

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)PRHLSNV SSTG (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 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;

———(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)PSLPTPPTRE (SEQ ID NO: 291), GTPGSRSRTP(pS)LPTPPTRE (SEQ ID

NO: 292), and GTPGSRSR(pT)P(pS)LTPPTRE (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).~~

Claims

1. An invention not claimed in any divisional application.