

CLAIMS

We claim:

1. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to a phosphorylated tau protein at a phosphorylated epitope comprising
 - (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 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 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: 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 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 having a polypeptide sequence of any of SEQ ID NOs: 26, 27, 28 and 29, and a light chain variable region 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 a heavy chain variable region 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 78, and a light chain variable region having a polypeptide sequence at least 95% identical to a V_L from a light chain of any of SEQ ID NOs: 31, 75, 77 and 79.
7. The isolated monoclonal antibody or antigen-binding fragment of claim 6 comprising a heavy chain variable region having a polypeptide sequence of a V_H from a heavy chain having a polypeptide sequence of any of SEQ ID NOs: 45, 74, 76 and 78, and a light chain variable region having a polypeptide sequence of a V_L from a light chain of any of SEQ ID NOs: 31, 75, 77 and 79.
8. The isolated monoclonal antibody or antigen-binding fragment of claim 3 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.
13. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment of any of claims 1-12.
14. A vector comprising the isolated nucleic acid of claim 13.
15. A host cell comprising the nucleic acid of claim 14.

16. A pharmaceutical composition comprising the isolated monoclonal antibody or antigen-binding fragment of any one of claims 1-12 and a pharmaceutically acceptable carrier.
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 16.
18. A method of treating a tauopathy in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 16.
19. The method of claim 18 wherein the tauopathy is selected from the group consisting of familial Alzheimer's disease, sporadic Alzheimer's disease, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), progressive supranuclear palsy, corticobasal degeneration, Pick's disease, progressive 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).
20. A method of producing the monoclonal antibody or antigen-binding fragment of any 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.
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 any one of claims 1-12 and detecting binding of the antibody or antigen-binding fragment to PHF-tau in the sample from the subject.

22. The method of claim 21 wherein the biological sample is a blood, serum, plasma, interstitial fluid, or cerebral spinal fluid sample.