

Claims

1. An isolated monoclonal antibody or a binding fragment thereof that binds to human tau, wherein the three 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.

2. The antibody or binding fragment of claim 1 comprising a mature heavy chain variable region comprising SEQ ID NO: 7 and a mature light chain variable region comprising SEQ ID NO: 11.

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

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

5. The humanized antibody of claim 4, comprising a humanized mature heavy chain variable region comprising an amino acid sequence at least 90% identical to SEQ ID NO: 18 and a humanized mature light chain variable region comprising an amino acid sequence at least 90% identical to SEQ ID NO: 21.

6. The humanized antibody of claim 4, comprising a mature heavy chain variable region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 18 and a mature light chain variable region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 21.

7. The humanized antibody of claim 4, comprising a mature heavy chain variable region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 18 and a mature light chain variable region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 21.

8. The humanized antibody of claim 4, wherein the mature heavy chain variable region comprises an amino acid sequence of SEQ ID NO: 18 and the mature light chain variable region comprises an amino acid sequence of SEQ ID NO: 21.

9. The antibody or binding fragment of any one of claims 1-8 that is an intact antibody.

10. The antibody or binding fragment of any one of claims 1-8 that is a binding fragment.

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

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

13. The humanized antibody of claim 4, 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. The humanized antibody of claim 13, 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. The humanized antibody of claim 13 or 14, wherein the heavy chain constant region is of IgG1 isotype.

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

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

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

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

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

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

23. A nucleic acid encoding the heavy chain and light chain of the antibody of any one of claims 1-9 and 12-21.

24. A recombinant expression vector comprising a nucleic acid of claim 23.

25. A host cell transformed with the recombinant expression vector of claim 24.

26. 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. A method of producing a ~~the~~ humanized, chimeric, or veneered antibody, 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. A method of producing a cell line producing a humanized, chimeric, or veneered antibody, 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.

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

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

31. The antibody or binding fragment of any one of claims 1-21 for use in reducing aberrant transmission of tau, inducing phagocytosis of tau, inhibiting tau aggregation or deposition, or inhibiting formation of tau tangles.

32. The antibody or binding fragment of any one of claims 1-21 for use in detecting tau protein deposits in a subject having or at risk of a disease associated with tau aggregation or deposition.

33. 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, 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. 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, 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.

35. 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.