WHAT IS CLAIMED IS:

1. A human monoclonal anti-tau antibody, or a tau binding fragment thereof, wherein the antibody binds to the same epitope of tau as an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

2. A monoclonal anti-tau antibody, or a tau binding fragment thereof which is characterized by one or more of:

(i) capable of binding recombinant human tau;

(ii) capable of binding pathologically modified tau;

(iii) binds to pathologically aggregated tau at the pre-tangle stage, in neurofibrillary tangles (NFT), neuropil threads and/or dystrophic neurites in the brain

(iv) does not substantially bind to physiological forms of tau in the brain;

(v) specifically binds any one of tau isoforms B to F or fetal tau represented by SEQ ID NOs: 1 to 6;

(vi) specifically binds a tau C-terminus;

(vii) specifically binds a tau N-terminus

(viii) specifically binds a tau epitope located in the microtubule binding domain which is masked in physiological microtubule-associated tau;

(ix) specifically binds pathologically aggregated tau at the pre-tangle stage, in neurofibrillary tangles (NFT), neuropil threads and/or dystrophic neurites in the brain; and

(x) specifically binds a tau epitope which comprises an amino acid sequence selected from the group consisting of residues 125-131, 397-441, 226-244, 217-227, 37-55, 387-406, 421-427, 427-439, 1-158, 197-207, 57-67, 355-441, 313-319, 309-319, and 221-231 of SEQ ID NO:6,

wherein the antibody binds to the same epitope of tau as an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

3. The monoclonal anti-tau antibody of claims 1 or 2 comprising a heavy chain variable region VH, wherein the heavy chain variable region comprises one, two or three VH CDRs of an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

4. The monoclonal anti-tau antibody of claim 3 comprising a VH CDR1, VH CDR2, and VH CDR3 of an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

5. The monoclonal anti-tau antibody of claim 3 comprising one or more of:

(a) a VH CDR1 selected from the group consisting of: SEQ ID NO: 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163;

(b) a VH CDR2 selected from the group consisting of: SEQ ID NO: 80, 86, 92, 98, 104, 110, 116, 122, 128, 134, 140, 146, 152, 158, and 164; and

(c) a VH CDR3 selected from the group consisting of: SEQ ID NO: 81, 87, 93, 99, 105, 111, 117, 123, 129, 135, 141, 147, 153, 159, and 165.

6. The monoclonal anti-tau antibody of claim 4 comprising:

(a) a VH CDR1 selected from the group consisting of: SEQ ID NO: 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151, 157, and 163;

(b) a VH CDR2 selected from the group consisting of: SEQ ID NO: 80, 86, 92, 98, 104, 110, 116, 122, 128, 134, 140, 146, 152, 158, and 164; and

(c) a VH CDR3 selected from the group consisting of: SEQ ID NO: 81, 87, 93, 99, 105, 111, 117, 123, 129, 135, 141, 147, 153, 159, and 165.

7. The monoclonal anti-tau antibody of claim 6 comprising the VH CDR1, VH CDR2, and VH CDR3 of an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4, wherein the VH CDR1, VH CDR2, and VH CDR3 are defined as listed in Table 2.

8. The monoclonal anti-tau antibody of any one of claims 1 to 7 comprising a light chain variable region VL, wherein the light chain variable region comprises one, two or three VL CDRs of an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

9. The monoclonal anti-tau antibody of claim 8 comprising a VL CDR1, VL CDR2, and VL CDR3 of an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

10. The monoclonal anti-tau antibody of claim 8 comprising one or more of:

(a) a VL CDR1 selected from the group consisting of: SEQ ID NO: 82, 88, 94, 100, 106, 112, 118, 124, 130, 136, 142, 148, 154, 160, 166 and 224;

(b) a VL CDR2 selected from the group consisting of: SEQ ID NO: 83, 89, 95, 101, 107, 113, 119, 125, 131, 137, 143, 149, 155, 161, and 167; and

(c) a VL CDR3 selected from the group consisting of: SEQ ID NO: 84, 90, 96, 102, 108, 114, 120, 126, 132, 138, 144, 150, 156, 162, and 168.

11. The monoclonal anti-tau antibody of claim 9 comprising:

(a) a VL CDR1 selected from the group consisting of: SEQ ID NO: 82, 88, 94, 100, 106, 112, 118, 124, 130, 136, 142, 148, 154, 160, 166 and 224;

(b) a VL CDR2 selected from the group consisting of: SEQ ID NO: 83, 89, 95, 101, 107, 113, 119, 125, 131, 137, 143, 149, 155, 161, and 167; and

(c) a VL CDR3 selected from the group consisting of: SEQ ID NO: 84, 90, 96, 102, 108, 114, 120, 126, 132, 138, 144, 150, 156, 162, and 168.

12. The monoclonal anti-tau antibody of claim 11 comprising the VL CDR1, VL CDR2, and VL CDR3 of an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4, wherein the VL CDR1, VL CDR2, and VL CDR3 are defined as listed in Table 2

13. The monoclonal anti-tau antibody of any one of claims 1 to 12 comprising a heavy chain variable region VH at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO: 44, 45, 47, 48, 50, 52, 54, 56, 58, 60, 62, 65, 67, 69, 71, 73, 75, 76, and 220.

14. The monoclonal anti-tau antibody of claim 13, wherein the heavy chain variable region comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 44, 45, 47, 48, 50, 52, 54, 56, 58, 60, 62, 65, 67, 69, 71, 73, 75, 76, and 220.

15. The monoclonal anti-tau antibody of any one of claims 1 to 14 comprising a light chain variable region VL at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to an amino acid sequence selected from the group consisting of: SEQ ID NO: 46, 49, 51, 53, 55, 57, 59, 61, 63, 64, 66, 68, 70, 72, 74, 77, 78, 221, and 222.

16. The monoclonal anti-tau antibody of claim 15, wherein the light chain variable region comprises an amino acid sequence selected from the group consisting of: SEQ ID NO: 46, 49, 51, 53, 55, 57, 59, 61, 63, 64, 66, 68, 70, 72, 74, 77, 78, 221, and 222.

17. The monoclonal anti-tau antibody of any one of claims 1 to 16 comprising a VH and VL pair selected from the group consisting of: a VH of SEQ ID NO: 45 and a VL of SEQ ID

NO: 46; a VH of SEQ ID NO: 45 and a VL of SEQ ID NO: 221; a VH of SEQ ID NO: 45 and a VL of SEQ ID NO: 222; a VH of SEQ ID NO: 48 and a VL of SEQ ID NO: 49; a VH of SEQ ID NO: 50 and a VL of SEQ ID NO: 51; a VH of SEQ ID NO: 52 and a VL of SEQ ID NO: 53; a VH of SEQ ID NO: 54 and a VL of SEQ ID NO: 55; a VH of SEQ ID NO: 220 and a VL of SEQ ID NO: 55; a VH of SEQ ID NO: 56 and a VL of SEQ ID NO: 57; a VH of SEQ ID NO: 58 and a VL of SEQ ID NO: 59; a VH of SEQ ID NO: 60 and a VL of SEQ ID NO: 61; a VH of SEQ ID NO: 62 and a VL of SEQ ID NO: 64; a VH of SEQ ID NO: 65 and a VL of SEQ ID NO: 66; a VH of SEQ ID NO: 67 and a VL of SEQ ID NO: 68; a VH of SEQ ID NO: 69 and a VL of SEQ ID NO: 70; a VH of SEQ ID NO: 71 and a VL of SEQ ID NO: 72; a VH of SEQ ID NO: 73 and a VL of SEQ ID NO: 74; a VH of SEQ ID NO: 76 and a VL of SEQ ID NO: 78; a VH of SEQ ID NO: 44 and a VL of SEQ ID NO: 46; a VH of SEQ ID NO: 47 and a VL of SEQ ID NO: 49; a VH of SEQ ID NO: 62 and a VL of SEQ ID NO: 63; and a VH of SEQ ID NO: 75 and a VL of SEQ ID NO: 77.

18. A monoclonal antibody which binds to the same epitope of tau as an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

19. A monoclonal antibody which competes for specific binding to tau with an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4.

20. The antibody or tau binding fragment thereof of any one of claims 2 to 19 which is a human antibody, humanized antibody, chimeric murine-human antibody or murinized antibody.

21. The antibody or tau binding fragment thereof of any one of claims 1 to 20, which is selected from the group consisting of a single chain Fv fragment (scFv), an F(ab') fragment, an F(ab) fragment, and an $F(ab')_2$ fragment.

22. An isolated polypeptide comprising a VH and/or a VL of the antibody of any one of claims 3 to 21.

23. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of claim 22.

24. The polynucleotide of claim 23 comprising a nucleotide sequence selected from the group consisting of: SEQ ID NO: 169-202 and 223.

25. A vector comprising the polynucleotide of claims 23 or 24.

26. A host cell comprising the polynucleotide of claims 23 or 24 or the vector of claim 25.

27. A method for preparing an anti-tau antibody or tau binding fragment thereof, comprising

(a) culturing the cell of claim 26; and

(b) isolating said antibody or tau binding fragment thereof from the culture.

28. An anti-tau antibody or tau binding fragment thereof obtained by the method of claim 27.

29. The anti-tau antibody or tau binding fragment thereof of any one of claims 1 to 21 or 28; which is

(a) detectably labeled wherein the detectable label is selected from the group consisting of an enzyme, a radioisotope, a fluorophore and a heavy metal; or

(b) which is attached to a drug.

30. A composition comprising the anti-tau antibody or tau binding fragment thereof of any one of claims 1 to 21 or 28.

31. The composition of claim 30, which is a pharmaceutical composition further comprising a pharmaceutically acceptable carrier.

32. The composition of claims 30 or 31 further comprising an additional agent useful for treating a neurodegenerative tauopathy.

33. The composition of claim 30, which is a diagnostic composition, and optionally comprises reagents conventionally used in immuno or nucleic acid based diagnostic methods.

34. A method of treating a neurodegenerative tauopathy in a subject in need thereof, comprising administering a therapeutically effective amount of the antibody of any one of claims 1 to 21 or 28.

35. Use of an antibody of any one of claims 1 to 21 or 28 for the preparation of a pharmaceutical or diagnostic composition for prophylactic and therapeutic treatment, monitoring the progression, or monitoring the response to a treatment of a neurodegenerative tauopathy in a subject.

36. A method of diagnosing or monitoring the progression of a neurodegenerative tauopathy in a subject, the method comprising

(a) measuring the level of pathologically modified or aggregated tau in a sample from the subject to be diagnosed with the antibody or tau binding fragment thereof of any one of claims 1 to 21 or 28 by IHC; and

(b) comparing the level of modified or aggregated tau to a reference standard that indicates the level of the pathologically modified or aggregated tau in one or more control subjects,

wherein a difference or similarity between the level of pathologically modified or aggregated tau and the reference standard indicates that the subject has a neurodegenerative tauopathy.

37. The use of claim 35 or the method of claims 34 or 36, wherein the neurodegenerative tauopathy is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis/parkinsonism–dementia complex, argyrophilic grain dementia, British type amyloid angiopathy, cerebral amyloid angiopathy, corticobasal degeneration, Creutzfeldt-Jakob disease, dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, frontotemporal lobar degeneration, Gerstmann-Sträussler-Scheinker disease, Hallervorden-Spatz disease, inclusion body myositis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive

subcortical gliosis, progressive supranuclear palsy, subacute sclerosing panencephalitis, Tangle only dementia, multi-infarct dementia and ischemic stroke.

38. A method for *in vivo* detection of or targeting a therapeutic or diagnostic agent to tau in the human or animal body, comprising administering a composition comprising the antibody or tau binding fragment thereof of any one of claims 1 to 21 or 28 attached to a therapeutic or diagnostic agent.

39. The method of claim 38, wherein the *in vivo* detection comprises positron emission tomography (PET), single photon emission tomography (SPECT), near infrared (NIR) optical imaging or magnetic resonance imaging (MRI).

40. A peptide having an epitope of tau specifically recognized by an antibody selected from the group consisting of: NI-105.17C1, NI-105.6C5, NI-105.29G10, NI-105.6L9, NI-105.40E8, NI-105.48E5, NI-105.6E3, NI-105.22E1, NI-105.26B12, NI-105.12E12, NI-105.60E7, NI-105.14E2, NI-105.39E2, NI-105.19C6, and NI-105.9C4, wherein the peptide comprises an amino acid sequence selected from the group consisting of residues 125-131, 397-441, 226-244, 217-227, 37-55, 387-406, 421-427, 427-439, 1-158, 197-207, 57-67, 355-441, 313-319, 309-319, and 221-231 of SEQ ID NO:6 and combinations thereof.

41. A method for diagnosing a neurodegenerative tauopathy in a subject, comprising detecting the presence of an antibody that binds to the peptide of claim 36 in a biological sample of said subject.

42. A kit useful in the diagnosis of a neurodegenerative tauopathy, said kit comprising the antibody or tau binding fragment thereof of any one of claims 1 to 21 or 28, with reagents or instructions for use.

CLAIMS

1. A human monoclonal anti-tau antibody, or a tau binding fragment thereof, comprising a heavy chain variable domain, wherein:

(a) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:79, CDR2 comprises the amino acids set forth in SEQ ID NO:80, and CDR3 comprises the amino acids set forth in SEQ ID NO:81;

(b) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:85, CDR2 comprises the amino acids set forth in SEQ ID NO:86, and CDR3 comprises the amino acids set forth in SEQ ID NO:87;

(c) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:91, CDR2 comprises the amino acids set forth in SEQ ID NO:92, and CDR3 comprises the amino acids set forth in SEQ ID NO:93;

(d) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:97, CDR2 comprises the amino acids set forth in SEQ ID NO:98, and CDR3 comprises the amino acids set forth in SEQ ID NO:99;

(e) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:103, CDR2 comprises the amino acids set forth in SEQ ID NO:104, and CDR3 comprises the amino acids set forth in SEQ ID NO:105;

(f) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:109, CDR2 comprises the amino acids set forth in SEQ ID NO:110, and CDR3 comprises the amino acids set forth in SEQ ID NO:111;

(g) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:115, CDR2 comprises the amino acids set forth in SEQ ID NO:116, and CDR3 comprises the amino acids set forth in SEQ ID NO:117;

(h) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:121, CDR2 comprises the amino acids set forth in SEQ ID NO:122, and CDR3 comprises the amino acids set forth in SEQ ID NO:123;

(i) wherein heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:127, CDR2 comprises the amino acids set forth in SEQ ID NO:128, and CDR3 comprises the amino acids set forth in SEQ ID NO:129;

(j) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:133, CDR2 comprises the amino acids set forth in SEQ ID NO:134, and CDR3 comprises the amino acids set forth in SEQ ID NO:135;

(k) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:139, CDR2 comprises the amino acids set forth in SEQ ID NO:140, and CDR3 comprises the amino acids set forth in SEQ ID NO:141;

(l) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:145, CDR2 comprises the amino acids set forth in SEQ ID NO:146, and CDR3 comprises the amino acids set forth in SEQ ID NO:147;

(m) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:151, CDR2 comprises the amino acids set forth in SEQ ID NO:152, and CDR3 comprises the amino acids set forth in SEQ ID NO:153;

(n) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:157, CDR2 comprises the amino acids set forth in SEQ ID NO:158, and CDR3 comprises the amino acids set forth in SEQ ID NO:159; and

(o) heavy chain CDR1 comprises the amino acids set forth in SEQ ID NO:163, CDR2 comprises the amino acids set forth in SEQ ID NO:164, and CDR3 comprises the amino acids set forth in SEQ ID NO:165.

2. A human monoclonal anti-tau antibody, or a tau binding fragment thereof, comprising a light chain variable domain, wherein:

(a) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:82, CDR2 comprises the amino acids set forth in SEQ ID NO:83, and CDR3 comprises the amino acids set forth in SEQ ID NO:84;

(b) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:88, CDR2 comprises the amino acids set forth in SEQ ID NO:89, and CDR3 comprises the amino acids set forth in SEQ ID NO:90;

(c) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:94, CDR2 comprises the amino acids set forth in SEQ ID NO:95, and CDR3 comprises the amino acids set forth in SEQ ID NO:96;

(d) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:100, CDR2 comprises the amino acids set forth in SEQ ID NO:101, and CDR3 comprises the amino acids set forth in SEQ ID NO:102;

(e) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:106, CDR2 comprises the amino acids set forth in SEQ ID NO:107, and CDR3 comprises the amino acids set forth in SEQ ID NO:108;

(f) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:112, CDR2 comprises the amino acids set forth in SEQ ID NO:113, and CDR3 comprises the amino acids set forth in SEQ ID NO:114;

(g) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:118, CDR2 comprises the amino acids set forth in SEQ ID NO:119, and CDR3 comprises the amino acids set forth in SEQ ID NO:120;

(h) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:124, CDR2 comprises the amino acids set forth in SEQ ID NO:125, and CDR3 comprises the amino acids set forth in SEQ ID NO:126;

(i) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:130, CDR2 comprises the amino acids set forth in SEQ ID NO:131, and CDR3 comprises the amino acids set forth in SEQ ID NO:132;

(j) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:136, CDR2 comprises the amino acids set forth in SEQ ID NO:137, and CDR3 comprises the amino acids set forth in SEQ ID NO:138;

(k) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:142, CDR2 comprises the amino acids set forth in SEQ ID NO:143, and CDR3 comprises the amino acids set forth in SEQ ID NO:144;

(l) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:148, CDR2 comprises the amino acids set forth in SEQ ID NO:149, and CDR3 comprises the amino acids set forth in SEQ ID NO:150;

(m) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:154, CDR2 comprises the amino acids set forth in SEQ ID NO:155, and CDR3 comprises the amino acids set forth in SEQ ID NO:156;

(n) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:160, CDR2 comprises the amino acids set forth in SEQ ID NO:161, and CDR3 comprises the amino acids set forth in SEQ ID NO:162;

(o) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:166, CDR2 comprises the amino acids set forth in SEQ ID NO:167, and CDR3 comprises the amino acids set forth in SEQ ID NO:168; and

(p) light chain CDR1 comprises the amino acids set forth in SEQ ID NO:224, CDR2 comprises the amino acids set forth in SEQ ID NO:83, and CDR3 comprises the amino acids set forth in SEQ ID NO:84.

3. The anti-tau antibody or tau binding fragment according to claim 1 or claim 2, comprising a heavy chain variable domain and a light chain variable domain, wherein:

(a) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:79, CDR2 comprises the amino acids set forth in SEQ ID NO:80, and CDR3 comprises the amino acids set forth in SEQ ID NO:81 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:82, CDR2 comprises the amino acids set forth in SEQ ID NO:83, and CDR3 comprises the amino acids set forth in SEQ ID NO:84;

(b) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:85, CDR2 comprises the amino acids set forth in SEQ ID NO:86, and CDR3 comprises the amino acids set forth in SEQ ID NO:87 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:88, CDR2 comprises the amino acids set forth in SEQ ID NO:89, and CDR3 comprises the amino acids set forth in SEQ ID NO:90;

(c) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:91, CDR2 comprises the amino acids set forth in SEQ ID NO:92, and CDR3 comprises the amino acids set forth in SEQ ID NO:93 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:94, CDR2 comprises the amino acids set forth in SEQ ID NO:95, and CDR3 comprises the amino acids set forth in SEQ ID NO:96;

(d) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:97, CDR2 comprises the amino acids set forth in SEQ ID NO:98, and CDR3 comprises the amino acids set forth in SEQ ID NO:99 and a light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:100, CDR2 comprises the amino acids set forth in SEQ ID NO:101, and CDR3 comprises the amino acids set forth in SEQ ID NO:102;

(e) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:103, CDR2 comprises the amino acids set forth in SEQ ID NO:104, and CDR3 comprises the amino acids set forth in SEQ ID NO:105 and a light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:106, CDR2 comprises the amino acids set forth in SEQ ID NO:107, and CDR3 comprises the amino acids set forth in SEQ ID NO:108;

(f) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:109, CDR2 comprises the amino acids set forth in SEQ ID NO:110, and CDR3 comprises the amino acids set forth in SEQ ID NO:111 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:112, CDR2 comprises the amino acids set forth in SEQ ID NO:113, and CDR3 comprises the amino acids set forth in SEQ ID NO:114;

(g) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:115, CDR2 comprises the amino acids set forth in SEQ ID NO:116, and CDR3 comprises the amino acids set forth in SEQ ID NO:117 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:118, CDR2 comprises the amino acids set forth in SEQ ID NO:119, and CDR3 comprises the amino acids set forth in SEQ ID NO:120;

(h) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:121, CDR2 comprises the amino acids set forth in SEQ ID NO:122, and CDR3 comprises the amino acids set forth in SEQ ID NO:123 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:124, CDR2 comprises the amino acids set forth in SEQ ID NO:125, and CDR3 comprises the amino acids set forth in SEQ ID NO:126;

(i) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:127, CDR2 comprises the amino acids set forth in SEQ ID NO:128, and CDR3 comprises the amino acids set forth in SEQ ID NO:129 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:130, CDR2 comprises the amino acids set forth in SEQ ID NO:131, and CDR3 comprises the amino acids set forth in SEQ ID NO:132;

(j) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:133, CDR2 comprises the amino acids set forth in SEQ ID NO:134, and CDR3 comprises the amino acids set forth in SEQ ID NO:135 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:136, CDR2 comprises the amino acids set forth in SEQ ID NO:137, and CDR3 comprises the amino acids set forth in SEQ ID NO:138;

(k) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:139, CDR2 comprises the amino acids set forth in SEQ ID NO:140, and CDR3 comprises the amino acids set forth in SEQ ID NO:141 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:142, CDR2 comprises the amino acids set forth in SEQ ID NO:143, and CDR3 comprises the amino acids set forth in SEQ ID NO:144;

(l) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:145, CDR2 comprises the amino acids set forth in SEQ ID NO:146, and CDR3 comprises the amino acids set forth in SEQ ID NO:147 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:148, CDR2 comprises the amino acids set forth in SEQ ID NO:149, and CDR3 comprises the amino acids set forth in SEQ ID NO:150;

(m) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:151, CDR2 comprises the amino acids set forth in SEQ ID NO:152, and CDR3 comprises the amino acids set forth in SEQ ID NO:153 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:154, CDR2 comprises the amino acids set forth in SEQ ID NO:155, and CDR3 comprises the amino acids set forth in SEQ ID NO:156;

(n) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:157, CDR2 comprises the amino acids set forth in SEQ ID NO:158, and CDR3 comprises the amino acids set forth in SEQ ID NO:159 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:160, CDR2 comprises the amino acids set forth in SEQ ID NO:161, and CDR3 comprises the amino acids set forth in SEQ ID NO:162;

(o) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:163, CDR2 comprises the amino acids set forth in SEQ ID NO:164, and CDR3 comprises the amino acids set forth in SEQ ID NO:165 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:166, CDR2 comprises the amino acids set forth in SEQ ID NO:167, and CDR3 comprises the amino acids set forth in SEQ ID NO:168; and

(p) heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:79, CDR2 comprises the amino acids set forth in SEQ ID NO:80, and CDR3 comprises the amino acids set forth in SEQ ID NO:81 and light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:224, CDR2 comprises the amino acids set forth in SEQ ID NO:83, and CDR3 comprises the amino acids set forth in SEQ ID NO:84.

4. The anti-tau antibody or tau binding fragment according to claim 3, wherein:

the heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:85, CDR2 comprises the amino acids set forth in SEQ ID NO:86, and CDR3 comprises the amino acids set forth in SEQ ID NO:87; and

the light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:88, CDR2 comprises the amino acids set forth in SEQ ID NO:89, and CDR3 comprises the amino acids set forth in SEQ ID NO:90.

5. The anti-tau antibody or tau binding fragment according to claim 3, wherein

the heavy chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:103, CDR2 comprises the amino acids set forth in SEQ ID NO:104, and CDR3 comprises the amino acids set forth in SEQ ID NO:105; and

the light chain variable domain CDR1 comprises the amino acids set forth in SEQ ID NO:106, CDR2 comprises the amino acids set forth in SEQ ID NO:107, and CDR3 comprises the amino acids set forth in SEQ ID NO:108.

6. The anti-tau antibody or tau binding fragment according to claim 1, wherein the heavy chain variable domain sequence is at least 90% identical to the amino acids set forth in SEQ ID NO:44; SEQ ID NO:45; SEQ ID NO:47; SEQ ID NO:48; SEQ ID NO:50; SEQ ID NO:52; SEQ ID NO:54; SEQ ID NO:56; SEQ ID NO:58; SEQ ID NO:60; SEQ ID NO:62; SEQ ID NO:65; SEQ ID NO:67; SEQ ID NO:69; SEQ ID NO:71; SEQ ID NO:73; SEQ ID NO:75; SEQ ID NO:76; or SEQ ID NO:220.

7. The anti-tau antibody or tau binding fragment according to claim 6, wherein the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:44; SEQ ID NO:45; SEQ ID NO:47; SEQ ID NO:48; SEQ ID NO:50; SEQ ID NO:52; SEQ ID NO:54; SEQ ID NO:56; SEQ ID NO:58; SEQ ID NO:60; SEQ ID NO:62; SEQ ID NO:65; SEQ ID NO:67; SEQ ID NO:69; SEQ ID NO:71; SEQ ID NO:73; SEQ ID NO:75; SEQ ID NO:76; or SEQ ID NO:220.

8. The anti-tau antibody or tau binding fragment according to claim 2, wherein the light chain variable domain sequence is at least 90% identical to the amino acids set forth in SEQ ID NO:46; SEQ ID NO:49; SEQ ID NO:51; SEQ ID NO:53; SEQ ID NO:55; SEQ ID NO:57; SEQ ID NO:59; SEQ ID NO:61; SEQ ID NO:63; SEQ ID NO:64; SEQ ID NO:66; SEQ ID NO:68; SEQ ID NO:70; SEQ ID NO:72; SEQ ID NO:74; or SEQ ID NO:77; SEQ ID NO:78; SEQ ID NO:221; or SEQ ID NO:222.

9. The anti-tau antibody, or tau binding fragment according to claim 8, wherein the light chain variable domain comprises the amino acids set forth in SEQ ID NO:46; SEQ ID NO:49; SEQ ID NO:51; SEQ ID NO:53; SEQ ID NO:55; SEQ ID NO:57; SEQ ID NO:59; SEQ ID NO:61; SEQ ID NO:63; SEQ ID NO:64; SEQ ID NO:66; SEQ ID NO:68; SEQ ID NO:70; SEQ ID NO:72; SEQ ID NO:74; or SEQ ID NO:77; SEQ ID NO:78; SEQ ID NO:221; or SEQ ID NO:222.

10. The anti-tau antibody or tau binding fragment according to claim 3, wherein:

(a) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:44 or SEQ ID NO:45 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:46, SEQ ID NO:221, or SEQ ID NO:222;

(b) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:47 or SEQ ID NO:48 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:49;

(c) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:50 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:51;

(d) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:52 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:53;

(e) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:54 or SEQ ID NO:220 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:55;

(f) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:56 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:57;

(g) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:58 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:59;

(h) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:60 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:61;

(i) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:62 or SEQ ID NO:63 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:64;

(j) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:65 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:66;

(k) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:67 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:68;

(l) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:69 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:70;

(m) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:71 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:72;

(n) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:73 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:74;

or

(o) the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:75 or SEQ ID NO:76 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:77 or SEQ ID NO:76.

11. The anti-tau antibody or tau binding fragment according to claim 10, wherein the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:48 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:49.

12. An anti-tau antibody, or tau binding fragment thereof, that binds to the same epitope as the antibody or binding fragment of claim 11.

13. The anti-tau antibody or tau binding fragment according to claim 10, wherein the heavy chain variable domain comprises the amino acids set forth in SEQ ID NO:220 and the light chain variable domain comprises the amino acids set forth in SEQ ID NO:55.

14. An anti-tau antibody, or a tau binding fragment thereof, that binds to the same epitope as the antibody or binding fragment of claim 13.

15. The anti-tau antibody or tau binding fragment according to claim 10, wherein the heavy chain comprises the amino acids set forth in SEQ ID NO:218 and the light chain comprises the amino acids set forth in SEQ ID NO:219.

16. The monoclonal anti-tau antibody or tau binding fragment according to any one of claims 1-15, wherein:

(a) the antibody or binding fragment is capable of binding recombinant human tau;

(b) the antibody or binding fragment is capable of binding pathologically modified tau;

(c) the antibody or binding fragment binds to pathologically aggregated tau at the pre-tangle stage, in neurofibrillary tangles (NFT), neuropil threads and/or dystrophic neurites in the brain;

(d) the antibody or binding fragment is does not substantially bind to physiological forms of tau in the brain;

(e) the antibody or binding fragment is specifically binds a tau epitope located in the microtubule binding domain which is masked in physiological microtubule-associated tau;

(f) the antibody or binding fragment is specifically binds pathologically aggregated tau at the pre-tangle stage, in neurofibrillary tangles (NFT), neuropil threads and/or dystrophic neurites in the brain; and

(g) the antibody or binding fragment is specifically binds a tau epitope which comprises an amino acid sequence selected from the group consisting of residues 125-131, 397-441, 226-244, 217-227, 37-55, 387-406, 421-427, 427-439, 1-158, 197-207, 57-67, 355-441, 313-319, 309-319, and 221-231 of SEQ ID NO:6.

17. The antibody or tau binding fragment of any one of claims 1-16, wherein the antibody is a human antibody or a humanized antibody, and/or the tau binding fragment is a single chain Fv fragment (scFv), an F(ab') fragment, an F(ab) fragment, or an $F(ab')_2$ fragment.

18. An isolated polynucleotide comprising a nucleotide sequence encoding the antibody or tau binding fragment of any one of claims 1-17.

19. The polynucleotide of claim 18 comprising:

(a) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:169 or SEQ ID NO:170 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:171;

(b) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:172 or SEQ ID NO:173 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:174;

(c) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:175 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:176;

(d) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:177 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:178;

(e) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:179 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:180;

(f) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:181 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:182;

(g) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:183 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:184;

(h) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:185 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:186;

(i) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:187 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:188 or SEQ ID NO:223;

(j) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:189 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:190;

(k) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:191 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:192;

(l) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:193 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:194;

(m) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:195 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:196;

(n) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:197 and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:198;

or

(o) a sequence of nucleotides encoding a heavy chain variable domain that comprises the nucleotides set forth in SEQ ID NO:199 or SEQ ID NO:200

and a sequence of nucleotides encoding a light chain variable domain that comprises the nucleotides set forth in SEQ ID NO:201 or SEQ ID NO:202.

20. A pharmaceutical composition comprising the anti-tau antibody or tau binding fragment of any one of claims 1-17 or the nucleotide sequence of claim 18 or 19 for use in treating a neurodegenerative tauopathy.

21. The composition for use according to claim 20, wherein the neurodegenerative tauopathy is selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis/parkinsonism–dementia complex, argyrophilic grain dementia, British type amyloid angiopathy, cerebral amyloid angiopathy, corticobasal degeneration, Creutzfeldt-Jakob disease, dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, frontotemporal lobar degeneration, Gerstmann-Sträussler-Scheinker disease, Hallervorden-Spatz disease, inclusion body myositis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C, non-Guamanian motor neuron disease with neurofibrillary tangles, Pick's disease, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, progressive supranuclear palsy, subacute sclerosing panencephalitis, Tangle only dementia, multi-infarct dementia and ischemic stroke.

22. A method of diagnosing or monitoring the progression of a neurodegenerative tauopathy in a subject, the method comprising

(a) measuring the level of pathologically modified or aggregated tau in a sample from the subject to be diagnosed with the antibody or tau binding fragment of any one of claims 1-16; and

(b) comparing the level of modified or aggregated tau to a reference standard that indicates the level of the pathologically modified or aggregated tau in one or more control subjects,

wherein a difference or similarity between the level of pathologically modified or aggregated tau and the reference standard indicates that the subject has a neurodegenerative tauopathy.