

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to human Tau, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 605; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 606; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 607.
2. The antibody of claim 1, wherein the antibody comprises HVR-L1 comprising the amino acid sequence of SEQ ID NO: 608; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 609; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 610.
3. An isolated antibody that binds to human Tau, wherein the antibody comprises HVR-L1 comprising the amino acid sequence of SEQ ID NO: 608; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 609; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 610.
4. An isolated antibody that binds to human Tau, wherein the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 605; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 606; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 607; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 608; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 609; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 610.
5. The antibody of claim 1, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau.
6. The antibody of claim 1 or claim 2, wherein the antibody binds an epitope within amino acids 2 to 24 of mature human Tau.
7. The isolated antibody of any one of claims 1 to 3, which is a monoclonal antibody.
8. The isolated antibody of any one of the preceding claims, which is a human, humanized, or chimeric antibody.
9. The antibody of any one of the preceding claims, which is an antibody fragment that binds human Tau.
10. The antibody of any one of the preceding claims, wherein the human Tau comprises the sequence of SEQ ID NO: 2.
11. The antibody of any one of the preceding claims, wherein the antibody comprises:
 - a) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 603;

- b) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 604;
 - c) a VH as in (a) and a VL as in (b);
 - d) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 614;
 - e) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 615;
 - f) a VH as in (d) and a VL as in (e);
 - g) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 619;
 - h) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 620;
 - i) a VH as in (g) and a VL as in (h).
12. The antibody of any one of the preceding claims, wherein the antibody comprises:
- a) a heavy chain variable region (VH) comprising SEQ ID NO: 603;
 - b) a light chain variable region (VL) comprising SEQ ID NO: 604;
 - c) a VH as in (a) and a VL as in (b);
 - d) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 614;
 - e) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 615;
 - f) a VH as in (d) and a VL as in (e);
 - g) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 619;
 - h) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 620;
 - i) a VH as in (g) and a VL as in (h).
13. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 603, 614, and 619; and a light chain variable region comprising a sequence selected from SEQ ID NOs: 604, 615, and 620.
14. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising a sequence selected from SEQ ID NOs:

340, 603, 614, and 619; and a light chain variable region comprising a sequence selected from SEQ ID NOs: 604, 615, and 620.

15. The isolated antibody of any one of the preceding claims, wherein the antibody comprises a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 603, 614, and 619; and a light chain variable region comprising a sequence selected from SEQ ID NOs: 341, 604, 615, and 620.

16. The isolated antibody of any one of the preceding claims, wherein the antibody comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 340 and a light chain variable region comprising a sequence selected from SEQ ID NOs: 604, 615, and 620; (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 603 and a light chain variable region comprising a sequence selected from SEQ ID NOs: 341, 604, 615, and 620; (c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 614 and a light chain variable region comprising a sequence selected from SEQ ID NOs: 341, 604, 615, and 620; (d) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 619 and a light chain variable region comprising a sequence selected from SEQ ID NOs: 341, 604, 615, and 620; (e) a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 603, 614, and 619 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 341; (f) a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 340, 603, 614, and 619 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 604; (g) a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 340, 603, 614, and 619 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 615; and (h) a heavy chain variable region comprising a sequence selected from SEQ ID NOs: 340, 603, 614, and 619 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 620.

17. The isolated antibody of any one of the preceding claims, wherein the antibody comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 603 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 604; (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 614 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 615; or (c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 619 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 620.

18. An isolated antibody that binds to human Tau, wherein the antibody comprises (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 603 and

a light chain variable region comprising the amino acid sequence of SEQ ID NO: 604; (b) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 614 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 615; or (c) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 619 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 620.

19. The isolated antibody of any one of the preceding claims, wherein the antibody comprises:

- a) a heavy chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 611 or SEQ ID NO: 612 and a light chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 613; or
- b) a heavy chain comprising the amino acid sequence of SEQ ID NO: 611 or SEQ ID NO: 612 and a light chain comprising the amino acid sequence of SEQ ID NO: 613; or
- c) a heavy chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 616 or SEQ ID NO: 617 and a light chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 618; or
- d) a heavy chain comprising the amino acid sequence of SEQ ID NO: 616 or SEQ ID NO: 617 and a light chain comprising the amino acid sequence of SEQ ID NO: 618; or
- e) a heavy chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 621 or SEQ ID NO: 622 and a light chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 623; or
- f) a heavy chain comprising the amino acid sequence of SEQ ID NO: 621 or SEQ ID NO: 622 and a light chain comprising the amino acid sequence of SEQ ID NO: 623.

20. An isolated antibody that binds to human Tau, wherein the antibody comprises (a) a heavy chain comprising the amino acid sequence of SEQ ID NO: 611 or SEQ ID NO: 612 and a light chain comprising the amino acid sequence of SEQ ID NO: 613; (b) a heavy chain

comprising the amino acid sequence of SEQ ID NO: 616 or SEQ ID NO: 617 and a light chain comprising the amino acid sequence of SEQ ID NO: 618; or (c) a heavy chain comprising the amino acid sequence of SEQ ID NO: 621 or SEQ ID NO: 622 and a light chain comprising the amino acid sequence of SEQ ID NO: 623.

21. An isolated antibody that binds to human Tau, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 611 or SEQ ID NO: 612 and a light chain consisting of the amino acid sequence of SEQ ID NO: 613; (b) a heavy chain consisting of the amino acid sequence of SEQ ID NO: 616 or SEQ ID NO: 617 and a light chain consisting of the amino acid sequence of SEQ ID NO: 618; or (c) a heavy chain consisting of the amino acid sequence of SEQ ID NO: 621 or SEQ ID NO: 622 and a light chain consisting of the amino acid sequence of SEQ ID NO: 623.

22. The isolated antibody of any one of the preceding claims, wherein the antibody is an IgG1 or an IgG4 antibody.

23. The isolated antibody of claim 22, wherein the antibody is an IgG4 antibody.

24. The isolated antibody of claim 23, wherein the antibody comprises M252Y, S254T, and T256E mutations.

25. The isolated antibody of claim 23 or claim 24, wherein the antibody comprises an S228P mutation.

26. The isolated antibody of any one of claims 1 to 18 and 22 to 25, which is an antibody fragment.

27. The isolated antibody of any one of the preceding claims, wherein the antibody binds each of monomeric Tau, phosphorylated Tau, non-phosphorylated Tau, and oligomeric Tau with a K_D of less than 100 nM, less than 75 nM, less than 50 nM, less than 10 nM, less than 5 nM, or less than 1 nM.

28. The isolated antibody of any one of the preceding claims, wherein the antibody binds to human monomeric Tau with a K_D of less than 1 nM.

29. The isolated antibody of claim 27 or claim 28, wherein K_D is determined by surface plasmon resonance at 37°C.

30. The isolated antibody of any one of the preceding claims, which binds cynomolgus monkey Tau.

31. An isolated nucleic acid that encodes the antibody of any one of the preceding claims.

32. A host cell comprising the nucleic acid of claim 31.

33. A method of producing an antibody comprising culturing the host cell of claim 32 under conditions suitable for producing the antibody.
34. An immunoconjugate comprising the isolated antibody of any one of claims 1 to 30 and a second therapeutic agent.
35. A labeled antibody comprising the antibody of any one of claims 1 to 30 and a detectable label.
36. A pharmaceutical composition comprising the isolated antibody of any one of claims 1 to 30 and a pharmaceutically acceptable carrier.
37. A method of treating a Tau protein associated disease comprising administering to an individual with a Tau protein related disease the antibody of any one of claims 1 to 30 or the pharmaceutical composition of claim 36.
38. The method of claim 37, wherein the Tau protein associated disease is a tauopathy.
39. The method of claim 38, wherein the tauopathy is a neurodegenerative tauopathy.
40. The method of claim 37 or claim 38, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.
41. The method of any one of claims 38 to 40, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.
42. A method of retaining or increasing cognitive memory capacity or slowing memory loss in an individual, comprising administering the antibody of any one of claims 1 to 30 or the pharmaceutical composition of claim 36.
43. A method of reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual, comprising

administering the antibody of any one of claims 1 to 30 or the pharmaceutical composition of claim 36.

44. The method of any one of claims 37 to 43, wherein the method comprises administering at least one additional therapy.

45. The method of claim 44, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, Tau inhibitors, anti-amyloid beta antibodies, beta-amyloid aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.

46. The isolated antibody of any one of claims 1 to 30 for use as a medicament.

47. The isolated antibody of any one of claims 1 to 30 for use in treating a tauopathy in an individual.

48. The isolated antibody of claim 47, wherein the tauopathy is a neurodegenerative tauopathy.

49. The isolated antibody of claim 47 or claim 48, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.

50. The isolated antibody of any one of claims 47 to 49, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

51. An isolated antibody of any one of claims 1 to 30 for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual.

52. An isolated antibody of any one of claims 1 to 30 for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual.

53. The isolated antibody of any one of claims 47 to 52, wherein the antibody is for use with at least one additional therapy.

54. The isolated antibody of claim 53, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, anti-amyloid beta antibodies, anti-BACE1 antibodies, and BACE1 inhibitors.

55. Use of an antibody of any one of claims 1 to 30 for manufacture of a medicament for treating a Tau protein associated disease in an individual.

56. The use of claim 55 wherein the Tau protein associated disease is a tauopathy.

57. The use of claim 56, wherein the tauopathy is a neurodegenerative tauopathy.

58. The use of claim 56 or claim 57, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy.

59. The use of any one of claims 56 to 58, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

60. Use of an antibody any one of claims 1 to 30 for manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual.

61. The use of any one of claims 55 to 60, wherein the medicament is for administration with at least one additional therapy.

62. The use of claim 61, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, anti-amyloid beta antibodies, anti-BACE1 antibodies, and BACE1 inhibitors.

63. A method of detecting neurofibrillary tangles, neuropil threads, or dystrophic neuritis comprising contacting a sample with the antibody of any one of claims 1 to 30.

64. The method of claim 63, wherein the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.