

Claim

1. An isolated antibody or antigen-binding antibody fragment that specifically binds to human tau, comprising:

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

a light chain variable region comprising CDR-L1 comprising SEQ ID NO: 12, CDR-L2 comprising SEQ ID NO: 150, and CDR-L3 comprising SEQ ID NO: 14, wherein the light chain variable region comprises a sequence that is at least 90% identical to SEQ ID NO: 122.

2. The antibody or antigen-binding antibody fragment of claim 1, wherein at least one of Kabat 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 Kabat 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 or antigen-binding antibody fragment of claim 1, wherein the heavy chain variable region comprises SEQ ID NO: 18 and the light chain variable region comprises SEQ ID NO: 93 or 127.

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

5. The antibody or antigen-binding antibody fragment of any one of claims 1-4 that is an antibody.

6. The antibody or antigen-binding antibody fragment of any one of claims 1-4 that is an antigen-binding antibody fragment.

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

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

9. The antibody or antigen-binding antibody fragment of claim 5, wherein the antibody is of human IgG1, human IgG2, or human IgG4 isotype.

10. The antibody or antigen-binding antibody fragment of any one of claims 1-4, comprising a light chain comprising the light chain variable region fused to a light chain constant region and a heavy chain comprising the heavy chain variable region fused to a heavy chain constant region.

11. The antibody or antigen-binding antibody fragment 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 or antigen-binding antibody fragment of claim 10 or 11, wherein the heavy chain constant region is of IgG1 isotype.

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

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

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

16. The antibody or antigen-binding antibody fragment of claim 14, wherein the heavy chain comprises an amino acid sequence of SEQ ID NO: 180 with or without the C-terminal lysine.

17. The antibody or antigen-binding antibody fragment of claim 10, wherein the light chain constant region comprises an amino acid sequence of SEQ ID NO: 177.

18. The antibody or antigen-binding antibody fragment of claim 10, wherein the light chain variable region comprises an amino acid sequence of SEQ ID NO: 93

19. The antibody or antigen-binding antibody fragment of claim 10, wherein the light chain variable region comprises an amino acid sequence of SEQ ID NO: 127.

20. The antibody or antigen-binding antibody fragment of claim 10 comprising at least one mutation in the heavy chain constant region.

21. The antibody or antigen-binding antibody fragment of claim 20, wherein the at least one mutation in the heavy chain constant region reduces complement fixation or activation by the heavy chain constant region.

22. The antibody or antigen-binding antibody fragment of claim 21, having a mutation at one or more of positions 241, 264, 265, 270, 296, 297, 318, 320, 322, 329, and 331 by EU numbering.

23. The antibody or antigen-binding antibody fragment of claim 22, having alanine at positions 318, 320, and 322 by EU numbering.

24. The antibody or antigen-binding antibody fragment of any one of claims 1-23, wherein the antibody is at least 95% w/w pure.

25. The antibody or antigen-binding antibody fragment of any one of claims 1-24,

wherein the antibody or antigen-binding antibody fragment is conjugated to a therapeutic, cytotoxic, cytostatic, neurotrophic, or neuroprotective agent.

26. A pharmaceutical composition comprising the antibody or antigen-binding antibody fragment of any one of claims 1-25 and a pharmaceutically-acceptable carrier.

27. A nucleic acid encoding the antibody or antigen-binding antibody fragment of any one of claims 1-25.

28. A method of producing an antibody or antigen-binding antibody fragment, the method comprising:

(a) culturing cells transformed with the nucleic acid of claim 27 in a cell culture medium, so that the cells secrete the antibody or antigen-binding antibody fragment; and

(b) purifying the antibody or antigen-binding antibody fragment from the cell culture medium.

29. A method of producing a cell line producing an antibody or antigen-binding antibody fragment, the method comprising:

(a) introducing a vector comprising the nucleic acid of claim 27 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 or antigen-binding antibody fragment.

30. Use of the antibody or antigen-binding antibody fragment of any one of claims 1-25 in the manufacture of a medicament for treating or effecting prophylaxis of a tau-related disease, 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).

31. The use of claim 30, wherein the tau-related disease is Alzheimer's disease.