

Claims

1. _____

- 1.—An isolated ~~monoclonal~~ antibody or antigen-binding fragment thereof ~~which~~that binds to ~~PHF~~a phosphorylated tau protein at a phosphorylated epitope comprising: a) a
(a)——phosphorylated T212 and phosphorylated T217 of the tau protein, and the phosphorylated epitope having or within the amino acid sequence of SEQ ID NO:48.
(b)——phosphorylated T217 of the tau protein, and the phosphorylated epitope having or within the amino acid sequence of SEQ ID NO:52; or
(c)——phosphorylated T212 of the tau protein, and the phosphorylated epitope having or within the amino acid sequence of SEQ ID NO:54.
- 2.—The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1 wherein the monoclonal antibody comprises an HCDR1 of any of SEQ ID NOs: 1, 4, 7, 10, 71, 80; an HCDR2 of any of SEQ ID NOs: 2, 5, 8, 11, 72, 81; an HCDR3 of any of SEQ ID NOs: 3, 6, 9, 12, 73; an LCDR1 of any of SEQ ID NOs: 13, 16, 19, 22, 70; an LCDR2 of any of SEQ ID NOs: 14, 17, 20, 23; an LCDR3 of any of SEQ ID NOs: 15, 18, 21, 24.
- 3.—The isolated monoclonal antibody or antigen-binding fragment of claim 2 comprising:
(a)——immunoglobulin heavy chain variable~~complementarity~~ determining regions (HCDRs) HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 7, 8 and 9, respectively and immunoglobulin light chain complementarity determining regions (LCDRs) LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 19, 20 and 21, respectively;
(b)——HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 1, 2 and 3, respectively and LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 13, 14 and 15, respectively;
(c)——HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 4, 5 and 6, respectively and LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 16, 17 and 18, respectively;

- (d) ~~HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 10, 11 and 12, respectively and LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 22, 23 and 24, respectively;~~
 - (e) ~~HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 80, 81 and 9, respectively and LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 70, 20 and 21, respectively;~~
 - (f) ~~HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 71, 72, 73, respectively and LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 70, 20 and 21, respectively;~~
 - (g) ~~HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 71, 72 and 73, respectively and LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 19, 20 and 21, respectively;~~
 - (h) ~~HCDR1, HCDR2 and HCDR3 of a V_H region CDR1 comprising having the amino acid polypeptide sequence of SEQ ID NO: 7, b) -26 and LCDR1, LCDR2 and LCDR3 of a V_L region having the polypeptide sequence of SEQ ID NO: 31;~~
 - (i) ~~HCDR1, HCDR2 and HCDR3 of a V_H region having the polypeptide sequence of SEQ ID NO: 28 and LCDR1, LCDR2 and LCDR3 of a V_L region having the polypeptide sequence of SEQ ID NO: 34;~~
 - (j) ~~HCDR1, HCDR2 and HCDR3 of a V_H region having the polypeptide sequence of SEQ ID NO: 26 and LCDR1, LCDR2 and LCDR3 of a V_L region having the polypeptide sequence of SEQ ID NO: 34; or~~
 - (k) ~~HCDR1, HCDR2 and HCDR3 of a V_H region having the polypeptide sequence of SEQ ID NO: 28 and LCDR1, LCDR2 and LCDR3 of a V_L region having the polypeptide sequence of SEQ ID NO: 31;~~
- ~~wherein the antibody or antigen-binding fragment thereof binds PHF-tau.~~

4. ~~The isolated monoclonal antibody or antigen-binding fragment of claim 3 comprising a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO: 8, c) having a polypeptide sequence at least 95% identical to any one of SEQ ID NOs: 26, 27, 28 and 29, and a light chain variable region having a polypeptide sequence at least~~

95% identical to any one of SEQ ID NOs: 31, 32, 33 and 34.

5. ~~The isolated monoclonal antibody or antigen-binding fragment of claim 4 comprising a heavy chain variable region CDR3 comprising the amino acid having a polypeptide sequence of any of SEQ ID NO:9, d) NOs: 26, 27, 28 and 29, and a light chain variable region CDR1 having a polypeptide sequence of any of SEQ ID NOs: 31, 32, 33 and 34.~~

6. ~~The isolated monoclonal antibody or antigen-binding fragment of claim 3 comprising the amino acid sequence of SEQ ID NO:19, e) a light heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:20, having a polypeptide sequence at least 95% identical to a V_H from a heavy chain having a polypeptide sequence of any of SEQ ID NOs: 45, 74, 76 and f) 78, and a light chain variable region CDR3 comprising the amino acid having a polypeptide sequence at least 95% identical to a V_L from a light chain of any of SEQ ID NO:21 NOs: 31, 75, 77 and 79.~~

2. _____

7. ~~The isolated monoclonal antibody or antigen-binding fragment thereof of claim 16 comprising: a) the heavy chain variable region CDR1 having the amino acid polypeptide sequence of SEQ ID NO:7, b) the V_H from a heavy chain variable region CDR2 having the amino acid polypeptide sequence of SEQ ID NO:8, c) the heavy chain variable region CDR3 having the amino acid sequence of SEQ ID NO:9, d) the any of SEQ ID NOs: 45, 74, 76 and 78, and a light chain variable region CDR1 having the amino acid polypeptide sequence of SEQ ID NO:19, e) the V_L from a light chain variable region CDR2 having the amino acid sequence of SEQ ID NO:20, and f) the light chain variable region CDR3 having the amino acid sequence of SEQ ID NO:21 any of SEQ ID NOs: 31, 75, 77 and 79.~~

3. _____

8. ~~The isolated monoclonal antibody or antigen-binding fragment of claim 23 comprising~~
~~—— (a) —— a V_H having the polypeptide sequence of SEQ ID NO: 26 and a V_L having the polypeptide sequence of SEQ ID NO: 31;~~
~~—— (b) —— a V_H having the polypeptide sequence of SEQ ID NO: 28 and a V_L having the polypeptide sequence of SEQ ID NO: 34;~~
~~—— (c) —— a V_H having the polypeptide sequence of SEQ ID NO: 26 and a V_L having the~~

- polypeptide sequence of SEQ ID NO: 34;
- (d) —— a V_H having the polypeptide sequence of SEQ ID NO: 28 and a V_L having the polypeptide sequence of SEQ ID NO: 31;
- (e) —— a V_H having the polypeptide sequence of SEQ ID NO: 27 and a V_L having the polypeptide sequence of SEQ ID NO: 31;
- (f) —— a V_H from a heavy chain of SEQ ID NO: 74 and a V_L from a light chain of SEQ ID NO: 75;
- (g) —— a V_H from a heavy chain of SEQ ID NO: 76 and a V_L from a light chain of SEQ ID NO: 77; or
- (h) —— a V_H from a heavy chain of SEQ ID NO: 78 and a V_L from a light chain of SEQ ID NO: 79.
9. ~~The isolated monoclonal antibody or antigen-binding fragment of claim 8 comprising a heavy chain having a polypeptide sequence at least 95% identical of any of SEQ ID NOs: 45, 74, 76 and 78, and a light chain having a polypeptide sequence at least 95% identical to any of SEQ ID NOs: 46, 75, 77 and 79.~~
10. ~~The isolated monoclonal antibody or antigen-binding fragment of claim 9 comprising a heavy chain having a polypeptide sequence of any of SEQ ID NOs: 45, 74, 76 and 78, and a light chain having a polypeptide sequence of any of SEQ ID NOs: 46, 75, 77 and 79.~~
11. ~~The isolated monoclonal antibody or antigen-binding fragment of claim 10 comprising:~~
- (a) —— a heavy chain of SEQ ID NO: 45, and a light chain of SEQ ID NO: 46;
- (b) —— a heavy chain of SEQ ID NO: 74, and a light chain of SEQ ID NO: 75;
- (c) —— a heavy chain of SEQ ID NO: 76, and a light chain of SEQ ID NO: 77; or
- (d) —— a heavy chain of SEQ ID NO: 78, and a light chain of SEQ ID NO: 79.
12. ~~The isolated monoclonal antibody or antigen-binding fragment of any of claims 1–~~
11 ~~comprising~~ a human heavy chain IgG1 constant region and a human light chain kappa

constant region.

4. _____

~~13.~~ An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment of claim 2~~any of claims 1-12~~.

5. _____

~~14.~~ A vector comprising the isolated nucleic acid of claim ~~4~~13.

6. _____

~~15.~~ A host cell comprising the nucleic acid of claim ~~5~~14.

7. _____

~~16.~~ A pharmaceutical composition comprising the isolated monoclonal antibody or antigen-binding fragment of claim 2~~any one of claims 1-12~~ and a pharmaceutically acceptable carrier.

8. _____
Use of the pharmaceutical composition of claim 7 in the manufacture of a medicament to~~A method of reducing~~

~~17.~~ ~~A method of reducing pathological tau aggregation or spreading of tauopathy in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 7~~16.

9. _____
Use of the pharmaceutical composition of claim 7 in the manufacture of a medicament to~~A method of slowing progression of~~

~~18.~~ ~~A method of treating a tauopathy in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 7~~16.

10. _____

~~The method use of claim 9~~18 wherein the tauopathy is selected from the group consisting of Alzheimer's~~familial Alzheimer's disease, sporadic Alzheimer's disease, frontotemporal dementia, and progressive supranuclear palsy.~~

11. _____
The method use of claim 10 wherein the tauopathy is Alzheimer's disease.

12. _____
The method use of claim 11 wherein the Alzheimer's disease is familial Alzheimer's disease.

13. _____
The method use of claim 11 wherein the Alzheimer's disease is sporadic Alzheimer's disease.

14. The method-use of claim 10 wherein the tauopathy is frontotemporal dementia.

15. The method-use of claim 14 wherein the frontotemporal dementia is frontotemporal dementia -with parkinsonism linked to chromosome 17 (FTDP-17).

16. The method-use of claim 10 wherein the tauopathy is), progressive supranuclear palsy, corticobasal degeneration, Pick's disease, progressive supranuclear palsy, subcortical gliosis, tangle only dementia, diffuse neurofibrillary tangles with calcification, argyrophilic grain dementia, amyotrophic lateral sclerosis parkinsonism dementia complex, Down syndrome, Gerstmann-Sträussler-Scheinker disease, Hallervorden-Spatz disease, inclusion body myositis, Creutzfeld-Jakob disease, multiple system atrophy, Niemann-Pick disease type C, prion protein cerebral amyloid angiopathy, subacute sclerosing panencephalitis, myotonic dystrophy, non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, chronic traumatic encephalopathy, and dementia pugilistica (boxing disease).

17.

20. A method of producing the monoclonal antibody or antigen-binding fragment of claim 2any one of claims 1-12 comprising culturing a cell comprising a nucleic acid encoding the antibody or antigen-binding fragment under conditions to produce the antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell or cell culture.

18.

21. A method of detecting the presence of PHF-tau in a biological sample from a subject, comprising contacting the biological sample with the antibody or antigen-binding fragment of claim 2any one of claims 1-12 and detecting binding of the antibody or antigen-binding fragment to PHF-tau in the sample from the subject.

19.

The method of claim 1821 wherein the biological sample is a blood, serum, plasma, interstitial fluid, or cerebral spinal fluid sample.

20. An isolated antibody or antigen binding fragment thereof which binds to PHF tau comprising: a) a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:80, b) a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ

ID NO:81, c) a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:9, d) a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:70, e) a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:20, and f) a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:21.

21. The isolated antibody or antigen binding fragment thereof of claim 20 comprising: a) the heavy chain variable region CDR1 having the amino acid sequence of SEQ ID NO:80, b) the heavy chain variable region CDR2 having the amino acid sequence of SEQ ID NO:81, c) the heavy chain variable region CDR3 having the amino acid sequence of SEQ ID NO:9, d) the light chain variable region CDR1 having the amino acid sequence of SEQ ID NO:70, e) the light chain variable region CDR2 having the amino acid sequence of SEQ ID NO:20, and f) the light chain variable region CDR3 having the amino acid sequence of SEQ ID NO:21.

22. An isolated antibody or antigen binding fragment thereof which binds to PHF tau comprising: a) a heavy chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:71, b) a heavy chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:72, c) a heavy chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:73, d) a light chain variable region CDR1 comprising the amino acid sequence of SEQ ID NO:70, e) a light chain variable region CDR2 comprising the amino acid sequence of SEQ ID NO:20, and f) a light chain variable region CDR3 comprising the amino acid sequence of SEQ ID NO:21.

23. The isolated antibody or antigen binding fragment thereof of claim 22 comprising: a) the heavy chain variable region CDR1 having the amino acid sequence of SEQ ID NO:71, b) the heavy chain variable region CDR2 having the amino acid sequence of SEQ ID NO:72, c) the heavy chain variable region CDR3 having the amino acid sequence of SEQ ID NO:73, d) the light chain variable region CDR1 having the amino acid sequence of SEQ ID NO:70, e) the light chain variable region CDR2 having the amino acid sequence of SEQ ID NO:20, and f) the light chain variable region CDR3 having the amino acid sequence of SEQ ID NO:21.

24. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain variable region having the polypeptide sequence of amino acids 1-188 of SEQ ID NO:74, and a light chain variable region having the polypeptide sequence of amino acids 1-107 of SEQ ID NO:75.

25. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain variable region having the polypeptide sequence of amino acids 1-118 of SEQ ID NO:76, and a light chain variable region having the polypeptide sequence of amino acids 1-107 of SEQ ID NO:77.

26. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain variable region having the polypeptide sequence of SEQ ID NO:27, and a light chain variable region having the polypeptide sequence of SEQ ID NO:31.

27. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment of claim 26.

28. A vector comprising the isolated nucleic acid of claim 27.

29. A host cell comprising the nucleic acid of claim 28.

30. A pharmaceutical composition comprising the isolated monoclonal antibody or antigen-binding fragment of claim 26 and a pharmaceutically acceptable carrier.

31. Use of the pharmaceutical composition of claim 30 in the manufacture of a medicament to ~~A method of reducing~~ pathological tau aggregation or spreading of tauopathy in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 30.

32. Use of the pharmaceutical composition of claim 30 in the manufacture of a medicament to ~~A method of~~ slowing progression of a tauopathy in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 30.

33. ~~The method~~ use of claim 32 wherein the tauopathy is selected from the group consisting of Alzheimer's disease, frontotemporal dementia, and progressive supranuclear palsy.

34. ~~The method~~ use of claim 33 wherein the tauopathy is Alzheimer's disease.

35. The method-use of claim 34 wherein the Alzheimer's disease is familial Alzheimer's disease.

36. The method-use of claim 34 wherein the Alzheimer's disease sporadic Alzheimer's disease.

37. The method-use of claim 33 wherein the tauopathy is frontotemporal dementia.

38. The method-use of claim 37 wherein the frontotemporal dementia is frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17).

39. The method-use of claim 33 wherein the tauopathy is progressive supranuclear palsy.

40. A method of producing the monoclonal antibody or antigen-binding fragment of claim 26 comprising culturing a cell comprising a nucleic acid encoding the antibody or antigen-binding fragment under conditions to produce the antibody or antigen-binding fragment, and recovering the antibody or antigen-binding fragment from the cell or cell culture.

41. The pharmaceutical composition of claim 7 or claim 30 for use in:

a) reducing pathological tau aggregation or spreading of tauopathy; or

22- b) slowing progression of a tauopathy in a subject in need thereof.