

ANTI-TAU ANTIBODIES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 62/431,180, filed December 7, 2016, which is incorporated by reference herein in its entirety for any purpose.

FIELD OF THE INVENTION

[0002] The present invention relates to anti-Tau antibodies and methods of using the same.

BACKGROUND

[0003] Neurofibrillary tangles and neuropil threads (NTs) are the major neuropathological hallmarks of Alzheimer's Disease (AD). NTs are composed of the microtubule-associated Tau protein that has undergone post-translational modifications including phosphorylation, and develop by aggregation of hyperphosphorylated Tau conformers. AD shares this pathology with many neurodegenerative tauopathies, in particular with certain types of frontotemporal dementia (FTD). Tau protein appears to be a major player in the cognitive demise in AD and related neurodegenerative tauopathies.

[0004] Therapeutic approaches that target Tau protein are scarce and comprise mainly inhibitors of the kinases that are thought to increase the phosphorylation of Tau to pathological levels, and compounds that block the cytoplasmic aggregation of hyper-phosphorylated Tau protein. These approaches suffer various draw-backs of specificity and efficacy. There is a need for additional therapeutic agents that target the pathological protein conformers that are known or presumed to cause neurodegenerative disorders.

SUMMARY

[0005] The disclosure provides anti-Tau antibodies and methods of using the same. In some examples, antibodies with high affinity for human and cynomolgus monkey Tau are provided. In some examples, the antibodies have an affinity for human Tau of less than 1 nM or less than 0.5 nM or less than 0.3 nM as measured, for example, by surface plasmon resonance.

[0006] In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated

Tau, and phosphorylated Tau. In some examples, the antibody binds an epitope within amino acids 2 to 24 of mature human Tau. In some examples, the antibody is a monoclonal antibody. In some examples, the antibody is a human, humanized, or chimeric antibody. In some examples, the antibody is an antibody fragment that binds human Tau. In some examples, the human Tau comprises the sequence of SEQ ID NO: 2.

[0007] In some examples, the antibody comprises HVR-H1 comprising an amino acid sequence of SEQ ID NO: 605; HVR-H2 comprising an amino acid sequence of SEQ ID NO: 606; and HVR-H3 comprising an amino acid sequence of SEQ ID NO: 607. Thus, in one example, there is provided 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.

[0008] In some examples, the antibody comprises HVR-L1 comprising an amino acid sequence of SEQ ID NO: 608; HVR-L2 comprising an amino acid sequence of SEQ ID NO: 609; and HVR-L3 comprising an amino acid sequence of SEQ ID NO: 610. Thus, in another example, there is provided 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.

[0009] In some examples, the antibody comprises HVR-H1 comprising an amino acid sequence of SEQ ID NO: 605; HVR-H2 comprising an amino acid sequence of SEQ ID NO: 606; HVR-H3 comprising an amino acid sequence of SEQ ID NO: 607; HVR-L1 comprising an amino acid sequence of SEQ ID NO: 608; HVR-L2 comprising an amino acid sequence of SEQ ID NO: 609; and HVR-L3 comprising an amino acid sequence of SEQ ID NO: 610. Thus, in one aspect, there is provided 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.

[0010] In some examples, 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).

[0011] In some examples, 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).

[0012] In some examples, 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. In some examples, 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. In some examples, 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.

[0013] In some examples, 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. In one aspect, there is provided 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.

[0014] In some examples, 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

[0015] In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises 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. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 611 and a light chain comprising the amino acid sequence of SEQ ID NO: 613. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 612 and a light chain comprising the amino acid sequence of SEQ ID NO: 613. In some examples, an isolated antibody that binds to human Tau is provided, 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. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 611 and a light chain consisting of the amino acid sequence of SEQ ID NO: 613. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 612 and a light chain consisting of the amino acid sequence of SEQ ID NO: 613.

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consisting of the amino acid sequence of SEQ ID NO: 618. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 617 and a light chain consisting of the amino acid sequence of SEQ ID NO: 618.

[0017] In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises 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. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 621 and a light chain comprising the amino acid sequence of SEQ ID NO: 623. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 622 and a light chain comprising the amino acid sequence of SEQ ID NO: 623. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises 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. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 621 and a light chain consisting of the amino acid sequence of SEQ ID NO: 623. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 622 and a light chain consisting of the amino acid sequence of SEQ ID NO: 623.

[0018] In any of the examples described herein, the antibody may be an IgG1 or an IgG4 antibody. In any of the examples described herein, the antibody may be an IgG4 antibody. In some such examples, the antibody comprises M252Y, S254T, and T256E mutations. In any of the examples described herein, the antibody may comprise an S228P mutation. In any of the examples described herein, the antibody may comprise S228P, M252Y, S254T, and T256E mutations. In any of the examples described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations. In some examples, the antibody is an antibody fragment. In any of the examples described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations, and lacking the C-terminal lysine (des-K) of the heavy chain constant region. The C-terminal lysine of the heavy chain constant region may be removed, for

example, during purification of the antibody or by recombinant engineering of the nucleic acid encoding the antibody such that the C-terminal lysine is not encoded.

[0019] In some examples, an isolated antibody that binds human Tau is provided, 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. In some examples, the antibody binds cynomolgus monkey Tau. In some examples, the antibody binds to human monomeric Tau and/or cynomolgus monkey monomeric Tau with a K_D of less than 1 nM.

[0020] In some aspects, an isolated nucleic acid is provided, wherein the isolated nucleic acid encodes an antibody described herein. In some aspects, a host cell is provided, wherein the host cell comprises an isolated nucleic acid that encodes an antibody described herein. In some aspects, a method of producing an antibody is provided, comprising culturing the host cell described herein under conditions suitable for producing the antibody.

[0021] In some aspects, an immunoconjugate is provided, wherein the immunoconjugate comprises an isolated antibody described herein and a second therapeutic agent. In some aspects, a labeled antibody is provided, comprising an antibody described herein and a detectable label.

[0022] In some aspects, a pharmaceutical composition is provided, comprising an isolated antibody described herein and a pharmaceutically acceptable carrier.

[0023] In some examples, a method of treating a Tau protein associated disease is provided, comprising administering to an individual with a Tau protein related disease an antibody described herein or a pharmaceutical composition comprising an antibody described herein. In some examples, the Tau protein associated disease is a tauopathy. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, 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. In some examples, the tauopathy is Alzheimer's disease or progressive supranuclear palsy. In some examples, the Tau protein associated disease is selected from PART (primary age-related Tauopathy), tangle predominant dementia, subacute sclerosis panencephalopathy, chronic traumatic encephalopathy (CTE), white matter tauopathy with globular glial inclusions, Lewy body dementia (LBD), mild cognitive impairment (MCI), glaucoma, familial British dementia, familial Danish dementia, Guadeloupean Parkinsonism, neurodegeneration with brain iron accumulation, SLC9A6-related mental retardation, multiple sclerosis, HIV-related dementia, senile cardiac amyloidosis, and Huntington's disease.

[0024] In some examples, a method of retaining or increasing cognitive memory capacity or slowing memory loss in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein.

[0025] In some examples, a method of reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein. In one aspect, there is provided use of an antibody described herein or the pharmaceutical composition described herein in the manufacture of medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a tauopathy.

[0026] In some aspects, an isolated antibody described herein is provided for use as a medicament. In some aspects, an isolated antibody described herein is provided for use in treating a tauopathy in an individual. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, 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. In some examples, the tauopathy is Alzheimer's disease or progressive supranuclear palsy. In some examples, the Tau protein associated disease is selected from PART (primary age-related Tauopathy), tangle predominant dementia, subacute

sclerosis panencephalopathy, chronic traumatic encephalopathy (CTE), white matter tauopathy with globular glial inclusions, Lewy body dementia (LBD), mild cognitive impairment (MCI), glaucoma, familial British dementia, familiar Danish dementia, Guadeloupean Parkinsonism, neurodegeneration with brain iron accumulation, SLC9A6-related mental retardation, multiple sclerosis, HIV-related dementia, senile cardiac amyloidosis, and Huntington's disease.

[0027] In some examples, an isolated antibody described herein is provided for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual. In some aspects, an isolated antibody described herein is provided for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a tauopathy. In some examples, an isolated antibody described herein is provided for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual. In some aspects, an isolated antibody described herein is provided for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a tauopathy.

[0028] In some examples, use of an antibody described herein or the pharmaceutical composition as described herein is provided for manufacture of a medicament for treating a Tau protein associated disease in an individual. In some aspects, use of an antibody described herein or the pharmaceutical composition as described herein is provided for manufacture of a medicament for treating a tauopathy in an individual. In some examples, the Tau protein associated disease is a tauopathy. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, 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. In some examples, the tauopathy is Alzheimer's disease or progressive supranuclear palsy. In some examples, the Tau protein associated disease is selected from PART (primary age-related Tauopathy), tangle predominant dementia, subacute sclerosis panencephalopathy, chronic traumatic encephalopathy (CTE), white matter tauopathy with globular glial inclusions, Lewy body dementia (LBD), mild cognitive impairment (MCI), glaucoma, familial British dementia, familiar Danish dementia, Guadeloupean Parkinsonism, neurodegeneration with brain iron accumulation, SLC9A6-related mental retardation, multiple sclerosis, HIV-related dementia, senile cardiac amyloidosis, and Huntington's disease.

[0029] In some examples, use of an antibody described herein or the pharmaceutical composition as described herein is provided for manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual. In some aspects, use of an antibody described herein or the pharmaceutical composition as described herein is provided for manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a tauopathy.

[0030] In some aspects, a method of detecting neurofibrillary tangles, neuropil threads, or dystrophic neuritis is provided, comprising contacting a sample with an antibody described herein. In some examples, the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.

[0031] In any of the examples described herein, a method or use may comprise administering an antibody described herein in combination with at least one additional therapy. Non-limiting examples of additional therapies include neurological drugs, corticosteroids, antibiotics, antiviral agents, and other therapeutic agents. Such other therapeutic agents include, but are not limited to, other anti-Tau antibodies, antibodies against amyloid-beta, antibodies against beta-secretase 1 (“BACE1”), and inhibitors of beta-secretase 1.

BRIEF DESCRIPTION OF THE FIGURES

[0032] Figure 1A-F. Binding of antibodies to hyperphosphorylated Tau (pTau) was compared to non-phosphorylated Tau using an ELISA. Results are expressed in optical densities (O.D.).

[0033] Figure 2A-E. Binding of antibodies to oligomeric Tau was assessed using an oligo- and monoTau capture ELISA. Results are expressed in optical densities (O.D.).

[0034] Figure 3. The three panTau antibodies tested show binding to soluble Tau in brain lysates from Alzheimer’s disease (AD) and matched control donors using a Western blot (WB) assay. Protein extracts from AD and control brain lysates, and six isoforms of recombinant human Tau, were run on SDS-PAGE and membranes blotted with three panTau antibodies (37D3-H9, 94B2-C1, and 125B11-H3). Lanes with AD samples are labeled as AD18, AD24, and AD27, and lanes with control samples are labeled as C25 and C21. The lanes run with six isoforms of recombinant human Tau are labeled as hTau ladder.

[0035] Figure 4A-C. PanTau antibodies show binding to soluble Tau in brain lysates from AD and matched control donors using a Tau capture ELISA. Data is shown for three panTau antibodies, 37D3-H9, 94B2-C1, and 125B11-H3. Results are expressed in optical densities (O.D.), with mean values $\pm$ SD, N=2.

[0036] Figure 5. Sensorgrams showing 37D3-H9 binding as a Fab (left panel) and as an IgG (right panel) to human Tau monomer covalently coupled to a Biacore chip surface. A

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; 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.

2. The antibody of claim 1, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau.

3. The antibody of claim 1 or claim 2, wherein the antibody binds an epitope within amino acids 2 to 24 of mature human Tau.

4. The isolated antibody of any one of claims 1 to 3, which is a monoclonal antibody.

5. The isolated antibody of any one of the preceding claims, which is a humanized or chimeric antibody.

6. The antibody of any one of the preceding claims, wherein the human Tau comprises the sequence of SEQ ID NO: 2.

7. 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; or
- i) a VH as in (g) and a VL as in (h).

8. 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; or
 - i) a VH as in (g) and a VL as in (h).

9. 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.

10. 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 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: 614 and a light chain variable region comprising a sequence selected from SEQ ID NOs: 604, 615, and 620; (c) 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: 604, 615, and 620; (d) 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: 604; (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: 615; or (f) 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: 620.

11. 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.

12. 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.

13. The isolated antibody of claim 12, 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.

14. 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.

15. 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.

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

17. The isolated antibody of claim 16, wherein the antibody is an IgG4 antibody.

18. The isolated antibody of claim 17, wherein the antibody comprises M252Y, S254T, and T256E mutations.

19. The isolated antibody of claim 17 or claim 18, wherein the antibody comprises an S228P mutation.

20. The isolated antibody of any one of claims 1 to 12, which is an antibody fragment.

21. 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.

22. 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.
23. The isolated antibody of claim 21 or claim 22, wherein K_D is determined by surface plasmon resonance at 37°C.
24. The isolated antibody of any one of the preceding claims, which binds cynomolgus monkey Tau.
25. An isolated nucleic acid that encodes the antibody of any one of the preceding claims.
26. A host cell comprising the nucleic acid of claim 25.
27. A method of producing an antibody comprising culturing the host cell of claim 26 under conditions suitable for producing the antibody.
28. An immunoconjugate comprising the isolated antibody of any one of claims 1 to 24 and a second therapeutic agent.
29. A labeled antibody comprising the antibody of any one of claims 1 to 24 and a detectable label.
30. A pharmaceutical composition comprising the isolated antibody of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.
31. Use of an antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 30 in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a tauopathy.
32. The isolated antibody of any one of claims 1 to 24 for use as a medicament.
33. The isolated antibody of any one of claims 1 to 24 for use in treating a tauopathy in an individual.
34. The isolated antibody for use of claim 33, wherein the tauopathy is a neurodegenerative tauopathy.
35. The isolated antibody for use of claim 33 or claim 34, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down 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, Hallervorden-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.

36. The isolated antibody for use of any one of claims 33 to 35, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

37. An isolated antibody of any one of claims 1 to 24 for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a tauopathy.

38. An isolated antibody of any one of claims 1 to 24 for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a tauopathy.

39. The isolated antibody for use of any one of claims 33 to 38, wherein the antibody is for use with at least one additional therapy.

40. The isolated antibody for use of claim 39, 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.

41. Use of an antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 30 for manufacture of a medicament for treating a tauopathy in an individual.

42. The use of claim 41, wherein the tauopathy is a neurodegenerative tauopathy.

43. The use of claim 41 or claim 42, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down 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, Hallervorden-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.

44. The use of claim 42 or claim 43, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

45. Use of an antibody any one of claims 1 to 24 or the pharmaceutical composition of claim 30 for manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a tauopathy.

46. The use of any one of claims 31, and 41 to 45, wherein the medicament is for administration with at least one additional therapy.

47. The use of claim 46, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, Tau inhibitors, anti-Tau antibodies, anti-amyloid beta antibodies, beta-amyloid aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.

48. 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 24.

49. The method of claim 48, wherein the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.