

TAU BINDING COMPOUNDS

RELATED APPLICATIONS

[0001] This International Patent Application claims priority to U.S. Provisional Patent Application No. 63/126,024, filed on December 16, 2020, the entire contents of which are hereby incorporated by reference in their entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been filed electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on December 14, 2021, is named 2057_1314USPRO_SL.txt and is 135,153 bytes in size.

FIELD OF THE DISCLOSURE

[0003] The present disclosure presents tau binding compounds. In particular, the present disclosure provides antibodies which bind to tau (e.g., human tau), e.g., antibodies which bind to phospho-epitopes on human tau.

BACKGROUND

[0004] Tauopathies are a group of neurodegenerative diseases characterized by the dysfunction and/or aggregation of the microtubule associated protein tau. Tau is normally a very soluble protein known to associate with microtubules based on the extent of its phosphorylation. Tau is considered a critical component of intracellular trafficking processes, particularly in neuronal cells, given their unique and extended structure. Hyperphosphorylation of tau depresses its binding to microtubules and microtubule assembly activity. Further, hyperphosphorylation of tau renders it prone to misfolding and aggregation. In tauopathies, the tau becomes hyperphosphorylated, misfolds and aggregates as neurofibrillary tangles (NFT) of paired helical filaments (PHF), twisted ribbons or straight filaments. These NFT are largely considered indicative of impending neuronal cell death and thought to contribute to widespread neuronal cell loss, leading to a variety of behavioral and cognitive deficits.

[0005] The first genetically defined tauopathy was described when mutations in the tau gene were shown to lead to an autosomal dominantly inherited tauopathy known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). This was the first causal evidence that changes in tau could lead to neurodegenerative changes in the brain. These molecules are considered to be more amyloidogenic, meaning they are more

likely to become hyperphosphorylated and more likely to aggregate into NFT (Hutton, M. et al., 1998, Nature 393(6686):702-5).

[0006] Several approaches have been proposed for therapeutically interfering with progression of tau pathology and preventing the subsequent molecular and cellular consequences. Given that NFT are composed of hyperphosphorylated, misfolded and aggregated forms of tau, interference at each of these stages has yielded a set of avidly pursued targets. Introducing agents that limit phosphorylation, block misfolding or prevent aggregation have all generated promising results. Passive and active immunization with late stage anti-phospho-tau antibodies in mouse models have led to dramatic decreases in tau aggregation and improvements in cognitive parameters. It has also been suggested that introduction of anti-tau antibodies can prevent the trans-neuronal spread of tau pathology.

[0007] There remains a need for anti-tau antibodies for use in tauopathy treatment, diagnostics, and other applications. The present disclosure addresses this need with related compounds and methods described herein.

SUMMARY

[0008] Provided herein are isolated, e.g., recombinant, antibodies which bind to tau (e.g., human tau). In particular, provided herein are anti-tau antibodies which are not only structurally unique, but also exhibit different binding patterns to various phospho-epitopes in tau compared to phospho-epitopes recognized by anti-tau antibodies widely used to study tau pathology (e.g., PT3 and AT8), despite binding to similar/overlapping regions in tau. In addition to therapeutic applications, the anti-tau antibodies provided herein may also serve as diagnostic tools for the detection of unique phosphorylation states of tau.

[0009] In some embodiments, the present disclosure provides an antibody that includes: a heavy chain variable domain (VH) with a complementarity determining region (CDR)H1, CDRH2, and CDRH3 including an amino acid sequence according to any of those listed in Table 4, or a fragment thereof; and a light chain variable domain (VL) with a CDRL1, CDRL2, and CDRL3 including an amino acid sequence according to any of those listed in **Table 1**, or a fragment thereof. The antibody may include a set of variable domain CDR amino acid sequences, wherein the variable domain CDR amino acid sequence set is selected from any of those listed in **Table 1**. The antibody may include a pair of variable domain CDR amino acid sequence sets, wherein the variable domain CDR amino acid sequence set pair is selected from any those listed in **Table 1**. The VH may include a framework region (FR)H1, FRH2, FRH3, and FRH4 that include an amino acid sequence selected from any of those

listed in **Table 1**, or a fragment thereof. The VL may include a FRL1, FRL2, FRL3, and FRL4 that include an amino acid sequence selected from any of those listed in **Table 1** or a fragment thereof. The VH may include an amino acid sequence selected from any of those listed in **Table 1** and/or may be encoded by a nucleic acid sequence selected from any of those listed in **Table 1**. The VL may include an amino acid sequence selected from any of those listed in **Table 1** and/or may be encoded by a nucleic acid sequence selected from any of those listed in **Table 1**. The antibody may include a variable domain pair selected from any of those listed in **Table 1**. The antibody may include a format selected from a monoclonal antibody, a multispecific antibody, a chimeric antibody, an antibody mimetic, a single chain Fv (scFv) format, and an antibody fragment. The antibody may include an antibody class selected from IgA, IgD, IgE, IgG, and IgM. The antibody may include one or more non-human constant domain. The antibody may include one or more human constant domain. The one or more human constant domain may be selected from any of those listed in **Table 5**. The antibody may include a human IgG, wherein the human IgG includes an isotype selected from IgG1, IgG2, IgG3, or IgG4. The antibody may be a human antibody. The antibody may bind to a tau protein epitope. The tau protein epitope may include or may be included within an amino acid sequence selected from any of those listed in **Table 4**. The tau protein epitope may include a region formed by a complex of at least two tau proteins. The antibody may bind to enriched paired helical filament tau protein (ePHF) with a half maximal effective concentration (EC50) of from about 0.01 nM to about 100 nM as determined by direct enzyme-linked immunosorbent assay (ELISA). The antibody may not bind to non-pathological tau. The antibody may bind to pathological tau tangles. The antibody may inhibit tau aggregation. The antibody may include a conjugate. The conjugate may include a therapeutic agent. The conjugate may include a detectable label.

[0010] In some embodiments, the present disclosure provides a construct encoding an antibody according to any of those described above or herein.

[0011] In some embodiments, the present disclosure provides a method of treating a therapeutic indication in a subject, the method including administering to the subject an antibody according to any of those described above or herein. The therapeutic indication may include a neurological indication. The neurological indication may include one or more of neurodegenerative disease, Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal

degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), a prion disease, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis.

[0012] In some embodiments, the present disclosure provides a method of diagnosing a therapeutic indication in a subject, the method including the use of an antibody according to any of those described above or herein. The therapeutic indication may include a neurological indication. The neurological indication may include one or more of neurodegenerative disease, AD, FTDP-17, FTL, FTD, CTE, PSP, Down's syndrome, Pick's disease, CBD, corticobasal syndrome, ALS, a prion disease, CJD, multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis. The antibody may be used to detect pathological tau in a subject tissue. The subject tissue may include CNS tissue. The subject tissue may include a thin tissue section. The thin tissue section may include a cryopreserved tissue section.

[0013] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following enumerated embodiments.

Enumerated embodiments

E1. An isolated, *e.g.*, recombinant, antibody that binds to human tau (*e.g.*, SEQ ID NO: 274), wherein the antibody comprises a heavy chain variable region (VH) comprising one, two, or three of a heavy chain complementary determining region 1 (HCDR1), a heavy chain complementary determining region 2 (HCDR2), and a heavy chain complementary determining region 3 (HCDR3), and/or a light chain variable region (VL) comprising one, two, or three of a light chain complementary determining region 1 (LCDR1), a light chain complementary determining region 2 (LCDR2), and a light chain complementary determining region 3 (LCDR3), *e.g.*, CDR sequences according to the Chothia numbering system, wherein:

- (i) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 82, 97, 115, 127, 141, and 159, respectively;
- (ii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 79, 94, 111, 127, 141, and 156, respectively;
- (iii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 80, 95, 112, 129, 143, and 157, respectively;
- (iv) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the

amino acid sequences of SEQ ID NOs: 81, 94, 114, 127, 141, and 156, respectively;

(v) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 82, 101, 119, 132, 149, and 164, respectively;

(vi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 77, 92, 109, 127, 141, and 154, respectively;

(vii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 93, 110, 128, 142, and 155, respectively;

(viii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 96, 113, 130, 144, and 158, respectively;

(xi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 83, 98, 116, 131, 145, and 160, respectively;

(x) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 84, 99, 117, 132, 146, and 161, respectively;

(xi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 85, 100, 118, 133, 147, and 162, respectively;

(xii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 85, 100, 118, 134, 148, and 163, respectively;

(xiii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 86, 102, 120, 127, 141, and 156, respectively;

(xiv) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 87, 103, 121, 132, 149, and 165, respectively;

(xv) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 104, 122, 135, 143, and 166, respectively;

(xvi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 104, 122, 136, 150, and 167, respectively;

(xvii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 88, 105, 123, 137, 151, and 168, respectively;

(xviii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 89, 106, 124, 138, 152, and 169, respectively;

(xix) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 90, 107, 125, 139, 151, and 170, respectively;

(xx) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 91, 108, 126, 140, 153, and 171, respectively;

(xxi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the

amino acid sequences of any of the HCDR and LCDR sequences provided in **Table 1**; or

(xxii) a variant, e.g., functional variant, of the antibodies of any one of (i)-(xxi), wherein any one, two, three, four, five or all of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and/or LCDR3 comprises one, two, or at most three substitutions (e.g., conservative substitutions); or wherein any one, two, three, four, five or all of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and/or LCDR3 comprises one, two, or at most three different amino acids relative to any of the sequences in (i)-(xxi).

E2. The antibody of embodiment E1, wherein the antibody comprises the HCDR1, HCDR2, and HCDR3 sequences of any one of (i)-(xxii).

E3. The antibody of embodiment E1 or E2, wherein the antibody comprises the LCDR1, LCDR2, and LCDR3 sequences of any one of (i)-(xxii).

E4. The antibody of any one of embodiments E1-E3, wherein the antibody comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences of any one of (i)-(xxii).

E4. An isolated, e.g., recombinant, antibody that binds to human tau (e.g., SEQ ID NO: 274), wherein the antibody comprises the heavy chain CDR1, CDR2, and CDR3, and/or light chain CDR1, CDR2, and CDR3 of an antibody comprising a heavy chain variable region (VH) and light chain variable region (VL) comprising: (i) SEQ ID NOs: 7 and 25, respectively; (ii) SEQ ID NOs: 3 and 21, respectively; (iii) SEQ ID NOs: 4 and 22, respectively; (iv) SEQ ID NOs: 6 and 24, respectively; (v) SEQ ID NOs: 11 and 30, respectively; (vi) SEQ ID NOs: 1 and 19, respectively; (vii) SEQ ID NOs: 2 and 20, respectively; (viii) SEQ ID NOs: 5 and 23, respectively; (ix) SEQ ID NOs: 8 and 26, respectively; (x) SEQ ID NOs: 9 and 27, respectively; (xi) SEQ ID NOs: 10 and 28, respectively; (xii) SEQ ID NOs: 10 and 29, respectively; (xiii) SEQ ID NOs: 12 and 31, respectively; (xiv) SEQ ID NOs: 13 and 32, respectively; (xv) SEQ ID NOs: 14 and 33, respectively; (xvi) SEQ ID NOs: 14 and 34, respectively; (xvii) SEQ ID NOs: 15 and 35, respectively; (xviii) SEQ ID NOs: 16 and 36, respectively; (xix) SEQ ID NOs: 17 and 37, respectively; or (xx) SEQ ID NOs: 18 and 38, respectively.

E5. The antibody of embodiment E4, wherein the CDR sequences are based on the Kabat numbering system, Chothia numbering system, or IMGT numbering system.

E6. The antibody of any one of the preceding embodiments, which comprises a VH comprising:

(i) the amino acid sequence of any VH provided in **Table 1**, or an amino acid

sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications relative to the amino acid sequence of any VH provided in **Table 1**;

(iii) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid sequences of any VH sequences provided in **Table 1**; or

(iv) an amino acid sequence encoded by a nucleotide sequence of any VH provided in Table 1X, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E7. The antibody of any one of the preceding embodiments, which comprises a VH comprising:

(i) the amino acid sequence of any of SEQ ID NOs: 7, 3, 4, 6, and 11, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any of SEQ ID NOs: 7, 3, 4, 6, and 11;

(iii) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid sequences of any of SEQ ID NOs: 7, 3, 4, 6, and 11; or

(iv) an amino acid sequence encoded by a nucleotide sequence of any of SEQ ID NOs: 51, 55, 54, 52, 47, 39, 56, 41, 50, 49, 48, 46, 45, 44, 43, 42, 53, or 40, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E8. The antibody of any one of the preceding embodiments, which comprises a VL comprising:

(i) the amino acid sequence of any VL provided in **Table 1**, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) an amino acid sequence comprising at least one, two or three modifications,

but not more than 30, 20 or 10 modifications relative to the amino acid sequence of any VL provided in **Table 1**;

(iii) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid sequences of any VL sequences provided in **Table 1**; or

(iv) an amino acid sequence encoded by a nucleotide sequence of any VL provided in **Table 1**, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E9. The antibody of any one of the preceding embodiments, which comprises a VL comprising:

(i) the amino acid sequence of any of SEQ ID NOs: 25, 21, 22, 24, and 30, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any of SEQ ID NOs: 25, 21, 22, 24, and 30;

(iii) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid sequences of any of SEQ ID NOs: 25, 21, 22, 24, and 30; or

(iv) an amino acid sequence encoded by a nucleotide sequence of any of SEQ ID NOs: 67, 75, 74, 72, 66, 57, 76, 59, 70, 69, 68, 65, 64, 62, 63, 61, 60, 73, or 58, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E10. The antibody of any one of the preceding embodiments, comprising:

(i) a VH comprising:

(a) the amino acid sequence of any VH provided in **Table 1**, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(b) an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications relative to the amino acid sequence of any VH provided in **Table 1**;

(c) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid

sequences of any VH sequences provided in **Table 1**; or

(d) an amino acid sequence encoded by a nucleotide sequence of any VH provided in **Table 1**, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and

(ii) a VL comprising:

(a) the amino acid sequence of any VL provided in **Table 1**, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(b) an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications relative to the amino acid sequence of any VL provided in **Table 1**;

(c) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid sequences of any VL sequences provided in **Table 1**; or

(d) an amino acid sequence encoded by a nucleotide sequence of any VL provided in **Table 1**, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E11. The antibody of any one of the preceding embodiments, comprising the amino acid sequence of any VH of an antibody provided in **Table 1**, and the amino acid sequence of the VL of the antibody provided in **Table 1**.

E12. The antibody of any one of the preceding embodiments, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 7; an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 7; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 7; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 25, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 25; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 25.

E13. The antibody of any one of embodiments E1-E11, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 3; an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 3; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 3; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 21, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 21; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 21.

E14. The antibody of any one of embodiments E1-E11, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 4; an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 4; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 4; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 22; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 22.

E15. The antibody of any one of embodiments E1-E11, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 6; an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 6; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 6; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 24; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 24.

E16. The antibody of any one of embodiments E1-E11, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 11; an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 11; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 11; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 30, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 30; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 30.

E17. An isolated, e.g., recombinant, antibody that binds to human tau (e.g., SEQ ID NO: 274), wherein the antibody comprises a heavy chain variable region (VH) and/or a light chain variable region (VL) comprising: (i) SEQ ID NOs: 7 and/or 25, respectively; (ii) SEQ ID NOs: 3 and/or 21, respectively; (iii) SEQ ID NOs: 4 and/or 22, respectively; (iv) SEQ ID NOs: 6 and/or 24, respectively; (v) SEQ ID NOs: 11 and/or 30, respectively; (vi) SEQ ID NOs: 1 and/or 19, respectively; (vii) SEQ ID NOs: 2 and/or 20, respectively; (viii) SEQ ID NOs: 5 and/or 23, respectively; (ix) SEQ ID NOs: 8 and/or 26, respectively; (x) SEQ ID NOs: 9 and/or 27, respectively; (xi) SEQ ID NOs: 10 and/or 28, respectively; (xii) SEQ ID NOs: 10 and/or 29, respectively; (xiii) SEQ ID NOs: 12 and/or 31, respectively; (xiv) SEQ ID NOs: 13 and/or 32, respectively; (xv) SEQ ID NOs: 14 and/or 33, respectively; (xvi) SEQ ID NOs: 14 and/or 34, respectively; (xvii) SEQ ID NOs: 15 and/or 35, respectively; (xviii) SEQ ID NOs: 16 and/or 36, respectively; (xix) SEQ ID NOs: 17 and/or 37, respectively; (xx) SEQ ID NOs: 18 and/or 38, respectively; (xxi) a variant, e.g., functional variant, of the antibodies of any one of (i)-(xx), wherein the VH and/or VL has an amino acid sequence

having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; or (xxii) a variant, e.g., functional variant, of the antibodies of any one of (i)-(xx), wherein the VH and/or VL comprises at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., amino acid substitutions, e.g., conservative substitutions) or wherein the VH and/or VL comprises at least one, two, or three, but not more than 30, 20, or 10 different amino acids.

E18. The antibody of any one of embodiments E1-E17, wherein the antibody comprises the VH and VL sequences of any one of (i)-(xxii) in embodiment E17.

E19. The antibody of any one of embodiments E1-E18, which binds to a tau protein at a half maximal effective concentration (EC₅₀) of from about 0.001 nM to about 10 nM, or about 0.01 nM to about 2 nM, e.g., as assessed by direct enzyme-linked immunosorbent assay (ELISA).

E20. The antibody of any one of embodiments E1-E19, which binds to enriched paired helical filament tau protein (ePHF), e.g., at a half maximal effective concentration (EC₅₀) of from about 0.001 nM to about 100 nM, or about 0.01 nM to about 20 nM e.g., as assessed by direct enzyme-linked immunosorbent assay (ELISA).

E21. The antibody of any one of embodiments E1-E20, which binds to iPHF with a dissociation constant (K_D) of about 0.1 to about 10 nM, or about 0.2-5 nM, e.g., as assessed by bio-layer interferometry.

E22. The antibody of any one of the preceding embodiments, wherein the antibody binds to a tau protein epitope comprising a region formed by a complex of at least two tau proteins.

E23. The antibody of any one of the preceding embodiments, wherein the antibody binds to all or a portion of amino acid residues of tau selected from: (a) 183-212, (b) 187-218, (c) 33-82, 159-182, 197-226, and 229-246; (d) 217-242, (e) 35-76 and 187-218, (f) 5-34, (g) 187-218, (h) 33-82, 159-188, and 191-230, (i) 35-62, 107-124, and 203-220, (j) 35-82, 159-188, and 197-224, and (k) 53-78, 329-348, or 381-408, wherein human tau is numbered according to SEQ ID NO: 274.

E24. An isolated, e.g., recombinant, antibody that binds to human tau (e.g., SEQ ID NO: 274), wherein the antibody binds to all or a portion of amino acid residues of tau selected from: (a) 183-212, (b) 187-218, (c) 33-82, 159-182, 197-226, and 229-246; (d) 217-242, (e) 35-76 and 187-218, (f) 5-34, (g) 187-218, (h) 33-82, 159-188, and 191-230, (i) 35-62, 107-124, and 203-220, (j) 35-82, 159-188, and 197-224, or (k) 53-78, 329-348, and 381-408,

wherein human tau is numbered according to SEQ ID NO: 274.

E25. The antibody of embodiment E23 or E24, wherein one or more of the serines, threonines, and/or tyrosines in the stretch of amino acids selected from (a)-(k) are phosphorylated.

E26. The antibody of any one of embodiments E23-E25, wherein all of the serines, threonines, and/or tyrosines in the stretch of amino acids selected from (a)-(k) are phosphorylated.

E27. The antibody of any one of embodiments E24-E26, wherein the antibody comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequence of any one of (i)-(xxii) in embodiment E3.

E28. The antibody of any one of embodiments E24-E27, wherein the antibody comprises the VH and VL sequences of any one of (i)-(xxii) in embodiment E17.

E29. The antibody of any one of embodiments E1-E28, which binds to all or a portion of amino acids 195-215 of tau with a dissociation constant (K_D) of about 1 pM to about 50 pM, or about 1-25 pM, e.g., as assessed by bio-layer interferometry.

E30. The antibody of any one of embodiments E1-E28, which binds to all or a portion of amino acids 191-214 of tau phosphorylated at S199 with a dissociation constant (K_D) of about 0.1 nM to about 10 nM, or about 0.5-5 nM, e.g., as assessed by bio-layer interferometry.

E31. The antibody of any one of embodiments E1-E28, which binds to all or a portion of amino acids 217-234 of tau phosphorylated at T217, T220, and T231 with a dissociation constant (K_D) of about 0.1 nM to about 10 nM, or about 0.1-5 nM, e.g., as assessed by bio-layer interferometry.

E32. The antibody of any one of embodiments E1-E28, which binds to all or a portion of amino acids 225-240 of tau phosphorylated at T231 with a dissociation constant (K_D) of about 0.1 nM to about 25 nM, or about 0.1-15 nM, e.g., as assessed by bio-layer interferometry.

E33. An isolated, e.g., recombinant, antibody that binds to human tau phosphorylated at amino acid residue S404, or a peptide comprising or consisting of the amino acid sequence DHGAEIVYKSPVVS GDT(pS)PRHLSNVSS TG (SEQ ID NO: 281), wherein p(S) corresponds to a phosphorylated serine residue.

E34. The antibody of embodiment E33, wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 89, 106, and 124, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 138, 152, and 169, respectively.

E35. The antibody of embodiment E33 or E34, wherein the antibody comprises VH and VL sequences comprising SEQ ID NOs: 16 and 36, respectively.

E36. An isolated, *e.g.*, recombinant, antibody that binds to:

(a) human tau phosphorylated at amino acid residue S199, but not at amino acid residues S202 and T205,

(b) human tau phosphorylated at amino acid residue S202, but not at amino acid residues S199 and T205,

(c) human tau phosphorylated at amino acid residue T205, but not at amino acid residues S199 and S202,

(d) human tau phosphorylated at a combination of amino acid residues S199 and T205, but not at amino acid residue S202 (*e.g.*, wherein binding tau phosphorylated at a combination of S199 and T205 is at least 3-times stronger (*e.g.*, at least 4-time stronger) than background (*e.g.*, non-specific) level of binding, *e.g.*, binding by hIgG1 isotype control),

(e) human tau phosphorylated at a combination of amino acid residues S202 and T205, but not at amino acid residue S199, but not human tau phosphorylated at a combination of residues S199 and S202, but not T205,

(f) human tau phosphorylated at a combination of amino acid residues (i) S202 and T205, but not S119, and (ii) S199 and T205, but not S202, at least 2 times (*e.g.*, at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more strongly than background (*e.g.*, non-specific) level of binding, *e.g.*, binding by hIgG1 isotype control).

(g) human tau phosphorylated at a combination of amino acid residues (i) S199 and S202, but not T205, (ii) S202 and T205, but not S199, (iii) S199 and T205, but not S202, and (iv) S199, S202, and T205 (*e.g.*, wherein binding to phosphorylated tau is at least 1.6-times stronger (*e.g.*, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-3 times, 1.6-2 times stronger) than background (*e.g.*, non-specific) level of binding, *e.g.*, binding by hIgG1 isotype control),

(h) a peptide comprising or consisting of the amino acid sequence

SGDRSGYS(pS)PGSPGTPGSRSRTPS (SEQ ID NO: 284),

(i) a peptide comprising or consisting of the amino acid sequence

SGDRSGYSSPG(pS)PGTPGSRSRTPS (SEQ ID NO: 285),

(j) a peptide comprising or consisting of the amino acid sequence

SGDRSGYSSPGSPG(pT)PGSRSRTPS (SEQ ID NO: 286), or

(k) a peptide comprising or consisting of the amino acid sequence

SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290) (e.g., wherein binding to the peptide is at least 3 times stronger (e.g., at least 4 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control),

(l) a peptide comprising or consisting of the amino acid sequence

SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), but not a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288),

(m) peptides comprising or consisting of the amino acid sequences

SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289) and

SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), wherein binding to the latter peptide is at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more stronger than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), or

(n) peptides comprising or consisting of the amino acid sequences

SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288),

SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289),

SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), and

SGDRSGYS(pS)PG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 287) (e.g., wherein binding to the peptides is at least 1.6 times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-4 times, 1.6-3 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control),

wherein p(S) and p(T) correspond to a phosphorylated serine and phosphorylated threonine, respectively,

optionally wherein binding is assessed, e.g., using one point ELISA as described in Example 7, and optionally wherein human tau has the sequence set forth in SEQ ID NO: 274.

E37. The antibody of embodiment E36, wherein the antibody comprises:

(a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively;

(b) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(c) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(d) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 77, 92, and 109, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 154, respectively; or

(e) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively.

E38. The antibody of embodiment E36 or E37, wherein the antibody comprises a VH and a VL, wherein the VH and the VL comprise the amino acid sequence of:

- (a) SEQ ID NOs: 7 and 25, respectively,
- (b) SEQ ID NOs: 8 and 21, respectively,
- (c) SEQ ID NOs: 6 and 24, respectively,
- (d) SEQ ID NOs: 1 and 19, respectively, or
- (e) SEQ ID NOs: 12 and 31, respectively.

E39. An isolated, *e.g.*, recombinant, antibody that binds to:

(a) human tau phosphorylated at amino acid residue S199, but not at amino acid residues S202 and T205, and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively;

(b) human tau phosphorylated at amino acid residue S202, but not at amino acid residues S199 and T205, and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(c) human tau phosphorylated at amino acid residue T205, but not at amino acid residues S199 and S202, and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(d) human tau phosphorylated at a combination of amino acid residues S199 and T205, but not at amino acid residue S202 (e.g., wherein binding tau phosphorylated at a combination of S199 and T205 is at least 3-times stronger (e.g., at least 4-time stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3

sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(e) human tau phosphorylated at a combination of amino acid residues S202 and T205, but not at amino acid residue S199, but not human tau phosphorylated at a combination of residues S199 and S202, but not T205, and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 77, 92, and 109, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 154, respectively;

(f) human tau phosphorylated at a combination of amino acid residues (i) S202 and T205, but not S119, and (ii) S199 and T205, but not S202, at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more strongly than background (non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(g) human tau phosphorylated at a combination of amino acid residues (i) S199 and S202, but not T205, (ii) S202 and T205, but not S199, (iii) S199 and T205, but not S202, and

(iv) S199, S202, and T205 (e.g., wherein binding to phosphorylated tau is at least 1.6-times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-3 times, 1.6-2 times stronger) than background (non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(h) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPGTPGSRSRTPS (SEQ ID NO: 284), and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively

(i) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PGTPGSRSRTPS (SEQ ID NO: 285), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3

sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(j) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPGSPG(pT)PGSRSRTPS (SEQ ID NO: 286), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(k) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290) (e.g., wherein binding to the peptide is at least 3 times stronger (e.g., at least 4 times stronger) than background (non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(l) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), but not a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288), and wherein the antibody comprises a heavy chain variable region (VH)

comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 77, 92, and 109, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 154, respectively

(m) peptides comprising or consisting of the amino acid sequences SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289) and SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), wherein binding to the latter peptide is at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more stronger than background (non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or

(n) peptides comprising or consisting of the amino acid sequences SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288), SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), and SGDRSGYS(pS)PG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 287) (e.g., wherein binding to the peptides is at least 1.6 times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-4 times, 1.6-3 times stronger) than background (non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising

CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

wherein p(S) and p(T) correspond to a phosphorylated serine and phosphorylated threonine, respectively,

optionally wherein binding is assessed, e.g., using one point ELISA as described in Example 7, and optionally wherein human tau has the sequence set forth in SEQ ID NO: 274.

E40. An isolated, *e.g.*, recombinant, antibody that binds to:

(a) tau phosphorylated at T217, but not at T212 or T214, or

(b) peptides comprising or consisting of the sequences

GTPGSRSRTPSLP(pT)PPTRE (SEQ ID NO: 293) and GTPGSRSRTP(pS)LP(pT)PPTRE (SEQ ID NO: 296), but not peptides comprising or consisting of the sequences

GTPGSRSR(pT)PSLTPPTRE (SEQ ID NO: 291), GTPGSRSRTP(pS)LPTPPTRE (SEQ ID NO: 292), and GTPGSRSR(pT)P(pS)LPTPPTRE (SEQ ID NO: 294),

wherein p(S) and p(T) correspond to a phosphorylated serine and phosphorylated threonine, respectively,

optionally wherein binding of the antibody to tau or the peptide is at least 1.5 times stronger (e.g., at least 1.6 times, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, 1.5-4 times, 1.5-3, 4-6 times stronger) than background (non-specific) level of binding, e.g., binding by hIgG1 isotype control),

optionally wherein binding of the antibody to tau or the peptide is assessed, e.g., using one point ELISA as described, e.g., in Example 8, and optionally wherein human tau has the sequence set forth in SEQ ID NO: 274.

- E41. The antibody of embodiment E40, wherein the antibody comprises:
- (a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 80, 95, and 112, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 129, 143, and 157, respectively;
 - (b) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 78, 104, and 122, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 136, 150, and 167, respectively; or
 - (c) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 90, 107, and 125, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 139, 151, and 170, respectively.
- E42. The antibody of embodiment E40 or E41, wherein the antibody comprises a VH and a VL, wherein the VH and the VL comprise the amino acid sequence of:
- (a) SEQ ID NOs: 4 and 22, respectively,
 - (b) SEQ ID NOs: 14 and 34, respectively, or
 - (c) SEQ ID NOs: 17 and 37, respectively.
- E43. The antibody of any one of the preceding embodiments, wherein the antibody is an IgA, IgD, IgE, IgG, or IgM antibody.
- E44. The antibody of embodiment E43, wherein the antibody is an IgG antibody.
- E45. The antibody of any one of the preceding embodiments, wherein the IgG is an isotype selected from IgG1, IgG2, IgG3, and IgG4.
- E46. The antibody of embodiment E45, wherein the antibody is an IgG1 antibody.
- E47. The antibody of any of the preceding embodiments, wherein the antibody comprises a heavy chain constant region selected from human IgG1, human IgG2, human IgG3, human IgG4, murine IgG1, murine IgG2a, murine IgG2b, murine IgG2c, and murine IgG3; and/or a light chain constant region selected from the light chain constant regions of kappa or lambda.
- E48. The antibody of embodiment E47, wherein the antibody comprises a heavy chain constant region of human IgG1.
- E49. The antibody of any one of the preceding embodiments, wherein the antibody

comprises:

(i) a heavy chain constant region (CH), e.g., a CH comprising an amino acid sequence of any of the heavy chain constant regions in **Table 5**, or a sequence having at least 80% (e.g., 85, 90, 95, 96, 97, 98, or 99%) sequence identity to the heavy chain constant region sequences in **Table 5**; an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications, relative to the amino acid sequence of the heavy chain constant region sequences in **Table 5**; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of the heavy chain constant region sequences in **Table 5**; and/or

(ii) a light chain constant region (CL), e.g., a CL comprising an amino acid sequence of any of the CL sequences in **Table 5**, or a sequence having at least 80% (e.g., 85, 90, 95, 96, 97, 98, or 99%) sequence identity to any of the CL sequences in **Table 5**; an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications, relative to the amino acid sequence of the light chain constant region sequences in **Table 5**; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of the light chain constant region sequences in **Table 5**.

E50. The antibody of any one of the preceding embodiments, wherein the antibody molecule comprises an Fc region or variant, e.g., functional variant, thereof.

E51. The antibody of any one of the preceding embodiments, wherein the antibody molecule comprises an Fc region which has modified, e.g., increased or reduced affinity (e.g., ablated), affinity for an Fc receptor, e.g., as compared to a reference, wherein the reference is a wild-type Fc receptor.

E52. The antibody of any one of embodiments E1-E51, wherein the antibody molecule comprises an Fc region which comprises a mutation at one, two, or all of positions I253 (e.g., I235A), H310 (e.g., H310A), and/or H435 (e.g., H435A), numbered according to the EU index as in Kabat.

E53. The antibody of any one of the preceding embodiments, wherein the antibody is a full-length antibody, a bispecific antibody, an intrabody, a Fab, a F(ab')₂, a Fv, a single chain Fv fragment (scFv), single domain antibody, or a camelid antibody.

E54. The antibody of any one of the preceding embodiments, wherein, in the antibody,

- (i) the VH and VL are connected directly, e.g., without a linker; or
- (ii) the VH and VL are connected via a linker.

E55. The antibody of any one of the preceding embodiments, wherein the antibody is a human, humanized, or chimeric antibody.

E56. The antibody of any one of the preceding embodiments, wherein the antibody comprises a signal sequence.

E57. The antibody of embodiment E56, wherein, in the antibody,

- (i) the signal sequence is located 5' relative to the VH and/or the heavy chain; and/or
- (ii) the signal sequence is located 5' relative to the VL and/or the light chain.

E58. The antibody of any one of the preceding embodiments, wherein the antibody molecule comprises a second antigen-binding region having a different binding specificity than the antigen-binding region that binds to tau.

E59. The antibody of any one of the preceding embodiments, wherein the antibody molecule is a multispecific antibody molecule comprising at least a first antigen-binding domain and a second antigen-binding domain, e.g., a bispecific antibody molecule.

E60. The antibody of any one of the preceding embodiments, wherein the antibody does not bind to non-pathological tau.

E61. The antibody of any one of the preceding embodiments, wherein the antibody binds to pathological tau tangles.

E62. The antibody of any one of the preceding embodiments, wherein the antibody inhibits tau aggregation.

E63. An isolated, e.g., recombinant, antibody that competes for binding to human tau with the antibody of any one of the preceding embodiments.

E64. An isolated, e.g., recombinant, antibody that binds to the same epitope, substantially the same epitope as, an epitope that overlaps with, or an epitope that substantially overlaps with, the epitope of the antibody of any one of the preceding embodiments.

E65. The antibody of any one of the preceding embodiments, wherein the antibody comprises a conjugate, e.g., a therapeutic agent or a detectable label.

E66. A composition (e.g., a pharmaceutical composition) comprising the antibody of any one of preceding embodiments and a carrier (e.g., a pharmaceutically-acceptable carrier).

E67. An isolated, e.g., recombinant, nucleic acid, or a combination of nucleic acids, encoding the antibody of any one of embodiments E1-E65.

E68. The nucleic acid, or combination of nucleic acids, of embodiment E67, comprising:

(a) the nucleotide sequence of any VH provided in **Table 1**, or a nucleic acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or

(b) the nucleotide sequence of any VL provided in **Table 1**, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E69. The nucleic acid, or combination of nucleic acids, of any one of embodiments E67 or E68, comprising:

(a) the nucleotide sequence of any one of SEQ ID NOs: 51, 55, 54, 52, 47, 39, 56, 41, 50, 49, 48, 46, 45, 44, 43, 42, 53, 40, or a nucleic acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or

(b) the nucleotide sequence of any one of SEQ ID NOs: 67, 75, 74, 72, 66, 57, 76, 59, 70, 69, 68, 65, 64, 62, 63, 61, 60, 73, 58, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

E70. The isolated nucleic acid sequence of any one of embodiments E67-E69, wherein the nucleic acid sequence encoding the heavy chain variable region and/or the light chain variable region is codon-optimized.

E71. An isolated, e.g., recombinant, antibody encoded by the nucleic acid of any one of embodiments E67-E70.

E72. A vector (e.g., an expression vector), or combination of vectors (e.g., combination of expression vectors), comprising the nucleic acid, or combination of nucleic acids, of any one of embodiments E67-E70.

E73. A host cell comprising the nucleic acid, or combination of nucleic acids, of any one of embodiments E67-E70, or the vector, or combination of vectors, of embodiment E62.

E74. The host cell of embodiment E73, wherein the host cell is a bacterial cell or a mammalian cell.

E75. A method of producing an antibody which binds to human tau, the method comprising culturing the host cell of embodiment E73 or E74, under conditions suitable for gene

expression.

E76. A method of delivering to a subject an exogenous antibody that binds to human tau, the method comprising administering to the subject an effective amount of the antibody of any one of embodiments E1-E65, or the composition (e.g., a pharmaceutical composition) of embodiment E66.

E77. The method of embodiment E76, wherein the subject has, has been diagnosed with having, or is at risk of having a disease associated with expression of tau.

E78. The method of embodiment E76 or E77, wherein the subject has, has been diagnosed with having, or is at risk of having a neurological, *e.g.*, neurodegenerative disorder.

E79. The method of any one of embodiments E76-E78, wherein the subject has, has been diagnosed with having, or is at risk of having a tauopathy.

E80. A method of treating a subject having or diagnosed with having a disease associated with expression of tau, the method comprising administering to the subject an effective amount of the antibody of any one of embodiments E1-E65, or the composition (e.g., a pharmaceutical composition) of embodiment E66.

E81. A method of treating a subject having or diagnosed with having a neurological, *e.g.*, neurodegenerative disorder, the method comprising administering to the subject an effective amount of the antibody of any one of embodiments E1-E65, or the composition (e.g., a pharmaceutical composition) of embodiment E66.

E82. A method of treating a subject having or diagnosed with having a tauopathy, the method comprising administering to the subject an effective amount of the antibody of any one of embodiments E1-E65, or the composition (e.g., a pharmaceutical composition) of embodiment E66.

E83. The method of any one of embodiments E77-E82, wherein the disease associated with tau expression, the neurological disorder, or the tauopathy comprises Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), prion diseases, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, or progressive subcortical gliosis.

- E84. The method of any one of embodiments E80-E83, wherein treating comprises prevention of progression of the disease or disorder in the subject.
- E85. The method of any one of embodiments E76-E84, wherein the subject is human.
- E86. The method of any one of embodiments E76-E85, wherein the antibody is administered intravenously.
- E87. The method of any one of embodiments E76-E86, wherein administration of the antibody results in a decreased presence, level, and/or activity of tau protein.
- E88. The method of any one of embodiments E76-E87, further comprising administration of an additional therapeutic agent and/or therapy suitable for treatment or prevention of a disorder associated with tau expression, a neurological, *e.g.*, neurodegenerative, disorder.
- E89. The method of embodiment E88, wherein the additional therapeutic agent and/or therapy comprises a cholinesterase inhibitor (*e.g.*, donepezil, rivastigmine, and/or galantamine), an N-methyl D-aspartate (NMDA) antagonist (*e.g.*, memantine), an antipsychotic drug, an anti-anxiety drug, an anticonvulsant, a dopamine agonist (*e.g.*, pramipexole, ropinirole, rotigotine, and/or apomorphine), an MAO B inhibitor (*e.g.*, selegiline, rasagiline, and/or safinamide), catechol O-methyltransferase (COMT) inhibitors (entacapone, opicapone, and/or tolcapone), anticholinergics (*e.g.*, benztropine and/or trihexyphenidyl), amantadine, carbidopa-levodopa, deep brain stimulation (DBS), or a combination thereof.
- E90. A method of diagnosing a neurological disorder, a neurodegenerative disorder, a disease associated with tau expression or activity, or a tau-related disease (*e.g.*, tauopathy) in a subject, the method comprising the use of the antibody of any one of embodiments E1-E65.
- E91. A method of detecting tau, the method comprising contacting a sample (*e.g.*, a biological sample such as human tissue, *e.g.*, human CNS tissue) with the antibody of any one of embodiments E1-E65 and detecting the formation of a complex between the antibody and tau.
- E92. The method of embodiment E91, wherein the tissue is a thin tissue section or cryopreserved tissue section.
- E93. The antibody of any one of embodiments E1-E65, or composition of embodiment E56, for use in a method of treating a neurological disorder, a neurodegenerative disorder, a disease associated with tau expression or activity, or a tau-related disease (*e.g.*, tauopathy).

E94. The antibody of any one of embodiments E1-E65, or composition of embodiment E56, for use in the manufacture of a medicament.

E95. The antibody of any one of embodiments E1-E65, or composition of embodiment E56, for use in the manufacture of a medicament for treating a neurological disorder, a neurodegenerative disorder, a disease associated with tau expression or activity, or a tau-related disease (e.g., tauopathy).

E96. Use of the antibody of any one of embodiments E1-E65, or composition of embodiment E66 in the manufacture of a medicament.

E97. Use of the antibody of any one of embodiments E1-E65, or composition of embodiment E66 in the manufacture of a medicament for treating a neurological disorder, a neurodegenerative disorder, a disease associated with tau expression or activity, or a tau-related disease (e.g., tauopathy).

Additional embodiments

1. An antibody comprising: (i) a heavy chain variable domain (VH), wherein the VH comprises: a complementarity determining region (CDR)H1 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; a CDRH2 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; and a CDRH3 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; and (ii) a light chain variable domain (VL), wherein the VL comprises: a CDRL1 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; a CDRL2 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; and a CDRL3 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof.
2. The antibody of embodiment 1, wherein the antibody comprises a set of variable domain CDR amino acid sequences, wherein the variable domain CDR amino acid sequence set is selected from the group consisting of any of those listed in **Table 1**.
3. The antibody of embodiment 1 or 2, wherein the antibody comprises a pair of variable domain CDR amino acid sequence sets, wherein the variable domain CDR amino acid sequence set pair is selected from the group consisting of any those listed in **Table 1**.

4. The antibody of any one of embodiments 1-3, wherein: (i) the VH comprises: a framework region (FR)H1 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; a FRH2 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; a FRH3 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; and a FRH4 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; and (ii) the VL comprises: a FRL1 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; a FRL2 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; a FRL3 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof; and a FRL4 comprising an amino acid sequence selected from the group consisting of any of those listed in **Table 1**, or a fragment thereof.
5. The antibody of any one of embodiments 1-4, wherein the VH comprises: an amino acid sequence selected from the group consisting of any of those listed in **Table 1**; and/or is encoded by a nucleic acid sequence selected from the group consisting of any of those listed in **Table 1**.
6. The antibody of any one of embodiments 1-5, wherein the VL comprises: an amino acid sequence selected from the group consisting of any of those listed in **Table 1**; and/or is encoded by a nucleic acid sequence selected from the group consisting of any of those listed in **Table 1**.
7. The antibody of any one of embodiments 1-6, wherein the antibody comprises a variable domain pair, the variable domain pair selected from the group consisting of any of those listed in **Table 1**.
8. The antibody of any one of embodiments 1-7, wherein the antibody comprises a format selected from the group consisting of a monoclonal antibody, a multispecific antibody, a chimeric antibody, an antibody mimetic, a single chain Fv (scFv) format, and an antibody fragment.
9. The antibody of any one of embodiments 1-7, wherein the antibody comprises an antibody class selected from the group consisting of IgA, IgD, IgE, IgG, and IgM.
10. The antibody of any one of embodiments 1-7, wherein the antibody comprises one or more non-human constant domain.

11. The antibody of any one of embodiments 1-7, wherein the antibody comprises one or more human constant domain.
12. The antibody of embodiment 11, wherein the one or more human constant domain is selected from the group consisting of any of those listed in **Table 5**.
13. The antibody of embodiment 12, wherein the antibody comprises a human IgG, wherein the human IgG comprises an isotype selected from the group consisting of IgG1, IgG2, IgG3, and IgG4.
14. The antibody of any one of embodiments 1-7, wherein the antibody comprises a human antibody.
15. The antibody of any one of embodiments 1-14, wherein the antibody binds to a tau protein epitope.
16. The antibody of embodiment 15, wherein the tau protein epitope comprises or is comprised within an amino acid sequence selected from the group consisting of any of those listed in **Table 4**.
17. The antibody of embodiment 15 or 16, wherein the tau protein epitope comprises a region formed by a complex of at least two tau proteins.
18. The antibody of any one of embodiments 15-17, wherein the antibody binds to enriched paired helical filament tau protein (ePHF) with a half maximal effective concentration (EC50) of from about 0.01 nM to about 100 nM as determined by direct enzyme-linked immunosorbent assay (ELISA).
19. The antibody of any one of embodiments 15-18, wherein the antibody does not bind to non-pathological tau.
20. The antibody of any one of embodiments 15-19, wherein the antibody binds to pathological tau tangles.
21. The antibody of any one of embodiments 15-20, wherein the antibody inhibits tau aggregation.
22. The antibody of any one of embodiments 1-21, wherein the antibody comprises a conjugate.
23. The antibody of embodiment 22, wherein the conjugate comprises a therapeutic agent.
24. The antibody of embodiment 22, wherein the conjugate comprises a detectable label.
25. A construct encoding the antibody of any one of embodiments 1-21.
26. A method of treating a therapeutic indication in a subject, the method comprising administering to the subject the antibody of any one of embodiments 1-24.

27. The method of embodiment 26, wherein the therapeutic indication comprises a neurological indication.
28. The method of embodiment 27, wherein the neurological indication comprises one or more of neurodegenerative disease, Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), a prion disease, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis.
29. A method of diagnosing a therapeutic indication in a subject, the method comprising the use of the antibody of any one of embodiments 1-24.
30. The method of embodiment 29, wherein the therapeutic indication comprises a neurological indication.
31. The method of embodiment 30, wherein the neurological indication comprises one or more of neurodegenerative disease, AD, FTDP-17, FTLD, FTD, CTE, PSP, Down's syndrome, Pick's disease, CBD, corticobasal syndrome, ALS, a prion disease, CJD, multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis.
32. The method of any one of embodiments 29-31, wherein the antibody is used to detect pathological tau in a subject tissue.
33. The method of embodiment 32, wherein the subject tissue comprises CNS tissue.
34. The method of embodiment 32 or 33, wherein the subject tissue comprises a thin tissue section.
35. The method of embodiment 34, wherein the thin tissue section comprises a cryopreserved tissue section.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **FIGs. 1A-1C** show the results of competition ELISA assays for binding of the indicated antibodies ($\pm$ competitors) to Peptide 12 (corresponding to SEQ ID NO: 277) (**FIG. 1A**), a TauS404 peptide (**FIG. 1B**), or the AC04 peptide (**FIG. 1C**).

[0015] **FIG. 2** shows the results of a competition ELISA assay for binding of AT8 in the presence or absence of VY003, VY007, VY006, VY001, or an isotype antibody control to PepScan Fragment 97 (corresponding to SEQ ID NO: 283).

[0016] FIG. 3 shows the results of a one point ELISA assay for binding of the indicated antibodies to Tau peptides having the following phosphorylated residues: pT231 (left bar), pS235 (right bar), or pT231/pS235 (middle bar).

DETAILED DESCRIPTION

I. COMPOSITIONS

[0017] In some embodiments, the present disclosure provides compositions that interact with human microtubule associated protein tau. Such compositions may be antibodies that bind tau protein epitopes, referred to herein as “anti-tau antibodies.” Dysfunction and/or aggregation of tau is found in a class of neurodegenerative diseases referred to as tauopathies. Tau hyperphosphorylation leads to aggregation and depressed tau-dependent microtubule assembly. In tauopathies, the tau aggregates form paired helical filaments (PHF) found in neurofibrillary tangles (NFTs). These aggregates lead to neuronal loss and cognitive decline. Anti-tau antibodies of the present disclosure may be useful for treating and/or diagnosing tauopathies, as well as other applications described herein.

Antibodies

[0018] In some embodiments, compounds (e.g., anti-tau antibodies) and compositions of the present disclosure include antibodies or fragments thereof. As used herein, the term “antibody” is referred to in the broadest sense and specifically covers various embodiments including, but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies formed from at least two intact antibodies), single chain Fv (scFv) formats, and antibody fragments (e.g., Fab, F(ab’), F(ab’)₂, or Fv), so long as they exhibit a functional or biological activity. Antibodies are primarily amino-acid based molecules but may also include one or more modifications (including, but not limited to the addition of sugar moieties, fluorescent moieties, chemical tags). In some embodiments, the antibody is a full-length antibody.

[0019] Antibodies of the present disclosure may include, but are not limited to, polyclonal, monoclonal antibodies, multispecific antibodies, bispecific antibodies, trispecific antibodies, human antibodies, humanized antibodies, chimeric antibodies, single chain antibodies, diabodies, linear antibodies, Fab fragments, F(ab’) fragments, F(ab’)₂ fragments, Fv fragments, single-chain Fv fragment (scFv), fragments produced by a Fab expression library, variable domains, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly made antibodies (i.e., intrabodies),

codon-optimized antibodies, tandem scFv antibodies, bispecific T-cell engagers, mAb2 antibodies, chimeric antigen receptors (CAR), tetravalent bispecific antibodies, biosynthetic antibodies, native antibodies, miniaturized antibodies, unibodies, maxibodies, intrabodies, camelid antibodies, and epitope-binding fragments of any of the above.

[0020] As used herein, the term "antibody fragment" refers to a portion of an intact antibody or fusion-protein thereof, in some cases including at least one antigen binding region. Examples of antibody fragments include Fab, Fab', F(ab')₂, Fv fragments, single-chain variable fragments (scFvs); diabodies; tri(a)bodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site. Also produced is a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')₂ fragment that has two antigen-binding sites and is still capable of cross-linking antigen. Antibodies of the present disclosure may include one or more of these fragments and may, for example, be generated through enzymatic digestion of whole antibodies or through recombinant expression.

[0021] "Native antibodies" are usually heterotetrameric glycoproteins of about 150,000 Daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Genes encoding antibody heavy and light chains are known and segments making up each have been well characterized and described (Matsuda, F. et al., 1998. The Journal of Experimental Medicine. 188(11); 2151-62 and Li, A. et al., 2004. Blood. 103(12): 4602-9, the content of each of which are herein incorporated by reference in their entirety). Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain at one end (V_L) and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0022] As used herein, the term "variable domain" refers to specific antibody domains found on both the antibody heavy and light chains that differ extensively in sequence among antibodies and are used in the binding and specificity of each particular antibody for its particular antigen. Variable domains include hypervariable regions. As used herein, the term "hypervariable region" refers to a region within a variable domain that includes amino acid

residues responsible for antigen binding. The amino acids present within the hypervariable regions determine the structure of the complementarity determining regions (CDRs) that become part of the antigen-binding site of the antibody. As used herein, the term “CDR” refers to a region of an antibody that includes a structure that is complimentary to its target antigen or epitope. Other portions of the variable domain, not interacting with the antigen, are each referred to as a “framework region” (FR). The antigen-binding site (also known as the antigen combining site or paratope) includes the amino acid residues necessary to interact with a particular antigen. The exact residues making up the antigen-binding site may be determined by CDR analysis. As used herein, the term “CDR analysis” refers to any process used to determine which antibody variable domain residues make up the CDRs. CDR analysis may be conducted by co-crystallography with bound antigen. In some embodiments, CDR analysis may include computational assessments based on comparisons with other antibodies (Strohl, W.R. *Therapeutic Antibody Engineering*. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety). CDR analysis may include the use of numbering schemes including, but not limited to, those taught by Kabat [Wu, T.T. et al., 1970, *JEM*, 132(2):211-50 and Johnson, G. et al., 2000, *Nucleic Acids Res.* 28(1): 214-8, the contents of each of which are herein incorporated by reference in their entirety], Chothia [Chothia and Lesk, *J. Mol. Biol.* 196, 901 (1987), Chothia et al., *Nature* 342, 877 (1989), and Al-Lazikani, B. et al., 1997, *J. Mol. Biol.* 273(4):927-48, the contents of each of which are herein incorporated by reference in their entirety], Lefranc (Lefranc, M.P. et al., 2005, *Immunome Res.* 1:3), and Honegger (Honegger, A. and Pluckthun, A. 2001. *J. Mol. Biol.* 309(3):657-70, the contents of which are herein incorporated by reference in their entirety).

[0023] The precise amino acid sequence boundaries of a given CDR can be determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (Kabat numbering scheme), Al-Lazikani et al., (1997) *JMB* 273,927-948 (Chothia numbering scheme). In some embodiments, the CDRs defined according the Chothia number scheme are also sometimes referred to as hypervariable loops.

[0024] For example, under Kabat, the CDR amino acid residues in the heavy chain variable domain (VH) are numbered 31-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3); and the CDR amino acid residues in the light chain variable domain (VL) are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3). Under Chothia the CDR

amino acids in the VH are numbered 26-32 (HCDR1), 52-56 (HCDR2), and 95-102 (HCDR3); and the amino acid residues in VL are numbered 26-32 (LCDR1), 50-52 (LCDR2), and 91-96 (LCDR3). By combining the CDR definitions of both Kabat and Chothia, the CDR amino acid residues are numbered 26-35 (HCDR1), 50-65 (HCDR2), and 95-102 (HCDR3) in human VH and the CDR amino acid residues are numbered 24-34 (LCDR1), 50-56 (LCDR2), and 89-97 (LCDR3) in human VL.

[0025] VH and VL domains have three CDRs each. VL CDRs are referred to herein as CDRL1, CDRL2 and CDRL3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. VH CDRs are referred to herein as CDRH1, CDRH2 and CDRH3, in order of occurrence when moving from N- to C- terminus along the variable domain polypeptide. Each of the CDRs have favored canonical structures with the exception of the CDRH3, which includes amino acid sequences that may be highly variable in sequence and length between antibodies resulting in a variety of three-dimensional structures in antigen-binding domains (Nikoloudis, D. et al., 2014. PeerJ. 2:e456). In some cases, CDRH3s may be analyzed among a panel of related antibodies to assess antibody diversity. Various methods of determining CDR sequences are known in the art and may be applied to known antibody sequences (Strohl, W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54, the contents of which are herein incorporated by reference in their entirety).

[0026] VH and VL domains each have four framework regions (FRs) located before, after, and between CDR regions. VH framework regions are referred to herein as FRH1, FRH2, FRH3, and FRH4 and VL framework regions are referred to herein as FRL1, FRL2, FRL3, and FRL4. On VH domains, FRs and CDRs are typically in the order of FRH1-CDRH1-FRH2-CDRH2-FRH3-CDRH3-FRH4, from N-terminus to C-terminus. On VL domains, FRs and CDRs are typically in the order of FRL1-CDRL1-FRL2-CDRL2-FRL3-CDRL3-FRL4, from N-terminus to C-terminus.

[0027] As used herein, the term “Fv” refers to an antibody fragment that includes the minimum fragment on an antibody needed to form a complete antigen-binding site. These regions consist of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. Fv fragments can be generated by proteolytic cleavage, but are largely unstable. Recombinant methods are known in the art for generating stable Fv fragments, typically through insertion of a flexible linker between the light chain variable domain and the heavy chain variable domain [to form a single chain Fv (scFv)] or through the introduction of a disulfide bridge between heavy and light chain variable domains (Strohl,

W.R. Therapeutic Antibody Engineering. Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p46-47, the contents of which are herein incorporated by reference in their entirety).

[0028] Antibody "light chains" from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda based on amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains, antibodies can be assigned to different classes.

[0029] As used herein, the term "single chain Fv" or "scFv" refers to a fusion protein of V_H and V_L antibody domains, wherein these domains are linked together into a single polypeptide chain by a flexible peptide linker. In some embodiments, the Fv polypeptide linker enables the scFv to form the desired structure for antigen binding. In some embodiments, scFvs are utilized in conjunction with phage display, yeast display or other display methods where they may be expressed in association with a surface member (e.g. phage coat protein) and used in the identification of high affinity peptides for a given antigen. In some embodiments, antibodies of the present disclosure are prepared as scFvFc antibodies. The term "scFvFc" refers to an antibody format which includes the fusion of one or more scFv with an antibody Fc domain.

[0030] The term "chimeric antibody" refers to an antibody with portions derived from two or more sources. Chimeric antibodies may include portions derived from different species. For example, chimeric antibodies may include antibodies with mouse variable domains and human constant domains. Further examples of chimeric antibodies and methods for producing them include any of those described in Morrison, S.L., *Transfectomas provide novel chimeric antibodies*. Science. 1985 Sep 20;229(4719):1202-7; Gillies, S.D. et al., *High-level expression of chimeric antibodies using adapted cDNA variable region cassettes*. J Immunol Methods. 1989 Dec 20;125(1-2):191-202.; and U.S. Pat. Nos. 5,807, 715; 4,816,567; and 4,816,397, the contents of each of which are incorporated herein by reference in their entirety.

[0031] The term "diabodies" refers to small antibody fragments with two antigen-binding sites, which fragments include a heavy chain variable domain V_H connected to a light chain variable domain V_L in the same polypeptide chain. By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993), the contents of each of which are incorporated herein by reference in their entirety.

[0032] The term “intrabody” refers to a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular protein(s). Intrabodies may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods of the present invention may include intrabody-based therapies. In some such embodiments, variable domain sequences and/or CDR sequences disclosed herein may be incorporated into one or more constructs for intrabody-based therapy. In some cases, intrabodies of the invention may target one or more glycosylated intracellular proteins or may modulate the interaction between one or more glycosylated intracellular protein and an alternative protein.

[0033] The term “chimeric antigen receptor” or “CAR” as used herein, refers to artificial receptors that are engineered to be expressed on the surface of immune effector cells resulting in specific targeting of such immune effector cells to cells expressing entities that bind with high affinity to the artificial receptors. CARs may be designed to include one or more segments of an antibody, antibody variable domain and/or antibody CDR, such that when such CARs are expressed on immune effector cells, the immune effector cells bind and clear any cells that are recognized by the antibody portions of the CARs. In some cases, CARs are designed to specifically bind cancer cells, leading to immune-regulated clearance of the cancer cells.

[0034] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous cells (or clones), i.e., the individual antibodies making up the population are identical and/or bind the same epitope, except for possible variants that may arise during production of the monoclonal antibody, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen

[0035] The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. The monoclonal antibodies herein include "chimeric" antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to

corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies.

[0036] Antibodies of the present disclosure may be from any animal origin including mammals, birds, reptiles, and insects. Mammalian antibodies may be, for example, of human, murine (e.g., mouse or rat), donkey, sheep, rabbit, goat, guinea pig, camel, bovine, or horse origin.

[0037] In some embodiments, antibodies of the present disclosure may be antibody mimetics. The term “antibody mimetic” refers to any molecule which mimics the function or effect of an antibody and which binds specifically and with high affinity to their molecular targets. In some embodiments, antibody mimetics may be monobodies, designed to incorporate the fibronectin type III domain (Fn3) as a protein scaffold (US 6,673,901; US 6,348,584). In some embodiments, antibody mimetics may be those known in the art including, but are not limited to affibody molecules, affilins, affitins, anticalins, avimers, DARPins, Fynomers and Kunitz and domain peptides. In other embodiments, antibody mimetics may include one or more non-peptide region.

[0038] As used herein, the term “antibody variant” refers to a biomolecule resembling an antibody in structure, sequence and/or function, but including some differences in their amino acid sequence, composition or structure as compared to another antibody or a native antibody.

Intrabody

[0039] In some embodiments, the antibody described herein is an intrabody. In some embodiments, an intrabody is a form of antibody that is not secreted from a cell in which it is produced, but instead targets one or more intracellular proteins. Intrabodies are expressed and function intracellularly, and may be used to affect a multitude of cellular processes including, but not limited to intracellular trafficking, transcription, translation, metabolic processes, proliferative signaling and cell division. In some embodiments, methods described herein include intrabody-based therapies.

[0040] In some embodiments, the intrabody is a single chain variable fragment (scFv) expressed from a recombinant nucleic acid molecule and engineered to be retained intracellularly (e.g., retained in the cytoplasm, endoplasmic reticulum, or periplasm). Intrabodies may be used, for example, to ablate the function of a protein to which the intrabody binds. Exemplary intrabodies are described and reviewed in: (Marasco et al., 1993 Proc. Natl. Acad. Sci. USA, 90: 7889-7893; Chen et al., 1994, Hum. Gene Ther. 5:595-601; Chen et al., 1994, Proc. Natl. Acad. Sci. USA, 91: 5932-5936; Maciejewski et al., 1995,

Nature Med., 1: 667-673; Marasco, 1995, Immunotech, 1: 1-19; Mhashilkar, et al., 1995, EMBO J. 14: 1542-51; Chen et al., 1996, Hum. Gene Therap., 7: 1515-1525; Marasco, Gene Ther. 4:11-15, 1997; Rondon and Marasco, 1997, Annu. Rev. Microbiol. 51:257-283; Cohen, et al., 1998, Oncogene 17:2445-56; Proba et al., 1998, J. Mol. Biol. 275:245-253; Cohen et al., 1998, Oncogene 17:2445-2456; Hassanzadeh, et al., 1998, FEBS Lett. 437:81-6; Richardson et al., 1998, Gene Ther. 5:635-44; Ohage and Steipe, 1999, J. Mol. Biol. 291:1119-1128; Ohage et al., 1999, J. Mol. Biol. 291:1129-1134; Wirtz and Steipe, 1999, Protein Sci. 8:2245-2250; Zhu et al., 1999, J. Immunol. Methods 231:207-222; Arafat et al., 2000, Cancer Gene Ther. 7:1250-6; der Maur et al., 2002, J. Biol. Chem. 277:45075-85; Mhashilkar et al., 2002, Gene Ther. 9:307-19; and Wheeler et al., 2003, FASEB J. 17: 1733-5; and references cited therein). In particular, a CCR5 intrabody has been produced by Steinberger et al., 2000, Proc. Natl. Acad. Sci. USA 97:805-810). See generally Marasco, WA, 1998, "Intrabodies: Basic Research and Clinical Gene Therapy Applications" Springer: New York; and for a review of scFvs, see Pluckthun in "The Pharmacology of Monoclonal Antibodies," 1994, vol. 113, Rosenberg and Moore eds. Springer-Verlag, New York, pp. 269-315; all of which are hereby incorporated by reference in their entirety.

[0041] Sequences from donor antibodies may be used to develop intrabodies. Intrabodies are often recombinantly expressed as single domain fragments such as isolated VH and VL domains or as a single chain variable fragment (scFv) antibody within the cell. For example, intrabodies are often expressed as a single polypeptide to form a single chain antibody comprising the variable domains of the heavy and light chains joined by a flexible linker polypeptide. Intrabodies typically lack disulfide bonds and are capable of modulating the expression or activity of target genes through their specific binding activity. Single chain antibodies can also be expressed as a single chain variable region fragment joined to the light chain constant region.

[0042] In some embodiments, an intrabody can be engineered into recombinant polynucleotide vectors to encode sub-cellular trafficking signals at its N or C terminus to allow expression at high concentrations in the sub-cellular compartments where a target protein is located. For example, intrabodies targeted to the endoplasmic reticulum (ER) are engineered to incorporate a leader peptide and, optionally, a C-terminal ER retention signal, such as the KDEL amino acid motif. Intrabodies intended to exert activity in the nucleus are engineered to include a nuclear localization signal. Lipid moieties are joined to intrabodies in order to tether the intrabody to the cytosolic side of the plasma membrane. Intrabodies can also be targeted to exert function in the cytosol. For example, cytosolic intrabodies are used

to sequester factors within the cytosol, thereby preventing them from being transported to their natural cellular destination.

[0043] Intrabodies may be promising therapeutic agents for the treatment of misfolding diseases, including tauopathies, prion diseases, Alzheimer's, Parkinson's, and Huntington's, because of their virtually infinite ability to specifically recognize the different conformations of a protein, including pathological isoforms, and because they can be targeted to the potential sites of aggregation (both intra- and extracellular sites). These molecules can work as neutralizing agents against amyloidogenic proteins by preventing their aggregation, and/or as molecular shunters of intracellular traffic by rerouting the protein from its potential aggregation site (Cardinale, and Biocca, *Curr. Mol. Med.* 2008, 8:2-11).

Antibody development

[0044] Antibodies according to the present disclosure may be developed using methods standard in the art. Two primary antibody preparation technologies are immunization and antibody display technology. In either case, desired antibodies are identified from a larger pool of candidates based on affinity for a specific target or epitope. An immune response is characterized by the reaction of the cells, tissues and/or organs of an organism to the presence of a foreign entity. Such an immune response typically leads to the production by the organism of one or more antibodies against the foreign entity, e.g., antigen or a portion of the antigen.

Antigens

[0045] Antibodies may be developed (e.g., through immunization) or selected (e.g., from pool of candidates), for example, using any naturally occurring or synthetic antigen. As used herein, an "antigen" is an entity which induces or evokes an immune response in an organism and may also refer to an antibody binding partner. An immune response is characterized by the reaction of the cells, tissues and/or organs of an organism to the presence of a foreign entity. Such an immune response typically leads to the production by the organism of one or more antibodies against the foreign entity. In some embodiments, antigens include tau proteins. As used herein, the term "tau protein" refers to proteins or protein complexes that include microtubule-associated protein tau or peptide fragments thereof. Tau proteins may include enriched paired helical filament tau protein (ePHF), also referred to as "sarkosyl insoluble tau," or fragments thereof. Tau proteins may include one or more phosphorylated residues. Such phosphorylated residues may correspond to tau proteins associated with disease (also referred to herein as "pathological tau.")

Immunization

[0046] In some embodiments, antibodies may be prepared by immunizing a host with an antigen of interest. Host animals (e.g., mice, rabbits, goats, or llamas) may be immunized with an antigenic protein to elicit lymphocytes that specifically bind to the antigen. Lymphocytes may be collected and fused with immortalized cell lines to generate hybridomas which can be cultured in a suitable culture medium to promote growth (e.g., see Kohler, G. et al., Continuous cultures of fused cells secreting antibody of predefined specificity. *Nature*. 1975 Aug 7;256(5517):495-7, the contents of which are herein incorporated by reference in their entirety). Alternatively, lymphocytes may be immunized in vitro.

[0047] In some embodiments, antibodies of the present disclosure may be prepared through immunization using mouse host animals. Such host animals may include transgenic mice. Transgenic mice may include those engineered to express human antibody sequences, in some cases, replacing mouse antibody sequences. Transgenic mice may express human variable domain sequences and/or constant domain sequences. In some embodiments, mouse host animals used for immunization may include any of the transgenic mice described in United States Patent Numbers 7,435,871, 7,547,817, 9,346,873, 9,580,491, or 10,555,506, the content of each of which is herein incorporated by reference in its entirety.

[0048] Lymphocytes may be fused with immortalized cell lines using suitable fusing agents (e.g., polyethylene glycol) to form a hybridoma cell (e.g., see Goding, J.W., *Monoclonal Antibodies: Principles and Practice*. Academic Press. 1986; 59-1031, the contents of which are herein incorporated by reference in their entirety). Immortalized cell lines may be transformed mammalian cells, particularly myeloma cells of rodent, rabbit, bovine, or human origin. In some embodiments, rat or mouse myeloma cell lines are employed. Hybridoma cells may be cultured in suitable culture media, typically including one or more substances that inhibit the growth or survival of unfused cells. For example, parental cells lacking the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT) may be used and culture media for resulting hybridoma cells may be supplemented with hypoxanthine, aminopterin, and thymidine ("HAT medium") to prevent growth of HGPRT-deficient (unfused) cells.

[0049] Desirable properties for immortalized cell lines may include, but are not limited to, efficient fusing, supportive of high level antibody expression by selected antibody-producing cells, and sensitivity to unfused cell-inhibitory media (e.g., HAT media). In some embodiments, immortalized cell lines are murine myeloma lines. Such cell lines may be

obtained, for example, from the Salk Institute Cell Distribution Center (San Diego, CA) or the American Type Culture Collection, (Manassas, VA). Human myeloma and mouse-human heteromyeloma cell lines may also be used for the production of human monoclonal antibodies (e.g., see Kozbor, D. et al., A human hybrid myeloma for production of human monoclonal antibodies. *J Immunol.* 1984 Dec;133(6):3001-5 and Brodeur, B. et al., *Monoclonal Antibody Production Techniques and Applications*. Marcel Dekker, Inc., New York. 1987; 33:51-63, the contents of each of which are herein incorporated by reference in their entirety).

[0050] Hybridoma cell culture media may be assayed for the presence of monoclonal antibodies with desired binding specificity. Assays may include, but are not limited to, immunoprecipitation assay, in vitro binding assay, radioimmunoassay (RIA), surface plasmon resonance (SPR) assay, and/or enzyme-linked immunosorbent assay (ELISA). In some embodiments, binding specificity of monoclonal antibodies may be determined by Scatchard analysis (Munson, P.J. et al., *Ligand: a versatile computerized approach for characterization of ligand-binding systems*. *Anal Biochem.* 1980 Sep 1;107(1):220-39, the contents of which are herein incorporated by reference in their entirety).

[0051] Antibodies produced by cultured hybridomas may be analyzed to determine binding specificity for target antigens. Once antibodies with desirable characteristics are identified, corresponding hybridomas may be subcloned through limiting dilution procedures and grown by standard methods. Antibodies produced by hybridomas may be isolated and purified using standard immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxyapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography. Alternatively, hybridoma cells may be grown in vivo as ascites in a mammal. In some embodiments, antibodies may be isolated directly from serum of immunized hosts.

[0052] In some embodiments, recombinant versions of antibodies generated through immunization may be prepared. Such antibodies may be prepared using genomic antibody sequences from selected hybridomas. Hybridoma genomic antibody sequences may be obtained by extracting RNA molecules from antibody-producing hybridoma cells and producing cDNA by reverse transcriptase polymerase chain reaction (PCR). PCR may be used to amplify cDNA using primers specific for antibody heavy and light chains. PCR products may then be subcloned into plasmids for sequence analysis. Antibodies may be produced by insertion of resulting antibody sequences into expression vectors. Some recombinant antibodies may be prepared using synthetic nucleic acid constructs that encode

amino acid sequences corresponding to amino acid sequences obtained from isolated hybridoma antibodies.

Antibody display

[0053] In some embodiments, antibodies may be developed using antibody display technologies. “Display technology” refers to systems and methods for expressing amino acid-based candidate compounds in a format where they are linked with nucleic acids encoding them and are accessible to a target or ligand. Candidate compounds are expressed at the surface of a host capsid or cell in most systems, however, some host-free systems (e.g., ribosomal display) exist. Display technologies may be used to generate display “libraries,” which include sets of candidate compound library members. Display libraries with antibodies (or variants or fragments thereof) as library members are referred to herein as “antibody display libraries.” Antibodies may be designed, selected, or optimized by screening target antigens using antibody display libraries. Antibody display libraries may include millions to billions of members, each expressing unique antibody domains. Antibody fragments displayed may be scFv antibody fragments, which are fusion proteins of V_H and V_L antibody domains joined by a flexible linker. Display libraries may include antibody fragments with differing levels of diversity between variable domain framework regions and CDRs. Display library antibody fragment CDRs may include unique variable loop lengths and/or sequences. Antibody variable domains or CDRs obtained from display library selection may be directly incorporated into antibody sequences for recombinant antibody production or mutated and utilized for further optimization through in vitro affinity maturation.

[0054] Antibody display libraries may include antibody phage display libraries. Antibody phage display libraries utilize phage virus particles as hosts with millions to billions of members, each expressing unique antibody domains. Such libraries may provide richly diverse sources that may be used to select potentially hundreds of antibody fragments with diverse levels of affinity for one or more antigens of interest (McCafferty, et al., 1990. *Nature*. 348:552-4; Edwards, B.M. et al., 2003. *JMB*. 334: 103-18; Schofield, D. et al., 2007. *Genome Biol.* 8, R254 and Pershad, K. et al., 2010. *Protein Engineering Design and Selection*. 23:279-88; the contents of each of which are herein incorporated by reference in their entirety). Antibody fragments displayed may be scFv antibody fragments. Phage display library members may be expressed as fusion proteins, linked to viral coat proteins (e.g. the N-terminus of the viral pIII coat protein). V_L chains may be expressed separately for assembly with V_H chains in the periplasm prior to complex incorporation into viral coats. Precipitated

library members may be sequenced from the bound phage to obtain cDNA encoding desired antibody domains.

[0055] In some embodiments, antibody display libraries may be generated using yeast surface display technology. Antibody yeast display libraries are made up of yeast cells with surface displayed antibodies or antibody fragments. Antibody yeast display libraries may include antibody variable domains expressed on the surface of *Saccharomyces cerevisiae* cells. Yeast display libraries may be developed by displaying antibody fragments of interest as fusion proteins with yeast surface proteins (e.g. Aga2p protein). Yeast cells displaying antibodies or antibody fragments with affinity for a specific target may be isolated according to standard methods. Such methods may include, but are not limited to, magnetic separation and flow cytometry.

Recombinant synthesis

[0056] Antibodies of the present disclosure may be prepared using recombinant DNA technology and related processes. Constructs (e.g., DNA expression plasmids) encoding antibodies may be prepared and used to synthesize full antibodies or portions thereof. In some embodiments, DNA sequences encoding antibody variable domains of the present disclosure may be inserted into expression vectors (e.g., mammalian expression vectors) encoding other antibody domains and used to prepare antibodies with the inserted variable domains. DNA sequences encoding antibody variable domains may be inserted downstream of upstream expression vector regions with promoter/enhancer elements and/or encoding immunoglobulin signal sequences. DNA sequences encoding antibody variable domains may be inserted upstream of downstream expression vector regions encoding immunoglobulin constant domains. Encoded constant domains may be from any class (e.g., IgG, IgA, IgD, IgE, and IgM) or species (e.g., human, mouse, rabbit, rat, and non-human primate). In some embodiments, encoded constant domains encode human IgG (e.g., IgG1, IgG2a, IgG2b, IgG2c, IgG3, or IgG4) constant domains. In some embodiments, encoded constant domains encode mouse IgG (e.g., IgG1, IgG2a, IgG2b, or IgG3) constant domains.

[0057] Expression vectors encoding antibodies of the present disclosure may be used to transfect cells for antibody production. Such cells may be mammalian cells. Cell lines with stable transfection of antibody expression vectors may be prepared and used to establish stable cell lines. Cell lines producing antibodies may be expanded for expression of antibodies which may be isolated or purified from cell culture media.

Anti-tau antibody sequences

[0058] Described herein are antibodies, *e.g.*, recombinant antibodies, which are characterized by particular functional and structural features or properties. For example, the antibodies specifically bind human tau (*e.g.*, human tau having the sequence set forth in SEQ ID NO: 274). Particular antibodies described herein are antibodies having the CDR and/or variable region (VH and/or VL) sequences of antibodies VY011, VY007, VY004, VY006, VY018, VY003, VY016, VY017, VY012, VY009, VY010, VY022, VY001, VY019, VY020, VY005, VY002, VY014, VY008, and VY013, as well as antibodies having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and antibodies having variable regions with at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (*e.g.*, 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as amino acid substitutions (*e.g.*, conservative substitutions)), relative to the VH and/or VL sequences of the VY antibodies listed above. The ability of variant antibodies to bind to tau (*e.g.*, wild-type tau (*e.g.*, SEQ ID NO: 274), ePHF, iPHF) can be determined using art-recognized binding assays, *e.g.*, the binding assays described in the Examples. **Table 1** summarizes the amino acid sequences and nucleotide sequences encoding the VY antibodies.

Table 1. Exemplary anti-tau antibodies

Ab ID	SEQ ID	Description	Sequence
VY011	82	HCDR1	GGGISNYY
	97	HCDR2	VYTSGSA
	115	HCDR3	ARDRGLYY
	175	FR H1	QVQLQESGPGLVKPSSETLSLTCTVS
	183	FR H2	WTWIRQPAGKGLEWIGR
	197	FR H3	NYNPSLKSRTMSVDTSKNQFSLTLSSVTAADTAVYYC
	209	FR H4	WGQGTILVTVSS
	127	LCDR1	QSLVHSDGNTY
	141	LCDR2	KIS
	159	LCDR3	MQATQFPLT
	219	FR L1	DIVMTQTPPLSSVLTGLQPASISCRSS
	230	FR L2	LSWLQQRPQGPPRLLIY
	250	FR L3	KRFFGVDPDRFSGSGAGTDFTLKINRVEAEDVGIYYC
	265	FR L4	FGGGTKVEIK
	7	VH	QVQLQESGPGLVKPSSETLSLTCTVSGGISNYYWTWIRQPAGKGLEWIGRVYTSGSANYNPSLKSRTMSVDTSKNQFSLTLSSVTAADTAVYYCARDRLYYWGQGTILVTVSS

VY007	25	VL	DIVMTQTPLSSLVTLGQPASISCRSSQSLVHSDGNTYLSWLQQRPGQ PPRLLIYKISKRFEGVPDRFSGSGAGTDFTLKINRVEAEDVGIYYCM QATQFPFLTFGGGTKVEIK
	51	VH (DNA)	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGA GACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAATT ACTACTGGACCTGGATCCGGCAGCCCGCCGGAAGGGACTGGAGTGG ATTGGGCGTGTCTATACAGTGGGAGCGCCAACCTACAACCCCTCCCT CAAGAGTCGAGTTACCATGTCTAGTACACGTCCAAGAACCAGTTCT CCCTGACGCTGAGCTCTGTGACCGCCGCGGACACGGCGGTGTATTAC TGTGCGAGAGATAGAGGACTCTACTACTGGGGCCAGGGAACCCCTGGT CACCGTCTCTCTCA
	71	VL (DNA)	GATATTGTGATGACCCAGACTCCACTCTCCTCACTTGTACCCCTTGG ACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTACACA GTGATGGAAACACCTATTTGAGTTGGCTTCAGCAGAGGCCAGGCCAG CCTCCAAGACTCCTAATTTATAAGATTTCTAAGCGGTCTTTGGGGT CCCAGACAGATTTCAGTGGCAGTGGGGCAGGGACAGATTTCACACTGA AAATCAACAGGGTGAAGCTGAGGATGTCTGGGATTTATTACTGCATG CAAGCTACACAATTTCCGCTCACTTTCGGCGGAGGGACCAAGGTGGA GATCAAA
	79	HCDR1	RFTFSNYN
	94	HCDR2	ISSSSSTI
	111	HCDR3	ASLGRGY
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS
	182	FR H2	MNWRQAPGKGLEWISY
	194	FR H3	YYADSVKGRFTISRDNKNSLSLQMNSLRDEDTAVYYC
	209	FR H4	WGQGTLLTVSS
	127	LCDR1	QSLVHSDGNTY
	141	LCDR2	KIS
	156	LCDR3	MQATQFPRT
	215	FR L1	DIVMTQTPLSSPVTTLGQPASISCRSS
	230	FR L2	LSWLQQRPGQPPRLLIY
	246	FR L3	NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC
	264	FR L4	FGQGSKEIK
	3	VH	EVQLVESGGGLVQPGGSLRLSCAASRFTFSNYNMNWRQAPGKGLEW ISYISSSSSTIYYADSVKGRFTISRDNKNSLSLQMNSLRDEDTAVY YCASLGRGYWGQGTLLTVSS
	21	VL	DIVMTQTPLSSPVTTLGQPASISCRSSQSLVHSDGNTYLSWLQQRPGQ PPRLLIYKISNRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCM QATQFPRTFGQGSKEIK
	55	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTAGATTACCTTCAGTAACCT ATAACATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG ATTTACATACATTAGTAGTAGTAGTAGTACCATATACTACGCAGACTC TGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAACTCAC TGTCTCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGAGTCTGGGGAGGGGCTACTGGGGCCAGGGAACCCCTGGT CACCGTCTCTCTCA
	75	VL (DNA)	GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTACCCCTTGG ACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTACACA

			GTGATGGAAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAG CCTCCAAGACTCCTAATTTATAAGATTTCTAACCGGTTCTCTGGGGT CCCAGACAGATTCACTGGCAGTGGGGCAGGGACAGATTCACACTGA AAATCAGCAGGGTGGAGCTGAGGATGTCGGGGTTTATTATTGTATG CAAGCTACTCAATTTCTCGCACTTTTGGCCAGGGGTCCAAGCTGGA GATCAAA
VY004	80	HCDR1	GFTFSDYS
	95	HCDR2	IRSSSSII
	112	HCDR3	ARRGHFDY
	174	FR H1	EVQLVESGGGLVQAGGSLRLSCAAS
	181	FR H2	MNWRQAPGKGLEWVS
	195	FR H3	YYADSVKGRFTISRDNAKNSLHLQMNSLRDEDTAVYYC
	209	FR H4	WGQGTILTVSS
	129	LCDR1	QSVSDY
	143	LCDR2	DVS
	157	LCDR3	QQRSNWPLT
	217	FR L1	EIVLTQSPATLSLSPGERATLSCRAS
	232	FR L2	LAWYQQKPGQAPRLFIY
	247	FR L3	KRATGIPARFSGSGSGTDFTLTISSELEPEDFAVYYC
	265	FR L4	FGGGTKVEIK
	4	VH	EVQLVESGGGLVQAGGSLRLSCAASGFTFSDYSMNWRQAPGKGLEW VSYIRSSSSIIYYADSVKGRFTISRDNAKNSLHLQMNSLRDEDTAVY YCARRGHFDYWGQGTILTVSS
	22	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSDYLAWYQQKPGQAPRLF IYDVSKRATGIPARFSGSGSGTDFTLTISSELEPEDFAVYYCQQRSNW PLTFGGGTKEIK
	54	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGGCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTGACT ATAGCATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG GTTTCATATATTAGGAGTAGTAGTAGTATCATATACTACGCAGACTC TGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAACTCAC TGCATTTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGAGACGGGGTCACTTTGACTACTGGGGCCAGGGAACCT GGTCACCGTCTCCTCA
	74	VL (DNA)	GAAATTGTGTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCGACT ACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCAGGCTCTTC ATCTATGATGTATCCAAGAGGGCCACTGGCATCCAGCCAGGTTTCAG TGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGCCTAG AGCCTGAAGATTTTGCAGTTTATTACTGTGAGCAGCGTAGCAACTGG CCGCTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA
VY006	81	HCDR1	GFTFSSYT
	94	HCDR2	ISSSSSTI
	114	HCDR3	ASLGRGDC
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS

	181	FR H2	MNWVRQAPGKGLEWVS
	192	FR H3	YYADSVKGRFTISRDNKNSLYLQMNSLRDEDTAVYYC
	209	FR H4	WGQGTILTVSS
	127	LCDR1	QSLVHSDGNTY
	141	LCDR2	KIS
	156	LCDR3	MQATQFPRT
	215	FR L1	DIVMTQTPLSSPVTILGQPASISCRSS
	230	FR L2	LSWLQQRPQGPPRLLIY
	249	FR L3	KRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC
	267	FR L4	FGQGTRLEIK
	6	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSYTMNWVRQAPGKGLEW VSYISSSSSTIYYADSVKGRFTISRDNKNSLYLQMNSLRDEDTAVY YCASLGRGDCWGQGTILTVSS
	24	VL	DIVMTQTPLSSPVTILGQPASISCRSSQSLVHSDGNTYLSWLQQRPQG PPRLLIYKISKRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCM QATQFPRTFGQGTRLEIK
	52	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGTT ATACCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG GTTTCATACATTAGTAGTAGTAGTAGTACCATATACTACGCAGACTC TGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGAGTCTGGGGAGAGGGGACTGCTGGGGCCAGGGAACCT GGTCACCGTCTCCTCA
	72	VL (DNA)	GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTACACCTTGG ACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTACACA GTGATGGAAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAG CCTCCAAGACTCCTAATTTATAAGATTTCTAAACGGTTCTCTGGGGT CCCAGACAGATTCACTGGCAGTGGGGCAGGGACAGATTCACACTGA AAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATG CAAGCTACACAATTTCTCGGACCTTCGGCCAAGGACACGACTGGA GATTAA
VY018	82	HCDR1	GGGISNYY
	101	HCDR2	IYTS GDT
	119	HCDR3	ARAGIVGTPGLGMDV
	175	FR H1	QVQLQESGPGLVKPSSETLSLTCTVS
	187	FR H2	WSWIRQPAGKGLEWIGR
	201	FR H3	YYNPSLQSRVTMSVDTSKNQFSLKLSAVTAADTAVYYC
	211	FR H4	WGQGTITVTVSS
	132	LCDR1	ALPKQY
	149	LCDR2	KDS
	164	LCDR3	QSADSSGTYRV

	224	FR L1	SYELTQPPSVSVSPGQTARITCSGE
	238	FR L2	AYWYQQKPGQAPVLIY
	252	FR L3	ERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYC
	263	FR L4	FGGGTKLTVL
	11	VH	QVQLQESGPGLVKPSSETLSLTCTVSGGSISNYYWSWIRQFAGKGLEW IGRIYTSGDTYYNPSLQSRVTMSVDTSKNQFSLKLSAVTAADTAVYY CARAGIVGTPGLGMDVWGQGTTTVTVSS
	30	VL	SYELTQPPSVSVSPGQTARITCSGEALPKQYAYWYQQKPGQAPVLI YKDSERPSPGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSDSSG TYRVFGGGTKLTVL
	47	VH (DNA)	CAGGTGCAGCTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGA GACCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAATT ACTACTGGAGTTGGATCCGGCAGCCCGCCGGAAGGGTCTGGAGTGG ATTGGGCGTATCTATACCAGTGGGGACACCTACTACAACCCCTCCCT CCAGAGTCGAGTCACCATGTCAGTAGACACGTCCAAGAACCAGTTCT CCCTGAAGCTGAGCGCTGTGACCGCCGCGGACACGGCCGTCTATTAC TGTGCGAGAGCGGGTATAGTGGAACTCCGGGACTCGGTATGGACGT CTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
	66	VL (DNA)	TCCTATGAGCTGACACAGCCACCCTCGGTGTCAAGTGTCCCCAGGACA GACGGCCAGGATCACCTGCTCTGGAGAAGCATTGCCAAAGCAATATG CTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCTGTGCTGGTGATA TATAAAGACAGTGAGAGGCCCTCAGGGATCCCTGAGCGATTCTCTGG CTCCAGCTCAGGGACAACAGTCACGTTGACCATCAGTGGAGTCCAGG CAGAAGATGAGGCTGACTATTACTGTCAATCAGCAGACAGCAGTGGT ACTTATCGGCTGTTTCGGCGGAGGGACCAAGCTGACCGTCCTA
VY003	77	HCDR1	GFTFSSYR
	92	HCDR2	ISSRSIAI
	109	HCDR3	ATLGIGY
	172	FR H1	EVQMVESGGGLVQPGGSLTLSCAAS
	181	FR H2	MNWVRQAPGKGLEWVSY
	192	FR H3	YYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYC
	209	FR H4	WGQGTLLTVSS
	127	LCDR1	QSLVHSDGNTY
	141	LCDR2	KIS
	154	LCDR3	MQVTQFPRT
	215	FR L1	DIVMTQTPLSSPVTLGQPASISCRSS
	230	FR L2	LSWLQQRPGQPPRLLIY
	244	FR L3	NRFSGVPDRFSGSGAGTDFTLKITRVEAEDVGIYYC
	262	FR L4	FGQGTKVEIR
	1	VH	EVQMVESGGGLVQPGGSLTLSCAASGFTFSSYRMNWVRQAPGKGLEW VSYISSRSIAIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVY YCATLGIGYWGQGTLLTVTVSS

	19	VL	DIVMTQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLSWLQQRPGQ PPRLLIYKISNRFSGVPDRFSGSGAGTDFTLKITRVEAEDVGIYYCM QVTQFPRTFGQGTKVEIR
	39	VH (DNA)	GAGGTGCAGATGGTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGG GTCCCTGACACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCT ATAGAATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG GTTTCATACATTAGCAGTAGTAGAAGTGCCATATACTACGCAGACTC TGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAATCAC TGTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGACCCTGGGGATAGGCTACTGGGGCCAGGGAACCTGGT CACCGTCTCTCA
	57	VL (DNA)	GATATTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCTTGG ACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTACACA GTGATGGAAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAG CCTCCAAGACTCCTAATTTATAAGATTTCTAACCAGTTCTCTGGGGT CCCAGACAGATTACAGTGGCAGTGGGGCAGGGACAGATTCACACTGA AAATCACCAGGGTGGAGGCTGAGGATGTCTGGGATTTATTACTGCATG CAAGTTACACAATTTCTCGGACGTTCTGGCCAAGGGACCAAGGTGGA AATCAGA
VY016	78	HCDR1	GFTFSSYS
	93	HCDR2	ISRSGSTI
	110	HCDR3	ARGNWAY
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS
	181	FR H2	MNWRVQAPGKGLEWVS
	193	FR H3	YYADSVGRFTISRDNAYNSLYLQMISLRDDDTAVYYC
	210	FR H4	WGQILVTSS
	128	LCDR1	SSNIGAGYD
	142	LCDR2	GNS
	155	LCDR3	QSYDSSLGSGV
	216	FR L1	QSVLTQPPSVSGAPGQRTISCTGS
	231	FR L2	VHWHYQQLPGTAPKLLIY
	245	FR L3	NRPSGVPDRFSGSKSGTSASLAITGLQAEDETDFYC
	263	FR L4	FGGGTKLTVL
	2	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWRVQAPGKLEW VSYISRSGSTIYYADSVGRFTISRDNAYNSLYLQMISLRDDDTAVY YCARGNWAYWGQILVTSS
	20	VL	QSVLTQPPSVSGAPGQRTISCTGSSNIGAGYDVHWHYQQLPGTAPK LLIYGNNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDETDFYCQSYD SSLGSGVFGGGTKLTVL
	56	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGTTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCT ATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG GTTTCATACATTAGTCGTAGTGGTAGTACCATATACTACGCAGACTC TGTGGAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAATCAC TGTATCTGCAAATGATCAGCCTGAGAGACGATGACACGGCTGTGTAT TACTGTGCGAGAGGGAAGTGGGCCTACTGGGGCCAGGGAATCCTGGT CACCGTCTCTCA

	76	VL (DNA)	CAGTCTGTGCTGACGCAGCCGCCCTCAGTGTCTGGGGCCCCAGGGCA GAGGGTCACCATCTCCTGCACTGGGAGCAGCTCCAACATCGGGGCAG GTTATGATGTACACTGGTACCAGCAGCTTCCAGGAACAGCCCCAAA CTCCTCATCTATGGTAACAGCAATCGGCCCTCAGGGGTCCTGACCG ATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCACTG GGCTCCAGGCTGAGGATGAGACTGATTTTTACTGCCAGTCCTATGAC AGCAGCCTGAGTGGTTCGGTTTTTCGGCGGAGGGACCAAGCTGACCGT CCTG
VY017	78	HCDR1	GFTFSSYS
	96	HCDR2	IRSSSSTI
	113	HCDR3	ARRSIADY
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS
	181	FR H2	MNWRQAPGKGLEWVSY
	196	FR H3	YYADSVKGRFTISRDNAKKSLYLQMNSLRDEDTAVYYC
	209	FR H4	WGQGTILTVSS
	130	LCDR1	QSVTSY
	144	LCDR2	DAS
	158	LCDR3	QQRSNWPYT
	218	FR L1	EIVLTQSPATLSSSPGERATLSCRAS
	233	FR L2	LNWYQQKPGQAPRLLIY
	248	FR L3	NRATGIPARFSGSGSGTDFTLTISSELEPEDFALYYC
	266	FR L4	FGQGTKLEIK
	5	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWRQAPGKGLEW VSYIRSSSSTIYYADSVKGRFTISRDNAKKSLYLQMNSLRDEDTAVY YCARRSIADYWGQGTILTVSS
	23	VL	EIVLTQSPATLSSSPGERATLSCRASQSVTSYLNWYQQKPGQAPRLI IYDASNRATGIPARFSGSGSGTDFTLTISSELEPEDFALYYCQQRSNW PYTFGQGTKLEIK
	41	VH (DNA)	GAGGTGCAGTTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCT ATAGCATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG GTTTCATACATTAGGAGTAGTAGTAGTACCATATACTACGCAGACTC TGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAAATCAT TGTATCTGCAAATGAATAGTCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGAGAAGGAGTATAGCTGACTACTGGGGCCAGGGAACCT GGTCACCGTCTCCTCA
	59	VL (DNA)	GAAATTGTGTGACACAGTCTCCAGCCACCCTGTCTTCGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTACCAGCT ACTTAACTGGTACCAACAGAAACCTGGCCAGGCTCCCAGGCTCCTC ATCTATGATGCATCCAACAGGGCCACTGGCATCCAGCCAGGTTTCAG TGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGCCTCG AGCCTGAAGATTTTGCACCTTATTACTGTGAGCAGCGTAGCAACTGG CCGTACACTTTTGGCCAGGGGACCAAACTGGAGATCAAA
VY012	83	HCDR1	GFTYSSYA
	98	HCDR2	ISGSSSIT

	116	HCDR3	AKGGRYGYFQH
	176	FR H1	EVQLLES GGGLVQPGGSLRLSCAAS
	184	FR H2	MSWVRRAPGKGLEWISI
	198	FR H3	YYADSMKGRFTISRDN SKNTLFLQMNSLRAEDTAVYYC
	209	FR H4	WGQGTLVTVSS
	131	LCDR1	NIGSKS
	145	LCDR2	DDS
	160	LCDR3	QVWDSSSDPVV
	220	FR L1	SYVLTQPPSVSVAPGQTARITCGGN
	234	FR L2	VHWYQQKPGQAPVLVY
	251	FR L3	DRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYC
	268	FR L4	FGGGTMLTVL
	8	VH	EVQLLES GGGLVQPGGSLRLSCAASGFTYSSYAMSWVRRAPGKGLEW ISIISSSSITYYADSMKGRFTISRDN SKNTLFLQMNSLRAEDTAVY YCAKGGRYGYFQHWGQGLTVTVSS
	26	VL	SYVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVY YDDSDRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYCQVWDSS DPVVFGGGTMLTVL
	50	VH (DNA)	GAGGTGCAGCTGTTGGAGTCTGGGGGAGGCTTGGTACAGCCGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCGGGATTACCTATAGCAGCT ATGCCATGAGCTGGGTCCGCCGGGCTCCAGGGAAGGGGCTGGAGTGG ATCTCAATTATTAGTGGTAGTAGTAGTATCACATACTACGCAGACTC CATGAAGGGCCGGTTCATCTCTCTAGAGACAATTCCAAGAACACGC TTTTTCTGCAAATGAATAGCCTGAGAGCCGAGGACACGGCCGTTTAT TACTGTGCGAAGGGGGGAGGTACGGGTACTTCCAACACTGGGGCCA GGCACCTGGTCAACCGTCTCCTCA
	70	VL (DNA)	TCCTATGTGCTGACTCAGCCACCCTCGGTGTGAGTGCCCCAGGACA GACGGCCAGGATTACCTGTGGGGGAAACAACATTGGAAGTAAAAGTG TGCACTGGTACCAGCAGAAGCCAGGCCAGGCCCTGTGCTGGTCGTC TATGATGATAGCGACCGGCCCTCAGGGATCCCTGAGCGATTCTCTGG CTCCAACCTCTGGGAACACGGCCACCCTGACCATCAGCAGGGTCGAAG CCGGGGATGAGGCCGACTATTACTGTGAGGTGTGGGATAGTAGTAGT GATCCTGTGGTATTTCGGCGGAGGGACCATGCTGACCGTCCTA
VY009	84	HCDR1	GFSLSTSEVG
	99	HCDR2	IYWNDHK
	117	HCDR3	ARRVTGEGFDP
	177	FR H1	QITLKESGPTLVKPTQTLLTCTLS
	185	FR H2	VGWIRQPPGKALEWLAI
	199	FR H3	RYSPLKNRLTFTKDTSKNQVVLMTNMDPVDATATYYC
	209	FR H4	WGQGTLVTVSS
	132	LCDR1	ALPKQY
	146	LCDR2	KDT

	161	LCDR3	QSADSSGSYV
	221	FR L1	SYELTQPPSVSVSPGQTARITCSGD
	235	FR L2	AYWYQQKPGQAPVLVIF
	252	FR L3	ERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYC
	269	FR L4	FGTGTKVTVL
	9	VH	QITLKESGPTLVKPTQTLLTCTLSGFSLSSTSEVGWGWIRQPPGKAL EWLAI IYWNCHKRYSPSLKNRLTFKDTSKNQVVLMTNMDPVD TAT YYCARRVTGEGFDPWGQGTLVTVSS
	27	VL	SYELTQPPSVSVSPGQTARITCSGDALPKQYAYWYQQKPGQAPVLVI FKDTERPSGIPERFSGSSSGTTVTLTISGVQAEDEADYYCQSADSSG SYVFGTGTKVTVL
	49	VH (DNA)	CAGATCACCTTAAAGGAGTCTGGTCTACGCTGGTGA AACCACACA GACCCTCACGCTGACCTGCACCCTCTCTGGGTTCTCACTCAGCACTA GTGAAGTGGGTGTGGGCTGGATCCGTCAGCCCCCAGGAAAGGCCCTG GAGTGGCTTGCAATCATT TATTGGAATGATCATAAGCGCTACAGCCC ATCTCTGAAGAACAGGCTCACCTTCACCAAGGACACCTCCAAAAACC AGGTGGTCTTACAATGACCAACATGGACCCTGTGGACACAGCCACA TATTATTGTGCACGCAGAGTA ACTGGGGAGGGGTTTCGACCCTGGGG CCAGGGAACCCTGGTCACCGTCTCCTCA
	69	VL (DNA)	TCCTATGAGCTGACACAGCCACCCTCGGTGT CAGTGTCCCCAGGACA GACGGCCAGGATCACCTGCTCTGGAGATGCATTGCCAAAGCAATATG CTTATTGGTACCAGCAGAAGCCAGGCCAGGCCCTGTGCTGGTGATA TTTAAAGACACTGAGAGGCCCTCAGGGATCCCTGAGCGATTCTCTGG CTCCAGCTCAGGGACAACAGTCACGTTGACCATCAGTGGAGTCCAGG CAGAAGATGAGGCTGACTATTACTGTCAATCAGCAGACAGCAGTGGT TCTTATGTCCTCGGA ACTGGGACCAAGGTCACCGTCTCTA
VY010	85	HCDR1	GFTFSTYS
	100	HCDR2	ISSGSSYI
	118	HCDR3	TVTTHFHH
	178	FR H1	EVQLVESGGGLVKPGGSLRLSCAAS
	186	FR H2	MNWVRQAPGKGLEWVSS
	200	FR H3	YYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVYYC
	209	FR H4	WGQGTLVTVSS
	133	LCDR1	QSLVYSDGNTY
	147	LCDR2	KVS
	162	LCDR3	MQGTHWPLT
	222	FR L1	DVVMTQSPSLPVT LGQPASISCRSS
	236	FR L2	LNWFQQRPGQSPRR LIY
	253	FR L3	NRDSGVPDFRSGSGSGTDFTLKISRVEAEDVGVYYC
	267	FR L4	FGQGRLEIK
	10	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSTYS MNWVRQAPGKLEW VSSISSGSSYIYYADSVKGRFTISRDN AKNSLYLQMNSLRAEDTAVY YCTVTHFHHWGQGTLVTVSS

	28	VL	DVVMTQSPSLSLPVTLGQPASISCRSSQSLVYSDGNTYLNWFQQRPGQ SPRRLIYKVSNRDSGVPDRFSGSGSGTDFTLKISRVEAEDVGVIYCM QGTHWPLTFGQGTLEIK
	48	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTACCT ATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGCTGGAGTGG GTCTCATCCATTAGTAGTGGTAGTAGTTACATATACTACGCAGACTC AGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGAATCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTAT TACTGTACAGTAACACTACACACTTCCACCCTGGGGCCAGGGCACCT GGTACCCTCTCTCA
	67	VL (DNA)	GATGTTGTGATGACTCAGTCTCCACTCTCCCTGCCCGTCAACCTTGG ACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTATACA GTGATGGAAACACCTACTTGAATTGGTTTCAGCAGAGGCCAGGCCAA TCTCCAAGGCGCCTAATTTATAAGGTTTCTAACGGGACTCTGGGGT CCCAGACAGATTACAGCGCAGTGGGTCAGGCACTGATTCACACTAA AAATCAGCAGGGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATG CAAGGTACACACTGGCCTCTCACCTTCGGCCAAGGGACAGACTGGA GATTAAA
VY022	85	HCDR1	GFTFSTYS
	100	HCDR2	ISSGSSYI
	118	HCDR3	TVTTHFHH
	178	FR H1	EVQLVESGGGLVKPGGSLRLSCAAS
	186	FR H2	MNWVRQAPGKGLEWVSS
	200	FR H3	YYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYC
	209	FR H4	WGQGTILTVSS
	134	LCDR1	SGINVGAYR
	148	LCDR2	YKSDSDK
	163	LCDR3	MIWHSSAWV
	223	FR L1	QAVLTQPSSLSASPGASARLTCTLR
	237	FR L2	LYWYQQKPGSPFPQYLLR
	254	FR L3	QQGSGVPSRFSGSKDASANAGILLISGLQSEDEADYYC
	263	FR L4	FGGGTKLTVL
	10	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSTYSMNWVRQAPGKGLEW VSSISSGSSYIYYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVY YCTVTTHFHHWGQGTILTVSS
	29	VL	QAVLTQPSSLSASPGASARLTCTLRSGINVGAYRLYWYQQKPGSPFPQ YLLRYKSDSDKQQGSGVPSRFSGSKDASANAGILLISGLQSEDEADY YCMIWSSAWVFGGGTKLTVL
	48	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCCTGGTCAAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTACCT ATAGCATGAACTGGGTCCGCCAGGCTCCAGGGAAGGGCTGGAGTGG GTCTCATCCATTAGTAGTGGTAGTAGTTACATATACTACGCAGACTC AGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGAATCAC TGTATCTGCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTAT TACTGTACAGTAACACTACACACTTCCACCCTGGGGCCAGGGCACCT GGTACCCTCTCTCA
	68	VL (DNA)	CAGGCTGTGCTGACTCAGCCGTCTTCCCTCTCTGCATCTCTGGAGC ATCAGCCAGACTACCTGCACCTTGCAGTGGCATCAATGTTGGTG

			CCTACAGGCTATACTGGTACCAGCAGAAGCCAGGAAGTCCTCCCCAG TATCTCCTGAGGTACAAATCAGACTCAGATAAGCAGCAGGGCTCTGG AGTCCCCAGCCGCTTCTCTGGATCCAAAGATGCTTCGGCCAATGCAG GGATTTTACTCATCTCTGGGCTCCAGTCTGAGGATGAGGCTGACTAT TACTGTATGATTTGGCACAGCAGCGCTTGGGTGTTTCGGCGGAGGGAC CAAGCTGACCGTCCTA
VY001	86	HCDR1	GFTFSSYN
	102	HCDR2	ISSSSNTI
	120	HCDR3	ATLGRGY
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS
	182	FR H2	MNWVRQAPGKGLEWISY
	202	FR H3	YYADSVKGRFTVSRDNAKNSLYLQMNSLRDEDTAVYYC
	212	FR H4	WGQGTLLVIASS
	127	LCDR1	QSLVHSDGNTY
	141	LCDR2	KIS
	156	LCDR3	MQATQFPRT
	225	FR L1	DVVMQTPLSSPVTLGQPASISCRSS
	230	FR L2	LSWLQQRPGQPPRLLIY
	246	FR L3	NRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYC
	266	FR L4	FGQGTKLEIK
	12	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYNMNWVRQAPGKGLEW ISYISSSSNTIYYADSVKGRFTVSRDNAKNSLYLQMNSLRDEDTAVY YCATLGRGYWGQGTLLVIASS
	31	VL	DVVMQTPLSSPVTLGQPASISCRSSQSLVHSDGNTYLSWLQQRPGQ PPRLLIYKISNRFSGVPDRFSGSGAGTDFTLKISRVEAEDVGVYYCM QATQFPRTFGQGTKLEIK
	46	VH (DNA)	GAGGTGCAACTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCT ATAACATGAACTGGGTTCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG ATTTTCATACATTAGTAGTAGTAGTAATACCATATACTACGCAGACTC TGTGAAGGGCCGATTACCGTCTCCAGGGACAATGCCAAGAACTCAC TGTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGACTCTGGGGAGGGGCTACTGGGGCCAGGGAACCTGGT CATCGCCTCCTCA
	65	VL (DNA)	GATGTTGTGATGACCCAGACTCCACTCTCCTCACCTGTCACCTTGG ACAGCCGGCCTCCATCTCCTGCAGGTCTAGTCAAAGCCTCGTACACA GTGATGGAACACCTACTTGAGTTGGCTTCAGCAGAGGCCAGGCCAG CCTCCAAGACTCCTAATTTATAAGATTCTAACC GGTTCTCTGGGGT CCCAGACAGATTCA GTGGCAGTGGGGCAGGGACAGATTTACACTGA AAATCAGCAGGGTGGAAGCTGAGGATGTCGGGGTTTATTACTGCATG CAAGCTACACAATTTCTCGCACTTTTGGCCAGGGGACCAAGCTGGA GATCAAA
VY019	87	HCDR1	GGSISSYY
	103	HCDR2	IDTSGST
	121	HCDR3	ARGGDGYRY
	175	FR H1	QVQLQESGPGLVKPSETLSLTCTVS

	183	FR H2	WTWIRQPAGKGLEWIGR
	203	FR H3	NYNPSLKSRVTMSIDTSKKQFSLKLSSVTAADTAVYYC
	209	FR H4	WGQGTILTVSS
	132	LCDR1	ALPKQY
	149	LCDR2	KDS
	165	LCDR3	QSTDSSGSWV
	221	FR L1	SYELTQPPSVSVSPGQTARITCSGD
	239	FR L2	ACWYQQKPGQAPVLIY
	255	FR L3	ERPSGIPERFSGSSSGTTVTLTITGVQAEDEADYYC
	263	FR L4	FGGGTKLTVL
	13	VH	QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWTWIRQPAGKGLEW IGRIDTSGSTNYNPSLKSRVTMSIDTSKKQFSLKLSSVTAADTAVYY CARGGDGYRYWGQGTILTVSS
	32	VL	SYELTQPPSVSVSPGQTARITCSGDALPKQYACWYQQKPGQAPVLI YKDSERPSPGIPERFSGSSSGTTVTLTITGVQAEDEADYYCQSTDSSG SWVFGGGTKLTVL
	45	VH (DNA)	CAGGTGCAGCTGCAGGAGTCGGGCCAGGACTGGTGAAGCCTTCGGA GACCCTGTCCCTCACCTGCACTGTCTCTGGTGGCTCCATCAGTAGTT ACTACTGGACCTGGATCCGGCAGCCCGCCGGAAGGGACTGGAGTGG ATTGGGCGTATCGATACCACTGGGAGCACCACTACAACCCCTCCCT CAAGAGTCGAGTCACCATGTCAATAGACACGTCCAAGAAACAGTTCT CCCTGAAGCTGAGCTCTGTGACCGCCGCGGACACGGCCGTGATTAC TGTGCGAGAGGGGGAGATGGCTACCGCTACTGGGGCCAGGGAACCT GGTCACCGTCTCCTCA
	64	VL (DNA)	TCCTATGAGCTGACACAGCCACCCTCGGTGTCACTGTCCCAGGACA GACGGCCAGGATCACCTGCTCTGGAGATGCATTGCCAAAGCAATATG CTTGTGGTACCAGCAGAAGCCAGGCCAGGCCCCGTGTCTGGTGATA TATAAAGACAGTGAGAGGCCCTCAGGGATCCCTGAGCGATTCTCTGG CTCCAGCTCAGGGACAACAGTCACGTTGACCATCACTGGAGTCCAGG CAGAAGATGAGGCTGACTATTACTGTCAATCCACAGACAGCAGTGGT TCTTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA
VY020	78	HCDR1	GFTFSSYS
	104	HCDR2	ISSNSTI
	122	HCDR3	ARRSLGDY
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS
	182	FR H2	MNWVRQAPGKGLEWISY
	204	FR H3	KYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYC
	213	FR H4	WGQGTILVIVSS
	135	LCDR1	QSVSSY
	143	LCDR2	DVS
	166	LCDR3	QQRNWPYT
	217	FR L1	EIVLTQSPATLSLSPGERATLSCRAS
	240	FR L2	LAWYLQKPGQAPRLLIY

	256	FR L3	NRATGIPARFSGSGSGTDFTLTISRLEPEDFAVYYC
	266	FR L4	FGQGTKLEIK
	14	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEW ISYISSNSTIKYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVY YCARRSLGDIWGQGTLLVIVSS
	33	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYLQKPGQAPRLL IYDVSNRATGIPARFSGSGSGTDFTLTISRLEPEDFAVYYCQQRNW PYTFGQGTKLEIK
	44	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCT ATAGCATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG ATTTACATACATTAGTAGTAGTAATAGTACCATAAAGTACGCAGACTC TGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAATCAC TGTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGAGAAGGAGTCTAGGTGACTACTGGGGCCAGGGAACCT GGTCATCGTCTCCTCA
	62	VL (DNA)	GAAATTGTGTGACACAGTCTCCAGCCACCCTGTCTTTGTCTCCAGG GGAAAGAGCCACCCTCTCCTGCAGGGCCAGTCAGAGTGTTAGCAGCT ACTTAGCCTGGTACCTACAGAAACCTGGCCAGGCTCCCAGGCTCCTC ATCTATGATGTGTCCAACAGGGCCACTGGCATCCCAGCCAGGTTTCAG TGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGACTAG AGCCTGAAGATTTTGCAGTTTATTACTGTGTCAGCAGCGTCGCAACTGG CCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA
VY005	78	HCDR1	GFTFSSYS
	104	HCDR2	ISSNSTI
	122	HCDR3	ARRSLGDI
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS
	182	FR H2	MNWRQAPGKGLEWISY
	204	FR H3	KYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYC
	213	FR H4	WGQGTLLVIVSS
	136	LCDR1	QGISCS
	150	LCDR2	AAS
	167	LCDR3	QQFNSYPFT
	226	FR L1	DIQLTQSPSFLSASVGDRTITCRAS
	241	FR L2	LAWYQQKPKAPKLLIY
	257	FR L3	TLQSGVPSRFSGSGSGTEFTLTISLQPEDFATYYC
	270	FR L4	FGPGTKVDIK
	14	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEW ISYISSNSTIKYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVY YCARRSLGDIWGQGTLLVIVSS
	34	VL	DIQLTQSPSFLSASVGDRTITCRASQGISCSLAWYQQKPKAPKLL IYAASLTQSGVPSRFSGSGSGTEFTLTISLQPEDFATYYCQQFNSY PFTFGPGTKVDIK
	44	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACCTTCAGTAGCT ATAGCATGAAGTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG ATTTACATACATTAGTAGTAGTAATAGTACCATAAAGTACGCAGACTC TGTGAAGGGCCGATTACCATCTCCAGAGACAATGCCAAGAATCAC

			TGTATCTGCAAATGAACAGCCTGAGAGACGAGGACACGGCTGTGTAT TACTGTGCGAGAAGGAGTCTAGGTGACTACTGGGGCCAGGGAACCT GGTCATCGTCTCCTCA
	63	VL (DNA)	GACATCCAGTTGACCCAGTCTCCATCCTTCCTGTCTGCATCTGTAGG AGACAGAGTCACCATCACTTGCCGGGCCAGTCAGGGCATTAGCTGTT CTTTAGCCTGGTATCAGCAAAAACCAGGGAAAGCCCCTAAGCTCCTG ATCTATGCTGCATCCACTTTGCAAAGTGGGGTCCCATCAAGGTTTCAG CGGCAGTGGATCTGGGACAGAATTCACTCTCACAATCAGCAGCCTGC AGCCTGAAGATTTTGCAACTTATTACTGTCAACAGTTTAATAGTTAC CCATTCACCTTCGGCCCTGGGACCAAAGTGGATATCAAA
VY002	88	HCDR1	GFTFSNAW
	105	HCDR2	IKSKTDGGTT
	123	HCDR3	VTDPKDV
	178	FR H1	EVQLVESGGGLVKPGGSLRLSCAAS
	188	FR H2	MSWVRQAPGKGLEWFGFR
	205	FR H3	DYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYC
	211	FR H4	WGQGTITVTVSS
	137	LCDR1	QSVLYSSKNKNY
	151	LCDR2	WAS
	168	LCDR3	QQYYSSPYT
	227	FR L1	DIVMTQSPDSLAVSLGERATINCKSS
	242	FR L2	LAWYQQKPGQPPKLLIY
	258	FR L3	TRESGVPDRFSGSGSGTDFTLAISSLQAEDVAVYYC
	266	FR L4	FGQGTKLEIK
	15	VH	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKLEW FGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTA VYYCVTDYPKDVWGQGTITVTVSS
	35	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSKNKNYLAWYQQKPG QPPKLLIYWASTRESGVPDRFSGSGSGTDFTLAISSLQAEDVAVYYC QQYYSSPYTFGQGTKLEIK
	43	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTAAAGCCTGGGGG GTCCCTTAGACTCTCCTGTGCAGCCTCTGGATTCACTTTCAGTAACG CCTGGATGAGCTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGG TTTGGCCGTATTAAAAGCAAACTGATGGTGGGACAACAGACTACGC TGCACCCGTGAAAGGCAGATTACCATCTCAAGAGATGACTCAAAAA ACACGCTGTATCTGCAAATGAACAGCCTGAAAACCGAGGACACAGCC GTGTATTACTGTGTACAGATTACCCGAAGGACGTCTGGGGCCAAGG GACCACGGTCACCGTCTCCTCA
	61	VL (DNA)	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGG CGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTATACA GCTCCAAAAATAAGAACTACTTAGCTTGGTACCAGCAGAAACCAGGA CAGCCTCCTAAGCTGCTCATTTACTGGGCATCTACCCGGAATCCGG GGTCCCTGACCGATTCAAGTGGCAGCGGTCTGGGACAGATTTCACTC TCGCCATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGT CAGCAATATTATAGTAGTCCGTACACTTTTGGCCAGGGGACCAAGCT GGAGATCAAA
VY014	89	HCDR1	GFTFNND
	106	HCDR2	IGAAGDT

	124	HCDR3	ARAGETLEGATIGYYYGMDV
	173	FR H1	EVQLVESGGGLVQPGGSLRLSCAAS
	189	FR H2	MHWVRQAAGKGLEWVST
	206	FR H3	YYPGSVKGRFIIISRENAKNSLYLQMNSLRAGDTAVYYC
	211	FR H4	WGQGTTTVTVSS
	138	LCDR1	QSLHNSNGYNY
	152	LCDR2	LGS
	169	LCDR3	MQALQIPLT
	228	FR L1	DILMTQSPLSLPVTGPGEPAISCRSS
	243	FR L2	LDWYLQKPGQSPQLLIY
	259	FR L3	NRASGVPDFRFSGSGSGTDFTLKFSRVEAEDVGLYYC
	265	FR L4	FGGGTKVEIK
	16	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNNDMHWVRQAAGKGLEW VSTIGAAGDTYYPGSVKGRFIIISRENAKNSLYLQMNSLRAGDTAVYY CARAGETLEGATIGYYYGMDVWGQGTTTVTVSS
	36	VL	DILMTQSPLSLPVTGPGEPAISCRSSQSLHNSNGYNYLDWYLQKPGQ SPQLLIYLGSNRASGVPDFRFSGSGSGTDFTLKFSRVEAEDVGLYYCM QALQIPLTFGGGKVEIK
	42	VH (DNA)	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGGGG GTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTACACCTCAATAACT ACGACATGCACTGGGTCCGCCAAGCTGCAGGAAAAGGTCTGGAGTGG GTCTCAACTATTGGTGCTGCTGGTGACACATATTATCCAGGCTCCGT GAAGGGCCGATTATCATCTCCAGAGAAAATGCCAAGAACTCCTTGT ATCTTCAAATGAACAGCCTGAGAGCCGGGGACACGGCTGTGTATTAC TGTGCAAGAGCCGGAGAGACCTTAGAGGGAGCTACTATCGGCTACTA CTACGGTATGGACGTCTGGGGCCAGGGGACCACGGTCACCGTCTCCT CA
	60	VL (DNA)	GATATTCTGATGACTCAGTCTCCACTCTCCCTGCCCCGTACCCCTGG AGAGCCGGCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATA GTAATGGATACAACACTATTTGGATTGGTACCTGCAGAAGCCAGGGCAG TCTCCACAGCTCCTGATCTATTTGGGTTCTAATCGGGCCTCCGGGGT CCCTGACAGGTTCACTGGCAGTGGATCAGGCACAGATTTTACACTGA AATTCAGCAGAGTGGAGGCTGAGGATGTTGGACTTTTACTGCAATG CAAGCTCTACAAATTCGCTCACTTTCGGCGGAGGGACCAAGGTGGA GATCAAA
VY008	90	HCDR1	GYTFTGYY
	107	HCDR2	INPNSSGT
	125	HCDR3	AGDAFDI
	179	FR H1	QVQLVQSGAEVKKPGASVKVSCAS
	190	FR H2	MHWVRQAPGQGLEWMGW
	207	FR H3	NYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYC
	214	FR H4	WGQGTMTVTVSS
	139	LCDR1	QSVLYSSNNKNY
	151	LCDR2	WAS

	170	LCDR3	QQYYSTPLT
	227	FR L1	DIVMTQSPDSLAVSLGERATINCKSS
	242	FR L2	LAWYQQKPGQPPKLLIY
	260	FR L3	TRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC
	265	FR L4	FGGGTKVEIK
	17	VH	QVQLVQSGAEVKKPGASVKVSKASGYTFTGYYMHWVRQAPGQGLEW MGWINPNSGGTNYAQKFQGRVTMRDTSISTAYMELSRLSDDTAVY YCAGDAFDIWGQGTMTVSS
	37	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQQKPG QPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC QQYYSTPLTFGGGKVEIK
	53	VH (DNA)	CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGGC CTCAGTGAAGGTCTCCTGCAAGGCTTCTGGATACACCTTACCCGGCT ACTATATGCACTGGGTGCGACAGGCCCTGGACAAGGGCTTGAGTGG ATGGGATGGATCAACCCTAACAGTGGTGGCACAACTATGCACAGAA GTTTCAGGGCAGGGTCACCATGACCAGGGACACGTCCATCAGCACAG CCTACATGGAGCTGAGCAGGCTGAGATCTGACGACACGGCCGTGTAT TACTGTGCTGGGGATGCTTTTGATATCTGGGGCCAAGGACAATGGT CACCGTCTCTTCA
VY013	73	VL (DNA)	GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGG CGAGAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTATACA GCTCCAACAATAAGAACTACTTAGCTTGGTACCAGCAGAAACCAGGA CAGCCTCCTAAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGG GGTCCCTGACCGATTTCAGTGGCAGCGGTCTGGGACAGATTTCACTC TCACCATCAGCAGCCTGCAGGCTGAAGATGTGGCAGTTTATTACTGT CAGCAATATTATAGTACTCCGCTCACTTTCGGCGGAGGGACCAAGGT GGAGATCAAA
	91	HCDR1	GFSLINARMA
	108	HCDR2	IFSNDEK
	126	HCDR3	ARIRGYSYNYGMDV
	180	FR H1	QVTLKESGPVLVKPTETLTLTCTVS
	191	FR H2	VSWIRQPPGKALEWLAH
	208	FR H3	SYSTSLKSRLTISKDTSKSQVVLIMTNMDPVDATATYYC
	211	FR H4	WGQGTITVTVSS
	140	LCDR1	QSLHLSNGYIY
	153	LCDR2	VGS
	171	LCDR3	MQTLQIPRT
	229	FR L1	DIVMTQSPLSLPVPVIGEPASISCRSS
	243	FR L2	LDWYLQKPGQSPQLLIY
	261	FR L3	NRASGVPDRFSGSGSGTDFTLTKISRVEAEDVGVYYC
	265	FR L4	FGGGTKVEIK
	18	VH	QVTLKESGPVLVKPTETLTLTCTVSGFSLINARMAVSWIRQPPGKAL EWLAHIFSNDEKSYSTSLKSRLTISKDTSKSQVVLIMTNMDPVDAT YYCARIRGYSYNYGMDVWGQGTITVTVSS

	38	VL	DIVMTQSPLSLPVIPGEPASISCRSSQSLHLSNGYIYLDWYLQKPGQSPQLLIYVGSNRASGVDPDRFSGSGSGTDFKLIKISRVEAEDVGVYYCMQTLQIPRTFGGGTKVEIK
	40	VH (DNA)	CAGGTCACCTTGAAGGAGTCTGGTCTGTGCTGGTGAACCCACAGAGACCCTCACGCTGACCTGCACCGTCTCTGGGTTCTCACTCATCAATGCTAGAATGGCTGTGAGCTGGATCCGTCAGCCCCCAGGGAAGGCCCTGGAGTGGCTTGACACATTTTTTCGAATGACGAAAAATCCTACAGCACATCTCTGAAGAGCAGACTCACCATCTCCAAGGACACCTCCAAAAGCCAGGTGGTCTTATCATGACCAACATGGACCCTGTGGACACAGCCACATATTACTGTGCACGGATCCGTGGATACAGCTATAACTACGGTATGGACGTCTGGGGCCAAGGGACCACGGTCACCGTCTCCTCA
	58	VL (DNA)	GATATTGTGATGACTCAGTCTCCACTCTCCCTGCCGTCATCCCTGGAGAGCCGGCTCCATCTCCTGCAGGTCTAGTCAGAGCCTCCTGCATAGTAATGGATACATCTATTGGATTGGTACCTGCAGAACCCAGGGCAGTCTCCACAGTCTCTGATCTATGTGGGTTCTAATCGGGCTCCGGGGTCCCTGACAGTTTCAGTGGCAGTGGATCAGGCACAGATTTCAAACCTGAATCAGCAGAGTGGAGGCTGAGGATGTTGGGGTTTATTACTGCATGCCAACTCTACAAATTCCGCGCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA

[0059] Anti-tau antibodies of the present disclosure may include variable domain amino acid sequences according to any of those listed in **Table 1**. In some embodiments, anti-tau antibody variable domains include fragments or variants of variable domain amino acid sequences listed. For instance, in some embodiments, the anti-tau antibody may comprise a VH comprising an amino acid sequence selected from SEQ ID NO: 7, 3, 4, 6, 11, 1, 2, 5, 8, 9, 10, 12, 13, 14, 15, 16, 17, or 18, or an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, or an amino acid sequence having at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as amino acid substitutions (e.g., conservative substitutions)) relative to the VH sequence. In some embodiments, the anti-tau antibody may comprise a VL comprising an amino acid sequence selected from SEQ ID NO: 25, 21, 22, 24, 30, 19, 20, 23, 26, 27, 28, 29, 31, 32, 33, 34, 35, 36, 37, or 38, or an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, or an amino acid sequence having at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as amino acid substitutions (e.g., conservative substitutions)) relative to the VL sequence. In some embodiment, the anti-tau antibody may comprise a VH and a VL, wherein (a) the VH comprises an amino acid sequence selected from SEQ ID NO: 7, 3, 4, 6, 11, 1, 2, 5, 8, 9, 10, 12, 13, 14, 15, 16, 17, or 18, or an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, or an amino acid sequence having at least one, two, or three modifications, but not more than 30, 20, or 10 modifications

(e.g., amino acid substitutions, such as conservative substitutions), relative to the VH sequence, and/or (b) the VL comprises an amino acid sequence selected from SEQ ID NO: 25, 21, 22, 24, 30, 19, 20, 23, 26, 27, 28, 29, 31, 32, 33, 34, 35, 36, 37, or 38, or an amino acid sequence at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, or an amino acid sequence having at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as amino acid substitutions (e.g., conservative substitutions)), relative to the VL sequence.

[0060] Provided herein are isolated, e.g., recombinant, antibodies which bind to human tau (e.g., human tau having the sequence set forth in SEQ ID NO: 274), comprising a VH and/or VL sequence selected from: (i) SEQ ID NOs: 7 and/or 25, respectively; (ii) SEQ ID NOs: 3 and/or 21, respectively; (iii) SEQ ID NOs: 4 and/or 22, respectively; (iv) SEQ ID NOs: 6 and/or 24, respectively; (v) SEQ ID NOs: 11 and/or 30, respectively; (vi) SEQ ID NOs: 1 and/or 19, respectively; (vii) SEQ ID NOs: 2 and/or 20, respectively; (viii) SEQ ID NOs: 5 and/or 23, respectively; (ix) SEQ ID NOs: 8 and/or 26, respectively; (x) SEQ ID NOs: 9 and/or 27, respectively; (xi) SEQ ID NOs: 10 and/or 28, respectively; (xii) SEQ ID NOs: 10 and/or 29, respectively; (xiii) SEQ ID NOs: 12 and/or 31, respectively; (xiv) SEQ ID NOs: 13 and/or 32, respectively; (xv) SEQ ID NOs: 14 and/or 33, respectively; (xvi) SEQ ID NOs: 14 and/or 34, respectively; (xvii) SEQ ID NOs: 15 and/or 35, respectively; (xviii) SEQ ID NOs: 16 and/or 36, respectively; (xix) SEQ ID NOs: 17 and/or 37, respectively; or (xx) SEQ ID NOs: 18 and/or 38, respectively. In some embodiments, the antibodies comprise a VH and/or VL sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequences of any one of (i)-(xx). In some embodiments, the antibodies comprise a VH and/or VL sequence having at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as amino acid substitutions (e.g., conservative substitutions)), relative to the VH and/or VL sequences of any one of (i)-(xx).

[0061] In some embodiments, the antibody which binds to human tau comprises VH and VL sequences selected from: (i) SEQ ID NOs: 7 and 25, respectively; (ii) SEQ ID NOs: 3 and 21, respectively; (iii) SEQ ID NOs: 4 and 22, respectively; (iv) SEQ ID NOs: 6 and 24, respectively; (v) SEQ ID NOs: 11 and 30, respectively; (vi) SEQ ID NOs: 1 and 19, respectively; (vii) SEQ ID NOs: 2 and 20, respectively; (viii) SEQ ID NOs: 5 and 23, respectively; (ix) SEQ ID NOs: 8 and 26, respectively; (x) SEQ ID NOs: 9 and 27, respectively; (xi) SEQ ID NOs: 10 and 28, respectively; (xii) SEQ ID NOs: 10 and 29,

respectively; (xiii) SEQ ID NOs: 12 and 31, respectively; (xiv) SEQ ID NOs: 13 and 32, respectively; (xv) SEQ ID NOs: 14 and 33, respectively; (xvi) SEQ ID NOs: 14 and 34, respectively; (xvii) SEQ ID NOs: 15 and 35, respectively; (xviii) SEQ ID NOs: 16 and 36, respectively; (xix) SEQ ID NOs: 17 and 37, respectively; or (xx) SEQ ID NOs: 18 and 38, respectively. In some embodiments, the antibodies comprise a VH and VL sequences having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to the sequences of any one of (i)-(xx). In some embodiments, the antibodies comprise a VH and/or VL sequence having at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as amino acid substitutions (e.g., conservative substitutions)), relative to the VH and VL sequences of any one of (i)-(xx).

[0062] Anti-tau antibody variable domains of the present disclosure may be encoded by nucleic acid sequences listed in **Table 1**. In some embodiments, nucleic acid sequences encoding anti-tau antibody variable domains of the present disclosure may include fragments or variants of the nucleic acid sequences listed. For instance, in some embodiments, the nucleic acid sequence encoding the VH may comprise a nucleotide sequence selected from SEQ ID NO: 51, 55, 54, 52, 47, 39, 56, 41, 50, 49, 48, 46, 45, 44, 43, 42, 53, or 40, or a nucleic acid sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the nucleic acid sequence encoding the VL may comprise a nucleotide sequence selected from SEQ ID NO: 67, 75, 74, 72, 66, 57, 76, 59, 70, 69, 68, 65, 64, 62, 63, 61, 60, 73, or 58, or a nucleic acid sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the nucleic acids described herein may encode an anti-tau antibody. In some embodiments, the anti-tau antibody may be encoded by a nucleic acid, or a combination of nucleic acids, comprising (a) a nucleotide sequence encoding a VH selected from SEQ ID NOs: 51, 55, 54, 52, 47, 39, 56, 41, 50, 49, 48, 46, 45, 44, 43, 42, 53, or 40, or a nucleic acid sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto, and/or (b) a nucleotide sequence encoding a VL selected from SEQ ID NOs: 67, 75, 74, 72, 66, 57, 76, 59, 70, 69, 68, 65, 64, 62, 63, 61, 60, 73, or 58, or a nucleic acid sequence having at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some embodiments, the anti-tau antibody may be encoded by a nucleic acid, or a combination of nucleic acids, comprising a nucleotide sequence encoding a VH and a nucleotide sequence encoding a VL

selected from: (i) SEQ ID NOs: 51 and 71, respectively, (ii) SEQ ID NOs: 55 and 75, respectively, (iii) SEQ ID NOs: 54 and 74, respectively, (iv) SEQ ID NOs: 52 and 72, respectively, (v) SEQ ID NOs: 47 and 66, respectively, (vi) SEQ ID NOs: 39 and 57, respectively, (vii) SEQ ID NOs: 56 and 76, respectively, (viii) SEQ ID NOs: 41 and 59, respectively, (ix) SEQ ID NOs: 50 and 70, respectively, (x) SEQ ID NOs: 49 and 69, respectively, (xi) SEQ ID NOs: 48 and 67, respectively, (xii) SEQ ID NOs: 48 and 68, respectively, (xiii) SEQ ID NOs: 46 and 65, respectively, (xiv) SEQ ID NOs: 45 and 64, respectively, (xv) SEQ ID NOs: 44 and 62, respectively, (xvi) SEQ ID NOs: 44 and 63, respectively, (xvii) SEQ ID NOs: 43 and 61, respectively, (xviii) SEQ ID NOs: 42 and 60, respectively, (ix) SEQ ID NOs: 53 and 73, respectively, or (xx) SEQ ID NOs: 40 and 58, respectively. In some embodiments, nucleic acid sequences encoding anti-tau antibody variable domains of the present disclosure include codon-optimized variants of the nucleic acid sequences listed.

[0063] In some embodiments, anti-tau antibodies of the present disclosure include one or more CDRs (e.g., 1, 2, 3, 4, 5, or all 6 CDRs), e.g., CDRs based on the Chothia numbering system, with amino acid sequences derived from one or more variable domain amino acid sequence provided in **Table 1**. In some embodiments, anti-tau antibodies of the present disclosure include one or more CDRs (e.g., 1, 2, 3, 4, 5, or all 6 CDRs) encoded by nucleic acid sequences derived from one or more variable domain nucleic acid sequences provided in **Table 1**. Anti-tau antibody CDRs may include one or more amino acid residues involved in antigen binding (e.g., as determined by co-crystallography with bound antigen). Anti-tau antibodies of the present disclosure may include CDRs identified through CDR analysis of variable domain sequences presented herein via co-crystallography with bound antigen; by computational assessments based on comparisons with other antibodies (e.g., see Strohl, W.R. *Therapeutic Antibody Engineering*, Woodhead Publishing, Philadelphia PA. 2012. Ch. 3, p47-54); or art-recognized Kabat, Chothia, Al-Lazikani, Lefranc, IMGT, or Honegger numbering schemes, as described previously. In some embodiments, anti-tau antibody CDR amino acid sequences may include any of those presented in **Table 1**, or fragments thereof. In some embodiments, anti-tau antibodies of the present disclosure include CDRs that include amino acid sequence variants of those listed. Amino acid fragments or variants included in anti-tau antibody CDRs may include from about 50% to about 99.9% sequence identity (e.g. from about 50% to about 60%, from about 55% to about 65%, from about 60% to about 70%, from about 65% to about 75%, from about 70% to about 80%, from about 75% to about 85%, from about 80% to about 90%, from about 85% to about 95%, from about 90% to about

99.9%, from about 95% to about 99.9%, about 97%, about 97.5%, about 98%, about 98.5%, about 99%, about 99.5%, about 99.6%, about 99.7% or about 99.8%) with one or more of the CDR sequences.

[0064] The anti-tau antibodies described herein may comprise a VH comprising one, two, or three of a heavy chain complementary determining region 1 (HCDR1), a heavy chain complementary determining region 2 (HCDR2), and a heavy chain complementary determining region 3 (HCDR3), and/or a VL comprising one, two, or three of a light chain complementary determining region 1 (LCDR1), a light chain complementary determining region 2 (LCDR2), and a light chain complementary determining region 3 (LCDR3), e.g., CDRs based on the Chothia numbering system, of any one of VY011, VY007, VY004, VY006, VY018, VY003, VY016, VY017, VY012, VY009, VY010, VY022, VY001, VY019, VY020, VY005, VY002, VY014, VY008, and VY013.

[0065] In some embodiments, provided herein is a recombinant antibody that binds to human tau, wherein the antibody comprises the heavy chain CDR1, CDR2, and CDR3, and/or light chain CDR1, CDR2, and CDR3 of an antibody comprising a heavy chain variable region (VH) and light chain variable region (VL) comprising: (i) SEQ ID NOs: 7 and 25, respectively; (ii) SEQ ID NOs: 3 and 21, respectively; (iii) SEQ ID NOs: 4 and 22, respectively; (iv) SEQ ID NOs: 6 and 24, respectively; (v) SEQ ID NOs: 11 and 30, respectively; (vi) SEQ ID NOs: 1 and 19, respectively; (vii) SEQ ID NOs: 2 and 20, respectively; (viii) SEQ ID NOs: 5 and 23, respectively; (ix) SEQ ID NOs: 8 and 26, respectively; (x) SEQ ID NOs: 9 and 27, respectively; (xi) SEQ ID NOs: 10 and 28, respectively; (xii) SEQ ID NOs: 10 and 29, respectively; (xiii) SEQ ID NOs: 12 and 31, respectively; (xiv) SEQ ID NOs: 13 and 32, respectively; (xv) SEQ ID NOs: 14 and 33, respectively; (xvi) SEQ ID NOs: 14 and 34, respectively; (xvii) SEQ ID NOs: 15 and 35, respectively; (xviii) SEQ ID NOs: 16 and 36, respectively; (xix) SEQ ID NOs: 17 and 37, respectively; or (xx) SEQ ID NOs: 18 and 38, respectively. In some embodiments, the CDR sequences are based on the Kabat numbering system, Chothia numbering system, or IMGT numbering system.

[0066] In some embodiments, provided herein are isolated, e.g., recombinant, antibodies which bind to human tau, comprising: (a) one, two, or all three HCDRs selected from a HCDR1 comprising an amino acid sequence selected from SEQ ID NO: 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, or 91, a HCDR2 comprising an amino acid sequence selected from SEQ ID NO: 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, or 108, and a HCDR3 comprising an amino acid sequence selected from SEQ ID NO:

109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, or 126, and/or (b) one, two, or all three LCDRs selected from a LCDR1 comprising an amino acid sequence selected from SEQ ID NO: 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, or 140, a LCDR1 comprising an amino acid sequence selected from SEQ ID NO: 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, or 153, a LCDR1 comprising an amino acid sequence selected from SEQ ID NO: 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, or 171. In some embodiments, one or more (1, 2, 3, 4, 5, or all 6 CDRs) of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 has one, two, or at most three amino acid substitutions (e.g., conservative substitutions).

[0067] In some embodiments, the anti-tau antibodies described herein comprise a VH and a VL, wherein the VH comprises the HCDR1, HCDR2, and HCDR3 combinations described in **Table 2**. In some embodiments, the anti-tau antibodies described herein comprise a VH and a VL, wherein the VL comprises the LCDR1, LCDR2, and LCDR3 combinations described in **Table 2**. In some embodiments, one or more (1, 2, or all 3) of the HCDR1, HCDR2, and HCDR3, and/or one or more (1, 2, or all 3) of the LCDR1, LCDR2, and LCDR3 has one, two, or at most three amino acid substitutions (e.g., conservative substitutions).

Table 2. Variable domain CDR amino acid sequence sets

ID#	Variable domain	CDR1 SEQ ID NO	CDR2 SEQ ID NO	CDR3 SEQ ID NO
VY003	VH	77	92	109
VY016	VH	78	93	110
VY007	VH	79	94	111
VY004	VH	80	95	112
VY017	VH	78	96	113
VY006	VH	81	94	114
VY011	VH	82	97	115
VY012	VH	83	98	116
VY009	VH	84	99	117
VY010	VH	85	100	118
VY022	VH	85	100	118
VY018	VH	82	101	119
VY001	VH	86	102	120
VY019	VH	87	103	121
VY020	VH	78	104	122
VY005	VH	78	104	122
VY002	VH	88	105	123
VY014	VH	89	106	124

VY008	VH	90	107	125
VY013	VH	91	108	126
VY003	VL	127	141	154
VY016	VL	128	142	155
VY007	VL	127	141	156
VY004	VL	129	143	157
VY017	VL	130	144	158
VY006	VL	127	141	156
VY011	VL	127	141	159
VY012	VL	131	145	160
VY009	VL	132	146	161
VY010	VL	133	147	162
VY022	VL	134	148	163
VY018	VL	132	149	164
VY001	VL	127	141	156
VY019	VL	132	149	165
VY020	VL	135	143	166
VY005	VL	136	150	167
VY002	VL	137	151	168
VY014	VL	138	152	169
VY008	VL	139	151	170
VY013	VL	140	153	171

[0068] In some embodiments, anti-tau antibodies of the present disclosure include pairs of variable domain CDR amino acid sequence sets presented herein. In some embodiments, anti-tau antibodies of the present disclosure include variable domain CDR amino acid sequence set pairs presented in **Table 3**.

Table 3. Variable domain CDR amino acid sequence set pairs

ID#	HCDR1 SEQ ID NO	HCDR2 SEQ ID NO	HCDR3 SEQ ID NO	LCDR1 SEQ ID NO	LCDR2 SEQ ID NO	LCDR3 SEQ ID NO
VY003	77	92	109	127	141	154
VY016	78	93	110	128	142	155
VY007	79	94	111	127	141	156
VY004	80	95	112	129	143	157
VY017	78	96	113	130	144	158
VY006	81	94	114	127	141	156
VY011	82	97	115	127	141	159
VY012	83	98	116	131	145	160
VY009	84	99	117	132	146	161
VY010	85	100	118	133	147	162
VY022	85	100	118	134	148	163
VY018	82	101	119	132	149	164
VY001	86	102	120	127	141	156

VY019	87	103	121	132	149	165
VY020	78	104	122	135	143	166
VY005	78	104	122	136	150	167
VY002	88	105	123	137	151	168
VY014	89	106	124	138	152	169
VY008	90	107	125	139	151	170
VY013	91	108	126	140	153	171

Provided herein are isolated, e.g., recombinant, antibodies that bind to human tau, wherein the antibody comprises a VH comprising one, two, or all three of a heavy chain complementary determining region 1 (HCDR1), a heavy chain complementary determining region 2 (HCDR2), and a heavy chain complementary determining region 3 (HCDR3), and/or a VL comprising one, two, or all three of a light chain complementary determining region 1 (LCDR1), a light chain complementary determining region 2 (LCDR2), and a light chain complementary determining region 3 (LCDR3), wherein: (i) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 82, 97, 115, 127, 141, and 159, respectively; (ii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 79, 94, 111, 127, 141, and 156, respectively; (iii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 80, 95, 112, 129, 143, and 157, respectively; (iv) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 81, 94, 114, 127, 141, and 156, respectively; (v) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 82, 101, 119, 132, 149, and 164, respectively; (vi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 77, 92, 109, 127, 141, and 154, respectively; (vii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 93, 110, 128, 142, and 155, respectively; (viii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 96, 113, 130, 144, and 158, respectively; (xi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 83, 98, 116, 131, 145, and 160, respectively; (x) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 84, 99, 117, 132, 146, and 161, respectively; (xi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 85, 100, 118, 133, 147, and 162, respectively; (xii) the HCDR1,

HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 85, 100, 118, 134, 148, and 163, respectively; (xiii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 86, 102, 120, 127, 141, and 156, respectively; (xiv) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 87, 103, 121, 132, 149, and 165, respectively; (xv) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 104, 122, 135, 143, and 166, respectively; (xvi) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 78, 104, 122, 136, 150, and 167, respectively; (xvii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 88, 105, 123, 137, 151, and 168, respectively; (xviii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 89, 106, 124, 138, 152, and 169, respectively; (xix) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 90, 107, 125, 139, 151, and 170, respectively; or (xx) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 91, 108, 126, 140, 153, and 171, respectively.

[0069] In some embodiments, the antibody comprises the HCDR1, HCDR2, and HCDR3 sequences of any one of (i)-(xx). In some embodiments, the antibody comprises the LCDR1, LCDR2, and LCDR3 sequences of any one of (i)-(xx). In some embodiments, the antibody comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences of any one of (i)-(xx).

[0070] In some embodiments, one or more (1, 2, 3, 4, 5, or all 6 CDRs) of the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 of the antibodies of (i)-(xx) has one, two, or at most three amino acid substitutions (e.g., conservative substitutions).

[0071] In some embodiments, anti-tau antibodies of the present disclosure include one or more framework regions (FRs). FRs may include amino acid sequences derived from variable domain amino acid sequences provided in Table 1. FRs may be encoded by nucleic acid sequences derived from one or more variable domain nucleic acid sequences provided in Table 1. In some embodiments, anti-tau antibody FRs may include amino acid sequences according to any of those presented in Table 1, or fragments thereof. In some embodiments, anti-tau antibodies of the present disclosure include FRs that include amino acid sequence variants of those listed. Amino acid fragments or variants included in anti-tau antibody FRs may include from about 50% to about 99.9% sequence identity (e.g. from about 50% to about

60%, from about 55% to about 65%, from about 60% to about 70%, from about 65% to about 75%, from about 70% to about 80%, from about 75% to about 85%, from about 80% to about 90%, from about 85% to about 95%, from about 90% to about 99.9%, from about 95% to about 99.9%, about 97%, about 97.5%, about 98%, about 98.5%, about 99%, about 99.5%, about 99.6%, about 99.7% or about 99.8%) with one or more of the amino acid sequences listed. In some embodiments, the FRs have at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity to the FR sequences listed in Table 1, or have at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modifications, such as amino acid substitutions (e.g., conservative substitutions)), relative to the FRs listed in Table 1.

[0072] Also provided herein are anti-tau antibodies which bind to tau protein antigens. Tau protein antigens may include human microtubule-associated protein tau, isoform 2 (SEQ ID NO: 274) or fragments thereof. Tau protein antigens may include ePHF or fragments thereof. Tau protein antigens may include one or more phosphorylated residues. Such phosphorylated residues may correspond to those found with pathological tau. In some embodiments tau protein antigens include any of those listed in **Table 4**. In the Table, phosphorylated residues associated with each antigen are denoted as (pS) for a phosphorylated serine and (pT) for phosphorylated threonine. In some embodiments, tau proteins may include variants (e.g., phosphorylated or unphosphorylated variants) or fragments of the sequences listed.

Table 4. Tau protein antigen sequences

Antigen	Sequence	SEQ ID NO
human microtubule-associated protein tau, isoform 2	MAEPRQEFVEMDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQ TPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTTEIP EGTTAAEEAGIGDTPSLEDEAAGHVTQARMVSKSKDGTGSDDKKAKGADG KTKIATPRGAAPPQKQGQANATRIPAKTPPAPKTPPSSGEPKSGDRSG YSSPGSPGTPGSRSRTPSLPTPTREP KKVAVVRTPPKSPSSAKSRLQT APVPM PDLKNVSKIGSTENLKHQPGGGKVQIIINKKLDLSNVQSKCGSK DNIKHVPGGGSVQIVYKPVDSLKVT SKCGSLGNIHHKPGGGQVEVKSEK LDFKDRVQSKIGSLDNI THVPGGGNKKIETHKLTFRENAKAKTDHGAEI VYKSPVVS GDTSPRHL SNVSSTG SIDMVDS PQLATL ADEV SASLAKQGL	274
PT3 epitope peptide (pT212/pT217)	TPGSRSR (pT) PSLP (pT) PPTREPK	275
Peptide 5 (tPeptide 5) (pT212/pS214/pT217)	GTPGSRSR (pT) P (pS) LP (pT) PPTRE	276
Peptide 12 (pS396/pS404/pS409)	RENAKAKTDHGAEIVYK (pS) PVVSGDT (pS) PRHL (pS) NVSSTG	277

Peptide 1 (AT120 epitope)	PTREPKKV	278
6C5 epitope peptide	ARMVSKS	279
UCB D & PT76 epitope peptide	SPSSAKSRLQTAPVPMPLDKNVKS	280
Tau(pS404)	DHGAEIVYKSPVVSGDT (pS) PRHLSNVSTG	281
AC04 peptide	CSR (pT) PSLP (pT) PPTREPK	282
PepScan 193-210 peptide	DR (pS) GY (pS) (pS) PG (pS) PG (pT) PG (pS) R (pS)	283
Tau191-214 phosphopeptide (pS199)	SGDRSGYS (pS) PGSPGTPGSRSRTPS	284
Tau191-214 phosphopeptide (pS202)	SGDRSGYSSPG (pS) PGTPGSRSRTPS	285
Tau191-214 phosphopeptide (pT205)	SGDRSGYSSPGSPG (pT) PGSRSRTPS	286
Tau191-214 phosphopeptide (pS199/pS202/pT205)	SGDRSGYSpSPG (pS) PG (pT) PGSRSRTPS	287
Tau191-214 phosphopeptide (pS199/pS202)	SGDRSGYS (pS) PG (pS) PGTPGSRSRTPS	288
Tau191-214 phosphopeptide (pS202/pT205)	SGDRSGYSSPG (pS) PG (pT) PGSRSRTPS	289
Tau191-214 phosphopeptide (pS199/pT205)	SGDRSGYS (pS) PGSPG (pT) PGSRSRTPS	290
Tau204-222 phosphopeptide (pT212)	GTPGSRSR (pT) PSLPTPPTRE	291
Tau204-222 phosphopeptide (pS214)	GTPGSRSRTP (pS) LPTPPTRE	292
Tau204-222 phosphopeptide (pT217)	GTPGSRSRTPSLP (pT) PPTRE	293
Tau204-222 phosphopeptide (pT212/pS214)	GTPGSRSR (pT) P (pS) LPTPPTRE	294
Tau204-222 phosphopeptide (pT212/pT217)	GTPGSRSR (pT) PSLP (pT) PPTRE	295
Tau204-222 phosphopeptide (pS214/pT217)	GTPGSRSRTP (pS) LP (pT) PPTRE	296
Tau204-222 phosphopeptide (pT212/pS214/pT217)	GTPGSRSR (pT) P (pS) LP (pT) PPTRE	297
Tau217-234 phosphopeptide (pT217/pT220/pT231)	(pT) PP (pT) REPKKVAVVR (pT) PPK	298
Tau225-240 phosphopeptide (pT231)	KVAVVR (pT) PPKSPSSAK	299
Tau phosphopeptide (pS235)	KVAVVRTPPK (pS) PSSAKPS	300
Tau phosphopeptide (pT231/pS235)	KVAVVR (pT) PPK (pS) PSSAKPS	301

[0073] In some embodiments, anti-tau antibodies of the present disclosure bind to tau protein epitopes on tau protein antigens described herein. Such tau protein epitopes may include or be included within a tau protein antigen amino acid sequence listed in **Table 4**. In

some embodiments, anti-tau antibodies of the present disclosure bind to tau protein epitopes that include a region formed by a complex of at least two tau proteins.

[0074] In some embodiments, anti-tau antibodies of the present disclosure exhibit binding that overlaps with a region of tau recognized by art-recognized antibodies, such as AT8 and PT3, but exhibit binding patterns to phosphorylated tau that differs from the art-recognized antibodies.

[0075] Accordingly, in one aspect, provided herein is an isolated, *e.g.*, recombinant, antibody that binds to human tau, wherein the antibody binds to all or a portion of amino acid residues of tau selected from: (a) 183-212, (b) 187-218, (c) 33-82, 159-182, 197-226, and 229-246; (d) 217-242, (e) 35-76 and 187-218, (f) 5-34, (g) 187-218, (h) 33-82, 159-188, and 191-230, (i) 35-62, 107-124, and 203-220, (j) 35-82, 159-188, and 197-224, or (k) 53-78, 329-348, and 381-408, wherein human tau is numbered according to SEQ ID NO: 274. In some embodiments, one or more of the serines, threonines, and/or tyrosines in the stretch of amino acids selected from (a)-(k) are phosphorylated. In some embodiments, all of the serines, threonines, and/or tyrosines in the stretch of amino acids selected from (a)-(k) are phosphorylated. In some embodiments, the antibody comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences, or the VH and VL sequences, of an antibody listed in **Table 1**.

[0076] In some embodiments, the anti-tau antibody binds to all or a portion of amino acids 195-215 of human tau (*e.g.*, phosphorylated at all serines, threonines, and/or tyrosines present in this stretch of amino acids) with a dissociation constant (K_D) of about 1 pM to about 50 pM, or about 1-25 pM, *e.g.*, as assessed by bio-layer interferometry.

[0077] In some embodiments, the anti-tau antibody binds to all or a portion of amino acids 191-214 of human tau phosphorylated at S199 (*e.g.*, phosphorylated only at S199 in this stretch of amino acids or throughout the entire tau protein) with a dissociation constant (K_D) of about 0.1 nM to about 10 nM, or about 0.5-5 nM, *e.g.*, as assessed by bio-layer interferometry.

[0078] In some embodiments, the anti-tau antibody binds to all or a portion of amino acids 217-234 of human tau phosphorylated at T217, T220, and T231 (*e.g.*, phosphorylated only at T217, T220, and T231 in this stretch of amino acids or throughout the entire tau protein) with a dissociation constant (K_D) of about 0.1 nM to about 10 nM, or about 0.1-5 nM, *e.g.*, as assessed by bio-layer interferometry.

[0079] In some embodiments, the anti-tau antibody binds to all or a portion of amino acids 225-240 of tau phosphorylated at T231 (*e.g.*, phosphorylated only at T231 in this stretch of

amino acids or throughout the entire tau protein) with a dissociation constant (K_D) of about 0.1 nM to about 25 nM, or about 0.1-15 nM, e.g., as assessed by bio-layer interferometry.

[0080] In another aspect, provided herein is an isolated, e.g., recombinant, antibody that binds to human tau phosphorylated at amino acid residue S404, or a peptide comprising or consisting of the amino acid sequence DHGAEIVYKSPVVSGDT(pS)PRHLSNVSTG (SEQ ID NO: 281), wherein p(S) corresponds to a phosphorylated serine residue. In some embodiments, the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 89, 106, and 124, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 138, 152, and 169, respectively. In some embodiments, the antibody comprises VH and VL sequences comprising SEQ ID NOs: 16 and 36, respectively.

[0081] In another aspect, provided herein is an isolated, e.g., recombinant, antibody that binds to: (a) human tau phosphorylated at amino acid residue S199, but not at amino acid residues S202 and T205; (b) human tau phosphorylated at amino acid residue S202, but not at amino acid residues S199 and T205; (c) human tau phosphorylated at amino acid residue T205, but not at amino acid residues S199 and S202; (d) human tau phosphorylated at a combination of amino acid residues S199 and T205, but not at amino acid residue S202 (e.g., wherein binding tau phosphorylated at a combination of S199 and T205 is at least 3-times stronger (e.g., at least 4-time stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control); (e) human tau phosphorylated at a combination of amino acid residues S202 and T205, but not at amino acid residue S199, but not human tau phosphorylated at a combination of residues S199 and S202, but not T205; (f) human tau phosphorylated at a combination of amino acid residues: (i) S202 and T205, but not S119, and (ii) S199 and T205, but not S202, at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more strongly than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control); (g) human tau phosphorylated at a combination of amino acid residues: (i) S199 and S202, but not T205, (ii) S202 and T205, but not S199, (iii) S199 and T205, but not S202, and (iv) S199, S202, and T205 (e.g., wherein binding to phosphorylated tau is at least 1.6-times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-3 times, 1.6-2 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control); (h) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPGTPGSRSRTPS (SEQ ID NO: 284); (i) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PGTPGSRSRTPS

(SEQ ID NO: 285); (j) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPGSPG(pT)PGSRSRTPS (SEQ ID NO: 286); (k) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290) (e.g., wherein binding to the peptide is at least 3 times stronger (e.g., at least 4 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control); (l) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), but not a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288); (m) peptides comprising or consisting of the amino acid sequences SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289) and SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290); wherein binding to the latter peptide is at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) stronger than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control); or (n) peptides comprising or consisting of the amino acid sequences SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288), SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), and SGDRSGYS(pS)PG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 287) (e.g., wherein binding to the peptides is at least 1.6 times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-4 times, 1.6-3 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control); wherein p(S) and p(T) correspond to a phosphorylated serine and phosphorylated threonine, respectively, optionally wherein binding is assessed, e.g., using one point ELISA as described in Example 7. In some embodiments, the antibody comprises (a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; (b) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (c) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (d) a heavy chain variable region (VH) comprising CDR1, CDR2, and

CDR3 sequences comprising SEQ ID NOs: 77, 92, and 109, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 154, respectively; (e) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (f) VH and VL sequences comprising SEQ ID NOs: 7 and 25, respectively; (g) VH and VL sequences comprising SEQ ID NOs: 8 and 21, respectively; (h) VH and VL sequences comprising SEQ ID NOs: 6 and 24, respectively; (i) VH and VL sequences comprising SEQ ID NOs: 1 and 19, respectively; or (j) VH and VL sequences comprising SEQ ID NOs: 12 and 31, respectively.

[0082] In another aspect, provided herein is an isolated, *e.g.*, recombinant, antibody that binds to: (a) tau phosphorylated at T217, but not at T212 or T214, or (b) peptides comprising or consisting of the sequences GTPGSRSRTPSLP(pT)PPTRE (SEQ ID NO: 293) and GTPGSRSRTP(pS)LP(pT)PPTRE (SEQ ID NO: 296), but not peptides comprising or consisting of the sequences GTPGSRSR(pT)PSLTPPTRE (SEQ ID NO: 291), GTPGSRSRTP(pS)LPTPPTRE (SEQ ID NO: 292), and GTPGSRSR(pT)P(pS)LPTPPTRE (SEQ ID NO: 294), wherein p(S) and p(T) correspond to a phosphorylated serine and phosphorylated threonine, respectively, optionally wherein binding of the antibody to tau or the peptide is at least 1.5 times stronger (*e.g.*, at least 1.6 times, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, 1.5-4 times, 1.5-3, 4-6 times stronger) than background (non-specific) level of binding, *e.g.*, binding by hIgG1 isotype control), and optionally wherein binding of the antibody to tau or the peptide is assessed, *e.g.*, using one point ELISA as described, *e.g.*, in Example 8. In some embodiments, the antibody comprises: (a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 80, 95, and 112, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 129, 143, and 157, respectively; (b) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 78, 104, and 122, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 136, 150, and 167, respectively; (c) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 90, 107, and 125, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 139,

151, and 170, respectively; (d) VH and VL sequences comprising SEQ ID NOs: 4 and 22, respectively; (e) VH and VL sequences comprising SEQ ID NOs: 14 and 24, respectively; or (f) VH and VL sequences comprising SEQ ID NOs: 17 and 37, respectively.

[0083] Specific binding to the aforementioned recited phosphorylated residues or peptides can be determined by comparison with the background level of binding of the assay (e.g., one point ELISA) or level of binding by a negative control, such as an isotype control antibody (e.g., a human IgG1 isotype control antibody), for example, as described in the Examples.

[0084] In some embodiments, provided herein are anti-tau antibodies which compete for binding to human tau, or human tau peptides, with any of the anti-tau antibodies described herein.

[0085] Also provided herein are anti-tau antibodies which exhibit similar epitope binding features, such as the ability to bind to phospho-epitopes on human tau, as the anti-tau antibodies described herein. Accordingly, in some embodiments, provided herein are antibodies which bind to the same epitope (e.g., phospho-epitope), substantially the same epitope as, an epitope that overlaps with, or an epitope that substantially overlaps with, the epitope recognized by an anti-tau antibody described herein. In some embodiments, the antibodies described herein bind to a discontinuous epitope, such as a conformational epitope.

[0086] Exemplary methods for determining whether an antibody binds to the same epitope (or substantially the same epitope, an epitope that overlaps with, or an epitope that substantially overlaps with) on human tau with the antibodies described herein include, e.g., epitope mapping methods such as x-ray analyses of crystals of antigen:antibody complexes which provides atomic resolution of the epitope. Other methods monitor the binding of the antibody to antigen fragments or mutated variations of the antigen where loss of binding due to a modification of an amino acid residue within the antigen sequence is often considered an indication of an epitope component. Computational combinatorial methods for epitope mapping can also be used. Methods may also rely on the ability of an antibody of interest to affinity isolate specific short peptides (either in native three dimensional form or in denatured form) from combinatorial phage display peptide libraries. Epitope mapping can also be performed using MS-based protein footprinting (e.g., HDX-MS, FPOP). Overlapping phospho-peptide scanning, as described in the Examples, can also be used for epitope mapping.

[0087] Anti-tau antibodies according to the present disclosure may be prepared using any of the antibody sequences (e.g., variable domain amino acid sequences, variable domain amino acid sequence pairs, CDR amino acid sequences, variable domain CDR amino acid

sequence sets, variable domain CDR amino acid sequence set pairs, and/or framework region amino acid sequences) presented herein, any may be prepared, for example, as monoclonal antibodies, multispecific antibodies, chimeric antibodies, antibody mimetics, scFvs, or antibody fragments. In some embodiments, anti-tau antibodies using any of the antibody sequences presented herein may be prepared as IgA, IgD, IgE, IgG, or IgM antibodies. When prepared as mouse IgG antibodies, anti-tau antibodies may be prepared as IgG1, IgG2a, IgG2b, or IgG3 isotypes. When prepared as human IgG antibodies, anti-tau antibodies may be prepared as IgG1, IgG2, IgG3, or IgG4 isotypes. Anti-tau antibodies prepared as human or humanized antibodies may include one or more human constant domains. Human constant domains included in anti-tau antibodies of the present disclosure may include, but are not limited to, any of those listed in **Table 5**.

[0088] In some embodiments, the anti-tau antibodies comprise: (i) a heavy chain constant region (CH), e.g., a CH comprising an amino acid sequence of a human CH, such as the CH of human IgG1, IgG2, IgG3, or IgG4 (e.g., a CH described in **Table 5**) or a murine CH, or a sequence having at least 80% (e.g., 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto, or an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as a substitution (e.g., a conservative substitution)), relative to the constant region sequence (e.g., a CH described in **Table 5**); and/or (ii) a light chain constant region (CL), e.g., a CL comprising an amino acid sequence of a human CL, such as the CL of a human lambda or kappa light chain (e.g., a CL described in **Table 5**) or a murine CL, or a sequence having at least 80% (e.g., 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto, or an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications (e.g., 1-30, 1-20, 1-10, 1-5, 1-4, 1-3, 1-2, or 1 amino acid modification, such as a substitution (e.g., a conservative substitution)), relative to the constant region sequence (e.g., a CH described in **Table 5**).

[0089] In some embodiments, the heavy chain constant region sequence (e.g., human heavy chain constant region sequence) has a C-terminal lysine (K), a C-terminal glycine (G), or a C-terminal glycine and lysine (GK). In some embodiments, the heavy chain constant region sequence (e.g., human heavy chain constant region sequence) lacks the C-terminal lysine (K), C-terminal glycine (G), or C-terminal glycine and lysine (GK).

[0090] In some embodiments, anti-tau antibodies of the present disclosure include constant domains that include amino acid sequence variants and/or fragments of those listed in **Table 5**. Amino acid fragments or variants included in anti-tau antibody constant domains

may include from about 50% to about 99.9% sequence identity (e.g. from about 50% to about 60%, from about 55% to about 65%, from about 60% to about 70%, from about 65% to about 75%, from about 70% to about 80%, from about 75% to about 85%, from about 80% to about 90%, from about 85% to about 95%, from about 90% to about 99.9%, from about 95% to about 99.9%, about 97%, about 97.5%, about 98%, about 98.5%, about 99%, about 99.5%, about 99.6%, about 99.7% or about 99.8%) with one or more of the amino acid sequences listed in **Table 5**. In some embodiments, the constant domains have at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity, or at least one, two, or three modifications, but not more than 30, 20, or 10 modifications (e.g., amino acid substitutions, such as conservative substitutions), relative to the amino acid sequences listed in **Table 5**.

[0091] A VH domain, or one or more CDRs thereof, described herein can be linked to a constant domain to form a heavy chain, e.g., a full length heavy chain. Similarly, a VL domain, or one or more CDRs thereof, described herein can be linked to a constant domain to form a light chain, e.g., a full length light chain. A full length heavy chain (with the exception of the C-terminal lysine (K), with the exception of the C-terminal glycine (G), or with the exception of the C-terminal glycine and lysine (GK), which may be absent) and full length light chain may combine to form a full length antibody.

Table 5. Constant domains

Constant domain	Sequence	SEQ ID NO
Human IgG1 heavy chain constant region (1)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVHLQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPG	271
Human IgG1 heavy chain constant region (2)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVHLQDW LNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPG	302
Human IgG2 heavy chain constant region	ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTV ERKCCVECPAPAPVAGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGK EYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVSCSVMHEALHNHYTQKSLSLSPGK	303
Human IgG3 heavy chain constant region	ASTKGPSVFPLAPCSRSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYTCNVNHKPSNTKVDKRV	304

80

region (secreted form)	PRVPITQNPCPPHQRVPPCAAPDLLGGPSVFIFFPKIKDVLMISSLSPMV TCVVVDVSEDDPDVQISWVNNVEVHTAQQTTHREDYNSTLRVVSALPI QHQDWMSGKEFKCKVNNRALPSPIEKTISKPRGPVRAPQVYVLPFPAAEE MTKKEFSLTCMITGFLPAEIAVDWTSNGRTEQNYKNTATVLDSDGSYFM YSKLRVQKSTWERGSLFACSVVHEVLHNHLTTKTISSRLGK	
Murine mIgG2b heavy chain constant region (secreted form)	KTTPPSVYPLAPGCGDTTGSSVTLGCLVKGYFPEPVTLTWNSSGLSSSV HTFPALLQSGLYTMSSSVTVPSSTWPSQTVTCVAHPASSTTVDDKKLEP SGPISTINPCPPCKECKCPAPNLEGGPSVFIFFPNIKDVLMISSLTPKV TCVVVDVSEDDPDVQISWVNNVEVHTAQQTTHREDYNSTIRVVSTLPI QHQDWMSGKEFKCKVNNKDLPSPIERTISKIKGLVRAPQVYILPFPAAEQ LSRKDVSLTCLVGFNPGDISVEWTSNGHTEENYKDTAPVLDSDGSYFI YSKLNMTKSKWEKTDSCNVRHEGLKNYYLKTTISRSPGLDLDICAEE AKDGELDGLWTTITIFISLFLLSVCYSASVTLFKVKWIFSSSVVELKQKI SPDYRNMIGQGA	314
Murine mIgG2b heavy chain constant region	KTTAPSVYPLAPVCGGTTGSSVTLGCLVKGYFPEPVTLTWNSSGLSSGV HTFPALLQSGLYTLSSSVTVTSNTWPSQITCNVAHPASSTKVDDKIEP RVPITQNPCPPLKECPPCAAPDLLGGPSVFIFFPKIKDVLMISSLSPMVT CVVVVDVSEDDPDVQISWVNNVEVHTAQQTTHREDYNSTLRVVSALPIQ HQDWMSGKEFKCKVNNRALPSPIEKTISKPRGPVRAPQVYVLPFPAAEEM TKKEFSLTCMITGFLPAEIAVDWTSNGRTEQNYKNTATVLDSDGSYFMY SKLRVQKSTWERGSLFACSVVHEGLHNHLTTKTISSRLGLDLDVCTEA QDGELDGLWTTITIFISLFLLSVCYSASVTLFKVKWIFSSSVVELKQKIS PDYRNMIGQGA	315
Murine mIgG3 heavy chain constant region (secreted form)	TTTAPSVYPLVPGCDTSGSSVTLGCLVKGYFPEPVTVKWNYGALSSGV RTVSSVLQSGFYLSSSLVTVPSSTWPSQTVICNVAHPASKTELKRIEP RIPKPSTPPGSSCPPGNILGGPSVFIFFPKPKDALMISLTPKVTCTVVVD VSEDDPDVHVSWFVDNKEVHTAWTQPREAQYNSTFRVVSALPIQHQDWM RGKEFKCKVNNKALPAPIERTISKPKGRAQTPQVYTIPPPREQMSKKKV SLTCLVTNFFSEATISVEWERNGELEQDYKNTPPILDSDGTYFLYSKLT DTSWLQGEIFTCSVVHEALHNHHTQKNLSRSPLELNETCAEAQDGEL DGLWTTITIFISLFLLSVCYSASVTLFKVKWIFSSVVQVKQTAIPDYRN MIGQGA	316
Murine kappa light chain constant region	ADAAPTIVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKIDGSRQN GVLNSWTDQDSKSTYSMSSTLTLTKEYERHNSYTCEATHKTSTSPIV KSFNRNEC	317
Murine lambda light chain constant region (subclass 1)	QPKSSPSVTLFPPSSEETNKATLVCTITDFYPGVTVVDWKVDGTPVT QGMETTQPSKQSNKYMASSTLTARAWERHSSYSCQVTHEGDTVEKS LSRADCS	318
Murine lambda light chain constant region (subclass 2)	QPKSTPTLTVPFPPSSEELKENKATLVCLISNFSPPSGVTVAWKANGTPI QGVDTSNPTKEGNKFMASSTLHLSQWRSHNSFTCQVTHEGDTVEKSL SPAECCL	319
Murine lambda light chain constant region (subclass 3)	QPKSTPTLTMTFPPSPEELQENKATLVCLISNFSPPSGVTVAWKANGTPI QGVDTSNPTKEDNKYMASSTLHLSQWRSHNSFTCQVTHEGDTVEKSL SPAECCL	320

[0092] In some embodiments, the anti-tau antibodies may comprise an Fc region or variant, e.g., functional variant, thereof.

[0093] In some embodiments, the antibody comprises an Fc region which has modified, e.g., increased or reduced affinity (e.g., ablated), affinity for an Fc receptor, e.g., as compared to a reference, wherein the reference is a wild-type Fc receptor.

[0094] In some embodiments, the antibody comprises an Fc region which comprises a mutation at one, two, or all of positions I253 (e.g., I235A), H310 (e.g., H310A), and/or H435 (e.g., H435A), numbered according to the EU index as in Kabat.

Antibody characterization

[0095] In some embodiments, antibodies of the present disclosure may be identified, selected, or excluded based on different characteristics. Such characteristics may include, but are not limited to, physical and functional characteristics. Physical characteristics may include features of antibody structures [e.g., amino acid sequence or residues; secondary, tertiary, or quaternary protein structure; post-translational modifications (e.g., glycosylations); chemical bonds, and stability]. Functional characteristics may include, but are not limited to, antibody affinity (i.e., for specific epitopes and/or antigens) and antibody activity (e.g., antibody ability to activate or inhibit a target, process, or pathway).

Antibody binding and affinity

[0096] In some embodiments, antibodies of the present disclosure may be identified, selected, or excluded based on binding and/or level of affinity for specific epitopes and/or antigens. Antibody binding and/or affinity level may be assessed with different antigen formats. In some embodiments, antibody affinity for different antigen formats may be tested *in vitro* (e.g., by ELISA). Anti-tau antibody *in vitro* testing may be carried out using brain samples or fractions. Such samples or fractions may be obtained from subjects with AD (e.g., human AD patients). In some embodiments, brain samples or fractions may be obtained from non-human subjects. Such non-human subjects may include non-human animals used in AD disease model studies (e.g., mice, rats, and primates). In some embodiments, brain samples or fractions used for antibody affinity testing may be derived from TG4510/P301S mouse strains. Antibody affinity may be compared against control samples lacking the particular antigen for which affinity is being analyzed. In some embodiments, control samples used for anti-tau antibody testing may include brain samples or fractions from non-diseased human subjects. In some embodiments, brain samples or fractions from wild type and/or Tau knockout mouse strains may be used as control samples.

[0097] *In vitro* affinity testing may be carried out (e.g., by ELISA) using recombinant or isolated protein antigens. For example, recombinant or isolated ePHF may be used for anti-tau antibody affinity testing. In some embodiments, anti-tau antibodies of the present disclosure may exhibit a half maximal effective concentration (EC₅₀) of from about 0.01 nM to about 100 nM for binding to ePHF when assessed by ELISA. In some embodiments, the

exhibited EC50 may be less than about 50 nM, less than about 20 nM, less than about 10 nM, or less than about 1 nM. In some embodiments, anti-tau antibodies of the present disclosure may exhibit an EC50 of from about 0.01 nM to about 100 nM for binding to any of the antigens listed in **Table 4**, or an epitope that includes or is included within any of the antigens (including, but not limited to conformational epitopes), when assessed by ELISA. In some embodiments, the exhibited EC50 may be less than about 50 nM, less than about 20 nM, less than about 10 nM, or less than about 1 nM.

[0098] In some embodiments, anti-tau antibodies of the present disclosure bind to pathological tau, but do not bind to non-pathological tau. Such antibodies may be referred to herein as being “selective” for pathological forms of tau. In some embodiments, anti-tau antibodies of the present disclosure bind to tau tangles.

[0099] In some embodiments, antibody affinity analysis may be used to identify, select, or exclude polyspecific antibodies. As used herein, the term “polyspecific antibody” refers to an antibody with affinity for more than one epitope or antigen. In some embodiments, polyspecific antibodies may be identified, selected, or excluded based on relative affinity for each epitope or antigen recognized. For example, a polyspecific antibody may be selected for use or further development based on higher affinity for one epitope or antigen over a second epitope or antigen for which the polyspecific antibody demonstrates affinity.

[0100] In some embodiments, anti-tau antibodies may be tested for competition with other anti-tau antibodies. Such testing may be carried out to provide information on the specific epitope recognized by an antibody and may yield information related to level of epitope affinity in comparison to the competing antibody. In some embodiments, anti-tau antibodies used in antibody binding and/or affinity analysis may include anti-tau antibody PT3, as described in United States Patent Number 9,371,376; anti-tau antibody C10.2, as described in United States Patent Number 10,196,439 (referred to as antibody “C10-2,” therein); anti-tau antibody IPN002, as described in US Patent Number 10,040,847; anti-tau antibody AT8 (ThermoFisher, Waltham, MA); anti-tau antibody AT100 (ThermoFisher, Waltham, MA); anti-tau antibody AT120 as described in United States Patent Number 5,843,779; or anti-tau antibody PT76, as described in Vandermeeren, M. et al., J Alzheimers Dis. 2018;65(1):265-281.

Antibody activity

[0101] In some embodiments, antibodies of the present disclosure may be identified, selected, or excluded based on their ability to promote or reduce a certain activity. Antibody

activity may be assessed using analytical assays. Such assays may be selected or designed to detect, screen, measure, and/or rank antibodies based on such antibody activity.

[0102] Anti-tau antibodies may be characterized by ability to inhibit tau aggregation. Inhibition may be based on physical disruption of tau aggregation or may be based on anti-tau antibody-dependent depletion (immunodepletion) of tau protein. Characterization based on tau aggregation inhibition may be assessed using one or more assays of tau aggregation. In some embodiments, anti-tau antibodies may be characterized by tau seeding assay. Tau seeding assays typically involve in vitro initiation of tau aggregation and assessment of aggregation inhibition by candidate compounds being tested. Tau seeding assays may be carried out using tau aggregation biosensor cells. Tau aggregation biosensor cells yield a detectable signal (e.g., a fluorescent signal) in response to tau aggregation. Tau aggregation biosensor cells may be cultured with recombinant or isolated tau or with samples from high tau brain tissues or fluids (to promote tau aggregation) and treated with or without candidate compounds to assess tau aggregation inhibition. In some embodiments, anti-tau antibodies may be used to deplete tau from media prior to incubation with biosensor cells. Aggregation levels with depleted media may be compared to aggregation levels with non-depleted media to assess anti-tau antibody inhibitory function. Tau aggregation biosensor cells may include, but are not limited to, tau RD Biosensor cells. In some embodiments, neurons expressing human tau may be used.

[0103] In some embodiments, anti-tau antibodies of the present disclosure may inhibit tau aggregation with a half maximal inhibitory concentration (IC₅₀) of from about 1 nM to about 30 nM as determined by immunodepletion assay (e.g., using tau RD Biosensor cells).

Antibody structure and variations

[0104] Antibodies of the present disclosure may exist as a whole polypeptide, a plurality of polypeptides or fragments of polypeptides, which independently may be encoded by one or more nucleic acids, a plurality of nucleic acids, fragments of nucleic acids or variants of any of the aforementioned. As used herein, “polypeptide” means a polymer of amino acid residues (natural or unnatural) linked together most often by peptide bonds. The term, as used herein, refers to proteins, polypeptides, and peptides of any size, structure, or function. Polypeptides smaller than about 50 amino acids may be referred to using the term “peptide.” Peptides may be at least about 2, 3, 4, or at least 5 amino acid residues long. Polypeptides of the present disclosure may include gene products, naturally occurring polypeptides, synthetic polypeptides, homologs, orthologs, paralogs, fragments, or other equivalents, variants, and

analogs of the foregoing. Polypeptides may be single molecules or may be multi-molecular complexes such as dimers, trimers, or tetramers. Polypeptides may also include single chain or multichain polypeptides, which may be associated or linked. Polypeptides may include amino acid polymers in which one or more amino acid residues are artificial chemical analogues of corresponding naturally occurring amino acids.

[0105] The term “polypeptide variant” refers to molecules which differ in their amino acid sequence from a native or reference sequence. Amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence, as compared to a native or reference sequence. Ordinarily, variants will possess at least about 50% identity (homology) to a native or reference sequence, and preferably, they will be at least about 80%, more preferably at least about 90% identical (homologous) to a native or reference sequence.

[0106] In some embodiments “variant mimics” are provided. As used herein, the term “variant mimic” is one which contains one or more amino acids which would mimic an activated sequence. For example, glutamate may serve as a mimic for phosphorylated threonine and/or phosphorylated serine. Alternatively, variant mimics may result in deactivation or in an inactivated product containing the mimic, e.g., phenylalanine may act as an inactivating substitution for tyrosine; or alanine may act as an inactivating substitution for serine.

[0107] The term “amino acid sequence variant” refers to molecules with some differences in their amino acid sequences as compared to a native or starting sequence. The amino acid sequence variants may possess substitutions, deletions, and/or insertions at certain positions within the amino acid sequence. “Native” or “starting” sequence should not be confused with a wild type sequence. As used herein, a native or starting sequence is a relative term referring to an original molecule against which a comparison may be made. “Native” or “starting” sequences or molecules may represent the wild-type (that sequence found in nature) but do not have to be the wild-type sequence.

[0108] Ordinarily, variants will possess at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5% at least 99.8%, or at least 99.9% sequence identity as compared to a native sequence.

[0109] By “homologs” as it applies to amino acid sequences is meant the corresponding sequence of other species having substantial identity to a second sequence of a second species.

[0110] "Analog" is meant to include polypeptide variants which differ by one or more amino acid alterations, e.g., substitutions, additions or deletions of amino acid residues that still maintain the properties of the parent polypeptide.

[0111] The present disclosure contemplates variants and derivatives of antibodies presented herein. These include substitutional, insertional, deletion and covalent variants and derivatives. For example, sequence tags or amino acids, such as one or more lysines, may be added to antibody peptide sequences (e.g., at the N-terminal or C-terminal ends). Sequence tags may be used for peptide purification or localization. Lysines may be used to increase peptide solubility or to allow for biotinylation. Alternatively, amino acid residues located at the carboxy and amino terminal regions of the amino acid sequence of a peptide or polypeptide may optionally be deleted providing for truncated sequences. Certain amino acids (e.g., C-terminal or N-terminal residues) may alternatively be deleted depending on the use of the sequence, as for example, expression of the sequence as part of a larger sequence which is soluble, or linked to a solid support.

[0112] "Substitutional variants" when referring to polypeptides are those that have at least one amino acid residue in a native or starting sequence removed and a different amino acid inserted in its place at the same position. The substitutions may be single, where only one amino acid in the molecule has been substituted, or they may be multiple, where two or more amino acids have been substituted in the same molecule.

[0113] As used herein the term "conservative amino acid substitution" refers to the substitution of an amino acid that is normally present in the sequence with a different amino acid of similar size, charge, or polarity. Examples of conservative substitutions include the substitution of a non-polar (hydrophobic) residue such as isoleucine, valine and leucine for another non-polar residue. Likewise, examples of conservative substitutions include the substitution of one polar (hydrophilic) residue for another such as between arginine and lysine, between glutamine and asparagine, and between glycine and serine. Additionally, the substitution of a basic residue such as lysine, arginine or histidine for another, or the substitution of one acidic residue such as aspartic acid or glutamic acid for another acidic residue are additional examples of conservative substitutions. Examples of non-conservative substitutions include the substitution of a non-polar (hydrophobic) amino acid residue such as isoleucine, valine, leucine, alanine, methionine for a polar (hydrophilic) residue such as cysteine, glutamine, glutamic acid or lysine and/or a polar residue for a non-polar residue.

[0114] The term "functional variant" refers to a polypeptide variant or a polynucleotide variant that has at least one activity of the reference sequence.

[0115] "Insertional variants" when referring to polypeptides are those with one or more amino acids inserted immediately adjacent to an amino acid at a particular position in a native or starting sequence. "Immediately adjacent" to an amino acid means connected to either the alpha-carboxy or alpha-amino functional group of the amino acid.

[0116] "Deletional variants" when referring to polypeptides, are those with one or more amino acids in the native or starting amino acid sequence removed. Ordinarily, deletional variants will have one or more amino acids deleted in a particular region of the molecule.

[0117] As used herein, the term "derivative" is used synonymously with the term "variant" and refers to a molecule that has been modified or changed in any way relative to a reference molecule or starting molecule. In some embodiments, derivatives include native or starting polypeptides that have been modified with an organic proteinaceous or non-proteinaceous derivatizing agent, and post-translational modifications. Covalent modifications are traditionally introduced by reacting targeted amino acid residues of a polypeptide with an organic derivatizing agent that is capable of reacting with selected side-chains or terminal residues, or by harnessing mechanisms of post-translational modifications that function in selected recombinant host cells. The resultant covalent derivatives are useful in programs directed at identifying residues important for biological activity, for immunoassays, or for the preparation of antibodies for immunoaffinity purification.

[0118] Certain post-translational modifications are the result of the action of recombinant host cells on the expressed polypeptide. Glutaminyl and asparaginyl residues are frequently post-translationally deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Either form of these residues may be present in polypeptides used in accordance with the present disclosure.

[0119] Other post-translational modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains (T. E. Creighton, *Proteins: Structure and Molecular Properties*, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)).

[0120] Covalent derivatives specifically include fusion molecules in which polypeptides are covalently bonded to non-proteinaceous polymers. Non-proteinaceous polymers may include hydrophilic synthetic polymers, i.e., polymers not otherwise found in nature. However, polymers which exist in nature and are produced by recombinant or in vitro methods are useful, as are polymers which are isolated from nature. Hydrophilic polyvinyl polymers may include polyvinylalcohol and/or polyvinylpyrrolidone. Particularly useful are polyvinylalkylene ethers such as polyethylene glycol and polypropylene glycol. Polypeptides

may be linked to various non-proteinaceous polymers, such as polyethylene glycol, polypropylene glycol or polyoxyalkylenes, in the manner set forth in U.S. Pat. No. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337, the contents of each of which are herein incorporated by reference in their entirety.

[0121] "Features" when referring to polypeptides are defined as distinct amino acid sequence-based components of a molecule. Polypeptide features may include surface manifestations, local conformational shape, folds, loops, half-loops, domains, half-domains, sites, termini or any combination thereof.

[0122] As used herein when referring to polypeptides the term "surface manifestation" refers to an amino acid-based component of a polypeptide appearing on an outermost surface.

[0123] As used herein when referring to polypeptides the term "local conformational shape" means an amino acid-based structural manifestation of a polypeptide which is located within a definable space of the polypeptide.

[0124] As used herein when referring to polypeptides the term "fold" means the resultant conformation of an amino acid sequence upon energy minimization. A fold may occur at the secondary or tertiary level of the folding process. Examples of secondary level folds include beta sheets and alpha helices. Examples of tertiary folds include domains and regions formed due to aggregation or separation of energetic forces. Regions formed in this way include hydrophobic and hydrophilic pockets, and the like.

[0125] As used herein the term "turn" as it relates to polypeptide conformation means a bend which alters the direction of the backbone of a peptide or polypeptide and may involve one, two, three or more amino acid residues.

[0126] As used herein when referring to polypeptides the term "loop" refers to a structural feature of a peptide or polypeptide which reverses the direction of the backbone of a peptide or polypeptide and includes four or more amino acid residues. Oliva et al. have identified at least 5 classes of polypeptide loops (J. Mol Biol 266 (4): 814-830; 1997, the contents of which are herein incorporated by reference in their entirety).

[0127] As used herein when referring to polypeptides the term "half-loop" refers to a portion of an identified loop having at least half the number of amino acid residues as the loop from which it is derived. It is understood that loops may not always contain an even number of amino acid residues. Therefore, in those cases where a loop contains or is identified to include an odd number of amino acids, a half-loop of the odd-numbered loop will include the whole number portion or next whole number portion of the loop (number of amino acids of

the loop/2+/-0.5 amino acids). For example, a loop identified as a 7 amino acid loop could produce half-loops of 3 amino acids or 4 amino acids ($7/2=3.5\pm0.5$ being 3 or 4).

[0128] As used herein when referring to polypeptides the term "domain" refers to a motif of a polypeptide having one or more identifiable structural or functional characteristics or properties (e.g., binding capacity), serving as a site for protein-protein interactions.

[0129] As used herein when referring to polypeptides the term "half-domain" means portion of an identified domain having at least half the number of amino acid residues as the domain from which it is derived. It is understood that domains may not always contain an even number of amino acid residues. Therefore, in those cases where a domain contains or is identified to include an odd number of amino acids, a half-domain of the odd-numbered domain will include the whole number portion or next whole number portion of the domain (number of amino acids of the domain/2+/-0.5 amino acids). For example, a domain identified as a 7 amino acid domain could produce half-domains of 3 amino acids or 4 amino acids ($7/2=3.5\pm0.5$ being 3 or 4). It is also understood that sub-domains may be identified within domains or half-domains, these subdomains possessing less than all of the structural or functional properties identified in the domains or half domains from which they were derived. It is also understood that the amino acids of any of the domain types herein need not be contiguous along the backbone of the polypeptide (i.e., nonadjacent amino acids may fold structurally to produce a domain, half-domain or subdomain).

[0130] As used herein when referring to polypeptides, the term "site" is synonymous with "amino acid residue" and "amino acid side chain." A site represents a position on a polypeptide that may be modified, manipulated, altered, derivatized or varied within the polypeptide.

[0131] As used herein the terms "termini or terminus" when referring to polypeptides refers to an extremity of a peptide or polypeptide. Such extremity is not limited only to the first or final site of the peptide or polypeptide but may include additional amino acids in the terminal regions. Polypeptide based molecules of the present disclosure may be characterized as having both an N-terminus (terminated by an amino acid with a free amino group) and a C-terminus (terminated by an amino acid with a free carboxyl group). Proteins of the present disclosure are in some cases made up of multiple polypeptide chains brought together by disulfide bonds or by non-covalent forces (multimers, oligomers). These sorts of proteins will have multiple N- and C-termini. Alternatively, the termini of the polypeptides may be modified such that they begin or end, as the case may be, with a non-polypeptide based moiety such as an organic conjugate.

Antibody modification

[0132] Antibodies may be modified to obtain variants with one or more altered properties. Such properties may include or relate to antibody structure, function, affinity, specificity, protein folding, stability, manufacturing, expression, and/or immunogenicity (i.e., immune reactions in subjects being treated with such antibodies). In some embodiments, antibody fragments or variants may be used to modify another antibody or may be incorporated into a synthetic antibody.

[0133] Antibody modification may include amino acid sequence modifications. Such modifications may include, but are not limited to, amino acid deletions, additions, and/or substitutions. Modifications may be informed by amino acid sequence analysis. Such analysis may include alignment of amino acid sequences between different antibodies or antibody variants. Two or more antibodies may be compared to identify residues or regions suitable for modification. Compared antibodies may include those binding to the same epitope. Compared antibodies may bind to different epitopes (separate or overlapping) of the same protein or target (e.g., to identify residues or regions conferring specificity to specific epitopes). Comparisons may include light and/or heavy chain sequence variation analysis, CDR sequence variation analysis, germline sequence analysis, and/or framework sequence analysis. Information obtained from such analysis may be used to identify amino acid residues, segments of amino acids, amino acid side chains, CDR lengths, and/or other features or properties that are conserved or variable among antibodies binding to the same or different epitopes.

Functional modifications

[0134] In some embodiments, antibodies of the present disclosure be modified to optimize one or more functional properties (e.g., antibody affinity or activity). Non-limiting examples of antibody functional properties include epitope or antigen affinity, ability to mobilize or immobilize targets, and ability to activate or inhibit a target, process, or pathway. In some embodiments, functional properties include or relate to ability to modulate protein-protein interactions, protein aggregation, enzyme activity, receptor-ligand interactions, cellular signaling pathways, proteolytic cascades, and/or biological or physiological responses.

[0135] Antibody modifications may optimize antibodies by modulating epitope affinity. Such modifications may be carried out by affinity maturation. Affinity maturation technology is used to identify sequences encoding CDRs with highest affinity for target antigens. In some embodiments, antibody display technologies (e.g., phage or yeast) may be used. Such

methods may include mutating nucleotide sequences encoding parental antibodies being optimized. Nucleotide sequences may be mutated randomly as a whole or to vary expression at specific amino acid residues to create millions to billions of variants. Sites or residues may be selected for mutation based on sequences or amino acid frequencies observed in natural human antibody repertoires. Variants may be subjected to repeated rounds of affinity screening [e.g., using display library screening technologies, surface plasmon resonance technologies, fluorescence-associated cell sorting (FACS) analysis, enzyme-linked immunosorbent assay (ELISA), etc.] for target antigen binding. Repeated rounds of selection, mutation, and expression may be carried out to identify antibody fragment sequences with highest affinity for target antigens. Such sequences may be directly incorporated into antibody sequences for production. In some cases, the goal of affinity maturation is to increase antibody affinity by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 100 fold, at least 500-fold, at least 1,000-fold, or more than 1,000-fold as compared to the affinity of an original or starting antibody. In cases where affinity is less than desired, the process may be repeated.

[0136] In some embodiments, antibody affinity may be assessed with different antigen formats. In some embodiments, antibody affinity for different antigen formats may be tested in vitro (e.g., by ELISA). In vitro testing may be carried out using brain samples or fractions. Such samples or fractions may be obtained from subjects with AD (e.g., human AD patients). In some embodiments, brain samples or fractions may be obtained from non-human subjects. Such non-human subjects may include non-human animals used in AD disease model studies (e.g., mice, rats, and primates). In some embodiments, brain samples or fractions used for antibody affinity testing may be derived from TG4510/P301S mouse strains. Antibody affinity may be compared against control samples lacking the particular antigen for which affinity is being analyzed. In some embodiments, control samples may include brain samples or fraction from non-diseased human subjects. In some embodiments, brain samples or fractions from wild type and/or Tau knockout mouse strains may be used as control samples. In vitro affinity testing may be carried out (e.g., by ELISA) using recombinant or isolated protein antigens. In some embodiments, recombinant or isolated ePHF is used for antibody affinity testing. In some embodiments, antigens listed in **Table 4** may be used.

[0137] In some embodiments, antibody affinity analysis may be used to modulate antibody polyspecificity (e.g., to reduce or enhance antibody polyspecificity). Such modulation may include modulating relative affinity for two or more epitopes or antigens.

For example, antibodies may be optimized for higher affinity for one epitope or antigen over a second epitope or antigen.

[0138] Antibodies may be modified to optimize antibody functional properties. Such functional properties may be assessed or engineered based on analytical assay results relating to one or more antibody functional properties. Assays may be used to screen multiple antibodies to identify or rank antibodies based on functional criteria. Anti-tau antibodies may be modified to optimize tau aggregation inhibition. Such inhibition may be based on physical disruption of tau aggregation or may be based on the ability of anti-tau antibodies to deplete tau protein from assay samples. Optimization based on tau aggregation inhibition may be assessed using one or more assays of tau aggregation (e.g., by tau seeding assay).

Production modifications

[0139] In some embodiments, modifications may be made to optimize antibody production. Such modifications may include or relate to one or more of protein folding, stability, expression, and/or immunogenicity. Modifications may be carried out to address one or more antibody features negatively impacting production. Such features may include, but are not limited to, unpaired cysteines or irregular disulfides; glycosylation sites (e.g., N-linked NXS/T sites); acid cleavage sites, amino acid oxidation sites, conformity with mouse germline sequences; asparagine deamidation sites; aspartate isomerization sites; N-terminal pyroglutamate formation sites; and aggregation-prone amino acid sequence regions (e.g., within CDR sequences).

Methods of production

[0140] In some embodiments, antibodies of the present disclosure may be prepared using recombinant DNA technology (e.g., see United States Patent No. 4,816,567, which is hereby incorporated by reference in its entirety). Antibody-encoding DNA may be isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). In some embodiments, hybridoma cells may be used as a preferred source of DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells. Host cells may include, but are not limited to HEK293 cells, HEK293T cells, simian COS cells, Chinese hamster ovary (CHO) cells, and myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place

of the homologous murine sequences (U.S. Pat. No. 4,816,567) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide.

[0141] Methods for producing the anti-tau antibodies described herein include, for example, expressing the heavy chain and the light chains of the antibody in a cell line comprising the nucleic acid sequences or vector(s) (e.g., expression vector(s)) expressing the heavy chain and light chains. Host cells comprising these nucleic acid sequences (e.g., the nucleic acid sequences described herein, such as in **Table 1**) are encompassed herein.

[0142] Once DNA fragments encoding VH and VL segments are obtained, these DNA fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a VL- or VH-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region (e.g., a constant region listed in **Table 5**) or a flexible linker. The term "operatively linked", as used in this context, is intended to mean that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

[0143] The isolated DNA encoding the VH region can be converted to a full-length heavy chain gene by operatively linking the VH-encoding DNA to another DNA molecule encoding heavy chain constant regions (hinge, CH1, CH2 and/or CH3), e.g., a heavy chain constant region described in **Table 5**. The sequences of human heavy chain constant region genes are known in the art (see e.g., Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, for example, an IgG1 region, as discussed *supra*. For a Fab fragment heavy chain gene, the VH-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

[0144] The isolated DNA encoding the VL region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the VL-encoding DNA to another DNA molecule encoding the light chain constant region, CL, e.g., a light chain constant region described in **Table 5**. The sequences of human light chain constant region genes are known in the art (see e.g., Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH

Publication No. 91-3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a kappa or lambda constant region, as discussed *supra*.

[0145] To express the antibodies described herein, nucleic acids encoding partial or full-length light and heavy chains, or a combination of nucleic acids encoding partial or full-length light and heavy chains, can be obtained by standard molecular biology techniques (*e.g.*, PCR amplification or cDNA cloning using a hybridoma that expresses the antibody of interest) and the DNAs can be inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. In this context, the term "operatively linked" is intended to mean that an antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vector or both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector(s) by standard methods (*e.g.*, ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). The light and heavy chain variable regions of the antibodies described herein can be used to create full-length antibody genes of any antibody isotype by inserting them into expression vectors already encoding heavy chain constant and light chain constant regions of the desired isotype such that the V_H segment is operatively linked to the C_H segment(s) within the vector and the V_L segment is operatively linked to the C_L segment within the vector.

[0146] Additionally, the recombinant expression vector can encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene can be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (*i.e.*, a signal peptide from a non-immunoglobulin protein).

[0147] For expression of the light and heavy chains, the expression vector (*e.g.*, when nucleic acids encoding the light and heavy chains are present in one vector), or combination of expression vectors (*e.g.*, when the nucleic acid encoding the light chain is present in one vector, and the nucleic acid encoding the heavy chain is present in a separate vector), is transfected into a host cell by standard techniques. The various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the

introduction of exogenous DNA into a prokaryotic (bacterial host cell) or eukaryotic host cell, *e.g.*, electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like.

[0148] Exemplary mammalian cells for expressing the recombinant antibodies described herein include Chinese Hamster Ovary (CHO cells) (including dhfr- CHO cells, described in Urlaub and Chasin, (1980) *Proc. Natl. Acad. Sci. USA* 77:4216-4220, used with a DHFR selectable marker, *e.g.*, as described in R. J. Kaufman and P. A. Sharp (1982) *Mol. Biol.* 159:601-621), NSO myeloma cells, COS cells and SP2 cells. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Antibody humanization

[0149] In some embodiments, anti-tau antibodies of the present disclosure may be prepared as humanized antibodies. "Humanized" antibodies are chimeric antibodies that contain minimal sequences (*e.g.*, variable domains or CDRs) derived from non-human immunoglobulins (*e.g.*, murine immunoglobulins). Humanized antibodies may be prepared from human (recipient) immunoglobulins in which residues from the hypervariable regions are replaced by hypervariable region residues from one or more non-human "donor" antibodies (*e.g.*, mouse, rat, rabbit, or nonhuman primate). Donor antibodies may be selected based on desired specificity, affinity, and/or capacity. Humanized antibodies may include one or more back-mutation that includes the reversion of one or more amino acids back to amino acids found in a donor antibody. Conversely, residues from donor antibodies included in humanized antibodies may be mutated to match residues present in human recipient antibodies. Back-mutations may be introduced to reduce human immune response to the humanized antibodies. In some embodiments, back-mutations are introduced to avoid issues with antibody manufacturing (*e.g.*, protein aggregation or post-translational modification).

[0150] For construction of expression plasmids encoding fully humanized antibodies with human constant regions, DNA sequences encoding antibody variable regions may be inserted into expression vectors (*e.g.*, mammalian expression vectors) between an upstream promoter/enhancer and immunoglobulin signal sequence and a downstream immunoglobulin constant region gene. DNA samples may then be transfected into mammalian cells for

antibody production. Constant domains from any class of human antibody may be used. There are five major classes of intact human antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2a, IgG2b, IgG2c, IgG3, IgG4, IgA, and IgA2.

[0151] Cell lines with stable transfection of DNA encoding humanized antibodies may be prepared and used to establish stable cell lines. Cell lines producing humanized antibodies may be expanded for expression of humanized antibodies that may be harvested and purified from cell culture media.

[0152] In some embodiments, humanized antibodies of the present disclosure may have cross-reactivity with non-human species. Species cross-reactivity may allow antibodies to be used in different animals for various purposes. For example, cross-reactive antibodies may be used in pre-clinical animal studies to provide information about antibody efficacy and/or toxicity. Non-human species may include, but are not limited to, mouse, rat, rabbit, dog, pig, goat, sheep, and nonhuman primates (e.g., *Cynomolgus* monkeys).

Antibody conjugates

[0153] In some embodiments, antibodies of the present disclosure may be or be prepared as antibody conjugates. As used herein, the term “conjugate” refers to any agent, cargo, or chemical moiety that is attached to a recipient entity or the process of attaching such an agent, cargo, or chemical moiety. As used herein, the term “antibody conjugate” refers to any antibody with an attached agent, cargo, or chemical moiety. Conjugates utilized to prepare antibody conjugates may include therapeutic agents. Such therapeutic agents may include drugs. Antibody conjugates that include a conjugated drug are referred to herein as “antibody drug conjugates.” Antibody drug conjugates may be used to direct conjugated drugs to specific targets based on the affinity of associated antibodies for proteins or epitopes associated with such targets. Such antibody drug conjugates may be used to localize biological activity associated with such conjugated drugs to targeted cells, tissues, organs, or other targeted entities. In some embodiments, conjugates utilized to prepare antibody conjugates include detectable labels. Antibodies may be conjugated with detectable labels for purposes of detection. Such detectable labels may include, but are not limited to, radioisotopes, fluorophores, chromophores, chemiluminescent compounds, enzymes, enzyme co-factors, dyes, metal ions, ligands, biotin, avidin, streptavidin, haptens, quantum dots, or any other detectable labels known in the art or described herein.

[0154] Conjugates may be attached to antibodies directly or via a linker. Direct attachment may be by covalent bonding or by non-covalent association (e.g., ionic bonds, hydrostatic bonds, hydrophobic bonds, hydrogen bonds, hybridization, etc.). Linkers used for conjugate attachment may include any chemical structure capable of connecting an antibody to a conjugate. In some embodiments, linkers include polymeric molecules (e.g., nucleic acids, polypeptides, polyethylene glycols, carbohydrates, lipids, or combinations thereof). Antibody conjugate linkers may be cleavable (e.g., through contact with an enzyme, change in pH, or change in temperature).

II. FORMULATION AND DELIVERY

Pharmaceutical Compositions

[0155] Compounds disclosed herein may be prepared as pharmaceutical compositions. As used herein the term “pharmaceutical composition” refers to compositions including at least one active ingredient and, most often, a pharmaceutically acceptable excipient.

[0156] Relative amounts of the active ingredient (e.g. an antibody), a pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of the subject being treated and further depending upon the route by which the composition is to be administered. For example, the composition may include between 0.1% and 99% (w/w) of the active ingredient. By way of example, the composition may include between 0.1% and 100%, e.g., between .5 and 50%, between 1-30%, between 5-80%, at least 80% (w/w) active ingredient.

[0157] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to any other animal, e.g., to non-human animals, e.g. non-human mammals. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with merely ordinary, if any, experimentation. Subjects to which administration of the pharmaceutical compositions is contemplated include, but are not limited to, humans and/or other primates; mammals, including commercially relevant mammals such as cattle, pigs, horses, sheep, cats, dogs, mice, rats, birds, including commercially relevant birds such as poultry, chickens, ducks, geese, and/or turkeys.

[0158] In some embodiments, compositions are administered to humans, human patients, or subjects.

Formulations

[0159] Compounds of the present disclosure can be formulated using one or more excipients to: (1) increase stability; (2) increase cell permeability; (3) permit the sustained or delayed release (e.g., from a sustained release formulation); and/or (4) alter the biodistribution (e.g., target an antibody to specific tissues or cell types). In addition to traditional excipients such as any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, formulations of the present disclosure can include, without limitation, liposomes, lipid nanoparticles, polymers, lipoplexes, core-shell nanoparticles, peptides, proteins, transfected cells (e.g., for transplantation into a subject) and combinations thereof.

[0160] Pharmaceutical compositions described herein may be prepared by methods known or hereafter developed in the art of pharmacology. Such preparatory methods may include the step of associating the active ingredient with an excipient and/or one or more other accessory ingredients.

[0161] A pharmaceutical composition in accordance with the present disclosure may be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a “unit dose” refers to a discrete amount of the pharmaceutical composition including a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0162] Relative amounts of active ingredient (e.g. antibody), pharmaceutically acceptable excipients, and/or any additional ingredients in pharmaceutical compositions in accordance with the present disclosure may vary, depending upon the identity, size, and/or condition of subjects being treated and further depending upon route of administration. For example, compositions may include between 0.1% and 99% (w/w) of active ingredient. By way of example, compositions may include between 0.1% and 100%, e.g., between 0.5 and 50%, between 1-30%, between 5-80%, or at least 80% (w/w) active ingredient.

[0163] According to the present disclosure, compounds may be formulated for CNS delivery. Agents that cross the brain blood barrier may be used. For example, some cell

penetrating peptides that can target molecules to the brain blood barrier endothelium may be used for formulation (e.g., Mathupala, *Expert Opin Ther Pat.*, 2009, 19, 137-140; the content of which is incorporated herein by reference in its entirety).

Excipients and Diluents

[0164] In some embodiments, a pharmaceutically acceptable excipient may be at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100% pure. In some embodiments, an excipient is approved for use for humans and for veterinary use. In some embodiments, an excipient may be approved by the United States Food and Drug Administration. In some embodiments, an excipient may be of pharmaceutical grade. In some embodiments, an excipient may meet the standards of the United States Pharmacopoeia (USP), the European Pharmacopoeia (EP), the British Pharmacopoeia, and/or the International Pharmacopoeia.

[0165] Excipients, as used herein, include, but are not limited to, any and all solvents, dispersion media, diluents, or other liquid vehicles, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, and the like, as suited to the particular dosage form desired. Various excipients for formulating pharmaceutical compositions and techniques for preparation are known in the art (see Remington: The Science and Practice of Pharmacy, 21st Edition, A. R. Gennaro, Lippincott, Williams & Wilkins, Baltimore, MD, 2006; incorporated herein by reference in its entirety). The use of conventional excipient media may be contemplated within the scope of the present disclosure, except insofar as any conventional excipient media may be incompatible with certain substances or their derivatives, such as by producing any undesirable biological effects or otherwise interacting in a deleterious manner with any other component(s) of pharmaceutical compositions of the present disclosure.

[0166] Exemplary diluents include, but are not limited to, calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, *etc.*, and/or combinations thereof.

Inactive Ingredients

[0167] In some embodiments, formulations of the present disclosure may include at least one inactive ingredient. As used herein, the term “inactive ingredient” refers to an agent that does not contribute to the activity of a pharmaceutical composition. In some embodiments,

all, none or some of the inactive ingredients which may be used in formulations of the present disclosure may be approved by the US Food and Drug Administration (FDA).

[0168] Formulations disclosed herein may include cations or anions. Formulations may include Zn^{2+} , Ca^{2+} , Cu^{2+} , Mn^{2+} , Mg^{+} , or combinations thereof. As a non-limiting example, formulations may include polymers and complexes with metal cations (*See e.g.*, U.S. Pat. Nos. 6265389 and 6555525, each of which is herein incorporated by reference in its entirety).

III. ADMINISTRATION AND DOSING

Administration

[0169] Compounds and compositions of the present disclosure may be administered by any delivery route which results in a therapeutically effective outcome. These include, but are not limited to, enteral (into the intestine), gastroenteral, epidural (into the dura mater), oral (by way of the mouth), transdermal, intracerebral (into the cerebrum), intracerebroventricular (into the cerebral ventricles), epicutaneous (application onto the skin), intradermal (into the skin itself), subcutaneous (under the skin), nasal administration (through the nose), intravenous (into a vein), intravenous bolus, intravenous drip, intra-arterial (into an artery), intramuscular (into a muscle), intracardiac (into the heart), intraosseous infusion (into the bone marrow), intrathecal (into the spinal canal), intraparenchymal (into the substance of a tissue, e.g., brain tissue), intraperitoneal (infusion or injection into the peritoneum), intravesical infusion, intravitreal (through the eye), intracavernous injection (into a pathologic cavity) intracavitary (into the base of the penis), intravaginal administration, intrauterine, extra-amniotic administration, transdermal (diffusion through the intact skin for systemic distribution), transmucosal (diffusion through a mucous membrane), transvaginal, insufflation (snorting), sublingual, sublabial, enema, eye drops (onto the conjunctiva), ear drops, auricular (in or by way of the ear), buccal (directed toward the cheek), conjunctival, cutaneous, dental (to a tooth or teeth), electro-osmosis, endocervical, endosinusial, endotracheal, extracorporeal, hemodialysis, infiltration, interstitial, intra-abdominal, intra-amniotic, intra-articular, intrabiliary, intrabronchial, intrabursal, intracartilaginous (within a cartilage), intracaudal (within the cauda equine), intracisternal (within the cisterna magna cerebellomedularis), intracorneal (within the cornea), dental intracoronaral, intracoronary (within the coronary arteries), intracorporus cavernosum (within the dilatable spaces of the corporus cavernosa of the penis), intradiscal (within a disc), intraductal (within a duct of a gland), intraduodenal (within the duodenum), intradural (within or beneath the dura), intraepidermal (to the epidermis), intraesophageal (to the esophagus), intragastric (within the

stomach), intragingival (within the gingivae), intraileal (within the distal portion of the small intestine), intralesional (within or introduced directly to a localized lesion), intraluminal (within a lumen of a tube), intralymphatic (within the lymph), intramedullary (within the marrow cavity of a bone), intrameningeal (within the meninges), intramyocardial (within the myocardium), intraocular (within the eye), intraovarian (within the ovary), intrapericardial (within the pericardium), intrapleural (within the pleura), intraprostatic (within the prostate gland), intrapulmonary (within the lungs or its bronchi), intrasinal (within the nasal or periorbital sinuses), intraspinal (within the vertebral column), intrasynovial (within the synovial cavity of a joint), intratendinous (within a tendon), intratesticular (within the testicle), intrathecal (within the cerebrospinal fluid at any level of the cerebrospinal axis), intrathoracic (within the thorax), intratubular (within the tubules of an organ), intratumor (within a tumor), intratympanic (within the aural media), intravascular (within a vessel or vessels), intraventricular (within a ventricle), iontophoresis (by means of electric current where ions of soluble salts migrate into the tissues of the body), irrigation (to bathe or flush open wounds or body cavities), laryngeal (directly upon the larynx), nasogastric (through the nose and into the stomach), occlusive dressing technique (topical route administration which is then covered by a dressing which occludes the area), ophthalmic (to the external eye), oropharyngeal (directly to the mouth and pharynx), parenteral, percutaneous, periarticular, peridural, perineural, periodontal, rectal, respiratory (within the respiratory tract by inhaling orally or nasally for local or systemic effect), retrobulbar (behind the pons or behind the eyeball), soft tissue, subarachnoid, subconjunctival, submucosal, topical, transplacental (through or across the placenta), transtracheal (through the wall of the trachea), transtympanic (across or through the tympanic cavity), ureteral (to the ureter), urethral (to the urethra), vaginal, caudal block, diagnostic, nerve block, biliary perfusion, cardiac perfusion, photophoresis, and spinal.

[0170] In some embodiments, compositions may be administered in a way which allows them to cross the blood-brain barrier, vascular barrier, or other epithelial barrier. Compounds and compositions of the present disclosure may be administered in any suitable form, including, but not limited to, as a liquid solution, as a suspension, or as a solid form suitable for liquid solution or suspension in a liquid solution.

[0171] In some embodiments, delivery to a subject may be via a single route administration. In some embodiments, delivery to a subject may be via multi-site route of administration. Administration may include a bolus infusion. Administration may include sustained delivery over a period of minutes, hours, or days. Administration by infusion may

include an infusion rate that may be changed depending on the subject, distribution, formulation, or other delivery parameter. Administration may be by more than one route of administration. As non-limiting examples, combination administrations may include intrathecal and intracerebroventricular administration, or intravenous and intraparenchymal administration.

Intravenous administration

[0172] Compounds and compositions of the present disclosure may be administered to a subject by systemic administration. Systemic administration may include intravenous administration. Systemic administration may include intraarterial administration.

[0173] Compounds and compositions of the present disclosure may be administered to a subject by intravenous administration. Intravenous administration may be achieved by subcutaneous delivery. Intravenous administration may be achieved by a tail vein injection (e.g., in a mouse model). Intravenous administration may be achieved by retro-orbital injection.

Administration to the CNS

[0174] Compounds and compositions of the present disclosure may be administered to a subject by direct injection into the brain. As a non-limiting example, the brain delivery may be by intrahippocampal administration. Administration may be by intraparenchymal administration. In one embodiment, the intraparenchymal administration is to tissue of the central nervous system. Administration may be by intracranial delivery (See, e.g., US Pat. No. 8119611; the content of which is incorporated herein by reference in its entirety). Administration may be by injection into the CSF pathway. Non-limiting examples of delivery to the CSF pathway include intrathecal and intracerebroventricular administration. Administration to the brain may be by systemic delivery. As a non-limiting example, the systemic delivery may be by intravascular administration. As a non-limiting example, the systemic or intravascular administration may be intravenous. Administration may be by intraocular delivery route. A non-limiting example of intraocular administration includes an intravitreal injection.

Dose and Regimen

[0175] The present disclosure provides methods of administering compounds and compositions in accordance with the disclosure to a subject in need thereof. Administration may be in any amount and by any route of administration effective for preventing, treating, managing, or diagnosing diseases, disorders, and/or conditions. The exact amount required

may vary from subject to subject, depending on species, age, general condition of the subject, severity of disease, particular composition, mode of administration, mode of activity, and the like. Subjects may be, but are not limited to, humans, mammals, or animals. Compositions may be formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of compositions of the present disclosure may be decided by an attending physician within the scope of sound medical judgment. Specific therapeutically effective, prophylactically effective, or appropriate diagnostic dose levels for any particular individual may vary depending upon a variety of factors including the disorder being treated and severity of the disorder; the activity of specific payloads employed; specific compositions employed; age, body weight, general health, sex, and diet of patients; time of administration, route of administration, and rate of excretion of compounds and compositions employed; duration of treatment; drugs used in combination or coincidental with compounds and compositions employed; and like factors well known in the medical arts.

[0176] In certain embodiments, compounds and compositions in accordance with the present disclosure may be administered at dosage levels sufficient to deliver from about 0.0001 mg/kg to about 100 mg/kg, from about 0.001 mg/kg to about 0.05 mg/kg, from about 0.005 mg/kg to about 0.05 mg/kg, from about 0.001 mg/kg to about 0.005 mg/kg, from about 0.05 mg/kg to about 0.5 mg/kg, from about 0.01 mg/kg to about 50 mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic, diagnostic, or prophylactic, effect.

[0177] In certain embodiments, the desired dosage may be delivered using multiple administrations (*e.g.*, two, three, four, or more than four administrations). When multiple administrations are employed, split dosing regimens such as those described herein may be used. As used herein, a “split dose” is the division of “single unit dose” or total daily dose into two or more doses, *e.g.*, two or more administrations of the “single unit dose”. As used herein, a “single unit dose” is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, *i.e.*, single administration event.

[0178] Compounds and compositions of the present disclosure may be administered as a “pulse dose” or as a “continuous flow.” As used herein, a “pulse dose” is a series of single unit doses of any therapeutic agent administered with a set frequency over a period of time. As used herein, a “continuous flow” is a dose of therapeutic agent administered continuously

for a period of time in a single route/single point of contact, i.e., continuous administration event. A total daily dose, an amount given or prescribed in a 24-hour period, may be administered by any of these methods, or as a combination of these methods, or by any other methods suitable for pharmaceutical administration.

Combinations

[0179] Compounds and compositions of the present disclosure may be used in combination with one or more other therapeutic, prophylactic, research or diagnostic agents. By “in combination with,” it is not intended to imply that the agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope of the present disclosure. Compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. In some embodiments, the present disclosure encompasses the delivery of pharmaceutical, prophylactic, research, or diagnostic compositions in combination with agents that may improve their bioavailability, reduce and/or modify their metabolism, inhibit their excretion, and/or modify their distribution within the body.

IV. METHODS AND USES OF THE COMPOSITIONS

[0180] In some embodiments, the present disclosure provides methods related to using and evaluating compounds and compositions for therapeutic and diagnostic applications.

Therapeutic applications

[0181] In some embodiments, methods of the present disclosure include methods of treating therapeutic indications using compounds and/or compositions disclosed herein. As used herein, the term “therapeutic indication” refers to any symptom, condition, disorder, or disease that may be alleviated, stabilized, improved, cured, or otherwise addressed by some form of treatment or other therapeutic intervention. In some embodiments, methods of the present disclosure include treating therapeutic indications by administering antibodies disclosed herein. In some embodiments, the therapeutic indication is a neurological, e.g., neurodegenerative disorder, a disease associated with tau expression or activity, and/or a tau-related disease (e.g., a tauopathy).

[0182] As used herein the terms “treat,” “treatment,” and the like, refer to relief from or alleviation of pathological processes. In the context of the present disclosure insofar as it relates to any of the other conditions recited herein below, the terms “treat,” “treatment,” and

the like mean to relieve or alleviate at least one symptom associated with such condition, or to slow or reverse the progression or anticipated progression of such condition.

[0183] By “lower” or “reduce” in the context of a disease marker or symptom is meant a significant decrease in such a level, often statistically significant. The decrease may be, for example, at least 10%, at least 20%, at least 30%, at least 40% or more, and is preferably down to a level accepted as within the range of normal for an individual without such a disorder.

[0184] By “increase” or “raise” in the context of a disease marker or symptom is meant a significant rise in such level, often statistically significant. The increase may be, for example, at least 10%, at least 20%, at least 30%, at least 40% or more, and is preferably up to a level accepted as within the range of normal for an individual without such disorder.

[0185] Efficacy of treatment or amelioration of disease can be assessed, for example by measuring disease progression, disease remission, symptom severity, reduction in pain, quality of life, dose of a medication required to sustain a treatment effect, level of a disease marker or any other measurable parameter appropriate for a given disease being treated or targeted for prevention. It is well within the ability of one skilled in the art to monitor efficacy of treatment or prevention by measuring any one of such parameters, or any combination of parameters. In connection with the administration of a compound or composition described herein, “effective against” a disease or disorder indicates that administration in a clinically appropriate manner results in a beneficial effect for at least a fraction of patients, such as an improvement of symptoms, a cure, a reduction in disease load, reduction in protein aggregation, reduction in neurofibrillary tangles, reduction in neurodegeneration, extension of life, improvement in quality of life, or other effect generally recognized as positive by medical doctors familiar with treating the particular type of disease or disorder.

[0186] A treatment or preventive effect is evident when there is a significant improvement, often statistically significant, in one or more parameters of disease status, or by a failure to worsen or to develop symptoms where they would otherwise be anticipated. As an example, a favorable change of at least 10% in a measurable parameter of disease, and preferably at least 20%, 30%, 40%, 50% or more may be indicative of effective treatment. Efficacy for a given compound or composition may also be judged using an experimental animal model for the given disease as known in the art. When using an experimental animal model, efficacy of treatment is evidenced when a statistically significant modulation in a marker or symptom is observed.

[0187] Compounds of the present disclosure and additional therapeutic agents and/or therapies can be administered in combination. Such combinations may be in the same composition, or the additional therapeutic agents can be administered as part of a separate composition or by another method described herein. In some embodiments, the additional therapeutic agent and/or therapy is a therapeutic agent and/or therapy that is suitable for treating or preventing a neurological, e.g., neurodegenerative disorder, a disease associated with tau expression or activity, and/or a tau-related disease (e.g., a tauopathy). In some embodiments, the additional therapeutic agent and/or therapy is a cholinesterase inhibitor (e.g., donepezil, rivastigmine, and/or galantamine), an N-methyl D-aspartate (NMDA) antagonist (e.g., memantine), an antipsychotic drug, an anti-anxiety drug, an anticonvulsant, a dopamine agonist (e.g., pramipexole, ropinirole, rotigotine, and/or apomorphine), an MAO B inhibitor (e.g., selegiline, rasagiline, and/or safinamide), catechol O-methyltransferase (COMT) inhibitors (entacapone, opicapone, and/or tolcapone), anticholinergics (e.g., benztropine and/or trihexyphenidyl), amantadine, carbidopa-levodopa, deep brain stimulation (DBS), or a combination thereof.

[0188] In some embodiments, therapeutic indications that may be addressed by methods of the present disclosure include neurological indications. As used herein, a “neurological indication” refers to any therapeutic indication relating to the central nervous system (CNS). Methods of treating neurological indications according to the present disclosure may include administering compounds (e.g., antibodies) and/or compositions described herein. Neurological indications may include neurological diseases and/or disorders involving irregular expression or aggregation of tau. Such indications may include, but are not limited to neurodegenerative disease, Alzheimer’s disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down’s syndrome, Pick’s disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), a prion disease, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, stroke, and progressive subcortical gliosis.

[0189] In some embodiments, methods of treating neurological diseases and/or disorders in a subject in need thereof may include one or more of the steps of: (1) deriving, generating, and/or selecting an anti-tau antibody or fragment or composition thereof; and (2) administering the anti-tau antibody or fragment or composition thereof to the subject. Administration to the subject may slow, stop, or reverse disease progression. As a non-

limiting example, disease progression may be measured by cognitive tests such as, but not limited to, the Mini-Mental State Exam (MMSE) or other similar diagnostic tool(s), known to those skilled in the art. As another non-limiting example, disease progression may be measured by change in the pathological features of the brain, CSF or other tissues of the subject, such as, but not limited to a decrease in levels of tau (either soluble or insoluble). In some embodiments, levels of insoluble hyperphosphorylated tau are decreased. In some embodiments, levels of soluble tau are decreased. In some embodiments, both soluble and insoluble tau are decreased. In some embodiments, levels of insoluble hyperphosphorylated tau are increased. In some embodiments, levels of soluble tau are increased. In some embodiments, both insoluble and soluble tau levels are increased. In some embodiments, neurofibrillary tangles are decreased in size, number, density, or combination thereof. In another embodiment, neurofibrillary tangles are increased in size, number, density or combination thereof.

Neurodegeneration

[0190] Neurodegenerative disease refers to a group of conditions characterized by progressive loss of neuronal structure and function, ultimately leading to neuronal cell death. Neurons are the building blocks of the nervous system(s) and are generally not able to reproduce and/or be replaced, and therefore neuron damage and/or death is especially devastating. Other, non-degenerating diseases that lead to neuronal cell loss, such as stroke, have similarly debilitating outcomes. Targeting molecules that contribute to deteriorating cell structure or function may prove beneficial generally for treatment of neurological indications, including neurodegenerative disease and stroke.

[0191] Certain molecules are believed to have inhibitory effects on neurite outgrowth, contributing to the limited ability of the central nervous system to repair damage. Such molecules include, but are not limited to, myelin associated proteins, such as, but not limited to, RGM (Repulsive guidance molecule), Nogo (Neurite outgrowth inhibitor), Nogo receptor, MAG (myelin associated glycoprotein), and MAI (myelin associated inhibitor). In some embodiments, anti-tau antibodies of the present disclosure may be utilized to target the aforementioned antigens (e.g., neurite outgrowth inhibitors).

[0192] Many neurodegenerative diseases are associated with aggregation of misfolded proteins, including, but not limited to, alpha synuclein, tau (as in tauopathies), amyloid β , prion proteins, TDP-43, and huntingtin (see, e.g. De Genst et al., 2014, *Biochim Biophys Acta*;1844(11):1907-1919, and Yu et al., 2013, *Neurotherapeutics*.; 10(3): 459–472,

references therein, all of which are herein incorporated by reference in their entirety). The aggregation results from disease-specific conversion of soluble proteins to an insoluble, highly ordered fibrillary deposit. This conversion is thought to prevent the proper disposal or degradation of misfolded proteins, thereby leading to further aggregation. Conditions associated with alpha synuclein misfolding and aggregation are referred to as “synucleinopathies.” In some embodiments, anti-tau antibodies of the present disclosure may be utilized to target misfolded or aggregated proteins.

Alzheimer's disease

[0193] Alzheimer Disease (AD) is a debilitating neurodegenerative disease currently afflicting more than 35 million people worldwide, with that number expected to double in coming decades. Symptomatic treatments have been available for many years but these treatments do not address the underlying pathophysiology. Recent clinical trials using these and other treatments have largely failed and, to date, no known cure has been identified.

[0194] The AD brain is characterized by the presence of two forms of pathological aggregates, the extracellular plaques composed of β -amyloid ($A\beta$) and the intracellular neurofibrillary tangles (NFT) comprised of hyperphosphorylated microtubule associated protein tau. Based on early genetic findings, β -amyloid alterations were thought to initiate disease, with changes in tau considered downstream. Thus, most clinical trials have been $A\beta$ -centric. Although no mutations of the tau gene have been linked to AD, such alterations have been shown to result in a family of dementias known as tauopathies, demonstrating that changes in tau can contribute to neurodegenerative processes. Tau is normally a very soluble protein known to associate with microtubules based on the extent of its phosphorylation. Hyperphosphorylation of tau depresses its binding to microtubules and microtubule assembly activity. In tauopathies, the tau becomes hyperphosphorylated, misfolds and aggregates as NFT of paired helical filaments (PHF), twisted ribbons or straight filaments. In AD, NFT pathology, rather than plaque pathology, correlates more closely with neuropathological markers such as neuronal loss, synaptic deficits, severity of disease and cognitive decline. NFT pathology marches through the brain in a stereotyped manner and animal studies suggest a trans-cellular propagation mechanism along neuronal connections.

[0195] Several approaches have been proposed for therapeutically interfering with progression of tau pathology and preventing the subsequent molecular and cellular consequences. Given that NFT are composed of a hyperphosphorylated, misfolded and aggregated form of tau, interference at each of these stages has yielded the most avidly

pursued set of targets. Introducing agents that limit phosphorylation, block misfolding or prevent aggregation have all generated promising results. Passive and active immunization with late stage anti-phospho-tau antibodies in mouse models have led to dramatic decreases in tau aggregation and improvements in cognitive parameters. It has also been suggested that introduction of anti-tau antibodies can prevent the trans-neuronal spread of tau pathology.

[0196] In some embodiments, anti-tau antibodies of the present disclosure may be used according to methods presented herein to treat subjects suffering from AD and other tauopathies. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing AD or other tauopathies.

Frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17)

[0197] Although Alzheimer's disease is, in part, characterized by the presence of tau pathology, no known mutations in the tau gene have been causally linked to the disease. Mutations in the tau gene have been shown to lead to an autosomal dominantly inherited tauopathy known as frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) and demonstrate that alterations in tau can lead to neurodegenerative changes in the brain. Mutations in the tau gene that lead to FTDP-17 are thought to influence splicing patterns, thereby leading to an elevated proportion of tau with four microtubule binding domains (rather than three). These molecules are considered to be more amyloidogenic, meaning they are more likely to become hyperphosphorylated and more likely to aggregate into NFT (Hutton, M. et al., 1998, Nature 393(6686):702-5, the contents of which are herein incorporated by reference in their entirety). Although physically and behaviorally, FTDP-17 patients can appear quite similar to Alzheimer's disease patients, at autopsy FTDP-17 brains lack the prominent A β plaque pathology of an AD brain (Gotz, J. et al., 2012, British Journal of Pharmacology 165(5):1246-59, the contents of which are herein incorporated by reference in their entirety). Therapeutically targeting the aggregates of tau protein may ameliorate and prevent degenerative changes in the brain and potentially lead to improved cognitive ability.

[0198] As of today, there is no treatment to prevent, slow the progression, or cure FTDP-17. Medication may be prescribed to reduce aggressive, agitated or dangerous behavior. There remains a need for therapy affecting the underlying pathophysiology, such as antibody therapies targeting tau protein.

[0199] In some embodiments, anti-tau antibodies of the present disclosure may be used to treat subjects suffering from FTDP-17. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing FTDP-17.

Chronic traumatic encephalopathy

[0200] Unlike the genetically linked tauopathies, chronic traumatic encephalopathy is a degenerative tauopathy linked to repeated head injuries. The disease was first described in boxers whom behaved “punch drunk” and has since been identified primarily in athletes that play American football, ice hockey, wrestling and other contact sports. The brains of those suffering from CTE are characterized by distinctive patterns of brain atrophy accompanied by accumulation of hyperphosphorylated species of aggregated tau in NFT. In CTE, pathological changes in tau are accompanied by a number of other pathobiological processes, such as inflammation (Daneshvar, D.H. et al., 2015 Mol Cell Neurosci 66(Pt B): 81-90, the contents of which are herein incorporated by reference in their entirety). Targeting the tau aggregates may provide reprieve from the progression of the disease and may allow cognitive improvement.

[0201] As of today, there is no medical therapy to treat or cure CTE. The condition is only diagnosed after death, due to lack of in vivo techniques to identify CTE specific biomarkers. There remains a need for therapy affecting the underlying pathophysiology, such as antibody therapies targeting tau protein.

[0202] In some embodiments, anti-tau antibodies of the present disclosure may be used to treat subjects suffering from CTE. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing CTE.

Prion diseases

[0203] Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a group of rare progressive conditions affecting the nervous system. The related conditions are rare and are typically caused by mutations in the PRNP gene which enables production of the prion protein. Gene mutations lead to an abnormally structured prion protein. Alternatively, the abnormal prion may be acquired by exposure from an outside source, e.g. by consumption of beef products containing the abnormal prion protein. Abnormal prions are misfolded, causing the brain tissue to degenerate rapidly. Prion diseases include, but are not limited to, Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal insomnia (FFI), variably protease-sensitive prionopathy (VPSPr), and kuru. Prion diseases are rare. Approximately 350 cases of prion diseases are diagnosed in the US annually.

[0204] CJD is a degenerative brain disorder characterized by problems with muscular coordination, personality changes including mental impairment, impaired vision, involuntary

muscle jerks, weakness and eventually coma. The most common categories of CJD are sporadic, hereditary due to a genetic mutation, and acquired. Sporadic CJD is the most common form affecting people with no known risk factors for the disease. The acquired form of CJD is transmitted by exposure of the brain and nervous system tissue to the prion. As an example, variant CJD (vCDJ) is linked to a bovine spongiform encephalopathy (BSE), also known as a ‘mad cow’ disease. CJD is fatal and patients typically die within one year of diagnosis.

[0205] Prion diseases are associated with an infectious agent consisting of an alternative conformational isoform of the prion protein, PrP^{Sc}. PrP^{Sc} replication is considered to occur through an induction of the infectious prion in the normal prion protein (PrP^C). The replication occurs without a nucleic acid.

[0206] As of today, there is no therapy to manage or cure CJD, or other prion diseases. Typically, treatment is aimed at alleviating symptoms and increasing comfort of the patient, e.g. with pain relievers. There remains a need for therapy affecting the underlying pathophysiology.

[0207] In some embodiments, anti-tau antibodies of the present disclosure may be used to treat subjects suffering from a prion disease. In some cases, methods of the present disclosure may be used to treat subjects suspected of developing a prion disease.

Diagnostic applications

[0208] In some embodiments, compounds (e.g., antibodies) and compositions of the present disclosure may be used as diagnostics. Anti-tau antibodies may be used to identify, label, or stain cells, tissues, organs, etc. expressing tau proteins. Anti-tau antibodies may be used to identify tau proteins present in tissue sections (e.g., histological tissue sections), including tissue known or suspected of having tau protein aggregates. Such antibodies may in some cases be used to identify subjects with neurological diseases and/or disorders. Tissue sections may be from CNS tissue.

[0209] In some embodiments, diagnostic methods of the present disclosure may include the analysis of one or more cells or tissues using immunohistochemical techniques. Such methods may include the use of one or more of any of the anti-tau antibodies described herein. Immunohistochemical methods may include staining tissue sections to determine the presence and/or level of one or more tau proteins or other markers. Tissue sections may be derived from subject CNS tissue (e.g., patient CNS, animal CNS, and CNS from animal models of disease). Tissue sections may come from formalin-fixed or unfixed fresh frozen

tissues. In some cases, tissue sections come from formalin fixed paraffin-embedded (FFPE) tissues. Anti-tau antibodies described herein may be used as primary antibodies. Primary antibodies are used to contact tissue sections directly and bind to target epitopes. Primary antibodies may be directly conjugated with a detectable label or may be detected through the use of a detection agent such as a secondary antibody. In some embodiments, primary antibodies or detection agents include an enzyme that can be used to react with a substrate to generate a visible product (e.g., precipitate). Such enzymes may include, but are not limited to horse radish peroxidase, alkaline phosphatase, beta-galactosidase, and catalase.

[0210] Anti-tau antibodies described herein may be used according to immunohistochemical methods of the present disclosure to detect tau proteins in tissues or cells. In some cases, these antibodies are used to detect and/or determine the level of tau proteins in tissues. Levels of anti-tau antibodies used in immunohistochemical staining techniques may be varied to increase visible staining or to decrease background levels of staining. In some embodiments, antibody concentrations of from about 0.01 µg/ml to about 50 µg/ml are used. For example, antibody concentrations of from about 0.01 µg/ml to about 1 µg/ml, from about 0.05 µg/ml to about 5 µg/ml, from about 0.1 µg/ml to about 3 µg/ml, from about 1 µg/ml to about 10 µg/ml, from about 2 µg/ml to about 20 µg/ml, from about 3 µg/ml to about 25 µg/ml, from about 4 µg/ml to about 30 µg/ml, or from about 5 µg/ml to about 50 µg/ml may be used.

[0211] Levels and/or identities of tau proteins may be determined according to any methods known in the art for identifying proteins and/or quantitating protein levels. In some embodiments, such methods may include, but are not limited to mass spectrometry, array analysis (e.g., antibody array or protein array), Western blotting, flow cytometry, immunoprecipitation, surface plasmon resonance analysis, and ELISA. Tau proteins may in some cases be immunoprecipitated from samples prior to analysis. Such immunoprecipitation may be carried out using anti-tau antibodies disclosed herein. In some embodiments, tau proteins are immunoprecipitated from biological samples using anti-tau antibodies and then identified and/or quantitated using mass spectrometry.

[0212] In some embodiments, a method for detecting tau (e.g., human tau) using the antibodies described herein comprises: (a) contacting a sample (e.g., a biological sample such as a tissue section) with an anti-tau antibody described herein for a time sufficient to allow specific binding of the anti-tau antibody to tau in the sample, and (b) contacting the sample with a detection reagent, e.g., an antibody, that specifically binds to the anti-tau antibody,

such as to the Fc region of the anti-tau antibody, to thereby detect tau bound by the anti-tau antibody.

[0213] Also provided are methods of detecting the presence of tau (e.g., human tau) in a sample, or measuring the amount of tau, comprising contacting a sample (e.g., biological sample such as a tissue sample) with an anti-tau antibody described herein under conditions that allow for formation of a complex between the antibody and tau, and detecting the formation of a complex. In some embodiments, the method may also include contacting the sample with a control antibody (e.g., an isotype control antibody) in parallel, wherein the difference in complex formation between the anti-tau antibody and sample and control antibody and sample is indicative of the presence of tau in the sample. In some embodiments, the anti-tau antibodies described herein can be used to purify tau (e.g., the various phospho-tau species recognized by the anti-tau antibodies described herein) via immunoaffinity purification.

[0214] In some embodiments, treatments are informed by diagnostic information generated using anti-tau antibodies. Accordingly, the present disclosure provides methods of treating neurological diseases and/or disorders that include obtaining a sample from a subject, diagnosing one or more neurological diseases and/or disorders using an anti-tau antibody, and administering a treatment selected based on the diagnosis. Such treatments may include treatment with anti-tau antibodies. Anti-tau antibodies administered according to such methods may include any of those described herein.

[0215] In some embodiments, the present disclosure provides methods of detecting and/or quantifying tau proteins in samples through the use of capture and detection antibodies. As used herein, a “capture antibody” is an antibody that binds an analyte in a way that it may be isolated or detected. Capture antibodies may be associated with surfaces or other carriers (e.g., beads). Detection antibodies are antibodies that facilitate observation of the presence or absence of an analyte. According to some methods of detecting and/or quantifying tau proteins, both capture antibodies and detection antibodies bind to tau proteins. Capture and detection antibodies may bind to different epitopes or regions of tau proteins to avoid competition for binding. In some embodiments, detection antibodies may be conjugated with a detectable label for direct detection. In some embodiments, binding of detection antibodies may be assessed using a secondary antibody that binds to a constant domain of the detection antibody or to a detectable label of the detection antibody. Capture, detection, and/or secondary antibodies may be derived from different species. This may prevent secondary antibodies from binding to both capture and detection antibodies.

V. KITS AND DEVICES

Kits

[0216] In some embodiments, compounds and composition of the present disclosure may be included in a kit. Such compounds and compositions may include anti-tau antibodies disclosed herein. In a non-limiting example, kits may include reagents for generating anti-tau antibodies, including tau protein antigens. Kits may include additional reagents and/or instructions for use, e.g., for creating or synthesizing anti-tau antibodies. Kits may include one or more buffers. Kits may include additional components, for example, solid supports or substrates for antibody or antigen attachment.

[0217] In some embodiments, the present disclosure includes kits for screening, monitoring, and/or diagnosis of a subject that include one or more anti-tau antibodies. Such kits may be used alone or in combination with one or more other methods of screening, monitoring, and/or diagnosis. Kits may include one or more of a buffer, a biological standard, a secondary antibody, a detection reagent, and a composition for sample pre-treatment (e.g., for antigen retrieval, blocking, etc.).

[0218] Kit components may be packaged. In some embodiments, kit components are packaged in aqueous media or in lyophilized form. Packaging may include one or more vial, test tube, flask, bottle, syringe or other container into which a component may be placed and/or suitably aliquoted. Where there are multiple kit components (labeling reagent and label may be packaged together), kits may include second, third or other additional containers into which additional components may be separately placed.

[0219] When kit components are provided in one and/or more liquid solutions, liquid solutions may be aqueous. Liquid solutions may be provided sterile. Kit components may be provided as dried powder(s). Dried powder components may be provided for reconstitution by kit users, e.g., by addition of suitable solvent. Solvents may also be provided in kits in one or more separate containers. In some embodiments, labeling dyes are provided in dried powder format.

[0220] Kits may include instructions for employing kit components as well other reagents not included in the kit. Instructions may include variations that can be implemented.

Devices

[0221] Any of the compounds and compositions described herein may be combined with, coated onto, or embedded in, or delivered by a device. Devices may include, but are not

limited to, implants, stents, bone replacements, artificial joints, valves, pacemakers, or other implantable therapeutic devices.

VI. DEFINITIONS

[0222] At various places in the present specification, substituents of compounds of the present disclosure are disclosed in groups or in ranges. It is specifically intended that the present disclosure include each and every individual sub combination of the members of such groups and ranges.

[0223] *About:* As used herein, the term “about” means +/- 10% of the recited value.

[0224] *Activity:* As used herein, the term “activity” refers to the condition in which things are happening or being done. Compositions may have activity and this activity may involve one or more biological events.

[0225] *Administered in combination:* As used herein, the term “administered in combination” or “combined administration” means that two or more agents are administered to a subject at the same time or within an interval such that there may be an overlap of an effect of each agent on the patient. In some embodiments, they are administered within about 60, 30, 15, 10, 5, or 1 minute of one another. In some embodiments, the administrations of the agents are spaced sufficiently closely together such that a combinatorial (*e.g.*, a synergistic) effect is achieved.

[0226] *Amelioration:* As used herein, the term “amelioration” or “ameliorating” refers to a lessening of severity of at least one indicator of a condition or disease. For example, in the context of neurodegeneration disorder, amelioration includes the reduction of neuron loss.

[0227] *Animal:* As used herein, the term “animal” refers to any member of the animal kingdom. In some embodiments, “animal” refers to humans at any stage of development. In some embodiments, “animal” refers to non-human animals at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, and worms. In some embodiments, the animal is a transgenic animal, genetically-engineered animal, or a clone.

[0228] *Approximately:* As used herein, the term “approximately” or “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term “approximately” or “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%,

6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0229] *Associated with:* As used herein, the terms “associated with,” “conjugated,” “linked,” “attached,” and “tethered,” when used with respect to two or more entities, means that the entities are physically associated or connected with one another, either directly or via a linker, to form a structure that is sufficiently stable so that the entities remain physically associated, e.g., under working conditions, e.g., under physiological conditions. An “association” need not be through covalent chemical bonding and may include other forms of association or bonding sufficiently stable such that the “associated” entities remain physically associated, e.g., ionic bonding, hydrostatic bonding, hydrophobic bonding, hydrogen bonding, or hybridization-based connectivity.

[0230] *Bifunctional:* As used herein, the term “bifunctional” refers to any substance, molecule or moiety which is capable of or maintains at least two functions. The functions may affect the same outcome or a different outcome. The structure that produces the function may be the same or different.

[0231] *Biocompatible:* As used herein, the term “biocompatible” means compatible with living cells, tissues, organs or systems posing little to no risk of injury, toxicity or rejection by the immune system.

[0232] *Biodegradable:* As used herein, the term “biodegradable” means capable of being broken down into innocuous products by the action of living things.

[0233] *Biologically active:* As used herein, the phrase “biologically active” refers to a characteristic of any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active.

[0234] *Chimeric antigen receptor (CAR):* As used herein, the term “chimeric antigen receptor” or “CAR” refers to an artificial chimeric protein comprising at least one antigen specific targeting region (ASTR), a transmembrane domain and an intracellular signaling domain, wherein the antigen specific targeting region comprises a full-length antibody or a fragment thereof. As a non-limiting example, the ASTR of a CAR may be any of the antibodies presented herein or fragments thereof. Any molecule that is capable of binding a target antigen with high affinity can be used in the ASTR of a CAR. The CAR may optionally have an extracellular spacer domain and/or a co-stimulatory domain. A CAR may also be used to generate a cytotoxic cell carrying the CAR.

[0235] *Compound*: Compounds of the present disclosure include all of the isotopes of the atoms occurring in the intermediate or final compounds. “Isotopes” refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

[0236] The compounds and salts of the present disclosure can be prepared in combination with solvent or water molecules to form solvates and hydrates by routine methods.

[0237] *Comprehensive Positional Evolution (CPETM)*: As used herein, the term “comprehensive positional evolution” refers to an antibody evolution technology that allows for mapping of the effects of amino acid changes at every position along an antibody variable domain’s sequence. This comprehensive mutagenesis technology can be used to enhance one or more antibody properties or characteristics.

[0238] *Comprehensive Protein Synthesis (CPSTM)*: As used herein, the term “comprehensive protein synthesis” refers to a combinatorial protein synthesis technology that can be used to optimize antibody properties or characteristics by combining the best properties into a new, high-performance antibody.

[0239] *Conditionally active*: As used herein, the term “conditionally active” refers to a mutant or variant of a wild-type polypeptide, wherein the mutant or variant is more or less active at physiological conditions than the parent polypeptide. Further, the conditionally active polypeptide may have increased or decreased activity at aberrant conditions as compared to the parent polypeptide. A conditionally active polypeptide may be reversibly or irreversibly inactivated at normal physiological conditions or aberrant conditions.

[0240] *Conserved*: As used herein, the term “conserved” refers to nucleotides or amino acid residues of a polynucleotide sequence or polypeptide sequence, respectively, that are those that occur unaltered in the same position of two or more sequences being compared. Nucleotides or amino acids that are relatively conserved are those that are conserved amongst more related sequences than nucleotides or amino acids appearing elsewhere in the sequences.

[0241] In some embodiments, two or more sequences are said to be “completely conserved” if they are 100% identical to one another. In some embodiments, two or more sequences are said to be “highly conserved” if they are at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be “highly conserved” if they are about 70% identical, about 80% identical, about 90% identical, about 95%, about 98%, or about 99% identical to one another. In some embodiments, two or more sequences are said to be

“conserved” if they are at least 30% identical, at least 40% identical, at least 50% identical, at least 60% identical, at least 70% identical, at least 80% identical, at least 90% identical, or at least 95% identical to one another. In some embodiments, two or more sequences are said to be “conserved” if they are about 30% identical, about 40% identical, about 50% identical, about 60% identical, about 70% identical, about 80% identical, about 90% identical, about 95% identical, about 98% identical, or about 99% identical to one another. Conservation of sequence may apply to the entire length of a polynucleotide or polypeptide or may apply to a portion, region or feature thereof.

[0242] *Cytotoxic*: As used herein, “cytotoxic” refers to killing or causing injurious, toxic, or deadly effect on a cell (*e.g.*, a mammalian cell (*e.g.*, a human cell)), bacterium, virus, fungus, protozoan, parasite, prion, or a combination thereof.

[0243] *Delivery*: As used herein, “delivery” refers to the act or manner of providing a compound, substance, entity, moiety, cargo, or payload to a subject or destination.

[0244] *Detectable label*: As used herein, “detectable label” refers to one or more markers, signals, or moieties which are attached, incorporated or associated with another entity, which markers, signals or moieties are readily detected by methods known in the art including radiography, fluorescence, chemiluminescence, enzymatic activity, absorbance and the like. Detectable labels include, but are not limited to, radioisotopes, fluorophores, chemiluminescent compounds, chromophores, enzymes, enzyme co-factors, dyes, metal ions, ligands, biotin, avidin, streptavidin, haptens, quantum dots, and the like. Detectable labels may be located at any position in or on an entity with which they are conjugated or otherwise attached, incorporated, or associated. For example, when conjugated or otherwise attached, incorporated, or associated with a peptide or protein, detectable labels may be on, within, or between amino acids or may be attached or associated with the N- or C- termini.

[0245] *Digest*: As used herein, the term “digest” means to break apart into smaller pieces or components. When referring to polypeptides or proteins, digestion results in the production of peptides.

[0246] *Distal*: As used herein, the term “distal” means situated away from the center or away from a point or region of interest.

[0247] *Dosing regimen*: As used herein, a “dosing regimen” is a schedule of administration or physician determined regimen of treatment, prophylaxis, or palliative care.

[0248] *Engineered*: As used herein, embodiments are “engineered” when they are designed to have a feature or property, whether structural or chemical, that varies from a starting compound, material or molecule (*e.g.*, from a wild type or native molecule).

[0249] *Effective Amount:* As used herein, the term “effective amount” of an agent is that amount sufficient to effect beneficial or desired results, for example, clinical results, and, as such, an “effective amount” depends upon the context in which it is being applied. For example, in the context of administering an agent that treats cancer, an effective amount of an agent is, for example, an amount sufficient to achieve treatment of a therapeutic indication as compared to the response obtained without administration of the agent.

[0250] *Epitope:* As used herein, an “epitope” refers to a surface or region on one or more entities that is capable of interacting with an antibody or other binding biomolecule. For example, a protein epitope may contain one or more amino acids and/or post-translational modifications (e.g., phosphorylated residues) which interact with an antibody. In some embodiments, an epitope may be a “conformational epitope,” which refers to an epitope involving a specific three-dimensional arrangement of the entity(ies) having or forming the epitope. For example, conformational epitopes of proteins may include combinations of amino acids and/or post-translational modifications from folded, non-linear stretches of amino acid chains.

[0251] *EvoMap™:* As used herein, an EvoMap™ refers to a map of a polypeptide, wherein detailed informatics are presented about the effects of single amino acid mutations within the length of the polypeptide and their influence on the properties and characteristics of that polypeptide.

[0252] *Expression:* As used herein, “expression” of a gene, nucleic acid, or protein refers to one or more of the following events: (1) production of an RNA template from a DNA sequence (e.g., by transcription); (2) processing of an RNA transcript (e.g., by splicing, editing, 5' cap formation, and/or 3' end processing); (3) translation of an RNA into a polypeptide or protein; and (4) post-translational modification of a polypeptide or protein.

[0253] *Feature:* As used herein, a “feature” refers to a characteristic, a property, or a distinctive element.

[0254] *Formulation:* As used herein, a “formulation” refers to a material or mixture prepared according to a formula. Formulations may include a compound (e.g., an antibody) or substance combined with a carrier or excipient.

[0255] *Fragment:* A “fragment,” as used herein, refers to a portion. For example, fragments of proteins may include polypeptides obtained by digesting full-length protein isolated from cultured cells.

[0256] *Functional:* As used herein, a “functional” biological molecule is a biological molecule in a form in which it exhibits a property and/or activity by which it is characterized.

For example, a “functional” antibody may include an antibody that binds a specific target or that activates or inhibits a specific biological process.

[0257] *Half maximal effective concentration:* As used herein, the term “half maximal effective concentration” or “EC50” refers to the concentration of a substance necessary to increase a given reaction, activity or process by half. For example, when measuring binding of an antibody in a sample to a target using a binding assay (e.g., an ELISA assay), the EC50 is the concentration of antibody in the sample needed to yield 50% of the maximum binding that can be observed with that assay. Similarly, the term “half maximal inhibitory concentration” or “IC50” refers to a concentration necessary to reduce a given reaction or process by half. For example, the IC50 for an antibody capable of inhibiting a biological process is the concentration of antibody necessary in a sample to reduce the biological process by 50%. EC50 and IC50 values may differ under specific time constraints and/or conditions.

[0258] *Homology:* As used herein, the term “homology” refers to the overall relatedness between polymeric molecules, e.g. between polynucleotide molecules (e.g. DNA molecules and/or RNA molecules) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be “homologous” to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical or similar. The term “homologous” necessarily refers to a comparison between at least two sequences (polynucleotide or polypeptide sequences). In accordance with the disclosure, two polynucleotide sequences are considered to be homologous if the polypeptides they encode are at least about 50%, 60%, 70%, 80%, 90%, 95%, or even 99% for at least one stretch of at least about 20 amino acids. In some embodiments, homologous polynucleotide sequences are characterized by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. For polynucleotide sequences less than 60 nucleotides in length, homology is determined by the ability to encode a stretch of at least 4–5 uniquely specified amino acids. In accordance with the disclosure, two protein sequences are considered to be homologous if the proteins are at least about 50%, 60%, 70%, 80%, or 90% identical for at least one stretch of at least about 20 amino acids.

[0259] *Heterologous Region:* As used herein the term “heterologous region” refers to a region which would not be considered a homologous region.

[0260] *Homologous Region:* As used herein the term “homologous region” refers to a region which is similar in position, structure, evolution origin, character, form or function.

[0261] *Identity*: As used herein, the term “identity” refers to the overall relatedness between polymeric molecules, *e.g.*, between polynucleotide molecules (*e.g.* DNA molecules and/or RNA molecules) and/or between polypeptide molecules. Calculation of the percent identity of two polynucleotide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second nucleic acid sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or 100% of the length of the reference sequence. The nucleotides at corresponding nucleotide positions are then compared. When a position in the first sequence is occupied by the same nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using methods such as those described in Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; each of which is incorporated herein by reference. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4:11-17), which has been incorporated into the ALIGN program (version 2.0) using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix. Methods commonly employed to determine percent identity between sequences include, but are not limited to those disclosed in Carillo, H. and Lipman, D., SIAM J Applied Math., 48:1073 (1988); incorporated herein by reference. Techniques for determining identity are codified in publicly available computer programs. Exemplary computer software to determine homology between two sequences

include, but are not limited to, GCG program package, Devereux, J., *et al.*, *Nucleic Acids Research*, 12(1), 387 (1984)), BLASTP, BLASTN, and FASTA Altschul, S. F. *et al.*, *J. Molec. Biol.*, 215, 403 (1990)).

[0262] *In vitro*: As used herein, the term “*in vitro*” refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, in a Petri dish, *etc.*, rather than within an organism (*e.g.*, animal, plant, or microbe).

[0263] *In vivo*: As used herein, the term “*in vivo*” refers to events that occur within an organism (*e.g.*, animal, plant, or microbe or cell or tissue thereof).

[0264] *Isolated*: As used herein, the term “isolated” refers to a substance or entity that has been separated from at least some of the components with which it was associated (whether in nature or in an experimental setting). Isolated substances may have varying levels of purity in reference to the substances from which they have been associated. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or more of the other components with which they were initially associated. In some embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or more than about 99% pure. As used herein, a substance is “pure” if it is substantially free of other components.

[0265] *Substantially isolated*: By “substantially isolated” is meant that a substance is substantially separated from the environment in which it was formed or detected. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compound of the present disclosure, or salt thereof. Methods for isolating compounds and their salts are routine in the art.

[0266] *Linker*: As used herein “linker” refers to a molecule or group of molecules which connects two molecules. In some embodiments, linkers may be cleavable (*e.g.*, through contact with an enzyme, change in pH, or change in temperature).

[0267] *Modified*: As used herein “modified” refers to a changed state or structure of a molecule. Molecules may be modified in many ways including chemically, structurally, and functionally.

[0268] *Naturally occurring*: As used herein, “naturally occurring” or “wild-type” means existing in nature without artificial aid, or involvement of the hand of man.

[0269] *Non-human vertebrate*: As used herein, a “non-human vertebrate” includes all vertebrates except *Homo sapiens*, including wild and domesticated species. Examples of non-

human vertebrates include, but are not limited to, mammals, such as alpaca, banteng, bison, camel, cat, cattle, deer, dog, donkey, gayal, goat, guinea pig, horse, llama, mule, pig, primate, rabbit, reindeer, sheep, water buffalo, and yak.

[0270] *Off-target:* As used herein, “off-target” refers to unintended activity or binding to an entity other than an expected target.

[0271] *Operably linked:* As used herein, the phrase “operably linked” refers to a functional connection between two or more molecules, constructs, transcripts, entities, moieties or the like.

[0272] *Patient:* As used herein, “patient” refers to a subject who may seek or be in need of treatment, requires treatment, is receiving treatment, will receive treatment, or a subject who is under care by a trained professional for a particular disease or condition.

[0273] *Peptide:* As used herein, “peptide” is less than or equal to 50 amino acids long, e.g., about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 amino acids long.

[0274] *Pharmaceutically acceptable:* The phrase “pharmaceutically acceptable” is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0275] *Pharmaceutically acceptable excipients or pharmaceutically acceptable carrier:* The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier,” as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a patient. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspension or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate,

sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0276] *Pharmaceutically acceptable salts:* The present disclosure also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form (e.g., by reacting the free base group with a suitable organic acid). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. Representative acid addition salts include acetate, acetic acid, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzene sulfonic acid, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418, *Pharmaceutical Salts: Properties, Selection, and Use*, P.H. Stahl and C.G. Wermuth (eds.), Wiley-VCH, 2008, and Berge et al.,

Journal of Pharmaceutical Science, 66, 1-19 (1977), each of which is incorporated herein by reference in its entirety.

[0277] *Pharmaceutically acceptable solvate*: The term “pharmaceutically acceptable solvate,” as used herein, means a compound wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. For example, solvates may be prepared by crystallization, recrystallization, or precipitation from a solution that includes organic solvents, water, or a mixture thereof. Examples of suitable solvents are ethanol, water (for example, mono-, di-, and tri-hydrates), *N*-methylpyrrolidinone (NMP), dimethyl sulfoxide (DMSO), *N,N'*-dimethylformamide (DMF), *N,N'*-dimethylacetamide (DMAC), 1,3-dimethyl-2-imidazolidinone (DMEU), 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (DMPU), acetonitrile (ACN), propylene glycol, ethyl acetate, benzyl alcohol, 2-pyrrolidone, benzyl benzoate, and the like. When water is the solvent, the solvate is referred to as a “hydrate.”

[0278] *Pharmacokinetic*: As used herein, “pharmacokinetic” refers to any one or more properties of a molecule or compound as it relates to the determination of the fate of substances administered to a living organism. Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as ADME where: (A) Absorption is the process of a substance entering the blood circulation; (D) Distribution is the dispersion or dissemination of substances throughout the fluids and tissues of the body; (M) Metabolism (or Biotransformation) is the irreversible transformation of parent compounds into daughter metabolites; and (E) Excretion (or Elimination) refers to the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

[0279] *Preventing*: As used herein, the term “preventing” refers to partially or completely delaying onset of an infection, disease, disorder and/or condition; partially or completely delaying onset of one or more symptoms, features, or clinical manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying onset of one or more symptoms, features, or manifestations of a particular infection, disease, disorder, and/or condition; partially or completely delaying progression from an infection, a particular disease, disorder and/or condition; and/or decreasing the risk of developing pathology associated with the infection, the disease, disorder, and/or condition.

[0280] *Proliferate*: As used herein, the term “proliferate” means to grow, expand or increase or cause to grow, expand or increase rapidly. “Proliferative” means having the

ability to proliferate. “Anti-proliferative” means having properties counter to or inapposite to proliferative properties.

[0281] *Prophylactic*: As used herein, “prophylactic” refers to a therapeutic or course of action used to prevent the spread of disease.

[0282] *Prophylaxis*: As used herein, a “prophylaxis” refers to a measure taken to maintain health and prevent the spread of disease.

[0283] *Protein of interest*: As used herein, the terms “proteins of interest” or “desired proteins” include those provided herein and fragments, mutants, variants, and alterations thereof.

[0284] *Purified*: As used herein, “purify,” “purified,” “purification” means to make substantially pure or clear from unwanted components, material defilement, admixture or imperfection. “Purified” refers to the state of being pure. “Purification” refers to the process of making pure.

[0285] *Region*: As used herein, the term “region” refers to a zone or general area. In some embodiments, when referring to a polypeptide or protein, a region may include a linear sequence of amino acids along the polypeptide or protein or may include a three-dimensional area, an epitope, or a cluster of epitopes. When referring to a polynucleotide, a region may include a linear sequence of nucleic acids along the polynucleotide or may include a three-dimensional area, secondary structure, or tertiary structure. Regions may include terminal regions. As used herein, the term “terminal region” refers to a region located at the end or “terminus” of a given entity. When referring to polypeptides, terminal regions may include N- and/or C-termini. N-terminus refers to the end of a polypeptide with a free amino acid amino group. C-terminus refers to the end of a polypeptide with a free amino acid carboxyl group. N- and/or C-terminal regions may refer to a single terminal functional group, single amino acid, or multiple amino acids located at either terminus. When referring to polynucleotides, terminal regions may include 5’ and 3’ termini. The 5’ terminus refers to the end of a polynucleotide that includes a free nucleic acid phosphate group. The 3’ terminus refers to the end of a polynucleotide that includes a free nucleic acid hydroxyl group. Polynucleotide terminal regions may refer to a single terminal functional group, single nucleotide, or multiple nucleotides located at a terminus.

[0286] *RNA and DNA*: As used herein, the term “RNA” or “RNA molecule” or “ribonucleic acid molecule” refers to a polymer of ribonucleotides; the term “DNA” or “DNA molecule” or “deoxyribonucleic acid molecule” refers to a polymer of deoxyribonucleotides. DNA and RNA can be synthesized naturally, e.g., by DNA replication

and transcription of DNA, respectively; or be chemically synthesized. RNA and DNA can be single-stranded (i.e., ssRNA or ssDNA, respectively) or multi-stranded (e.g., double stranded, i.e., dsRNA and dsDNA, respectively). The term “messenger RNA” or “mRNA,” as used herein, refers to a single stranded RNA that encodes an amino acid sequence of one or more polypeptide chains.

[0287] *Sample:* As used herein, the term “sample” refers to a portion or subset of larger entity. A sample from a biological organism or material is referred to herein as a “biological sample” and may include, but is not limited to, tissues, cells, and body fluids (e.g., blood, mucus, lymphatic fluid, synovial fluid, cerebrospinal fluid, saliva, amniotic fluid, amniotic cord blood, urine, vaginal fluid, and semen). Samples may further include a homogenate, lysate or extract prepared from a whole organism or a subset of its tissues, cells or component parts, or a fraction or portion thereof, including but not limited to, for example, plasma, serum, spinal fluid, lymph fluid, the external sections of the skin, respiratory, intestinal, and genitourinary tracts, tears, saliva, milk, blood cells, tumors, and organs. Samples may further include a medium, such as a nutrient broth or gel, which may contain cellular components, such as proteins or nucleic acid molecules.

[0288] *Signal Sequences:* As used herein, the phrase “signal sequences” refers to a sequence which can direct the transport or localization of a protein.

[0289] *Single unit dose:* As used herein, a “single unit dose” is a dose of any therapeutic administered in one dose/at one time/single route/single point of contact, i.e., single administration event. In some embodiments, a single unit dose is provided as a discrete dosage form (e.g., a tablet, capsule, patch, loaded syringe, vial, etc.).

[0290] *Split dose:* As used herein, a “split dose” is the division of single unit dose or total daily dose into two or more doses.

[0291] *Stable:* As used herein “stable” refers to a state of an entity that is sufficiently robust to survive a certain degree of perturbation. For example, a stable compound or protein may remain intact during isolation to a useful degree of purity from a reaction mixture.

[0292] *Stabilized:* As used herein, the term “stabilize” or “stabilized” means to make or become stable.

[0293] *Subject:* As used herein, the term “subject” refers to any organism to which a compound, composition, method, kit, or device according to the present disclosure may be administered or applied, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Subjects can include animals (e.g., mammals such as mice, rats, rabbits, non-

human primates, and humans) and plants. A subject receiving, requiring, eligible for, or seeking medical treatment is referred to herein as a “patient.”

[0294] *Substantially*: As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0295] *Suffering from*: An individual who is “suffering from” a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of a disease, disorder, and/or condition.

[0296] *Susceptible to*: An individual who is “susceptible to” a disease, disorder, and/or condition has not been diagnosed with and/or may not exhibit symptoms of the disease, disorder, and/or condition but harbors a propensity to develop a disease or its symptoms. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition (for example, neurodegenerative disease) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity or dysfunction of a protein and/or nucleic acid associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, and/or condition; (5) a family history of the disease, disorder, and/or condition; and (6) exposure to and/or infection with a microbe associated with development of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[0297] *Sustained release*: As used herein, the term “sustained release” refers to release of a compound or agent over a specific period of time, typically at a relatively controlled or consistent rate.

[0298] *Synthetic*: The term “synthetic” means produced, prepared, and/or manufactured by the hand of man. Synthetic polynucleotides, polypeptides, or other molecules of the present disclosure may be prepared using chemical or enzymatic processes.

[0299] *Target:* As used herein, the term “target” refers to an entity of interest or attention, which may include a subject, an organ, a tissue, a cell, a protein, a nucleic acid, biomolecule, or a group, complex, or portion of any of the foregoing. In some embodiments, a target may be a protein or epitope thereof for which an antibody has affinity or for which an antibody is desired, designed, or developed to have affinity for. As used herein, the term “target” may also be used to refer to an activity of an agent that is directed to a particular object. For example, an antibody that has affinity for a specific protein “X” may be said to *target* protein X or may be referred to as an antibody *targeting* protein X or referred to as a protein X-*targeting* antibody. Similarly, an object that is the subject of an agent’s activity may be referred to as a “targeted” object. For example, where an antibody has affinity for a specific protein “X,” protein X may be referred to as being *targeted* by the antibody.

[0300] *Therapeutic Agent:* The term “therapeutic agent” refers to any agent that, when administered to a subject, has a therapeutic, diagnostic, and/or prophylactic effect and/or elicits a desired biological and/or pharmacological effect. Therapeutic agents capable of producing a biological effect in living organisms are referred to herein as “drugs.”

[0301] *Therapeutically effective amount:* As used herein, the term “therapeutically effective amount” means an amount of an agent (*e.g.*, antibody or other therapeutic agent) to be delivered to a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, that when delivered or administered in that amount is sufficient to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is provided in a single dose. In some embodiments, a therapeutically effective amount is administered in a dosage regimen that includes a plurality of doses. Those skilled in the art will appreciate that in some embodiments, a unit dosage form may be considered to include a therapeutically effective amount of a particular agent or entity if it includes an amount that is effective when administered as part of such a dosage regimen.

[0302] *Therapeutically effective outcome:* As used herein, the term “therapeutically effective outcome” means an outcome that is sufficient in a subject suffering from or susceptible to an infection, disease, disorder, and/or condition, to treat, improve symptoms of, diagnose, prevent, and/or delay the onset of the infection, disease, disorder, and/or condition.

[0303] *Total daily dose:* As used herein, a “total daily dose” is an amount given or prescribed in 24 hr period. It may be administered as a single unit dose.

[0304] *Treating:* As used herein, the term “treating” refers to partially or completely alleviating, ameliorating, improving, relieving, delaying onset of, inhibiting progression of,

reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular infection, disease, disorder, and/or condition. For example, “treating” neurodegenerative disease in a subject may refer to inhibiting neurodegeneration; promoting the health of neuronal cells; reversing, preventing, or reducing the formation of plaques or tangles in the brain; and/or reversing, preventing, or reducing memory loss or loss of other neurological functions or activities of the subject. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

[0305] *Unmodified:* As used herein, “unmodified” refers to any substance, compound or molecule prior to being changed in any way. Unmodified may refer to the wild type or native form of a biomolecule. Molecules may undergo a series of modifications whereby each modified molecule may serve as the “unmodified” starting molecule for a subsequent modification.

[0306] *Vector:* As used herein, a “vector” is any molecule or moiety which transports, transduces or otherwise acts as a carrier of a heterologous molecule. Vectors of the present disclosure may be produced recombinantly.

VII. EQUIVALENTS AND SCOPE

[0307] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments in accordance with the invention described herein. The scope of the present invention is not intended to be limited to the above Description, but rather is as set forth in the appended claims.

[0308] In the claims, articles such as “a,” “an,” and “the” may mean one or more than one unless indicated to the contrary or otherwise evident from the context. Claims or descriptions that include “or” between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention includes embodiments in which more than one, or the entire group members are present in, employed in, or otherwise relevant to a given product or process.

[0309] It is also noted that the term “comprising” is intended to be open and permits but does not require the inclusion of additional elements or steps. When the term “comprising” is used herein, the term “consisting of” is thus also encompassed and disclosed.

[0310] Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

[0311] All cited sources, for example, references, publications, databases, database entries, and art cited herein, are incorporated into this application by reference, even if not expressly stated in the citation.

[0312] Section and table headings are not intended to be limiting.

EXAMPLES

Example 1. Antigen preparation

[0313] Antigen preparation was carried out to support generation and characterization of anti-human tau antibodies. Enriched paired helical filament (ePHF; sarkosyl insoluble tau) including human microtubule-associated protein tau, isoform 2 (SEQ ID NO: 274) was prepared along with several tau protein antigens with different phosphorylated residues corresponding to pathological tau. Related sequences are presented in **Table 6**. Phosphorylated residues are underlined in the Table.

Table 6. Tau protein antigens

Antigen	Sequence	SEQ ID NO
human microtubule-associated protein tau, isoform 2	MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAG LKESPLQTPTEDGSEEPGSETSDAKSTPTAEDVTAPLVDEGAPGKQ AAAPHTPEIPEGTTAEAGIGDTPSLEDEAAGHVTQARMVSKSKD GTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIAPAKTPP APKTPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLTPPTREPCK VAVVRTPPKSPSSAKSRLQTAPVPMPLKLVKSKIGSTENLKHQP GGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDL SKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNIT HVPGGGNKKIETHKLTFRENAKAKTDHGAEIVYKSPVVSGDTSR HLSNVSTGSIDMVDSPQLATLADEV SASLAKQGL	274
PT3 epitope peptide (pT212/pT217)	TPGSRSRTPSLTPPTREPCK	275
Peptide 5 (pT212/pS214/pT217)	GTPGSRSRTPSLTPPTRE	276
Peptide 12 (pS396/pS404/pS409)	RENAKAKTDHGAEIVYKSPVVSGDTSRHLNVSTG	277

Peptide 1 (AT120 epitope)	PTREPKKV	278
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[0314] Tau protein antigens were conjugated with keyhole limpet hemocyanin (KLH) for immunization. For ePHF antigen preparation, ePHF was isolated from fractions of AD or non-AD frontal cortical tissue. Cortical tissue fractions were prepared according to methods described by Greenberg and Davies (1990) with minor modification (Liu et al., J Neuroscience, 2016, the contents of which are herein incorporated by reference in their entirety). Briefly, brain tissue was homogenized with cold homogenization buffer (10 mM Tris/1 mM EDTA/0.8 M NaCl/10% sucrose, pH 7.4) with protease inhibitor (Roche Molecular Systems, Inc., Branchburg, NJ) and phosphatase inhibitors cocktail (ThermoFisher, Waltham, MA, catalog #78437) or 1 mM NaF/1 mM Na₃VO₄ in a Teflon glass homogenizer. Brain homogenate was then centrifuged at 27,000 x g for 30 min at 4°C. The resulting supernatant was subjected to extraction with 1% (w/v) N-lauroylsarcosine in the presence of 1% (v/v) 2-mercaptoethanol at 37°C for 2.5 h followed by centrifugation at 108,000 x g for 30 min at room temperature. The pellet recovered from this centrifugation was quickly rinsed one time with 0.5 mL of PBS/tube. The rinsed PBS was discarded. Another 0.5 mL of PBS was added to each tube to dissolve PHF. PHF from 6 tubes were pooled and the pooled PHF solution was sonicated. The resulting solution was concentrated to ~5X and further sonicated. PHF samples were then analyzed by HT7 western for qualitative and PT3 ELISA quantitative assessment. PHF samples were then stored at -80°C.

Example 2. Immunization

[0315] Transgenic mice developed to express antibodies with human variable domains were used for immunization with ePHF (prepared as described in Example 1). Sera from immunized mice were screened by enzyme-linked immunosorbent assay (ELISA) for the presence of antibodies binding to tau protein antigens. Immunized mice with sera testing positive for antigen-specific antibodies were used to prepare hybridoma cells. Supernatants from hybridoma cell culture medium were screened by direct ELISA to identify cells producing antigen-specific antibodies. Hybridoma clones producing antibodies with positive antigen binding were selected for subcloning and antibody sequence analysis.

[0316] Variable domain amino acid sequences for selected clones included those presented in **Table 1**, with each ID# corresponding to an antibody expressed by a selected hybridoma clone. Complementarity determining region (CDR) analysis was carried out to identify heavy chain CDRH1, CDRH2, and CDRH3 sequences and light chain CDRL1,

CDRL2, and CDRL3 sequences. CDR amino acid sequences identified include those presented in **Table 1**.

Example 3. Tau binding

[0317] A set of recombinant human IgG1 antibodies were prepared with clone-specific variable domain pairs selected from those presented in **Table 1** and human IgG1 constant domains. These candidate antibodies were analyzed for binding to ePHF and specificity for ePHF over wild type tau by direct ELISA.

[0318] For direct ePHF and wildtype tau ELISA, plates were first coated with ePHF or wild type tau. Antigen solutions were prepared in PBS and 50 μ L were pipetted into each well. Plates were covered and incubated for one hour at 37°C or overnight at 4°C. Plates were then washed and blocked by addition of 150 μ L of blocking buffer to each well and incubated one hour at room temperature. Plates were then washed before addition of serially diluted candidate antibody samples prepared in blocking buffer. Detection of candidate antibody binding was carried out by washing plates and adding a solution of enzyme-labeled secondary antibody in blocking buffer to each well. Secondary antibody binding was detected by addition of substrate and spectrophotometric analysis of resulting reaction product. Half maximal effective concentration (EC50) for antibody binding to ePHF and wild type tau are presented in **Table 7**.

Table 7. ELISA results

ID#	ePHF EC50 (nM)	Wild type Tau EC50 (nM)
VY001	0.02	No binding
VY002	0.03	No binding
VY003	0.06	No binding
VY004	0.07	No binding
VY005	0.07	No binding
VY006	0.11	No binding
VY007	0.18	No binding
VY008	0.27	No binding
VY009	1.74	No binding
VY010	8.99	No binding
VY011	0.03	No binding
VY012	0.04	0.01
VY013	0.06	0.98
VY014	6.23	0.04
VY016	No binding	No binding
VY017	No binding	No binding
VY018	No binding	No binding

VY019	No binding	No binding
VY020	No binding	No binding

Example 4. Epitope affinity analysis

[0319] Anti-human tau antibodies were assessed for affinity for iPHF by Octet (ForteBio, Menlo Park, CA) analysis. A set of recombinant human IgG1 antibodies were prepared with clone-specific variable domain pairs selected from those presented in **Table 1** and human IgG1 constant domains. Candidate antibodies were immobilized on biosensor tips (ForteBio) in kinetic buffer (ForteBio). Biosensor tips were then washed before introduction of a solution of iPHF in kinetic buffer for analysis of association and dissociation with candidate antibodies. Affinity measurements (K_D) were obtained using Data Analysis HT version 11.1 and corrected for background and high-frequency noise. Results are presented in **Table 8**.

Table 8. Affinity analysis results

ID#	iPHF K_D (nM)
VY007	0.6
VY005	1.0
VY002	1.0
VY009	1.1
VY006	1.5
VY010	1.5
VY011	2.0
VY008	2.3
VY020	2.6
VY013	2.9
VY018	3.0
VY004	3.7
VY017	3.7
VY003	4.6
VY012	5.1
VY014	5.3
VY001	7.7

[0320] The antibodies shown in **Table 8** all demonstrated K_D values less than 10 nM, with antibodies VY002, VY005, and VY007 demonstrating K_D values less than or equal to 1 nM.

Example 5. Epitope binning by peptide antigen

[0321] Anti-human tau antibodies were subjected to PHF tau epitope binning analysis by sandwich ELISA. A set of recombinant human IgG1 antibodies were prepared with clone-specific variable domain pairs selected from those presented in **Table 1** and human IgG1

constant domains. Anti-tau antibodies AT120 (directed to peptide 1), PT3 (directed to peptide 5), and C10.2 (directed to peptide 12) were used as capture antibodies in the assay. Capture antibodies were diluted in PBS at a concentration of 1 µg/ml and 50 µl of the solution was used to coat each assay plate well. Plates were covered and incubated overnight at 4°C. Plates were then washed and blocked by addition of 150 µl of blocking buffer to each well and incubated one hour at room temperature. Plates were again washed before coating with ePHF or wild type tau in blocking buffer followed by incubation for 1 hour at room temperature. Plates were then washed before addition of serially diluted candidate antibody samples prepared in blocking buffer. Detection of candidate antibody binding was carried out by washing plates and adding a solution of enzyme-labeled secondary antibody in blocking buffer to each well. Secondary antibody binding was detected by addition of substrate and spectrophotometric analysis of resulting reaction product. Epitope “bins” were determined for each candidate antibody tested based on observed competition (epitope blocking) by each anti-tau capture antibody tested. Results are shown in **Table 9**.

Table 9. Epitope binning results

ID#	Epitope bin
VY017	AT120
VY013	C10.2
VY004	PT3
VY005	PT3
VY014	C10.2
VY002	PT3
VY008	PT3

[0322] Multiple antibodies competed for epitope binding with PT3, with one antibody competing for AT120, and two antibodies competing for epitope binding with C10.2.

[0323] Additional competition assays were performed to further characterize the binding specificity of VY014. Specifically, the binding of VY014 to a Tau(pS404) peptide with only S404 phosphorylated (DHGAEIVYKSPVVS GDTpSPRHLSNV SSTG; SEQ ID NO: 281) was tested. As shown in **FIG. 1A**, competitive ELISA using peptide-12 (bound by C10.2/PHF1) from **Table 6** (SEQ ID NO: 277) showed that the Tau(pS404) peptide competitively inhibited the binding of VY014 to peptide-12. While PHF-1 showed binding to the C-terminus of tau (peptide 12) (**FIG. 1A**), it did not bind to the Tau(pS404) peptide (**FIG. 1B**). Finally, the AC04 peptide (recognized by antibody PT3 (**FIG. 1C**) and corresponding to the dual phosphorylated peptide: CSRpTPSLPpTPPTREPK; SEQ ID NO: 282) did not inhibit VY014 binding to TauS404 (**FIG. 1B**). These results suggest that VY014

binds to tau phosphorylated at S404 and exhibits a distinct binding pattern to phosphorylated tau species compared to PHF-1.

Example 6. Epitope binning of anti-human Tau antibodies by PepScan overlapping phosphorylated peptide library

[0324] Epitope binning of 15 additional anti-Tau antibodies (i.e., VY003, VY007, VY004, VY006, VY011, VY012, VY009, VY018, VY001, VY019, VY020, VY005, VY002, VY008, and VY013) was performed using a PepScan overlapping phospho-peptide library strategy.

[0325] Briefly, the PepScan library used included 212 phosphorylated overlapping 18-mer peptides, with each fragment containing at least one phosphorylated site (with the exception of 5 fragments). Tau has 45 serines, 35 threonines, and 5 tyrosines, for a total of 85 possible sites.

[0326] In a control run, PT3, PHF1, and C10.2 antibodies were tested for binding to the PepScan library and found to bind to their expected epitopes. Specifically, PT3 bound to amino acids 201-228, PHF1 to amino acids 13-34 and 377-408, and C10.2 to amino acids 39-56, 205-222, and 383-402.

[0327] **Table 10** summarizes the epitopes recognized by the tested antibodies using the PepScan library.

Table 10. Epitope mapping

Antibody	Peptide epitopes (amino acid residues)
PT3	201-228
PHF1	13-34; 377-408
C10.2	39-56, 205-222, 383-402
MC1	1-22
IPN002	2-24
AT8	187-218
AT180	215-238
VY003	35-62, 53-76, 187-218
VY007	187-218
VY006	187-218
VY004	33-64; 53-82, 159-178, 165-182, 197-214, 201-226, 229-246
VY011	183-201; 187-212
VY012	5-34
VY009	217-242
VY018	217-242
VY001	187-218
VY019	217-242
VY020	187-218
VY005	33-64, 53-82, 159-178, 165-188, 191-230
VY002	35-62, 107-124, 203-220
VY008	35-64, 53-82, 159-188, 197-214, 201-224

VY013	53-78, 329-348, 381-408
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*amino acid residues are in relation to human tau having the sequence of SEQ ID NO: 274 from **Table 10**.

[0328] Similar to MC1 and IPN002, VY012 exhibited strong binding to the N-terminal region of Tau.

[0329] VY003, VY007, VY006, VY011, VY001, and VY020 exhibited binding to a peptide region similar to the AT8 antibody. However, competitive ELISA using the phospho-peptide spanning amino acids 193-210 (DRpSGYpSpSPGpSPGpTPGpSRpS; SEQ ID NO: 283) did not demonstrate competition between AT8 and VY003, VY007, VY006, and VY001 (**FIG. 2**), suggesting that these antibodies may have a different binding specificity to the 193-210 region compared to AT8.

[0330] VY009 and VY018 exhibited binding to a peptide region containing pT231 (Tau217-242).

[0331] VY004, VY005, and VY008 showed strong binding to the proline-rich domain, similar to PT3 (Tau201-228), while VY002 showed very weak binding to PepScan overlapping phosphorylated peptides (Tau203-220). VY004, VY005, VY002, and VY008 also showed strong binding to other regions of tau, especially the N-terminal region (Tau33-64 and Tau53-82).

[0332] VY013 showed strong binding to the C-terminal region of tau (Tau381-408), as well as the N-terminal region (Tau53-78).

Example 7. Fine epitope mapping of AT8 bin antibodies

[0333] This Example describes the further characterization of the binding specificity of antibodies tentatively categorized as belonging to the AT8 bin (i.e., VY003, VY007, VY006, VY011, VY001, and VY020).

[0334] As an initial experiment, the ability of the antibodies to bind to the AT8 peptide (amino acids 195-215 of tau) was tested by bio-layer interferometry (BLI; Octet assay). Briefly, phospho-peptides were immobilized on streptavidin biosensor tips and the binding ability of each antibody was assessed using an eight-point concentration gradient.

[0335] As shown in **Table 11**, VY003, VY007, VY006, VY011, and VY001 showed strong binding to the AT8 peptide, whereas VY020 showed no binding to the peptide.

Table 11. Affinity of AT8 bin antibodies for AT8 peptide by BLI

Antibody	KD (pM)
AT8 (positive control)	309

hIgG1 isotype control	no binding
VY003	12.4
VY007	18.2
VY006	3.82
VY011	8.9
VY001	4.35
VY020	no binding

[0336] To further assess the binding characteristics of VY003, VY007, VY006, VY011, and VY001, the ability of these antibodies to bind to different phosphorylated species of the AT8 peptide were tested by one point ELISA using a high resolution sub-phospho-peptide library.

[0337] Briefly, peptides were generated that showed all possible combinations of phosphorylation patterns within known epitopes containing multiple possible phosphorylation sites. One-point ELISA was used to determine differential binding based on the individual phosphorylation patterns of each peptide. OD values (450nm) were collected (as shown in Table 13), where a stronger positive signal is shown as a higher OD value, which is indicative of increased binding.

[0338] Table 12 lists the Tau191-214 phospho-peptides used in the binding assay, and Table 13 summarizes the specific binding patterns of the antibodies to the phospho-peptides.

Table 12. Tau191-214 phospho-peptides used in binding assay

SEQ ID	Description	Sequence
284	pS199	SGDRSGYS (pS) PGSPGTPGSRSRTPS
285	pS202	SGDRSGYSSPG (pS) PGTPGSRSRTPS
286	pT205	SGDRSGYSSPGSPG (pT) PGSRSRTPS
287	pS199-pS202-pT205	SGDRSGYS (pS) PG (pS) PG (pT) PGSRSRTPS
288	pS199-pS202	SGDRSGYS (pS) PG (pS) PGTPGSRSRTPS
289	pS202-pT205	SGDRSGYSSPG (pS) PG (pT) PGSRSRTPS
290	pS199-pT205	SGDRSGYS (pS) PGSPG (pT) PGSRSRTPS

Table 13. Binding assay for AT8 bin antibodies (OD values*)

SCBio-4PEG-Peptide (Tau191-214)	VY003	VY007	VY006	VY011	VY001	AT8 Mab	pS199 Rab	pS202 Rab	hIgG1 isotype cont
pS199-old	0.062	0.057	0.063	0.544	0.059	0.056	3.168		0.060
pS199	0.065	0.057	0.054	0.103	0.059	0.056	3.207		0.058
pS202	0.065	1.142	0.345	0.060	2.996	0.058		3.203	0.055

pT205	0.060	2.023	0.365	0.060	3.117	0.065		0.208	0.054
pS199-pS202-pT205	3.083	3.082	3.124	1.691	3.152	3.069		1.085	0.245
pS199-pS202	0.082	0.544	0.435	1.222	1.906	2.389		3.203	0.062
pS202-pT205	3.064	3.063	3.087	0.402	3.149	2.940		0.740	0.249
pS199-pT205	0.119	3.134	3.124	0.518	3.163	0.139	3.162		0.090

*values are readings at OD450 nm

[0339] As shown in **Table 13**, many of the antibodies showed a distinct binding pattern compared to AT8 for Tau191-214 phospho-peptide species. AT8 did not bind to any of the singly phosphorylated peptides, exhibited binding to all doubly phosphorylated peptides, albeit weakly to the pS199/pT205 peptide, and bound strongly to the triple phosphorylated peptide (pS199/pS202/pT205).

[0340] VY003, VY007, VY006, VY011, and VY001 all exhibited binding to the triple phosphorylated peptide (pS199/pS202/pT205). VY003 exhibited binding when the peptide was doubly phosphorylated at pS202/pT205. VY007 exhibited binding to the peptide when S202 and T205 were singly phosphorylated, and to all doubly phosphorylated peptides, although binding was weaker for the peptide doubly phosphorylated at pS199/pS202 compared to the other two doubly phosphorylated peptides (pS202/pT205 and pS199/pT205). VY006 exhibited binding to the peptide when S202 and T205 were singly phosphorylated; however, no binding was observed with when only pS199 was phosphorylated, and strongest binding was observed when the peptide was doubly phosphorylated at pS202/pT205 and pS199/pT205. This suggests that VY006 likely binds strongly to pT205 and an additional epitope, such as pS199 and/or pS202. Both VY007 and VY006 showed strongest binding when T205 and at least one other site on the peptide were phosphorylated. VY001 exhibited binding to the peptide when S202 and T205 were singly phosphorylated, and all three doubly phosphorylated peptides.

[0341] VY011 exhibited binding to the peptide when S199 was singly phosphorylated, as well as when the peptide was doubly phosphorylated at pS199/pT205, pS202/pT205, and pS199/pS202. VY011 showed strongest binding to the peptide when all three sites (pS199/pS202/pT205) were phosphorylated. Notably, VY011 was the only antibody which exhibited binding to the peptide when S199 was singly phosphorylated. As shown in **Table 14**, VY011 exhibited nanomolar binding to the pS199 peptide, whereas neither VY020 nor AT8 exhibited binding to the peptide, as assessed by BLI.

Table 14. Specificity of VY011 for pS199 by BLI

Antibody	KD (nM)
pS199 Ab (positive control)	0.004

hIgG1 isotype control	no binding
AT8	no binding
VY011	1.049
VY020	no binding
VY003	no binding
VY006	no binding
VY007	no binding
VY001	no binding

[0342] In addition, neither VY011 nor VY020 were found to bind to the AT270 peptide (pT181; Tau172-186) by one point ELISA.

[0343] These results collectively suggest that the VY003, VY007, VY006, VY011, and VY001 antibodies exhibit a distinct pattern of binding to phosphorylated tau species compared to AT8, and that VY011 uniquely binds to the tau peptide singly phosphorylated at S199. Distinct binding patterns of these four antibodies were also observed relative to each other.

Example 8. Fine epitope mapping of PT3 bin antibodies

[0344] This Example describes the further characterization of the binding specificity of antibodies tentatively categorized as belonging to the PT3 bin (i.e., VY004, VY005, VY002, and VY008).

[0345] To assess the binding characteristics of VY004, VY005, VY002, and VY008, the ability of these antibodies to bind to different phosphorylated species of the Tau204-222 peptide was tested by one point ELISA using a high resolution sub-phospho-peptide library, in the manner described in Example 7. OD values (450nm) were collected (as shown in Tables 16 and 18), where a stronger positive signal is shown as a higher OD value, which is indicative of increased binding.

[0346] **Table 15** lists the Tau204-222 phospho-peptides used in the binding assay, and **Table 16** summarizes the specific binding patterns of the antibodies to the phospho-peptides.

Table 15. Tau204-222 phospho-peptides

SEQ ID	Description	Sequence
291	pT212	GTPGSRSR (pT) PSLPTPPTRE
292	pS214	GTPGSRSRTP (pS) LPTPPTRE
293	pT217	GTPGSRSRTPSLP (pT) PPTRE
294	pT212/pS214	GTPGSRSR (pT) P (pS) LPTPPTRE

295	pT212/pT217	GTPGSRSR (pT) PSLP (pT) PPTRE
296	pS214/pT217	GTPGSRSRTP (pS) LP (pT) PPTRE
297	pT212/pS214/pT217	GTPGSRSR (pT) P (pS) LP (pT) PPTRE

Table 16. Binding assay for PT3 bin antibodies (OD values at 450nm)

SCBiot-(dPEG4)- peptide (Tau204- 222)	VY004	VY005	VY002	VY008	hIgG1 isotype cont.	PT3- hIgG1	AT100
pT212	0.082	0.087	0.055	0.112	0.060	3.162	0.069
pS214	0.069	0.092	0.058	0.143	0.061	3.142	0.065
pT217	0.287	2.967	0.068	3.134	0.083	3.132	0.068
pT212, pS214, pT217	0.795	0.789	0.060	2.418	0.053	3.166	0.187
pT212, pS214	0.067	0.111	0.055	0.186	0.059	3.142	0.071
pS214, pT217	0.207	2.468	0.062	2.825	0.059	3.131	0.067
pT212, pT217	2.623	2.593	0.060	3.123	0.057	3.158	0.069

[0347] As shown in **Table 16**, VY004, VY005, VY002, and VY008 showed distinct binding patterns compared to PT3 for Tau204-222 phospho-peptide species. PT3 exhibited binding to all single, double, and triple phosphorylated peptides tested.

[0348] VY004 exhibited binding when the peptide was singly phosphorylated at T217, when doubly phosphorylated at pS214/pT217 and pT212/pT217 (albeit substantially more weakly for pS214/pT217), and when triply phosphorylated (pT212/pS214/pT217). VY005 and VY008 showed similar binding patterns, with both binding when the peptide was singly phosphorylated at T217, doubly phosphorylated at pS214/pT217 and pT212/pT217, and when triply phosphorylated (pT212/pS214/pT217). VY002 did not bind to any of the phosphorylated peptides in this experiment.

[0349] Further testing was done with additional peptides spanning the PT3 epitope having a different length than the Tau204-222 phospho-peptides described above. **Table 17** lists the peptides used in this experiment.

Table 17. Additional PT3 peptides

Peptide	Specificity	Sequence	SEQ ID NO:
AC04	pT212, pT217	CSR (pT) PSLP (pT) PPTREPK	282
wtTau C2	AT120	219-227	-
tPeptide 5 (204-222)	pT212, pS214, pT217	GTPGSRSR (pT) P (pS) LP (pT) PPTRE	276

[0350] As expected, PT3 exhibited binding to all 3 peptides (**Table 18**). Consistent with the results described above, VY004, VY005, and VY008 all showed binding to the doubly

phosphorylated (pT212/pT217) AC04 peptide. VY004, VY005, and VY008 also showed binding to tpeptide5 (pT212/pS214/pT217), although the binding was weak for VY004 and VY005.

Table 18. Binding assay for PT3 bin antibodies (OD values at 450nm)

Peptides	VY004	VY005	VY008	PT3-hIgG1	IPN002-hIgG1	hIgG1 isotype control
AC04	2.850	2.825	2.963	2.802	0.211	0.147
wtTau C2	0.169	0.153	0.125	1.202	0.161	0.124
tPeptide5	0.382	0.288	2.872	2.806	0.281	0.141

[0351] These results collectively suggest that the VY004, VY005, and VY008 exhibit a distinct pattern of binding to phosphorylated tau species compared to PT3. Additionally, VY005 and VY008 appear to require phosphorylation of T217 for binding.

Example 9. Fine epitope mapping of AT180 bin antibodies

[0352] This Example describes the further characterization of the binding specificity of antibodies tentatively categorized as belonging to the AT180 bin (i.e., VY009, VY018, and VY019).

[0353] Screening of the overlapping phospho-peptide library identified all three antibodies as binding to a similar region as AT180, as demonstrated by their binding to the phospho-peptide (pT)PP(pT)REPKKVAVVR(pT)PPK (Tau217-234; SEQ ID NO: 298) (Table 19), as assessed by BLI.

Table 19. Binding affinity of AT180 bin antibodies for Tau217-234 phospho-peptide

Antibody	KD (nM)
AT180	0.005
VY009	0.31
VY018	4.08
VY019	3.7

[0354] Next, the ability of the three antibodies to bind to an AT180 peptide singly phosphorylated at T231 was tested (Tau225-240: KVAVVR(pT)PPKSPSSAK; SEQ ID NO: 299). As shown in Table 20, all three antibodies exhibited binding to the pT231 peptide in the nanomolar/subnanomolar range, as assessed by BLI.

Table 20. Binding affinity of AT180 bin antibodies for pT231 phospho-peptide

Antibody	KD (nM)
AT180	0.006

hIgG1 isotype control	no binding
pT231 mAb	1.950
VY009	0.439
VY018	3.649
VY019	11.539

[0355] Finally, the ability of the three antibodies to bind to an AT180 peptide having different combinations of phosphorylated residues were tested using ELISA. The phospho-peptides used in the experiment are shown in **Table 21**.

Table 21. AT180 phospho-peptides

SEQ ID	Description	Sequence
299	pT231	KVAVVR (pT) PPKSPSSAK
300	pS235	KVAVVRTPPK (pS) PSSAKPS
301	pT231/pS235	KVAVVR (pT) PPK (pS) PSSAKPS

[0356] As shown in **FIG. 3**, while VY009, VY018, and AT180 (and to a small extent VY019) exhibited binding to the pT231 phospho-peptide and pT231/pS235 phospho-peptide, none of the antibodies exhibited binding to the pS235 phospho-peptide.

We Claim:

1. An isolated, *e.g.*, recombinant, antibody that binds to human tau, wherein the antibody comprises a heavy chain variable region (VH) comprising a heavy chain complementary determining region 1 (HCDR1), a heavy chain complementary determining region 2 (HCDR2), and a heavy chain complementary determining region 3 (HCDR3), and a light chain variable region (VL) comprising a light chain complementary determining region 1 (LCDR1), a light chain complementary determining region 2 (LCDR2), and a light chain complementary determining region 3 (LCDR3), wherein:

(i) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 82, 97, 115, 127, 141, and 159, respectively;

(ii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 79, 94, 111, 127, 141, and 156, respectively;

(iii) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 80, 95, 112, 129, 143, and 157, respectively;

(iv) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of SEQ ID NOs: 81, 94, 114, 127, 141, and 156, respectively; or

(v) the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the amino acid sequences of any of the HCDR and LCDR sequences provided in **Table 1**.

2. The antibody of claim 1, which comprises a VH comprising:

(i) the amino acid sequence of any VH provided in **Table 1**, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications relative to the amino acid sequence of any VH provided in **Table 1**;

(iii) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid sequences of any VH sequences provided in **Table 1**; or

(iv) an amino acid sequence encoded by a nucleotide sequence of any VH provided in **Table 1**, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

3. The antibody of claim 1 or 2, which comprises a VL comprising:

(i) the amino acid sequence of any VL provided in **Table 1**, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications relative to the amino acid sequence of any VL provided in **Table 1**;

(iii) an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to any one of the amino acid sequences of any VL sequences provided in **Table 1**; or

(iv) an amino acid sequence encoded by a nucleotide sequence of any VL provided in **Table 1**, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.

4. The antibody of any one of the preceding claims, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 7; an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 7; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 7; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 25, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 25; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 25.

5. The antibody of any one of claims 1-4, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 3; an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 3; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 3; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 21, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10

different amino acids relative to SEQ ID NO: 21; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 21.

6. The antibody of any one of claims 1-4, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 4; an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 4; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 4; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 22; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 22.

7. The antibody of any one of claims 1-4, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 6; an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 6; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 6; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 24; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 24.

8. The antibody of any one of claims 1-4, comprising:

(i) a VH comprising the amino acid sequence of SEQ ID NO: 11; an amino acid

sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 11; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 11; and

(ii) a VL comprising the amino acid sequence of SEQ ID NO: 30, or an amino acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids relative to SEQ ID NO: 30; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 modifications, e.g., substitutions (e.g., conservative substitutions) relative to SEQ ID NO: 30.

9. The antibody of any one of claims 1-8, wherein the antibody binds to:

(a) a tau protein at a half maximal effective concentration (EC₅₀) of from about 0.001 nM to about 10 nM, or about 0.01 nM to about 2 nM, e.g., as assessed by direct enzyme-linked immunosorbent assay (ELISA);

(b) enriched paired helical filament tau protein (ePHF), e.g., at a half maximal effective concentration (EC₅₀) of from about 0.001 nM to about 100 nM, or about 0.01 nM to about 20 nM e.g., as assessed by direct enzyme-linked immunosorbent assay (ELISA);

(c) iPHF with a dissociation constant (K_D) of about 0.1 to about 10 nM, or about 0.2-5 nM, e.g., as assessed by bio-layer interferometry;

(d) a tau protein epitope comprising a region formed by a complex of at least two tau proteins; and/or

(e) all or a portion of amino acid residues of tau selected from: (a) 183-212, (b) 187-218, (c) 33-82, 159-182, 197-226, and 229-246; (d) 217-242, (e) 35-76 and 187-218, (f) 5-34, (g) 187-218, (h) 33-82, 159-188, and 191-230, (i) 35-62, 107-124, and 203-220, (j) 35-82, 159-188, and 197-224, or (k) 53-78, 329-348, and 381-408, wherein human tau is numbered according to SEQ ID NO: 274, optionally wherein one or more of the serines, threonines, and/or tyrosines in the stretch of amino acids selected from (a)-(k) are phosphorylated, optionally wherein all of the serines, threonines, and/or tyrosines in the stretch of amino acids selected from (a)-(k) are phosphorylated.

10. The antibody of any one of claims 1-9, which binds to:

(a) all or a portion of amino acids 195-215 of tau with a dissociation constant (K_D) of

about 1 pM to about 50 pM, or about 1-25 pM, e.g., as assessed by bio-layer interferometry;

(b) all or a portion of amino acids 191-214 of tau phosphorylated at S199 with a dissociation constant (K_D) of about 0.1 nM to about 10 nM, or about 0.5-5 nM, e.g., as assessed by bio-layer interferometry;

(c) all or a portion of amino acids 217-234 of tau phosphorylated at T217, T220, and T231 with a dissociation constant (K_D) of about 0.1 nM to about 10 nM, or about 0.1-5 nM, e.g., as assessed by bio-layer interferometry; or

(d) all or a portion of amino acids 225-240 of tau phosphorylated at T231 with a dissociation constant (K_D) of about 0.1 nM to about 25 nM, or about 0.1-15 nM, e.g., as assessed by bio-layer interferometry.

11. An isolated, *e.g.*, recombinant, antibody that binds to human tau phosphorylated at amino acid residue S404, or a peptide comprising or consisting of the amino acid sequence DHGAEIVYKSPVVSGDT(pS)PRHLSNVSSSTG (SEQ ID NO: 281), wherein p(S) corresponds to a phosphorylated serine residue, and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 89, 106, and 124, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 138, 152, and 169, respectively.

12. An isolated, *e.g.*, recombinant, antibody that binds to:

(a) human tau phosphorylated at amino acid residue S199, but not at amino acid residues S202 and T205,

(b) human tau phosphorylated at amino acid residue S202, but not at amino acid residues S199 and T205,

(c) human tau phosphorylated at amino acid residue T205, but not at amino acid residues S199 and S202,

(d) human tau phosphorylated at a combination of amino acid residues S199 and T205, but not at amino acid residue S202 (e.g., wherein binding tau phosphorylated at a combination of S199 and T205 is at least 3-times stronger (e.g., at least 4-time stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control),

(e) human tau phosphorylated at a combination of amino acid residues S202 and T205, but not at amino acid residue S199, but not human tau phosphorylated at a combination of residues S199 and S202, but not T205,

(f) human tau phosphorylated at a combination of amino acid residues (i) S202 and T205, but not S119, and (ii) S199 and T205, but not S202, at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more strongly than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control).

(g) human tau phosphorylated at a combination of amino acid residues (i) S199 and S202, but not T205, (ii) S202 and T205, but not S199, (iii) S199 and T205, but not S202, and (iv) S199, S202, and T205 (e.g., wherein binding to phosphorylated tau is at least 1.6-times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-3 times, 1.6-2 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control),

(h) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPGTPGSRSRTPS (SEQ ID NO: 284),

(i) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PGTPGSRSRTPS (SEQ ID NO: 285),

(j) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPGSPG(pT)PGSRSRTPS (SEQ ID NO: 286), or

(k) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290) (e.g., wherein binding to the peptide is at least 3 times stronger (e.g., at least 4 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control),

(l) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), but not a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288),

(m) peptides comprising or consisting of the amino acid sequences SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289) and SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), wherein binding to the latter peptide is at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more stronger than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), or

(n) peptides comprising or consisting of the amino acid sequences SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288), SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289),

SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), and
SGDRSGYS(pS)PG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 287) (e.g., wherein binding to
the peptides is at least 1.6 times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9
times, at least 2 times, at least 3 times, 1.6-4 times, 1.6-3 times stronger) than background
(e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control),

wherein p(S) and p(T) correspond to a phosphorylated serine and
phosphorylated threonine, respectively,

optionally wherein binding is assessed, e.g., using one point ELISA as
described in Example 7.

13. The antibody of claim 12, wherein the antibody comprises:

(a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3
sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable
region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127,
141, and 159, respectively;

(b) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3
sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable
region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127,
141, and 156, respectively;

(c) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3
sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable
region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127,
141, and 156, respectively;

(d) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3
sequences comprising SEQ ID NOs: 77, 92, and 109, respectively, and a light chain variable
region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127,
141, and 154, respectively; or

(e) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3
sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable
region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127,
141, and 156, respectively.

14. The antibody of claim 12 or 13, wherein the antibody comprises a VH and a VL,
wherein the VH and the VL comprise the amino sequence of:

- (a) SEQ ID NOs: 7 and 25, respectively,
- (b) SEQ ID NOs: 8 and 21, respectively,
- (c) SEQ ID NOs: 6 and 24, respectively,
- (d) SEQ ID NOs: 1 and 19, respectively, or
- (e) SEQ ID NOs: 12 and 31, respectively.

15. An isolated, *e.g.*, recombinant, antibody that binds to:

(a) human tau phosphorylated at amino acid residue S199, but not at amino acid residues S202 and T205, and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively;

(b) human tau phosphorylated at amino acid residue S202, but not at amino acid residues S199 and T205, and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(c) human tau phosphorylated at amino acid residue T205, but not at amino acid residues S199 and S202, and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain

variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(d) human tau phosphorylated at a combination of amino acid residues S199 and T205, but not at amino acid residue S202 (e.g., wherein binding tau phosphorylated at a combination of S199 and T205 is at least 3-times stronger (e.g., at least 4-time stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(e) human tau phosphorylated at a combination of amino acid residues S202 and T205, but not at amino acid residue S199, but not human tau phosphorylated at a combination of residues S199 and S202, but not T205, and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 77, 92, and 109, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 154, respectively;

(f) human tau phosphorylated at a combination of amino acid residues (i) S202 and T205, but not S119, and (ii) S199 and T205, but not S202, at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more strongly than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy

chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(g) human tau phosphorylated at a combination of amino acid residues (i) S199 and S202, but not T205, (ii) S202 and T205, but not S199, (iii) S199 and T205, but not S202, and (iv) S199, S202, and T205 (e.g., wherein binding to phosphorylated tau is at least 1.6-times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-3 times, 1.6-2 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(h) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPGTPGSRSRTPS (SEQ ID NO: 284), and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127,

141, and 159, respectively

(i) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PGTPGSRSRTPS (SEQ ID NO: 285), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(j) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPGSPG(pT)PGSRSRTPS (SEQ ID NO: 286), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(k) a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290) (e.g., wherein binding to the peptide is at least 3 times stronger (e.g., at least 4 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light

chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

(l) a peptide comprising or consisting of the amino acid sequence SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), but not a peptide comprising or consisting of the amino acid sequence SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288), and wherein the antibody comprises a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 77, 92, and 109, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 154, respectively

(m) peptides comprising or consisting of the amino acid sequences SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289) and SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), wherein binding to the latter peptide is at least 2 times (e.g., at least 3 times, at least 4 times, at least 5 times, 2-6 times, 2-5 times, 2-4 times, 2-3 times, 3-5 times or 4-5 times) more stronger than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; or

(n) peptides comprising or consisting of the amino acid sequences SGDRSGYS(pS)PG(pS)PGTPGSRSRTPS (SEQ ID NO: 288), SGDRSGYSSPG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 289), SGDRSGYS(pS)PGSPG(pT)PGSRSRTPS (SEQ ID NO: 290), and SGDRSGYS(pS)PG(pS)PG(pT)PGSRSRTPS (SEQ ID NO: 287) (e.g., wherein binding to the peptides is at least 1.6 times stronger (e.g., at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, 1.6-4 times, 1.6-3 times stronger) than background (e.g., non-specific) level of binding, e.g., binding by hIgG1 isotype control), and wherein the antibody comprises (i) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 79, 94, and 111, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (ii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 81, 94, and 114, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively; (iii) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 82, 97, and 115, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 159, respectively; or (iv) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 86, 102, and 120, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 127, 141, and 156, respectively;

wherein p(S) and p(T) correspond to a phosphorylated serine and phosphorylated threonine, respectively,

optionally wherein binding is assessed, e.g., using one point ELISA as described in Example 7.

16. An isolated, *e.g.*, recombinant, antibody that binds to:

(a) tau phosphorylated at T217, but not at T212 or T214, or

(b) peptides comprising or consisting of the sequences

GTPGSRSRTPSLP(pT)PPTRE (SEQ ID NO: 293) and GTPGSRSRTP(pS)LP(pT)PPTRE (SEQ ID NO: 296), but not peptides comprising or consisting of the sequences GTPGSRSR(pT)PSLTPPPTRE (SEQ ID NO: 291), GTPGSRSRTP(pS)LPTPPTRE (SEQ ID NO: 292), and GTPGSRSR(pT)P(pS)LPTPPTRE (SEQ ID NO: 294),

wherein p(S) and p(T) correspond to a phosphorylated serine and phosphorylated threonine, respectively,

optionally wherein binding of the antibody to tau or the peptide is at least 1.5 times stronger (e.g., at least 1.6 times, at least 1.7 times, at least 1.8 times, at least 1.9 times, at least 2 times, at least 3 times, at least 4 times, at least 5 times, at least 6 times, 1.5-4 times, 1.5-3, 4-6 times stronger) than background (non-specific) level of binding, e.g., binding by hIgG1 isotype control),

optionally wherein binding of the antibody to tau or the peptide is assessed, e.g., using one point ELISA as described, e.g., in Example 8.

17. The antibody of claim 16, wherein the antibody comprises:

(a) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 80, 95, and 112, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 129, 143, and 157, respectively;

(b) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 78, 104, and 122, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 136, 150, and 167, respectively; or

(c) a heavy chain variable region (VH) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 90, 107, and 125, respectively, and a light chain variable region (VL) comprising CDR1, CDR2, and CDR3 sequences comprising SEQ ID NOs: 139, 151, and 170, respectively.

18. The antibody of claim 16 or 17, wherein the antibody comprises a VH and a VL, wherein the VH and the VL comprise the amino acid sequence of:

(a) SEQ ID NOs: 4 and 22, respectively,

(b) SEQ ID NOs: 14 and 34, respectively, or

(c) SEQ ID NOs: 17 and 37, respectively.

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

(a) is an IgA, IgD, IgE, IgG, or IgM antibody;

(b) is an isotype selected from IgG1, IgG2, IgG3, and IgG4; and/or

(c) comprises a heavy chain constant region selected from human IgG1, human IgG2,

human IgG3, human IgG4, murine IgG1, murine IgG2a, murine IgG2b, murine IgG2c, and murine IgG3; and/or a light chain constant region selected from the light chain constant regions of kappa or lambda.

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

(i) a heavy chain constant region (CH), e.g., a CH comprising an amino acid sequence of any of the heavy chain constant regions in **Table 5**, or a sequence having at least 80% (e.g., 85, 90, 95, 96, 97, 98, or 99%) sequence identity to the heavy chain constant region sequences in **Table 5**; an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications, relative to the amino acid sequence of the heavy chain constant region sequences in **Table 5**; or an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of the heavy chain constant region sequences in **Table 5**; and/or

(ii) a light chain constant region (CL), e.g., a CL comprising an amino acid sequence of any of the CL sequences in **Table 5**, or a sequence having at least 80% (e.g., 85, 90, 95, 96, 97, 98, or 99%) sequence identity to any of the CL sequences in **Table 5**; an amino acid sequence comprising at least one, two or three modifications, but not more than 30, 20 or 10 modifications, relative to the amino acid sequence of the light chain constant region sequences in **Table 5**; an amino acid sequence comprising at least one, two or three, but not more than 30, 20 or 10 different amino acids, relative to the amino acid sequence of the light chain constant region sequences in **Table 5**.

21. The antibody of any one of the preceding claims, wherein the antibody is a full-length antibody, a bispecific antibody, an intrabody, a Fab, a F(ab')₂, a Fv, a single chain Fv fragment (scFv), single domain antibody, or a camelid antibody.

22. The antibody of any one of the preceding claims, wherein the antibody molecule comprises a second antigen-binding region having a different binding specificity than the antigen-binding region that binds to tau, optionally wherein the antibody molecule is a multispecific antibody molecule comprising at least a first antigen-binding domain and a second antigen-binding domain, e.g., a bispecific antibody molecule.

23. The antibody of any one of the preceding claims, wherein the antibody:

- (a) does not bind to non-pathological tau;
 - (b) binds to pathological tau tangles; and/or
 - (c) inhibits tau aggregation.
24. A composition (e.g., a pharmaceutical composition) comprising the antibody of any one of preceding claims and a carrier (e.g., a pharmaceutically-acceptable carrier).
25. An isolated, e.g., recombinant, nucleic acid, or a combination of nucleic acids, encoding the antibody of any one of claims 1-23.
26. The nucleic acid, or combination of nucleic acids, of claim 25, comprising:
- (a) the nucleotide sequence of any VH provided in **Table 1**, or a nucleic acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or
 - (b) the nucleotide sequence of any VL provided in **Table 1**, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
27. The nucleic acid, or combination of nucleic acids, of claim 25 or 26, comprising:
- (a) the nucleotide sequence of any one of SEQ ID NOs: 51, 55, 54, 52, 47, 39, 56, 41, 50, 49, 48, 46, 45, 44, 43, 42, 53, 40, or a nucleic acid sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or
 - (b) the nucleotide sequence of any one of SEQ ID NOs: 67, 75, 74, 72, 66, 57, 76, 59, 70, 69, 68, 65, 64, 62, 63, 61, 60, 73, 58, or a nucleotide sequence having at least 70%, 75%, 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
28. The isolated nucleic acid sequence of any one of claims 25-27, wherein the nucleic acid sequence encoding the heavy chain variable region and/or the light chain variable region is codon-optimized.
29. An isolated, e.g., recombinant, antibody encoded by the nucleic acid of any one of claims 25-28.
30. A vector (e.g., an expression vector), or combination of vectors (e.g., combination of

expression vectors), comprising the nucleic acid, or combination of nucleic acids, of any one of claims 25-28.

31. A host cell comprising the nucleic acid, or combination of nucleic acids, of any one of claims 25-28, or the vector, or combination of vectors, of claim 30, optionally wherein host cell is a bacterial cell or a mammalian cell.

32. A method of producing an antibody which binds to human tau, the method comprising culturing the host cell of claim 31, under conditions suitable for gene expression.

33. A method of delivering to a subject an exogenous antibody that binds to human tau, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-23, or the composition (e.g., a pharmaceutical composition) of claim 24, optionally wherein the subject is human.

34. The method of claim 33, wherein the subject has, has been diagnosed with having, or is at risk of having:

- (a) a disease associated with expression of tau;
- (b) a neurological, *e.g.*, neurodegenerative disorder; and/or
- (c) a tauopathy.

35. A method of treating a subject having or diagnosed with having a disease associated with tau expression or activity, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-23, or the composition (e.g., a pharmaceutical composition) of claim 24, optionally wherein the subject is human.

36. A method of treating a subject having or diagnosed with having a neurological, *e.g.*, neurodegenerative disorder, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-23, or the composition (e.g., a pharmaceutical composition) of claim 24, optionally wherein the subject is human.

37. A method of treating a subject having or diagnosed with having a tauopathy, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-23, or the composition (e.g., a pharmaceutical composition) of claim 24,

optionally wherein the subject is human.

38. The method of any one of claims 34-37, wherein the disease associated with tau expression or activity, the neurological, *e.g.*, neurodegenerative disorder, or the tauopathy comprises Alzheimer's disease (AD), frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), frontotemporal dementia (FTD), chronic traumatic encephalopathy (CTE), progressive supranuclear palsy (PSP), Down's syndrome, Pick's disease, corticobasal degeneration (CBD), corticobasal syndrome, amyotrophic lateral sclerosis (ALS), prion diseases, Creutzfeldt-Jakob disease (CJD), multiple system atrophy, tangle-only dementia, or progressive subcortical gliosis.

39. The method of any one of claims 33-38, wherein the antibody is administered intravenously.

40. The method of any one of claims 33-39, further comprising administration of an additional therapeutic agent and/or therapy suitable for treatment or prevention of a disorder associated with tau expression or activity, a neurological, *e.g.*, neurodegenerative disorder, or a tauopathy, optionally wherein the additional therapeutic agent and/or therapy comprises a cholinesterase inhibitor (*e.g.*, donepezil, rivastigmine, and/or galantamine), an N-methyl D-aspartate (NMDA) antagonist (*e.g.*, memantine), an antipsychotic drug, an anti-anxiety drug, an anticonvulsant, a dopamine agonist (*e.g.*, pramipexole, ropinirole, rotigotine, and/or apomorphine), an MAO B inhibitor (*e.g.*, selegiline, rasagiline, and/or safinamide), catechol O-methyltransferase (COMT) inhibitors (entacapone, opicapone, and/or tolcapone), anticholinergics (*e.g.*, benztropine and/or trihexyphenidyl), amantadine, carbidopa-levodopa, deep brain stimulation (DBS), or a combination thereof.

41. The antibody of any one of claims 1-23, or composition of claim 24, for use in a method of treating a neurological, *e.g.*, neurodegenerative disorder, a disease associated with tau expression or activity, or a tau-related disease (*e.g.*, tauopathy).

42. The antibody of any one of claims 1-23, or composition of claim 24, for use in the manufacture of a medicament.

43. The antibody of any one of claims 1-23, or composition of claim 24, for use in the manufacture of a medicament for treating a neurological, *e.g.*, neurodegenerative disorder, a disease associated with tau expression or activity, or a tau-related disease (*e.g.*, tauopathy).
44. Use of the antibody of any one of claims 1-23, or composition of claim 24 in the manufacture of a medicament.
45. Use of the antibody of any one of claims 1-23, or composition of claim 24 in the manufacture of a medicament for treating a neurological, *e.g.*, neurodegenerative disorder, a disease associated with tau expression or activity, or a tau-related disease (*e.g.*, tauopathy).