

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, 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.

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.