

CLAIMS

What is claimed is:

1. ~~An isolated, e.g., recombinant, antibody that binds to tau comprising a heavy chain variable region (VH) comprising an HC CDR1, an HC CDR2, and an HC CDR3, and a light chain variable region (VL) comprising an LC CDR1, an LC CDR2, and an LC CDR3, wherein:~~
 - (i) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 315, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 474, 529, and 571, respectively;~~
 - (ii) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 314, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1154, 529, and 571, respectively;~~
 - (iii) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 316, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 475, 530, and 571, respectively;~~
 - (iv) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 325, 362, and 435, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 495, 540, and 587, respectively;~~
 - (v) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 304, 347, and 400, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 464, 523, and 562, respectively;~~
 - (vi) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 299, 343, and 395, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 460, 518, and 557, respectively; or~~
 - (vii) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of any of the HC CDR sequences of Tables 1, 6, 2A-2C, 4, or 5; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of any of the~~

LC CDR sequences of Tables 1, 6, 2A-2C, 4, or 5.

2. An isolated, *e.g.*, recombinant, antibody that binds to tau comprising a heavy chain variable region (VH) comprising an HC CDR1, an HC CDR2, and an HC CDR3, and a light chain variable region (VL) comprising an LC CDR1, an LC CDR2, and an LC CDR3, wherein:

- (i) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1180, 341, 410, 1181, 1182, and 571, respectively;
- (ii) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1183, 1184, 410, 1185, 1182, and 571, respectively; or
- (iii) the HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1186, 1187, 1167, 1188, 528, and 571, respectively;

optionally wherein the antibody binds to a region of a human tau protein comprising residues 409-436, numbered according to SEQ ID NO: 920.

3. The antibody of claim 2, wherein the antibody binds to the region of the human tau protein comprising residues 409-436, numbered according to SEQ ID NO: 920, and wherein:

- (i) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1180, 341, and 410, respectively; and
- (ii) the LC CDR1, LC CDR2, and LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1181, 1182 and 571, respectively.

4. The antibody of any one of claims 1-3, wherein:

- (i) the VH comprises the amino acid sequence of SEQ ID NO: 22, 21, 23, 51, 9, or 4, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
- (ii) the VH comprises an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 22, 21, 23, 51, 9, or 4;
- (iii) the VH comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 168, 167, 169, 197, 155, or 150, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence

identity thereto; or

- (iv) the VH comprises an amino acid sequence of any VH provided in Table 3 or 4, or an amino acid sequence having at least 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 of the amino acid sequence of any VH provided in Table 3 or 4.

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

- (i) the VL comprises the amino acid sequence of SEQ ID NO: 94, 93, 95, 122, 83, or 78, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;
- (ii) the VL comprises an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 94, 93, 95, 122, 83, or 78;
- (iii) the VL comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 242, 241, 243, 270, 229, or 224, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; or
- (iv) the VL comprises the amino acid sequence of any VL provided in Table 3 or 4, or an amino acid sequence having at least 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 of the amino acid sequence of any VL provided in Table 3 or 4.

6. The antibody of any one of claims 1-5, wherein:

- (i) the VH comprises the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof, and the VL comprises the amino acid sequence of SEQ ID NO: 94 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof;
- (ii) the VH comprises the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99%

sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof, and the VL comprises the amino acid sequence of SEQ ID NO: 93 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof;

- (iii) the VH comprises the amino acid sequence of SEQ ID NO: 23 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof, and the VL comprises the amino acid sequence of SEQ ID NO: 95 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof;
- (iv) the VH comprises the amino acid sequence of SEQ ID NO: 51 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof, and the VL comprises the amino acid sequence of SEQ ID NO: 122 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof;
- (v) the VH comprises the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof, and the VL comprises the amino acid sequence of SEQ ID NO: 83 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof; or,
- (vi) the VH comprises the amino acid sequence of SEQ ID NO: 4 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof, and the VL comprises the amino

acid sequence of SEQ ID NO: 78 or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications thereof.

7. ~~The antibody of any one of claims 1-6, wherein:~~
 - (i) ~~the nucleotide sequence encoding the VH comprises the nucleotide sequence of SEQ ID NO: 168, 167, 169, 197, 155, or 150, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or~~
 - (ii) ~~the nucleotide sequence encoding the VL comprises the nucleotide sequence of SEQ ID NO: 242, 241, 243, 270, 229, or 224, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.~~
8. ~~The antibody of any one of claims 1-7, which is a full length antibody, a bispecific antibody, an Fab, an F(ab')₂, an Fv, or a single chain Fv fragment (scFv).~~
9. ~~The antibody of any one of claims 1-8, comprising a heavy chain constant region selected from human IgG1, human IgG2, human IgG3, and human IgG4, murine IgG1, murine IgG2a, murine IgG2b, murine IgG2c, and murine IgG3; and/or a light chain constant region chosen from the light chain constant regions of kappa or lambda, e.g., human or mouse kappa, or human or mouse lambda.~~
10. ~~The antibody of any one of claims 1-9, comprising a heavy chain constant region comprising an amino acid of a heavy chain constant region provided in Table X, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or a light chain constant region comprising the amino acid sequence of a light chain constant region provided in Table X, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.~~
11. ~~The antibody of any one of claims 1-10, which binds:~~
 - (1) ~~the C terminus of a tau protein, e.g., residues 409-436 numbered according to SEQ ID NO: 920;~~
 - (2) ~~a microtubule binding domain of a tau protein;~~
 - (3) ~~a proline-rich domain of a tau protein;~~

- (4) ~~a tau protein which comprises at least one, two, three or more phosphorylated residues, e.g., residue T212, T217, S396, S404, S409, or combination thereof, numbered according to SEQ ID NO: 920;~~
 - (5) ~~enriched paired helical filament tau protein (ePHF); and/or,~~
 - (6) ~~an epitope comprising a region formed by a complex of at least two tau proteins, e.g., a tau dimer.~~
12. ~~The antibody of any one of claims 1-11, which binds to a tau protein with a dissociation constant (K_D) of less than about 120 nM (e.g., as measured by Octet, e.g., as described in Example 8).~~
13. ~~The antibody of any one of claims 1-12, which reduces or inhibits aggregation of tau, e.g., inhibits aggregation of tau at a half maximal inhibitory concentration (IC50) of from about 1 nM to about 30 nM (e.g., as measured by an immunodepletion assay (e.g., with tau RD Biosensor cells), e.g., as described in Example 6).~~
14. ~~An isolated, e.g., recombinant, antibody that competes for binding to tau with the antibody of any one of the preceding claims.~~
15. ~~An isolated, e.g., recombinant, antibody that binds to the same epitope as, substantially the same epitope as, or an epitope that overlaps with, the epitope of the antibody of any one of the preceding claims.~~
16. ~~An isolated, e.g., recombinant, nucleic acid encoding the antibody of any one of the preceding claims.~~
17. ~~An isolated, e.g., recombinant, nucleic acid encoding an antibody comprising a VH comprising an HC CDR1, an HC CDR2, and an HC CDR3, and a VL comprising an LC CDR1, an LC CDR2, and an LC CDR3, wherein:~~
- (i) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 315, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 474, 529, and 571, respectively;~~
 - (ii) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 314, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1154, 529, and 571, respectively;~~
 - (iii) ~~the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence~~

- of SEQ ID NOs: 316, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 475, 530, and 571, respectively;
- (iv) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 325, 362, and 435, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 495, 540, and 587, respectively;
- (v) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 304, 347, and 400, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 464, 523, and 562, respectively;
- (vi) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 299, 343, and 395, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 460, 518, and 557, respectively; or
- (vii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of any of the HC CDR sequences of Tables 1, 6, 2A-2C, 4, or 5; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of any LC CDR sequence of Tables 1, 6, 2A-2C, 4, or 5.
18. The nucleic acid of claim 17, wherein:
- (i) the VH comprises the amino acid sequence of SEQ ID NO: 22, 21, 23, 51, 9, or 4, or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications of the amino acid sequence thereof; and/or
- (ii) the VL comprises the amino acid sequence of SEQ ID NO: 94, 93, 95, 122, 83, or 78, or an amino acid sequence either having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto or having at least one, two or three modifications, but not more than 10 modifications of the amino acid sequence thereof.
19. The nucleic acid of claims 17 or 18, comprising:
- (i) the nucleotide sequence of any VH provided in Table 3 or 4, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence

- identity thereto; and/or
- (ii) the nucleotide sequence of any VL provided in Table 3 or 4, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
20. The nucleic acid of any one of claims 17-19, comprising:
- (i) the nucleotide sequence of SEQ ID NO: 168, 167, 169, 197, 155, or 150, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or
- (ii) the nucleotide sequence of SEQ ID NO: 242, 241, 243, 270, 229, or 224, or a nucleotide sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
21. The nucleic acid of any one of claims 17-20, wherein the antibody comprises:
- (i) a heavy chain constant region comprising an amino acid of a heavy chain constant region provided in Table X, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto; and/or
- (ii) a light chain constant region comprising the amino acid sequence of a light chain constant region provided in Table X, or an amino acid sequence having at least 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto.
22. The isolated nucleic acid sequence of any one of claims 17-21, wherein the nucleic acid sequence encoding the heavy chain variable region and/or the light chain variable region is codon optimized.
23. An isolated, *e.g.*, recombinant antibody, encoded by the nucleic acid of any one of claims 17-22.
24. An isolated nucleic acid encoding a payload, wherein the encoded payload comprises the antibody of any one of claims 1-15 or 23, or an antibody encoded by the nucleic acid of any one of claims 17-22.
25. The nucleic acid of claim 24, further encoding a signal sequence and optionally a second signal sequence, optionally wherein the nucleotide sequence encoding the signal sequence, and/or the second signal sequence (if present), comprises the nucleotide sequence of any of the signal sequences listed in Table 14, or a nucleotide sequence with at least 95% sequence identity thereto.

26. The nucleic acid of claim 24 or 25, wherein the:
- (i) the nucleotide sequence encoding the signal sequence is located 5' relative to the nucleotide sequence encoding the VH; and/or
 - (ii) the nucleotide sequence encoding the signal sequence is located 5' relative to the nucleotide sequence encoding the VL.
27. The nucleic acid of any one of claims 24-26, wherein:
- (i) the sequences of the encoded VH and VL are connected directly (*e.g.*, without a linker); or
 - (ii) the sequences of the encoded VH and VL are connected via a linker, optionally, the linker comprises the nucleotide sequence of any of the linker sequences provided in Table 15, or a nucleotide sequence with at least 95% sequence identity thereto.
28. The nucleic acid of any one of claims 24-27, wherein the encoded payload is a full length antibody, a bispecific antibody, an Fab, an F(ab')₂, an Fv, a single chain Fv fragment (scFv), single domain antibody, or a camelid antibody.
29. A viral genome comprising a promoter operably linked to the nucleic acid encoding a payload comprising the antibody of any one of claims 1-15 and 23, optionally, wherein the promoter:
- (i) is chosen from human elongation factor 1 α subunit (EF1 α), cytomegalovirus (CMV) immediate early enhancer and/or promoter, chicken β actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron specific enolase (NSE), platelet derived growth factor (PDGF), platelet derived growth factor B chain (PDGF β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl CpG binding protein 2 (MeCP2), Ca²⁺/calmodulin dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β globin minigene n β 2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), or a fragment, *e.g.*, a truncation, or a functional variant thereof; and/or
 - (ii) comprises the nucleotide sequence of any of the promoter sequences provided in Table 11, or a nucleotide sequence at least 95% identical thereto.

30. The viral genome of claim 29, which further comprises an enhancer, optionally wherein the enhancer is a CMV immediate early (CMVie) enhancer.
31. The viral genome of claim 29 or 30, which further comprises:
- (i) a polyadenylation (polyA) signal region, optionally, wherein the polyA signal region comprises the nucleotide sequence of any of SEQ ID NO: 1134-1136, or a nucleotide sequence with at least 95% identity thereto;
 - (ii) an ITR sequence, optionally wherein:
 - (a) the ITR sequence is positioned 5' relative to the encoded payload and/or the ITR sequence is positioned 3' relative to the encoded; and/or
 - (b) the ITR sequence comprises a nucleotide sequence of any one of SEQ ID NOs: 1035-1038, or a nucleotide sequence with at least 80%, 85%, 90%, or 95% sequence identity thereto;
 - (iii) at least 1, 2, or 3 intron regions, optionally, wherein each intron region independently comprises a nucleotide sequence of any of the intron regions listed in Table 13, or a nucleotide sequence with at least 95% identity thereto;
 - (iv) at least 1, 2, or 3 exon regions; optionally, wherein each exon region independently comprises a nucleotide sequence of any of the exon sequences in Table 12, or a nucleotide sequence with at least 95% identity thereto; and/or
 - (v) a Kozak sequence, optionally wherein the Kozak sequence comprises the nucleotide sequence of GCCGCCACCATG (SEQ ID NO: 1079) or GAGGAGCCACC (SEQ ID NO: 1089).
32. The viral genome of any one of claims 29-31, which further comprises a nucleotide sequence encoding a miR binding site, *e.g.*, a miR binding site that modulates, *e.g.*, reduces, expression of the payload encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed.
33. The viral genome of claim 32, which comprises at least 1-5 copies of an encoded miR binding site, *e.g.*, at least 1, 2, 3, 4, or 5 copies.
34. The viral genome of claim 32 or 33, which comprises at least 3 or 4 copies of the encoded miR binding site, optionally wherein all copies comprise the same miR binding site, or at least one, two, three or all of the copies comprise a different miR

binding site.

35. The viral genome of any one of claims 32-34, wherein the encoded miR binding site comprises a miR122 binding site, a miR183 binding site, a miR-142-3p, or a combination thereof, optionally wherein:
- (i) the encoded miR122 binding site comprises the nucleotide sequence of SEQ ID NO: 1029, or a nucleotide sequence substantially identical (*e.g.*, having at least 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1029;
 - (ii) the encoded miR183 binding site comprises the nucleotide sequence of SEQ ID NO: 1032, or a nucleotide sequence substantially identical (*e.g.*, having at least 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1032; and/or
 - (iii) the encoded miR-142-3p binding site comprises the nucleotide sequence of SEQ ID NO: 1031, or a nucleotide sequence substantially identical (*e.g.*, having at least 90%, 92%, 95%, 97%, 98%, or 99% sequence identity) thereto; or a nucleotide sequence having at least one, two, three, four, five, six, or seven modifications, but no more than ten modifications of SEQ ID NO: 1031.
36. The viral genome of any one of claims 29-35, which is single stranded.
37. A vector comprising the viral genome of any one claims 29-36, optionally wherein the vector further comprises:
- (i) a nucleotide sequence encoding a Rep protein, *e.g.*, a non-structural protein, wherein the Rep protein comprises a Rep78 protein, a Rep68, Rep52 protein, and/or a Rep40 protein, optionally wherein the Rep78 protein, the Rep68 protein, the Rep52 protein, and/or the Rep40 protein are encoded by at least one Rep gene; and/or
 - (ii) a nucleotide sequence encoding a capsid protein, *e.g.*, a structural protein, wherein the capsid protein comprises a VP1 polypeptide, a VP2 polypeptide, and/or a VP3 polypeptide, optionally wherein the VP1 polypeptide, the VP2 polypeptide, and/or the VP3 polypeptide are encoded by at least one Cap gene.

38. An isolated, *e.g.*, recombinant AAV particle comprising:
- (i) a capsid protein, and;
 - (ii) the nucleic acid of any one of claims 16 and 17-28, the viral genome of any one of claims 29-36, or the vector of claim 37.
39. The isolated AAV particle of claim 38, wherein:
- (i) the capsid protein comprises the amino acid sequence of SEQ ID NO: 1003, or an amino acid sequence with at least 80% (*e.g.*, at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto;
 - (ii) the capsid protein comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 1003;
 - (iii) the capsid protein comprises the amino acid sequence of SEQ ID NO: 1011, or an amino acid sequence with at least 80% (*e.g.*, at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto;
 - (iv) the capsid protein comprises an amino acid sequence having at least one, two or three modifications but not more than 30, 20 or 10 modifications of the amino acid sequence of SEQ ID NO: 1011;
 - (v) the capsid protein comprises an amino acid sequence encoded by the nucleotide sequence of SEQ ID NO: 1002, or a sequence with at least 80% (*e.g.*, at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto; and/or
 - (vi) the nucleotide sequence encoding the capsid protein comprises the nucleotide sequence of SEQ ID NO: 1002, or a sequence with at least 80% (*e.g.*, at least about 85, 90, 95, 96, 97, 98, or 99%) sequence identity thereto.
40. The isolated AAV particle of claim 38 or 39, wherein the capsid protein comprises:
- (i) an amino acid substitution at position K449, *e.g.*, a K449R substitution, numbered according to SEQ ID NO:1003;
 - (ii) an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151), optionally wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO:1003;
 - (iii) an amino acid other than "A" at position 587 and/or an amino acid other than "Q" at position 588, numbered according to SEQ ID NO: 1003; and/or

- (iv) the amino acid substitution of A587D and/or Q588G, numbered according to SEQ ID NO: 1003.
41. The isolated AAV particle of any one of claims 38-40, wherein the capsid protein comprises:
- (i) (a) the amino acid substitution of K449R numbered according to SEQ ID NO: 1003; and (b) an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151), optionally wherein the insert is present immediately subsequent to position 588 of SEQ ID NO: 1003;
 - (ii) (a) the amino acid substitution of K449R numbered according to SEQ ID NO: 1003; (b) an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151), optionally wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 1003; and (c) the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 1003; or
 - (iii) (a) an insert comprising the amino acid sequence of TLAVPFK (SEQ ID NO: 1151), optionally wherein the insert is present immediately subsequent to position 588, relative to a reference sequence numbered according to SEQ ID NO: 1003; and (b) the amino acid substitutions of A587D and Q588G, numbered according to SEQ ID NO: 1003.
42. The AAV particle of any one of claims 38-41, wherein the capsid protein comprises:
- (i) a VOY101, VOY201, AAVPHP.B (PHP.B), AAVPHP.A (PHP.A), AAVG2B-26, AAVG2B-13, AAVTH1.1-32, AAVTH1.1-35, AAVPHP.B2 (PHP.B2), AAVPHP.B3 (PHP.B3), AAVPHP.N/PHP.B-DGT, AAVPHP.B-EST, AAVPHP.B-GGT, AAVPHP.B-ATP, AAVPHP.B-ATT-T, AAVPHP.B-DGT-T, AAVPHP.B-GGT-T, AAVPHP.B-SGS, AAVPHP.B-AQP, AAVPHP.B-QQP, AAVPHP.B-SNP(3), AAVPHP.B-SNP, AAVPHP.B-QGT, AAVPHP.B-NQT, AAVPHP.B-EGS, AAVPHP.B-SGN, AAVPHP.B-EGT, AAVPHP.B-DST, AAVPHP.B-DST, AAVPHP.B-STP, AAVPHP.B-PQP, AAVPHP.B-SQP, AAVPHP.B-QLP, AAVPHP.B-TMP, AAVPHP.B-TTP, AAVPHP.S/G2A12, AAVG2A15/G2A3 (G2A3), AAVG2B4 (G2B4), AAVG2B5 (G2B5), AAVPHP.N (PHP.N), PHP.S, AAV1, AAV2, AAV2 variant, AAV2/3 variant, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9.47, AAV9(hu14), AAV9, AAV9-K449R, AAV10,

AAV11, AAV12, AAVrh8, AAVrh10, AAVDJ, AAVDJ8, or AAV2G9 capsid protein, or a functional variant thereof; optionally, the capsid protein comprises a VOY101 capsid protein; and/or

- (ii) any of the capsid proteins listed in Table 1 or a functional variant thereof.
43. ~~A host cell comprising the nucleic acid of any one of claims 16-22 and 24-28, the viral genome of any one of claims 29-36, or the AAV particle of any one of claims 38-42, optionally wherein the host cell is an insect cell, a bacterial cell or a mammalian cell.~~
44. ~~A method of producing an antibody, the method comprising culturing the host cell of claim 43 under conditions suitable for gene expression.~~
45. ~~A pharmaceutical composition comprising the antibody of any one of claims 1-15 and 23, the isolated nucleic acid of any one of claims 16-22 and 24-28, an AAV particle comprising the viral genome of any one of claims 29-36, or the AAV particle of any one of claims 38-42; and a pharmaceutically acceptable excipient.~~
46. ~~A method of delivering an exogenous antibody that binds to tau, to a subject, comprising administering an effective amount of the antibody of any one of claims 1-15 and 23, the isolated nucleic acid of any one of claims 16-22 and 24-28, an AAV particle (e.g., a plurality of AAV particles) comprising the viral genome of any one of claims 29-36, the AAV particle (e.g., a plurality of AAV particles) of any one of claims 38-42, or the pharmaceutical composition of claim 44; optionally,~~
- ~~(i) the subject has, has been diagnosed with having, or is at risk of having a disease associated with expression of tau;~~
 - ~~(ii) the subject has, has been diagnosed with having, or is at risk of having a neurological, e.g., neurodegenerative disorder; and/or,~~
 - ~~(iii) the subject has, has been diagnosed with having, or is at risk of having a tauopathy.~~
47. ~~A method of treating a subject having or diagnosed with having a neurological or neurodegenerative disorder, e.g., a tauopathy, comprising administering to the subject an effective amount of the antibody of any one of claims 1-15 and 23, the isolated nucleic acid of any one of claims 16-22 and 24-28, an AAV particle (e.g., a plurality of AAV particles) comprising the viral genome of any one of claims 29-36, the AAV particle (e.g., a plurality of AAV particles) of any one of claims 38-42, or the~~

pharmaceutical composition of claim 45.

48. The method of claim 47, wherein the neurological disorder comprises:
 - (i) a tauopathy; and/or
 - (ii) AD, FTDP-17, FTL, FTD, CTE, PSP, Down's syndrome, Pick's disease, CBD, Corticobasal syndrome, ALS, Prion diseases, CJD, Multiple system atrophy, Tangle-only dementia, or Progressive subcortical gliosis.
49. The method of any one of claims 46-48, wherein the subject is a human.
50. The method of any one of claims 46-49, wherein the AAV particle is administered to the subject intravenously, intramuscularly, via intraparenchymal administration, intracerebroventricularly, via intra-cisterna magna (ICM) injection, intrathecally, via focused ultrasound (FUS), *e.g.*, coupled with the intravenous administration of microbubbles (FUS-MB), or MRI-guided FUS coupled with intravenous administration; optionally, the AAV particle is administered to the subject intravenously; or via intra-cisterna magna injection (ICM).
51. The method of any one of claims 46-50, further comprising administration of an additional therapeutic agent and/or therapy suitable for treatment or prevention of a neurological or neurodegenerative disorder, *e.g.*, 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 tolecapone), anticholinergics (*e.g.*, benztropine and/or trihexyphenidyl), amantadine, carbidopa-levodopa, deep brain stimulation (DBS), or a combination thereof.
52. The antibody of any one of claims 1-15 and 23, the isolated nucleic acid of any one of claims 16-22 and 24-28, the AAV particle comprising the viral genome of any one of claims 29-36, the AAV particle of any one of claims 38-42, or the pharmaceutical composition of claim 45, for use in the manufacture of a medicament.
53. The antibody of any one of claims 1-15 and 23, the isolated nucleic acid of any one of claims 16-22 and 24-28, the AAV particle comprising the viral genome of any one of claims 29-36, the AAV particle of any one of claims 38-42, or the pharmaceutical

~~composition of claim 45, for use in treating a neurological or neurodegenerative disorder, e.g., a tauopathy.~~

54. ~~Use of an effective amount of the antibody of any one of claims 1-15 and 23, the isolated nucleic acid of any one of claims 16-22 and 24-28, the AAV particle comprising the viral genome of any one of claims 29-36, the AAV particle of any one of claims 38-42, or the pharmaceutical composition of claim 45, in the manufacture of a medicament for the treatment of a neurological or neurodegenerative disorder, e.g., a tauopathy in a subject.~~

CLAIMS

1. An antibody that binds to tau comprising a heavy chain variable region (VH) comprising an HC CDR1, an HC CDR2, and an HC CDR3, and a light chain variable region (VL) comprising an LC CDR1, an LC CDR2, and an LC CDR3, wherein:

(i) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1183, 1184, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1185, 1182, and 571, respectively;

(ii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1186, 1187, and 1167, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1188, 528, and 571, respectively; or

(iii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1180, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1181, 1182, and 571, respectively.

2. The antibody of claim 1, wherein:

(i) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1144, 1145, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1146, 529, and 571, respectively;

(ii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1147, 1148, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 474, 529, and 571, respectively; or

(iii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1149, 1150, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 475, 530, and 571, respectively.

3. The antibody of claim 1 or 2, wherein:

(i) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1144, 1145, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1146, 529, and 571, respectively;

(ii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1165, 1166, and 1167, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise

the amino acid sequence of SEQ ID NOs: 473, 528, and 571, respectively; or

(iii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 314, 341, and 410, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1154, 529, and 571, respectively.

4. The antibody of any one of claims 1-3, wherein:

(i) the VH comprises the amino acid sequence of any one of SEQ ID NOs: 21, 22, or 23, or an amino acid sequence having at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto;

(ii) the VH comprises an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 21, 22, or 23; or

(iii) the VH comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 167, 168, or 169, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

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

(i) the VL comprises the amino acid sequence of any one of SEQ ID NOs: 93, 94, or 95, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(ii) the VL comprises an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 93, 94, or 95; or

(iii) the VL comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 241, 242, or 243, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

6. The antibody of any one of claims 1-5, wherein:

(i) the VH comprises the amino acid sequence of SEQ ID NO: 21, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and the VL comprises the amino acid sequence of SEQ ID NO: 93, or an amino acid sequence at least

80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(ii) the VH comprises the amino acid sequence of SEQ ID NO: 22, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and the VL comprises the amino acid sequence of SEQ ID NO: 94, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; or

(iii) the VH comprises the amino acid sequence of SEQ ID NO: 23, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and the VL comprises the amino acid sequence of SEQ ID NO: 95, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

7. The antibody of any one of claims 1-6, wherein the VH comprises the amino acid sequence of SEQ ID NO: 21, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; and the VL comprises the amino acid sequence of SEQ ID NO: 93, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

8. The antibody of any one of claims 1-7, wherein:

(i) the nucleotide sequence encoding the VH comprises any one of SEQ ID NOs: 167, 168, or 169, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; and/or

(ii) the nucleotide sequence encoding the VL comprises any one of SEQ ID NOs: 241, 242, or 243, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

9. An antibody that binds to tau comprising a heavy chain variable region (VH) comprising an HC CDR1, an HC CDR2, and an HC CDR3, and a light chain variable region (VL) comprising an LC CDR1, an LC CDR2, and an LC CDR3, wherein:

(i) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1152, 1153, and 435, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 495, 540, and 587, respectively;

(ii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1142, 1143, and 400, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 464, 523, and 562, respectively;

(iii) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of SEQ ID NOs: 1140, 1141, and 395, respectively; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of SEQ ID NOs: 460, 518, and 557, respectively; or

(vi) the HC CDR1, HC CDR2, and HC CDR3 comprise the amino acid sequence of any of the HC CDR sequences of Tables 1, 6, 2A-2C, 4, or 5; and the LC CDR1, LC CDR2, LC CDR3 comprise the amino acid sequence of any of the LC CDR sequences of Tables 1, 6, 2A-2C, 4, or 5.

10. The antibody of claim 9, wherein:

(i) the VH comprises the amino acid sequence of any one of SEQ ID NOs: 51, 9, or 4, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(ii) the VH comprises an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 51, 9, or 4;

(iii) the VH comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 197, 155, or 150, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; or

(iv) the VH comprises an amino acid sequence of any VH provided in Table 3 or 4, or an amino acid sequence at least 80%, 85% 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; or an amino acid sequence having at least one, two or three modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any VH provided in Table 3 or 4.

11. The antibody of claim 9 or 10, wherein:

(i) the VL comprises the amino acid sequence of any one of SEQ ID NOs: 122, 83, or 78, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(ii) the VL comprises an amino acid sequence having at least one, two or three

modifications, but not more than 30, 20 or 10 modifications of the amino acid sequence of any one of SEQ ID NOs: 122, 83, or 78;

(iii) the VL comprises an amino acid sequence encoded by the nucleotide sequence of any one of SEQ ID NOs: 270, 229, or 224, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; or

(iv) the VL comprises the amino acid sequence of any VL provided in Table 3 or 4, or an amino acid sequence having at least 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 of the amino acid sequence of any VL provided in Table 3 or 4.

12. The antibody of any one of claims 9-11, wherein:

(i) the VH comprises the amino acid sequence of SEQ ID NO: 51, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and the VL comprises the amino acid sequence of SEQ ID NO: 122, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(ii) the VH comprises the amino acid sequence of SEQ ID NO: 9, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and the VL comprises the amino acid sequence of SEQ ID NO: 83, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto;

(iii) the VH comprises the amino acid sequence of SEQ ID NO: 4, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto, and the VL comprises the amino acid sequence of SEQ ID NO: 78, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; or

(iv) the nucleotide sequence encoding the VH comprises any one of SEQ ID NOs: 197, 155, or 150, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto; and/or the nucleotide sequence encoding the VL comprises any one of SEQ ID NOs: 270, 229, or 224, or a nucleotide sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical thereto.

13. The antibody of any one of claims 1-12, which is a full length antibody, a bispecific

antibody, an Fab, an F(ab')₂, an Fv, or a single chain Fv fragment (scFv).

14. The antibody of any one of claims 1-13, which is a humanized antibody.

15. The antibody of any one of claims 1-14, comprising a heavy chain constant region selected from human IgG1, human IgG2, human IgG3, and human IgG4, murine IgG1, murine IgG2a, murine IgG2b, murine IgG2c, and murine IgG3; and/or a light chain constant region chosen from the light chain constant regions of kappa or lambda, e.g., human or mouse kappa, or human or mouse lambda.

16. The antibody of any one of claims 1-15, comprising a human IgG4 heavy chain constant region and a human kappa light chain constant region.

17. The antibody of any one of claims 1-16, which:

(i) binds the C-terminus of a tau protein, e.g., residues 409-436 numbered according to SEQ ID NO: 920;

(ii) binds a microtubule binding domain of a tau protein;

(iii) binds a proline rich domain of a tau protein;

(iv) binds a tau protein which comprises at least one, two, three or more phosphorylated residues;

(v) binds enriched paired helical filament tau protein (ePHF);

(vi) binds an epitope comprising a region formed by a complex of at least two tau proteins, e.g., a tau dimer;

(vii) binds to a tau protein with a dissociation constant (K_D) of less than about 120 nM (e.g., as measured by Octet, e.g., as described in Example 8); and/or

(viii) reduces or inhibits aggregation of tau, e.g., inhibits aggregation of tau at a half maximal inhibitory concentration (IC₅₀) of from about 1 nM to about 30 nM (e.g., as measured by an immunodepletion assay (e.g., with tau RD Biosensor cells), e.g., as described in Example 6).

18. An antibody that competes for binding to tau with the antibody of any one of claims 1-17; or

that binds to the same epitope as, substantially the same epitope as, or an epitope that overlaps with, the epitope of the antibody of any one of claims 1-17.

19. A nucleic acid encoding the antibody of any one of claims 1-18.

20. A viral genome comprising a promoter operably linked to a nucleic acid encoding the antibody of any one of claims 1-18.

21. The viral genome of claim 20, wherein:

(i) the sequences of the encoded VH and VL are connected directly; or

(ii) the sequences of the encoded VH and VL are connected via a linker, optionally,

wherein the linker comprises the nucleotide sequence of any of the linker sequences provided in Table 15, or a nucleotide sequence at least 95% identical thereto.

22. The viral genome of claim 20 or 21, wherein the promoter is chosen from human elongation factor 1 α -subunit (EF1 α), cytomegalovirus (CMV) immediate-early enhancer and/or promoter, chicken β -actin (CBA) and its derivative CAG, β glucuronidase (GUSB), or ubiquitin C (UBC), neuron-specific enolase (NSE), platelet-derived growth factor (PDGF), platelet-derived growth factor B-chain (PDGF- β), intercellular adhesion molecule 2 (ICAM-2), synapsin (Syn), methyl-CpG binding protein 2 (MeCP2), Ca²⁺/calmodulin-dependent protein kinase II (CaMKII), metabotropic glutamate receptor 2 (mGluR2), neurofilament light (NFL) or heavy (NFH), β -globin minigene n β 2, preproenkephalin (PPE), enkephalin (Enk) and excitatory amino acid transporter 2 (EAAT2), glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), or a fragment, e.g., a truncation, or a functional variant thereof.

23. The viral genome of any one of claims 20-22, which further comprises:

(i) an enhancer;

(ii) a polyadenylation (polyA) signal region;

(ii) an ITR sequence, optionally wherein the ITR sequence is positioned 5' relative to the nucleic acid encoding the antibody and/or the ITR sequence is positioned 3' relative to the nucleic acid encoding the antibody;

(iii) at least 1, 2, or 3 intron regions;

(iv) at least 1, 2, or 3 exon regions; and/or
(v) a nucleotide sequence encoding a miR binding site, e.g., a miR binding site that modulates, e.g., reduces, expression of the payload encoded by the viral genome in a cell or tissue where the corresponding miRNA is expressed.

24. A vector comprising the nucleic acid of claim 19, the viral genome of any one claims 20-23, or a nucleotide sequence encoding the antibody of any one of claims 1-18.

25. An AAV particle comprising:

- (i) a capsid protein; and
- (ii) the viral genome of any one of claims 20-23.

26. The AAV particle of claim 25, wherein the capsid protein comprises an AAV5 capsid protein or variant thereof; or an AAV9 capsid protein or variant thereof.

27. A host cell comprising the antibody of any one of claims 1-18, the nucleic acid of claim 19, the viral genome of any one of claims 20-23, the vector of claim 24, or the AAV particle of claim 25 or 26, optionally wherein the host cell is an insect cell, a bacterial cell or a mammalian cell.

28. A method of producing an antibody, the method comprising culturing the host cell of claim 27 under conditions suitable for gene expression.

29. A pharmaceutical composition comprising the antibody of any one of claims 1-18, an AAV particle comprising the viral genome of any one of claims 20-23, or the AAV particle of claim 25 or 26; and a pharmaceutically acceptable excipient.

30. Use of the antibody of any one of claims 1-18, an AAV particle comprising the viral genome of any one of claims 20-23, the AAV particle of claim 25 or 26, or the pharmaceutical composition of claim 29, in the manufacture of a medicament for delivering an exogenous antibody that binds to tau to a subject.

31. The use of claim 30, wherein:

(i) the subject has, has been diagnosed with having, or is at risk of having a disease associated with expression of tau;

(ii) the subject has, has been diagnosed with having, or is at risk of having a neurological, e.g., neurodegenerative disorder; and/or,

(iii) the subject has, has been diagnosed with having, or is at risk of having a tauopathy.

32. Use of the antibody of any one of claims 1-18, an AAV particle comprising the viral genome of any one of claims 20-23, the AAV particle of claim 25 or 26, or the pharmaceutical composition of claim 29, in the manufacture of a medicament for treating a neurological or neurodegenerative disorder, e.g., a tauopathy, in a subject.

33. The Use of claim 31 or 32, wherein the neurological or neurodegenerative disorder comprises:

(i) a tauopathy; and/or

(ii) AD, FTDP-17, FTLT, FTD, CTE, PSP, Down's syndrome, Pick's disease, CBD, Corticobasal syndrome, ALS, Prion diseases, CJD, Multiple system atrophy, Tangle-only dementia, or Progressive subcortical gliosis.

34. The use of any one of claims 30-33, wherein the antibody or the AAV particle is formulated for intravenous administration, intramuscular administration, intraparenchymal administration, intracerebroventricular administration, intra-cisterna magna (ICM) injection, or intrathecal administration.

35. The use of any one of claims 30-34, further comprising administration of an additional therapeutic agent and/or therapy suitable for treatment or prevention of a neurological or neurodegenerative disorder, e.g., 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.