

Claims

1. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to a tau protein at an epitope of the tau protein consisting of or within the amino acid sequence of SEQ ID NO: 1, wherein the antibody or antigen-binding fragment thereof binds paired helical filament (PHF)-tau, preferably human PHF-tau.
2. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1 , wherein:
 - (a) the epitope of the tau protein comprises either one of phosphorylated S433 or phosphorylated S435 of the tau protein, but does not comprise phosphorylated S433 and phosphorylated S435;
 - (b) the epitope of the tau protein comprises one or more of phosphorylated T427, phosphorylated S433 and phosphorylated S435 of the tau protein, but does not comprise all of phosphorylated T427, phosphorylated S433 and phosphorylated S435;
 - (c) the epitope of the tau protein comprises one or more of phosphorylated T427 and phosphorylated S433 of the tau protein, but does not comprise phosphorylated S435, and does not comprise all of phosphorylated T427, phosphorylated S433 and phosphorylated S435; or
 - (d) the epitope of the tau protein comprises phosphorylated T427 of the tau protein, but does not comprise phosphorylated S433 or phosphorylated S435.
3. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1 or 2 comprising:
 - (a) immunoglobulin heavy chain HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 4, 5 and 6, respectively; and immunoglobulin light chain FCDR1, FCDR2 and FCDR3 having the polypeptide sequences of SEQ ID NOs: 7, 8 and 9, respectively;
 - (b) immunoglobulin heavy chain HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 14, 15 and 16, respectively; and immunoglobulin light chain LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 17, 18 and 19, respectively;

- (c) immunoglobulin heavy chain HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 24, 25 and 26, respectively; and immunoglobulin light chain LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 27, 18 and 19, respectively;
 - (d) immunoglobulin heavy chain HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 32, 33 and 34, respectively; and immunoglobulin light chain LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 17, 18 and 35, respectively; or
 - (e) immunoglobulin heavy chain HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 40, 41 and 42, respectively; and immunoglobulin light chain LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 17, 18 and 43, respectively.
4. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 3, comprising a heavy chain variable region having a polypeptide sequence at least 90% identical to SEQ ID NO: 2, 12, 22, 30 or 38, or a light chain variable region having a polypeptide sequence at least 90% identical to SEQ ID NO: 3, 13, 23, 31 or 39.
5. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 4, comprising a heavy chain variable region having a polypeptide sequence of SEQ ID NO: 2, 12, 22, 30 or 38, or a light chain variable region having a polypeptide sequence of SEQ ID NO: 3, 13, 23, 31 or 39.
6. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 5, comprising:
- (a) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 2, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 3;
 - (b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 12, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 13;
 - (c) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 22, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 23;

- (d) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 30, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 31; or
 - (e) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 38, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 39.
7. The isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 6, comprising:
- (a) a heavy chain having the polypeptide sequence of SEQ ID NO: 10, and a light chain having the polypeptide sequence of SEQ ID NO: 11;
 - (b) a heavy chain having the polypeptide sequence of SEQ ID NO: 20, and a light chain having the polypeptide sequence of SEQ ID NO: 21;
 - (c) a heavy chain having the polypeptide sequence of SEQ ID NO: 28, and a light chain having the polypeptide sequence of SEQ ID NO: 29;
 - (d) a heavy chain having the polypeptide sequence of SEQ ID NO: 36, and a light chain having the polypeptide sequence of SEQ ID NO: 37; or
 - (e) a heavy chain having the polypeptide sequence of SEQ ID NO: 44, and a light chain having the polypeptide sequence of SEQ ID NO: 45.
8. An isolated monoclonal antibody or antigen-binding fragment thereof, comprising:
- (a) an immunoglobulin heavy chain HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 4, 5 and 6, respectively; and immunoglobulin light chain LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 7, 8 and 9, respectively;
 - (b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 2, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 3; or
 - (c) a heavy chain having the polypeptide sequence of SEQ ID NO: 10, and a light chain having the polypeptide sequence of SEQ ID NO: 11.
9. An isolated monoclonal antibody or antigen-binding fragment thereof, comprising:
- (a) immunoglobulin heavy chain HCDR1, HCDR2 and HCDR3 having the polypeptide sequences of SEQ ID NOs: 14, 15 and 16, respectively; and immunoglobulin light chain

LCDR1, LCDR2 and LCDR3 having the polypeptide sequences of SEQ ID NOs: 17, 18 and 19, respectively;

(b) a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 12, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 13; or

(c) a heavy chain having the polypeptide sequence of SEQ ID NO: 20, and a light chain having the polypeptide sequence of SEQ ID NO: 21.

10. An isolated nucleic acid encoding the isolated monoclonal antibody or antigen-binding fragment thereof of any of claims 1 to 9.

11. A vector comprising the isolated nucleic acid of claim 10.

12. A host cell comprising the isolated nucleic acid of claim 10.

13. A pharmaceutical composition comprising the isolated monoclonal antibody or antigen binding fragment thereof of any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13 for use in blocking tau seeding in a subject in need thereof.

15. The pharmaceutical composition of claim 13 for use in treating a tauopathy in a subject in need thereof.

16. The pharmaceutical composition of claim 13 for use in reducing pathological tau aggregation or spreading of tauopathy in a subject in need thereof.

17. The pharmaceutical composition of claim 15 or 16, 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-Straussler-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).

18. A method of producing the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 9, comprising culturing a cell comprising a nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof under conditions to produce the monoclonal antibody or antigen-binding fragment thereof, and recovering the monoclonal antibody or antigen-binding fragment thereof from the cell or cell culture.

19. A method of detecting the presence of PHF-tau in a biological sample from a subject, comprising contacting the biological sample with the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 9, and detecting binding of the monoclonal antibody or antigen-binding fragment thereof to PHF-tau in the sample from the subject.

20. The method of claim 19, wherein the biological sample is a blood, serum, plasma, interstitial fluid, or cerebral spinal fluid sample.