ID NO: 149~~, and CDR-H3 comprising SEQ ID NO: 10, wherein the heavy chain variable region is at least 90% identical to SEQ ID NO: 18; and

a ~~mature~~ light chain variable region comprising CDR-L1 comprising SEQ ID NO: 12, CDR-L2 comprising SEQ ID NO: ~~168, 150, 151, 153, 156, 158, 159, 160, 163, 165, 166, 167, 168, 169, 170, 171, 172, 173 or 174~~, and CDR-L3 comprising SEQ ID NO: 14, wherein the light chain variable region is at least 90% identical to SEQ ID NO: 122.

2. The antibody of claim 1, wherein at least one of positions H12, H13, H17, H24, H40, H43, H48, H66, H67, H76, H80, H81, and H91 is occupied by V, K, T, A, R, Q, I, R, A, D, L, Q, and F, respectively, and at least one of positions L2, L12, L15, L37, L39, L45, L60, and L100 is occupied by V, P, L, Q, R, R, D, and Q respectively.

~~3. The antibody of claim 1, wherein CDR-L2 comprises SEQ ID NO: 150, 151, 163, 167, 168, or 169.~~

~~3.4. The antibody of claim 23, wherein the heavy chain variable region comprises SEQ ID NO: 18 and the light chain variable region comprises SEQ ID NO: 122, 140, 121, 122 or 123.~~

~~4. The antibody of any one of claims 1-3, wherein the antibody is a chimeric, veneered, or humanized antibody.~~

~~5. The antibody of claim 3, wherein the heavy chain variable region comprises SEQ ID NO: 146 and the light chain variable region comprises SEQ ID NO: 94 or SEQ ID NO: 122.~~

~~6. The antibody of claim 3, wherein the heavy chain variable region comprises SEQ ID NO: 18 and the light chain variable region comprises SEQ ID NO: 122.~~

~~5.7.)~~ The antibody of any one of claims ~~1-4~~ ~~1-6~~ that is an intact antibody.

6.8. The antibody of any one of claims 1-41-6 that is a an antigen binding fragment.

7. The antibody of claim 6, wherein the antigen-binding fragment is a single-chain antibody, a Fab, or a Fab'2 fragment.

8. The antibody of claim 6, wherein the antigen-binding fragment is a Fab fragment or a single chain Fv.

9. The antibody of any one of claims 1-5~~the preceding claims~~, wherein the isotype is human IgG1, human IgG2, or human IgG4.

10. The antibody of any one of claims 1-51-7 and 9, comprising a light chain comprising ~~wherein the~~ mature-light chain variable region ~~is~~ fused to a light chain constant region and a heavy chain comprising the ~~mature~~-heavy chain variable region ~~is~~ fused to a heavy chain constant region.

11. The antibody of claim 10, 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.

12. The antibody of claim 10 or ~~claim~~-11, wherein the heavy chain constant region is of IgG1 isotype.

13. The antibody of claim 12, wherein the heavy chain constant region has an amino acid sequence of SEQ ID NO: 176 with or without the C-terminal lysine

14. The antibody of claim 10, wherein the mature-heavy chain variable region fused to ~~the~~a heavy chain constant region has an amino acid sequence of SEQ ID NO: 178 with or without the C-terminal lysine.

15. The antibody of claim 10, further comprising a signal peptide fused to the ~~mature~~ heavy and/or light chain variable region.

16. The antibody of claim 14, wherein the heavy chain has an amino acid sequence of SEQ ID NO:_180 with or without the C-terminal lysine.

17. The antibody of claim 10, wherein the light chain constant region has an amino acid sequence of SEQ ID NO:_177.

18. The antibody of claim 10, wherein the ~~mature~~-light chain variable region is fused to a light chain constant region has an amino acid sequence of SEQ ID NO:_179.

19. The antibody of claim 18, wherein the light chain has an amino acid sequence of SEQ ID NO:_181.

20. The antibody of claim 14, wherein the heavy chain has an amino acid sequence of SEQ ID NO:_178 with or without the C-terminal lysine and the light chain has an amino acid sequence of SEQ ID NO:_179.

21. The antibody of claim 16, wherein the heavy chain has an amino acid sequence of SEQ ID NO:_180 with or without the C-terminal lysine and the light chain has an amino acid sequence of SEQ ID NO:_181.

22. The antibody of claim 10~~any one of the preceding claims~~ having at least one mutation in the heavy chain constant region.

23. The antibody of claim 22, wherein the mutation reduces complement fixation or activation by the heavy chain constant region.

24. The antibody of claim 23, having a mutation at one or more of positions 241, 264, 265, 270, 296, 297, 318, 320, 322, 329, or 331 by EU numbering.

25. The antibody of claim 24, having alanine at positions 318, 320, and 322.

26. The antibody of any one of claims 1-25, wherein the antibody is at least 95% w/w pure.

27. The antibody of any one of claims 1-26, wherein the antibody is conjugated to a therapeutic, cytotoxic, cytostatic, neurotrophic, or neuroprotective agent.

28.24. A pharmaceutical composition comprising an antibody as defined in any of claims 1-27+23 and a pharmaceutically-acceptable carrier.

29.25. A nucleic acid encoding the heavy chain and/or light chain of an antibody as described in any one of claims 1-27+23.

30.26. The nucleic acid of claim 2925, wherein the heavy chain is encoded by a sequence comprising SEQ ID NO:_182 and the light chain is encoded by a sequence comprising SEQ ID NO:_183.

31.27. A method of producing an the antibody of claim 1, the method comprising:

- (a) culturing cells transformed with the nucleic acid of claim 30 ~~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.

32.28. A method of producing a cell line producing an the antibody of claim 1, the method comprising:

- (a) introducing a vector comprising the nucleic acid of claim 30 ~~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 the antibody.

~~29. Use of an antibody of any one of claims 1-23 in the manufacture of a medicament for inhibiting or reducing aggregation of tau.~~

~~33.~~30. Use of an antibody as defined by any one of claims ~~1-27~~1-23 in the manufacture of a medicament for- treating or effecting prophylaxis of a tau-related disease~~;~~;

~~31. The use of claim 30~~ 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), or progressive supranuclear palsy (PSP).

34. The use of claim 33, wherein the tau-related disease is Alzheimer's disease.