

CLAIMS

It is claimed:

1. An isolated monoclonal antibody or antigen-binding fragment thereof comprising a heavy chain variable region having a polypeptide sequence selected from SEQ ID NO: 71, 45, 51, 57, 63, 69, 39, 41, 43, 47, 49, 53, 55, 59, 61, 65, or 67, or a light chain variable region having a polypeptide sequence selected from SEQ ID NO: 72, 46, 52, 58, 64, 70, 40, 42, 44, 48, 50, 54, 56, 62, 66, or 68, wherein the monoclonal antibody or antigen-binding fragment thereof specifically binds paired helical filament (PHF)-tau, preferably human PHF-tau.
2. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the monoclonal antibody or antigen-binding fragment thereof comprises:
 - a. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 71, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 72;
 - b. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 45, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 46;
 - c. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 51, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 52;
 - d. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 57, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 58;
 - e. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 63, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 64;
 - f. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 69, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 70;
 - g. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 39, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 40;

- h. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 41, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 42;
 - i. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 43, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 44;
 - j. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 47, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 48;
 - k. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 49, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 50;
 - l. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 53, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 54;
 - m. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 55, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 56;
 - n. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 59, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 60;
 - o. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 61, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 62;
 - p. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 65, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 66; or
 - q. a heavy chain variable region having the polypeptide sequence of SEQ ID NO: 67, and a light chain variable region having the polypeptide sequence of SEQ ID NO: 68.
3. The isolated monoclonal antibody or antigen-binding fragment thereof of claim 1, wherein the monoclonal antibody or antigen-binding fragment thereof comprises:

- a. a heavy chain having the polypeptide sequence of SEQ ID NO: 37, and a light chain having the polypeptide sequence of SEQ ID NO: 38;
- b. a heavy chain having the polypeptide sequence of SEQ ID NO: 11, and a light chain having the polypeptide sequence of SEQ ID NO: 12;
- c. a heavy chain having the polypeptide sequence of SEQ ID NO: 17, and a light chain having the polypeptide sequence of SEQ ID NO: 18;
- d. a heavy chain having the polypeptide sequence of SEQ ID NO: 23, and a light chain having the polypeptide sequence of SEQ ID NO: 24;
- e. a heavy chain having the polypeptide sequence of SEQ ID NO: 29, and a light chain having the polypeptide sequence of SEQ ID NO: 30;
- f. a heavy chain having the polypeptide sequence of SEQ ID NO: 35, and a light chain having the polypeptide sequence of SEQ ID NO: 36;
- g. a heavy chain having the polypeptide sequence of SEQ ID NO: 5, and a light chain having the polypeptide sequence of SEQ ID NO: 6;
- h. a heavy chain having the polypeptide sequence of SEQ ID NO: 7, and a light chain having the polypeptide sequence of SEQ ID NO: 8;
- i. a heavy chain having the polypeptide sequence of SEQ ID NO: 9, and a light chain having the polypeptide sequence of SEQ ID NO: 10;
- j. a heavy chain having the polypeptide sequence of SEQ ID NO: 13, and a light chain having the polypeptide sequence of SEQ ID NO: 14;
- k. a heavy chain having the polypeptide sequence of SEQ ID NO: 15, and a light chain having the polypeptide sequence of SEQ ID NO: 16;
- l. a heavy chain having the polypeptide sequence of SEQ ID NO: 19, and a light chain having the polypeptide sequence of SEQ ID NO: 20;
- m. a heavy chain having the polypeptide sequence of SEQ ID NO: 21, and a light chain having the polypeptide sequence of SEQ ID NO: 22;
- n. a heavy chain having the polypeptide sequence of SEQ ID NO: 25, and a light chain having the polypeptide sequence of SEQ ID NO: 26;
- o. a heavy chain having the polypeptide sequence of SEQ ID NO: 27, and a light chain having the polypeptide sequence of SEQ ID NO: 28;
- p. a heavy chain having the polypeptide sequence of SEQ ID NO: 31, and a light chain having the polypeptide sequence of SEQ ID NO: 32; or
- q. a heavy chain having the polypeptide sequence of SEQ ID NO: 33, and a light chain having the polypeptide sequence of SEQ ID NO: 34.

4. An isolated nucleic acid encoding the monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 3.
5. A vector comprising the isolated nucleic acid of claim 4.
6. A host cell comprising the nucleic acid of claim 5.
7. A pharmaceutical composition comprising the isolated monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 3 and a pharmaceutically acceptable carrier.
8. 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.
9. A method of treating a tauopathy in a subject in need thereof, comprising administering to the subject the pharmaceutical composition of claim 7.
10. The method of claim 9 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).
11. A method of producing a monoclonal antibody or antigen-binding fragment thereof of any one of claims 1 to 3, the method 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.

12. 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 3 and detecting binding of the monoclonal antibody or antigen-binding fragment thereof to PHF-tau in the sample from the subject.

13. The method of claim 12, wherein the biological sample is a blood, serum, plasma, interstitial fluid, or cerebral spinal fluid sample.